Cannabinoids in arterial, pulmonary and portal hypertension – mechanisms of action and potential therapeutic significance

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The endocannabinoid system is overactivated in arterial, pulmonary and portal hypertension. In this paper, we present limited clinical data concerning the role of cannabinoids in human hypertension including polymorphism of endocannabinoid system components. We underline differences between the acute cannabinoid administration and their potential hypotensive effect after chronic application in experimental hypertension. We discuss pleiotropic effects of cannabinoids on the cardiovascular system mediated via numerous neuronal and non-neuronal mechanisms both in normotension and in hypertension. The final results are dependent on the model of hypertension, age, sex, the cannabinoid ligands used or the action via endocannabinoid metabolites. More experimental and clinical studies are needed to clarify the role of endocannabinoids in hypertension, not only in the search for new therapeutic strategies but also in the context of cardiovascular effects of cannabinoids and the steadily increasing legalization of cannabis use for recreational and medical purposes.

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Abbreviations
2-AG, 2-arachidonoylglycerol; ACEA, arachidonyl-2-chloroethylamide; AEA, anandamide; AM1241, (2-Jodo-5-nitrophe none)-[1-[(1-methylpiperidin-2-yl)methyl]indol-3-yl]methanone; AM251, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-piperidin-1-ylpyrazole-3-carboxamide; AM3506, 5-(4-hydroxyphenyl)pentane-1-sulfonyl fluoride; AM404, (5Z,8Z,11Z,14Z)-N-(4-hydroxyphenyl)icoso-5,8,11,14-tetraenamide; AM6545, 5-[4-(4-cyanobut-1-ynyl)phenyl]-1-(2,4-dichlorophenyl)-N-(1,1-dioxo-1,4-thiazinan-4-yl)-4-methylpyrazole-3-carboxamide; Ang II, angiotensin II; CB1, cannabinoid CB1 receptor gene; CB2, cannabinoid CB2 receptor gene; CP55940, 2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-5-(2-methyloctan-2-yl)phenol; DOCA, 11-deoxycorticosterone acetate; eCBs, endocannabinoids; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; G3 vessels, third-order branches of the isolated mesenteric artery; HR, heart rate; HU210, (6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol; JWH-015, (2-methyl-1-propylindol-3-yl)-naphthalen-1-ylmethanone; JZL184, 4-nitrophenyl 4-[bis(2H-1,3-benzodioxol-5-yl)hydroxy]methyl]piperidine-1-carboxylate; MethAEA, methanandamide; NTS, nucleus tractus solitarii; OMDM-2, (Z)-N-[(2R)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl]octadec-9-enamide; PAH, pulmonary arterial hypertension; PEA, N-palmitoylethanolamine; PH, portal hypertension; PVN, paraventricular nucleus of hypothalamus; SHR, spontaneously hypertensive rats; SR144528, 5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)ethyl]-N-[(1S,4R,6S)-1,5,5-trimethyl-6-bicyclo[2.2.2]heptanyl]pyrazole-3-carboxamide; U46619, (Z)-7-[(1S,4R,5R,6S)-5-[(E,3S)-3-hydroxyoctyl-1-enyl]-3-oxabicyclo[2.2.1]heptan-6-yl]hept-5-enioic acid; URB597, 3-(3-carbamoylphenyl)phenyl N-cyclohexylcarbamate; WIN55522-2, (1R)-2-methyl-11-(morpholin-4-y1methyl)-3-[(naphthalen-1-yl)carbonyl]-9-oxa-1-azatricyclo[6.3.1.0^4,12]dodeca-2,4,6,8(12)-tetraene; Δ^9-THC, Δ^9-tetrahydrocannabinol

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Introduction

Marijuana is the most widely used illicit drug, with approximately 200 million users worldwide (see Orsini et al., 2016). Δ⁹-Tetrahydrocannabinol (Δ⁹-THC) is the major psychoactive component of the cannabis plant, but beyond the so-called phytocannabinoids, there are synthetic compounds, such as nabilone which is used for therapeutic purposes, and CB55940 and WIN55212-2 which are used for experimental purposes (for structures, see Malinowska et al., 2012).

Another group of cannabinoids is the endogenously formed endocannabinoids (eCBs), including arachidonoyl ethanolamide [anandamide (AEA)] and 2-arachidonoylglycerol (2-AG). They are formed from arachidonic acid and degraded by fatty acid amidase (FAAH) and monoacylglycerol lipase respectively. In addition, AEA is subject to an uptake process (Figure 1; see Cascio and Marini, 2015). The final component of this so-called eCB system (ECS) are receptors targeted by Δ⁹-THC, synthetic and eCBs, namely, the metabotropic cannabinoid CB1 and CB2 receptors. The eCBs have additional targets; the most well-known is the ionotropic TRPV1 receptor, which is activated by AEA (Figure 1; see Pertwee, 2015). The ECS plays an important role both in a quantitative and qualitative manner. For example, the density of CB1 receptors in various brain regions is higher than that of many other metabotropic receptors and these receptors are tonically active on numerous sites (see Pertwee, 2015).

At the moment, we are witnessing an increased legalization of cannabis use for recreational and medical purposes, particularly in the USA (Alshaarawy and Elbaz, 2016). For this reason, a clear-cut analysis of the risks of cannabis beyond the well-known addictive potential is important. For example, the ECS is implicated in cardiovascular functions, and there is concern that cannabis smoking increases cardiovascular disease risk in middle-aged adults (Hall, 2015). On the other hand, in their study dedicated to the role of the ECS in several hypertension models of the rat, Bátkai et al. (2004) reached the conclusion that ‘targeting the ECS offers novel therapeutic strategies in the treatment of hypertension’.

The aim of the current study is to critically review the association of the ECS and increased BP levels and to consider the effects of cannabinoids on BP in hypertensive humans and animals.

Cannabinoids in human arterial hypertension

In humans, tachycardia is the most well known and consistent acute physiological change produced by cannabis preparations and also serves as a useful cannabinoid biomarker. This holds true for the major psychotropic cannabis constituent, Δ⁹-THC (whether delivered p.o., i.v. or through smoking), for the oromucosal spray Sativex® (containing Δ⁹-THC: cannabidiol (CBD) ≈ 1:1) and for the orally administered synthetic cannabinoid nabilone (Cesamet®). Tachycardia may be accompanied by a modest increase in BP (particularly when supine) (see Malinowska et al., 2012; Ho and Kelly, 2017). The combination of tachycardia and a decrease in BP in response to inhaled Δ⁹-THC has been described as well (Crawford and Merritt, 1979). The epidemiological estimates from the US National Health and Nutrition Examination Survey (NHANES; 2005–2012; n = 12 426)
showed that, compared with “never use”, “recent” cannabis use (at least once in the 30 days prior to the interview) was associated with higher systolic but not diastolic BP in an age-adjusted and sex-adjusted model (Alshaarawy and Elbaz, 2016). When administered alone, the non-psychoactive phytocannabinoid CBD decreased resting BP and the stress-induced increase in BP (Jadoon et al., 2017). In contrast to acute administration, chronic use of cannabis may elicit a long-lasting bradycardia and prolonged reduction in BP (see Malinowska et al., 2012). Abrupt cessation of heavy (Vandrey et al., 2011) but not recreational (Bonnet, 2016), long-term daily cannabis use was followed by increases in BP.

Unfortunately, the possible involvement of eCBs in human arterial hypertension has been rarely investigated. No association was detected between cannabis use and hypertension or pre-hypertension in the NHANES studies (Alshaarawy and Elbaz, 2016). However, in the study by Crawford and Merritt (1979), differences between normotensive and hypertensive subjects were found but these were in small groups of subjects ($n = 8$ per group). Thus, the maximal positive chronotropic acute response to 2.8% Δ$^9$-THC inhalation was higher in sitting normotensive than in hypertensive patients, but the basal heart rate (HR) did not differ. By contrast, the intensity and duration of the depressor response to Δ$^9$-THC was greater in hypertensive than normotensive subjects. The latter difference may be, however, related to the different level of basal BP rather than to a specific alteration of the ECS.

A positive correlation between plasma levels of eCBs and BP has been found in hypertensive patients with obstructive sleep apnoea (Engeli et al., 2012) and in depressed women (Ho et al., 2012). Thus, the venous levels of AEA and the sum of 1-arachidonoylglycerol, 2-AG and oleoylethanolamide (but not arachidonic acid) were higher in sleep apnoea patients ($n = 55$) than in obese individuals ($n = 21$) without disordered nocturnal breathing. Importantly, AEA level was a stronger determinant of BP than sleep apnoea severity, obesity, insulin resistance and inflammation (Engeli et al., 2012). Moreover, serum contents of AEA and 2-AG strongly and positively correlated with BP in depressed ($n = 28$) but not healthy ($n = 27$) women, suggesting that serum eCBs might compensate for an elevated BP in depression. However, an additional factor that might affect the final conclusion was that the depressed subjects were obese (with BMI $\geq 30$ kg·m$^{-2}$), compared with their matched controls (Ho et al., 2012).

A potential compensatory role of AEA in lowering BP has also been suggested for peritoneal dialysis patients during volume expansion ($n = 105$; Bai et al., 2012). Thus, plasma AEA level was higher in patients with controlled hypertension (and high volume), as compared with patients with uncontrolled hypertension (and normal volume).

Genetic studies have partly confirmed the potential involvement of eCBs in hypertension. Thus, in a study including 1452 adult Japanese, male, but not female, carriers of the CC genotype of base 4895 in the 3’ untranslated region of exon 4 of the cannabinoid CB$_1$ receptor gene (CNR1), are more likely to be obese and hypertensive than the TT or TC allele carriers (Mutombo et al., 2012). By contrast, a large case–control study of 1968 individuals from Germany showed that 13 common single-nucleotide polymorphisms in the cannabinoid CB$_2$ receptor gene (CNR2) were not significantly implicated in the development of classic cardiovascular risk factors including hypertension (Reinhard et al., 2008). Interestingly, two FAAH defective gene variants exert different influence on BP. In young Caucasian students ($n = 215$) but not older male obese hypertensive patients ($n = 185$), the mutation associated with the exchange of Pro in position 129 by Thr led to a lower BP (Sarzani et al., 2008). On the other hand, homozygous TT and heterozygous CT in position rs6703669 of the FAAH gene were associated with a higher BP in European adult men than homozygous CC ($n = 420$; Burguete et al., 2009).

Four large-scale multicentre phase III clinical trials [Rimonabant in Obesity (RIO)-Europe, RIO-Lipids, RIO-Diabetes and RIO-North America] were carried out to test the effect of the CB$_1$ receptor antagonist rimonabant (20 mg·day$^{-1}$; for 1 year combined with a moderately hypocaloric diet) on body weight (total $n = 6625$; 37% of patients had hypertension). Rimonabant reduced body weight and also decreased BP in hypertensive but not in normotensive obese patients, in a manner dependent on the body weight loss, suggesting that its hypotensive effect is related to the weight loss (Ruilope et al., 2008). When rimonabant administration in the RIO-Europe Study was extended to 2 years, there was still a tendency towards a hypotensive effect, which, however, was no longer statistically significant ($n = 1507$; 41% with hypertension) (Van Gaal et al., 2008).

### Effects of acute cannabinoid administration on cardiovascular parameters in normotensive and hypertensive rats

In anaesthetized rats, rapid i.v. injection of AEA or its stable analogue methanandamide (MethAEA) induces typical triphasic changes in cardiovascular parameters: (I) a rapid, pronounced bradycardia and a transient drop in BP, (II) a brief pressor response and (III) a marked and prolonged decrease in BP and a slight decrease in HR. Only phases II and III occur after injection of Δ$^9$-THC and only phase III in response to WIN55212-2, CP55940 and HU210. By contrast, in conscious rats, AEA, MethAEA, Δ$^9$-THC and WIN55212-2 elicit a pressor response associated with vasoconstriction in the renal and mesenteric and vasodilatation in the hindquarters vascular bed as well as minor bradycardia (see Malinowska et al., 2012; O’Sullivan, 2015; Ho and Kelly, 2017).

Cannabinoids (AEA, MethAEA and HU210) and inhibitors of FAAH (URB597 and AM3506) or AEA transport (AM404 and OMDM-2) markedly decreased BP in anaesthetized or conscious rats with primary [spontaneously hypertensive (SHR)] and in different models of secondary hypertension. The same dose of the cannabinoid ligand did not affect BP, induced a modest decrease in BP only or even increased BP in the respective normotensive controls (Table 1). These depressor effects were connected with bradycardia (AEA and AM3506 but not URB597), decreased cardiac contractility and total peripheral resistance and renal, mesenteric and hindquarters vasodilatation. Again, these
## Table 1

Effects of acute i.v. (if not stated otherwise) administration of cannabinoid ligands on cardiovascular parameters in hypertensive rats and their normotensive controls

| Model of hypertension | Cannabinoid ligand | Dose (mg·kg⁻¹) | Anaesthesia | Effects: Hypertension | Effects: Normotension | References |
|-----------------------|-------------------|----------------|-------------|-----------------------|-----------------------|------------|
| SHR                   | AEA               | 10             | Pentobarbital | Sustained ↓ BP, ↓ HR, ↓ LVSP, ↓ dP/dt and ↓ TPR | WKY: modest ↓ BP and ↓ LVSP | Bátkai et al. (2004) |
| HU210                 | 0.001             | Isoflurane     |             | Sustained ↓ BP         | WKY: modest ↓ BP      | Godlewski et al. (2010) |
| URB597                | 10                | Pentobarbital  |             | ↓ BP, ↓ LVSP, ↓ dP/dt and ↓ TPR | WKY: no effect         | Bátkai et al. (2004) |
| AM3506                | 1                 | Isoflurane     |             | Sustained ↓ BP, ↓ HR, ↓ LVSP, ↓ dP/dt, ↓ TPR, ↓ CO and ↓ [NAdr] | WKY: modest ↓ BP      | Godlewski et al. (2010) |
| AM404                 | 10                | Pentobarbital  |             | ↓ BP                  | WKY: no effect         | Bátkai et al. (2004) |
| OMDM-2                | 5                 |               |             |                       |                       |            |
| MethAEA               | 5                 | Conscious      |             | (I) transient ↓ BP, (II) brief ↑ BP and (III) prolonged ↓ BP (phase III much stronger than in WKY) | WKY: (I) transient ↑ BP, (II) brief ↑ BP and (III) prolonged ↓ BP | Li et al. (2003) |
| Δ⁹-THC                | 5 p.o.            | Conscious      |             | ↓ BP                  | ↓ BP                  | Nahas et al. (1973) |
| Induced by Ang II     | AEA               | 10             | Pentobarbital | ↓ BP                  | Sprague–Dawley: no effect | Bátkai et al. (2004) |
|                       | URB597            | 10             |             |                       |                       |            |
| Both SHR and hypertension induced by chronic NOS inhibition and acute hypertension induced by Ang II/AVP | AEA | 3 | Conscious | (I) ↑ BP, renal and mesenteric vasoconstriction and (II) ↓ BP, renal and mesenteric vasodilatation | ↑ BP, renal and mesenteric vasoconstriction | Wheal et al. (2007a,b) and Ho and Gardiner (2009) |
|                       | MethAEA           | 3 or 0.25      |             |                       |                       |            |
|                       | WIN55212-2        | 0.15 or 0.25   |             |                       |                       |            |
| Induced by high-salt intake | MethAEA | 5 or 15 | Conscious | (I) transient ↓ BP, (II) brief ↑ BP and (III) prolonged ↓ BP (phase III much stronger than in WKY) | Wistar on normal-salt intake: (I) transient ↓ BP, (II) brief ↑ BP and (III) prolonged ↓ BP | Wang et al. (2007) |
| Induced by chronic inhibition of NOS | Δ⁹-THC | 1 infusionᵇ | Conscious | ↑ BP and ↓ HR, renal and mesenteric vasoconstriction and smaller | ↑ BP, renal and mesenteric vasoconstriction | O’Sullivan et al. (2007) |

*b* Indicates administration of Δ⁹-THC by infusion.
| Model of hypertension | Cannabinoid ligand | Dose (mg·kg⁻¹) | Anaesthesia | Effects Hypertension | Effects Normotension | References |
|-----------------------|-------------------|----------------|-------------|----------------------|----------------------|------------|
| 1K1C                  | Δ⁹-THC            | 1.5 i.p.       | Conscious   | ↑ BP and ↓ HR        | and hindquarters vasodilatation | Varma and Goldbaum (1975) |
| Transgenic (mRen-2)27 | WIN55212-2        | 0.25           | Conscious   | ↑ BP and ↓ HR, renal and mesenteric vasoconstriction and hindquarters vasodilatation | Sprague–Dawley: ↑ BP and ↓ HR, renal and mesenteric vasoconstriction | Gardiner et al. (2001) |
|                       | Rimonabant       | 10 p.o.        | Conscious   | ↓ BP and ↓ HR        | Sprague–Dawley: no effect | Schach et al. (2014) |
| Both SHR and hypertension induced by chronic NOS inhibition and acute hypertension induced by Ang II/AVP | URB597 | 3 | Conscious | No effect | No effect | Ho and Gardiner (2009) and Wheal et al. (2007a, b) |
|                       | AM251             | 1 or 3 both infusion* | Conscious | No effect | No effect | Ho and Gardiner (2009) and Wheal et al. (2007a, b) |
| SHR                   | Rimonabant       | 3              | Pentobarbital | ↑ BP, ↑ LVSP, ↑ dP/dt and ↑ CO | WKY: no effect | Bátkai et al. (2004) |
|                       | SR144528          | 3              | Pentobarbital | No effect | WKY: no effect | Bátkai et al. (2004) |
| Induced by Ang II    | AM251             | 3              | Pentobarbital | ↑ BP | Sprague–Dawley: no effect | Bátkai et al. (2004) |
| Salt-sensitive Dahl rats kept on 8% NaCl | Rimonabant | 3              | Pentobarbital | ↑ BP | Salt-sensitive Dahl rats kept on low-salt diet: no effect | Bátkai et al. (2004) |

↑, increase; ↓, decrease; 1K1C, one-kidney one-clip; AVP, arginine vasopressin; CO, cardiac output; dP/dt, slope of systolic pressure increment; LVSP, left ventricular systolic pressure; [NAdr], plasma noradrenaline concentration; TPR, total peripheral resistance.

*Infusion of 2 mL·h⁻¹ over 30 min.

Infusion in 0.5 mL of vehicle over 20 min.
alterations occurred in hypertensive but not normotensive animals (Table 1). In conscious rats with hypertension induced by chronic inhibition of NOS the fall in BP in response to AEA, MethAEA and WIN55212-2 were connected with a vasodilatation in vascular beds and preceded by a pressor response, accompanied by renal and mesenteric vasoconstriction. Δ⁰-THC given to SHR and renal hypertensive rats decreased BP and/or HR (see Table 1).

There are two exceptions from this pattern of cardiovascular responses to cannabinoids (Table 1). First, infusion of Δ⁰-THC into conscious rats made hypertensive by chronic inhibition of NOS and their normotensive controls caused comparable increases in BP associated with renal and mesenteric vasoconstriction; bradycardia occurred in hypertensive but not normotensive animals, and hindquarters vasodilatation was less in hypertensive than in normotensive rats. Second, in conscious hypertensive transgenic (mRen-2)27 rats and their normotensive controls, WIN55212-2-induced pressor and bradycardic responses were accompanied by renal and mesenteric vasoconstriction and hindquarters vasodilatation (the latter was less in hypertensive animals).

Neither cannabinoid receptor antagonists nor FAAH inhibitors nor genetic deletion of the latter components of the ECS affect BP or other cardiovascular parameters under physiological conditions (see Malinowska et al., 2012; O’Sullivan, 2015; Ho and Kelly, 2017). By contrast, the following observations underline the involvement of the ECS in the regulation of the cardiovascular system in hypertension (Table 1). Firstly, FAAH inhibitors or inhibitors of the AEA transport exerted cardiovascular effects in hypertensive animals. Furthermore, chronic inhibition of NOS and their normotensive controls caused comparable increases in BP associated with renal and mesenteric vasoconstriction; bradycardia occurred in hypertensive but not normotensive animals, and hindquarters vasodilatation was less in hypertensive than in normotensive rats. Second, in conscious hypertensive transgenic (mRen-2)27 rats and their normotensive controls, WIN55212-2-induced pressor and bradycardic responses were accompanied by renal and mesenteric vasoconstriction and hindquarters vasodilatation (the latter was less in hypertensive animals).

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Potential mechanisms involved in the cardiovascular effects of endocannabinoids in arterial hypertension

Under physiological conditions, cannabinoids act on the cardiovascular system via numerous central and peripheral mechanisms (see Malinowska et al., 2012; O’Sullivan, 2015; Ho and Kelly, 2017). Are these mechanisms involved in the hypotensive action of cannabinoids in hypertension?

Role of CB₁ and TRPV1 receptors

The AEA-induced prolonged hypotension in normotensive rats is mediated via CB₁ receptors (Malinowska et al., 2012; O’Sullivan, 2015; Ho and Kelly, 2017). Are these receptors also responsible for the hypotensive actions of cannabinoid ligands in hypertension (Figure 2)? Indeed, as already mentioned above for different hypertension models, the CB₁ receptor antagonists rimonabant or AM251 showed cardiovascular effects opposite in direction to those induced by agonists. Moreover, rimonabant and AM251 prevented or attenuated (i) the cardiovascular effects of the FAAH inhibitor AM3506 in anaesthetized SHR (Godlewski et al., 2010), (ii) the haemodynamic responses to WIN55212-2 in conscious rats with acute hypertension induced by infusion of Ang II/vasopressin (Ho and Gardiner, 2009) and (iii) the pressor and vasoconstrictor effects of Δ⁰-THC in conscious rats treated chronically with the NOS inhibitor L-NAME (O’Sullivan et al., 2007b). The situation is more complicated for conscious SHR (Wheal et al., 2007a). AM251 attenuated the pressor and vasoconstrictor effects of WIN55212-2 and the AEA-induced bradycardia, whereas the WIN55212-2-induced and AEA-induced hypotension and vasodilatation were not modified.
The eCB AEA does not only act on cannabinoid but also on vanilloid TRPV1 receptors (see Li et al., 2003). TRPV1 receptors (which are also activated by the AEA uptake inhibitor AM404; Zygmunt et al., 2000) occur on sensory nerves and mediate the vasodilator action of AEA via the release of CGRP (for literature, see Li et al., 2003). Is this mechanism important also in hypertension (Figure 2)? The answer is yes, as the prolonged hypotensive effect of MethAEA in SHR (Li et al., 2003) and in hypertensive rats fed a high-salt diet (Wang et al., 2007) was blocked not only by rimonabant but also by the TRPV1 receptor antagonist capsazepine. Importantly, MethAEA increased plasma CGRP level in mesenteric arteries and capsazepine increased BP by itself, and both effects were stronger in rats on high-salt than those on normal diet. Moreover, dietary consumption of the TRPV1 receptor agonist capsaicin, over 1 year, decreased BP and improved endothelial function in SHR (Yang et al., 2010). The pivotal role of vasodilatory TRPV1 receptors located on vascular sensory nerves in hypertension has also been confirmed in experiments on isolated vessels (see below). A role of TRPV1 receptors in hypertension is also suggested by the study of Marshall et al. (2013) on mice, although the protective effect of TRPV1 receptor deletion against obesity-induced hypertension and vascular hypertrophy is the opposite of what was expected.

**Neuronal mechanisms in the central and peripheral nervous system**

The involvement of central mechanisms in the cardiovascular effects of AM3506 has been clearly demonstrated in SHR (Godlewski et al., 2010). Thus, the pronounced hypotension and bradycardia induced by this FAAH inhibitor were reduced by the CNS-penetrating CB1 receptor antagonist AM251 but not by the peripherally restricted CB1 receptor antagonist AM6545. Moreover, HU210 led to a much greater hypotension in SHR than in Wistar Kyoto (WKY) rats, whereas the non-brain penetrant CB1/CB2 receptor mixed agonist CB13 evoked similar hypotensive responses in both strains. Interestingly, CB1 receptor density was similar in WKY rat and SHR brain but CB1 receptor coupling efficiency was increased in brain membrane preparations from SHR compared with the WKY rats, suggesting that this effect might be responsible for the strong hypotensive effects of AM3506 and HU210 in SHR. These decreases in BP resulted probably from a CB1 receptor-mediated decrease in sympathetic tone since they were (i) accompanied by a reduction in plasma noradrenaline levels and (ii) strongly reduced by ganglionic blockade with hexamethonium.

Sympathetic tone is mediated centrally by the rostral ventrolateral medulla (RVLM) and the paraventricular nucleus of the hypothalamus (PVN) (see Grzeda et al., 2017; Wang et al., 2017), two CNS nuclei, the function of which in hypertension is modified by cannabinoid ligands (Figure 2). Thus, it has been shown that microinjection of the CB1 receptor agonist arachidonyl-2-chloroethylamide (ACEA) into the RVLM increased BP, HR and renal sympathetic nerve activity (RSNA). All the above changes were more pronounced and lasted longer in SHR than in normotensive controls. AM251 microinjected into the RVLM not only blocked all cardiovascular effects of ACEA but also decreased BP, HR and RSNA more markedly in SHR than in normotensive controls. Expression of CB1 receptors was higher in the

**Figure 2**

Involvement of the ECS in experimental arterial (red colours), pulmonary (grey colours) and portal (brown colours) hypertension. Activation (+) or blockade (−) of CB1, CB2 or TRPV1 receptors or of eCB degradation by FAAH have beneficial effects, dependent on the site and the type of hypertension, † increase; ‡ decrease; CB, cannabinoid; CVLM, caudal ventrolateral medulla; DOCA, 11-deoxycorticoesterone acetate; FAAH1, 2 weeks of FAAH inhibition by URB597 1 mg·kg−1 twice daily; n. X, vagal nerve; NA, nucleus ambiguus; PoSN, postganglionic sympathetic nerve.
RVLM of SHR, but levels of AEA and 2-AG were similar when compared with control rats (Wang et al., 2017). In our own studies (Grzędz et al., 2017 and unpublished) on anaesthetized rats, a CB1 receptor-mediated depressor response could be evoked by microinjection of CP55940 into the PVN, which was reversed into a pressor response by i.v. AM251. The pressor response was enhanced in DOCA-salt hypertension but not in SHR, whereas the depressor response was not affected in either hypertensive model.

Sympathetic tone might also be diminished by the activation of presynaptic inhibitory CB1 receptors, which are located on sympathetic nerve endings innervating resistance vessels and lead to a reduction of noradrenaline release (Figure 2; see Malinowska et al., 2012). We have shown that the CB1 receptor-dependent inhibitory effect of CP55940 on the neurogenic vasopressor response was enhanced in DOCA-salt hypertension but not in SHR (Toczek et al., 2015; Malinowska et al., 2017).

Baroreflex sensitivity is known to be diminished in hypertension (see Brozoski et al., 2009). Microinjection of AEA into the nucleus tractus solitarii (NTS; the primary site for termination of baroreceptor afferent neurons) prolonged the baroreflex-related inhibition of RSNA in a manner dependent on CB1 receptors (Figure 2). The expression of CB1 receptors was reduced in SHR, in comparison with WKY rats. Accordingly, the baroreflex response evoked by AEA and the AEA uptake inhibitor AM404 was prolonged in normotensive, but not in hypertensive, rats (Brozoski et al., 2009).

Rimonabant increased BP and cardiac contractility in SHR only after i.v. but not i.c.v. administration suggesting that its effects are related to a peripheral but not a central site of action (Batkaı et al., 2004).

### Non-neuronal peripheral mechanisms

Cannabinoids are known for their vasodilatory effects (see Stanley and O’Sullivan, 2014) that might play a protective role in hypertension. However, as shown in Table 2 (references therein refer to male rats if not stated otherwise), there are marked differences in terms of hypertension model, vascular bed and cannabinoid ligand. Thus, the vasodilatory response to AEA, MethAEA and CBD in third-order branches of the isolated mesenteric artery (G3 vessels) and/or in the perfused mesenteric bed was reduced in SHR but enhanced in hypertension induced by DOCA-salt or chronic inhibition of NOS. AEA-induced vasodilatation was enhanced in the isolated aorta of SHR. Moreover, the effect of Δ⁹-THC but not AEA was enhanced in isolated G3 vessels in rats made hypertensive by NOS inhibition. Interestingly, in the latter model of hypertension, Δ⁹-THC increased BP and decreased mesenteric vascular conductance (O’Sullivan et al., 2007). The possible mechanisms responsible for the different responses to cannabinoid ligands in hypertension and the related references are listed in Table 2.

The potential hypotensive influence of cannabinoids might also result from the fact that they decrease the vasoconstriction or increase the vasodilatation induced by other agents (Table 2). Accordingly, CBD decreased the vasoconstrictor responses to phenylephrine and to the TXA2 analogue U46619 and increased the vasodilator effect of ACh and sodium nitroprusside in the aorta from SHR and DOCA-salt hypertensive rats when compared with their normotensive controls. Recently, a novel protective vascular mechanism of eCBs against various vasoconstrictors has been identified in the systemic and pulmonary circulations (Karpinski et al., 2017). Thus, U46619, phenylephrine and Ang II may stimulate rapid endothelial release of eCBs, leading to a CB1 receptor-dependent vasorelaxation, which via a negative feedback mechanism restrains vasoconstriction. We have detected this mechanism in G3 vessels but not in aorta isolated from SHR and WKY rats; the CB1 receptor antagonist AM251 enhanced the vasoconstrictor response to phenylephrine and U46619 probably by preventing the vasodilatory effect of eCBs released by the latter vasconstrictors (for details see Table 2).

Apart from factors such as the model of hypertension, vascular bed and cannabinoid ligand, sex-related effects have also been considered (Table 2). Thus, in SHR, the response to AEA in G3 vessels was decreased in hypertensive males, but not changed in female rats. Moreover, the vasodilator response to AEA was enhanced by 17β-oestradiol in G3 vessels isolated from male but not female SHR or male WKY rat. On the other hand, testosterone did not modify the AEA effect in G3 vessels from female WKY rat and SHR. 17β-Oestradiol modifies FAAH, and exactly the same pattern of AEA response modification has been obtained in the presence of URB597, as seen with 17β-oestradiol. Finally, the inhibitors of AEA and 2-AG degradation, URB597 and JZL184, respectively, diminished the vasoconstrictor response to Ang II in uterine artery isolated from rats in early stages of hypertensive pregnancy but not from normotensive controls (see Table 2).

We have examined whether the potential hypotensive effect of chronic FAAH inhibition by URB597 found in hypertensive DOCA-salt rats but not in SHR correlated with its vascular effects and/or changes in cardiac performance. The effect of chronic URB597 on BP only partly correlated with structural and functional changes in conductance and resistance vessels and was independent of Kca2.3/Kca3.1 channel-based vasodilatation. Thus, URB597 did not modify the response to MetAEA in G3 vessels from both hypertensive models. However, it reduced the vasoconstrictor effect of phenylephrine in DOCA-salt, but not in SHR. On the other hand, it enhanced the vasodilatory effect of ACh in SHR but not in DOCA-salt rats and reduced hypertrophy of aorta (but not G3) in DOCA-salt but not in SHR (see Table 2).

Reduction of increased cardiac contractility in hypertension could be one of the major components of the antihypertensive action of acute injection of FAAH inhibitors (Batkaı et al., 2004; Godlewski et al., 2010). Thus, in DOCA-salt but not in SHR, chronic URB597 administration reduced left ventricular hypertrophy and diastolic stiffness enhanced in hypertension. Importantly, it normalized the negative inotropic effect of CP55940 in left atria and the positive inotropic influence of isoprenaline in isolated heart both of which were diminished in hypertension. By contrast, in SHR, only normalization of the positive inotropic effect of isoprenaline was observed (Pedzińska-Betiku et al., 2017). Moreover, chronic FAAH inhibition improved the morphology of coronary vessels and myocardial glucose metabolism and slightly modified lipid metabolism in DOCA-salt hypertension (Polak et al., 2017a,b).
| Model of hypertension | Cannabinoid ligand | Plus other CB or non-CB agents | Vascular preparation | Degree of vasodilatation (if not stated otherwise) in comparison with the respective control | Mechanisms | Involved | Excluded | References |
|-----------------------|-------------------|-------------------------------|----------------------|------------------------------------------------------------------------------------------------|-----------|---------|---------|------------|
| SHR                   | AEA               | –                             | Mesenteric arterial bed<sup>b</sup> | ↓ NO-dependent relaxation and ENDO | ↓ | NO-dependent relaxation and ENDO | Changes in sensory nerve activity | Wheal and Randall (2009) |
| MethAEA               |                   | –                             | G3<sup>a</sup> | ↓ | H: CB<sub>1</sub> | – | – | Kloza et al. (2017a) |
| AEA                   |                   | –                             | G3<sup>a</sup> | ↓ TRPV1 and ENDO | ↓ | TRPV1 and ENDO | – | Ho (2013) |
| AEA                   |                   | –                             | Thoracic aorta<sup>a</sup> | ↑ | ENDO | – | CB<sub>1</sub> and TRPV1 | – | Wheal and Randall (2009) |
| CBD                   |                   | –                             | G3<sup>a</sup> | ↓ | – | – | – | Baranowska-Kuczko et al. (2016b) |
| Oleamide              |                   | –                             | Abdominal aorta<sup>a</sup> | ↑ PG | NO, FAAH, TRPV1, and ENDO | – | – | Hopps et al. (2012) |
| Induced by chronic inhibition of NOS | AEA               | –                             | G3<sup>a</sup> | ⇆ | – | – | – | Wheal et al. (2007b) |
|                       |                   | –                             | Mesenteric arterial bed<sup>b</sup> | ↑ | ↑ sensory nerve-mediated activity | ↑ | ↑ sensory nerve-mediated activity | – | Wheal et al. (2007b) and Wheal and Randall (2009) |
|                       | AEA               | –                             | Thoracic aorta<sup>a</sup> | ⇆ | – | – | CB<sub>1</sub>, TRPV1, NO and PG | – | Wheal and Randall (2009) |
|                       | Δ<sup>9</sup>-THC  | –                             | Aorta<sup>a</sup> | ⇆ | – | – | – | O'Sullivan et al. (2007) |
|                       | Δ<sup>9</sup>-THC  | –                             | G0<sup>a</sup> | ↑ | – | – | – | O'Sullivan et al. (2007) |
|                       |                   | –                             | G3<sup>a</sup> | ↑ | ↑ sensory nerve-mediated activity TRPV1, H: PG | ↑ | ↑ sensory nerve-mediated activity TRPV1, H: PG | CB<sub>1</sub> | – | Guo et al. (2015) |
| 2K1C                  | AEA               | –                             | Thoracic aorta<sup>a</sup> | ↑ | CB<sub>1</sub>, CB<sub>2</sub>, phosphorylation of endothelial NOS and ENDO | ↑ | ↑ phosphorylation of endothelial NOS and ENDO | – | – | Guo et al. (2015) |

<sup>a</sup> Indicates a significant difference compared to control. <sup>b</sup> Indicates the presence of changes in sensory nerve activity.
| Model of hypertension | Cannabinoid ligand | Plus other CB or non-CB agents | Vascular preparation | Degree of vasodilatation (if not stated otherwise) in comparison with the respective control | Mechanisms | References |
|-----------------------|-------------------|-------------------------------|---------------------|---------------------------------------------------------------------------------|------------|------------|
| DOCA-salt             | MethAEA           | –                             | G3<sup>a</sup>      | ↑                                                                             | TRPV1 and H: CB<sub>1</sub> –      | Baranowska-Kuczko et al. (2016a) |
| CBD                   | –                 | G3<sup>a</sup>                | –                   | –                                                                              | –          | Baranowska-Kuczko et al. (2016b) |
| SHR                   | AM251             | Phe                           | G3<sup>a</sup> but not in aorta<sup>a</sup> | ↑ contraction induced by Phe and U46619                                      | CB<sub>1</sub> –               | Kloza et al. (2017a) |
| Both DOCA-salt and SHR| URB597 (chronic) | MethAEA                       | G3<sup>a</sup>      | No changes in the vasodilator response to MethAEA                              | – – –      | Baranowska-Kuczko et al. (2016a, 2017) and Kloza et al. (2017a) |
|                       | URB597 (chronic) | Phe                           | G3<sup>a</sup> but not in aorta<sup>a</sup> | ↓ contraction induced by Phe in DOCA-salt (but not in SHR)                    | – – –      | Baranowska-Kuczko et al. (2016a, 2017) and Kloza et al. (2017a) |
|                       | URB597 (chronic) | Ach                           | G3<sup>a</sup> Aorta | H: vasodilator response to Ach in SHR (but not in DOCA-salt)                  | CB<sub>1</sub> –               | Baranowska-Kuczko et al. (2016a, 2017) |
| DOCAsalt              | URB597 (chronic) | ACh                           | G3<sup>a</sup>      | No changes in non-NO, non-PG-mediated relaxation in the presence of K<sub>Ca</sub> channel blockers | – – –      | Kloza et al. (2017b) |
|                       | URB597 (chronic) | NS309                         | G3<sup>a</sup>      | No changes in the vasodilator response to NS309                               | – – –      | Baranowska-Kuczko et al. (2016a, 2017) |
| CBD                   | Phe               | Aorta<sup>a</sup>             | –                   | ↓ contraction induced by Phe and U46619                                        | ENDO –     | Baranowska-Kuczko et al. (2016a, 2017) |
| CBD                   | ACh               | Aorta<sup>a</sup>             | –                   | ↑ vasodilator response to ACh                                                  | ENDO –     | Baranowska-Kuczko et al. (2016a, 2017) |

<sup>a</sup> Significance: DOCA-salt, SHR, CBD, URB597 (chronic), MethAEA, Phe, U46619, ACh, G3<sup>a</sup> (Goralska et al. 2016).
| Model of hypertension | Cannabinoid ligand | Plus other CB or non-CB agents | Vascular preparation | Degree of vasodilation (if not stated otherwise) in comparison with the respective control | Mechanisms | References |
|-----------------------|-------------------|--------------------------------|----------------------|------------------------------------------------------------------------------------------------|-----------|-----------|
| SHR                   | AEA               | 17β-Oestradiol                 | G3                   | ↑ vasodilator response to AEA in male but not in female, similarly in WKY | TRPV1     | Ho (2013) |
|                       |                   |                               |                      |                                                                                                | ENDO      |           |
|                       | AEA               | Testosterone                   | G3                   | Female: no change in the vasodilator response to AEA                                           | –         | END0     |
|                       |                   |                               |                      |                                                                                                |           |           |
|                       | AEA               | URB597                         | G3                   | ↑ vasodilator response to AEA in male but not in female, similarly in WKY                     | ENDO      |           |
|                       |                   |                               |                      |                                                                                                | –         |           |
| Hypertensive pregnancy| URB597            | Ang II                         | Uterine artery       | H↓ contraction induced by Ang II                                                              | CB1 and ENDO |          |
|                       |                   |                               |                      |                                                                                                | –         | Pulgar et al. (2014) |
|                      | JZL184            |                               |                      |                                                                                                |           |           |

↔ no changes; ↑ increase; ↓ decrease; CB, cannabinoid; ENDO, endothelium dependent; G0 and G3, superior mesenteric arteries and their third-order (small resistance) branches respectively; H, mechanisms determined in hypertension but not in normotension; 2K1C, two-kidney one-clip; NS309, activator of potassium K<sub>Ca2.3</sub>/K<sub>Ca3.1</sub> channels; Phe, phenylephrine (their involvement determined by the use of the COX inhibitor indomethacin).

*Isolated vessels taken from male (if not stated otherwise) hypertensive rats.

*Perfused vascular beds taken from male (if not stated otherwise) hypertensive rats.
Interaction of the endocannabinoid with the renin–angiotensin system

There is an increasing number of reports linking the ECS to the renin–angiotensin system (RAS). Interestingly, the cardiovascular effects of rimonabant in RAS-dependent hypertensive (mRen2)27 rats were opposite in direction to those observed in SHR (Table 1). Thus, its acute and chronic oral administration reduced rather than increased BP and HR in (mRen2)27 rats (Schaich et al., 2014). Acutely administered rimonabant might decrease BP via CB1 receptors located in the PVN, because its microinjection into this nucleus prevented the pressor effect of Ang II given into the PVN (determined in normotensive rats only; Gyombolai et al., 2012). The reason for the hypotensive effect after chronic CB1 receptor blockade may be the enhancement of baroreceptor sensitivity including an increase and decrease in the parasympathetic and sympathetic components respectively (Schaich et al., 2014). By contrast, CB1 receptor stimulation in the NTS of WKY rat but not SHR prolonged the baroreflex response (see above; Brozoski et al., 2009). Moreover, microinjection of rimonabant into the NTS did not modify baroreceptor sensitivity in normotensive rats, decreased it in ASRAGEN rats with low glial angiotensinogen and increased it in (mRen2)27 rats with up-regulated brain RAS expression, that is, animals with enhanced and impaired resting baroreceptor sensitivity respectively. The level of 2-AG (but not AEA) was increased in the NTS of (mRen2)27 but not of other rat strains, suggesting that an up-regulated brain ECS in Ang II-dependent hypertension may contribute to the impaired baroreceptor sensitivity in this model of hypertension (Schaich et al., 2016).

An interesting interaction in brainstem astrocytes has been determined between Ang II and CB1 receptors, which have been shown to elevate and to neutralize the inflammatory state respectively. Basal expression of CB1 receptors in brainstem astrocytes, which may play a role in hypertension (Haspula and Clark, 2016), was lower for SHR than for Wistar rats. Ang II infusion further decreased CB1 receptor expression via AT1 receptors. The authors have also examined cerebellar astrocytes, which may play a role in attention-deficit hyperactivity disorder. In this set of experiments, basal expression of CB1 receptors was higher in SHR than in WKY rats. Ang II infusion further increased CB1 receptor expression via both AT1 and AT2 receptors.

Moreover, the AEA transporter activity that is dependent on AT1 receptors and an increase in ROS production was decreased by Ang II in SHR when compared with WKY rats (Shi et al., 2012). The protective role of CB1 receptors against the vasoconstrictor effect of Ang II in uterine artery isolated from rats with hypertensive pregnancy has been described above (Pulgar et al., 2014).

The endocannabinoid system in pulmonary and portal hypertension

Pulmonary arterial hypertension (PAH) is a progressive, potentially lethal disease. The eCBs are known as potent vasodilators of isolated human and rat pulmonary arteries (see Stanley and O’Sullivan, 2014). However, their potential significance in PAH therapy is still to be established. On the one hand, AEA, which has an inhibitory effect on the two-pore domain potassium (K2P) channel, has been shown to reduce the hypoxia-induced vasoconstriction (one of the pathogenetic factors in PAH) in murine intra-acinar and pre-acinar arteries and had virtually no effect on the vascular calibre under normoxia (Murtaza et al., 2017). On the other hand, in the isolated perfused lung of the mouse (Wenzel et al., 2013) and the rabbit (Wahn et al., 2005), AEA increased the perfusion pressure via COX-2-generated metabolites, following enzymic degradation by FAAH into arachidonic acid products (Figure 2). Accordingly, the onset of PAH was prevented in FAAH−/− mice or by treating wild-type mice with the FAAH inhibitor URB597 for 3 weeks of hypoxia (Wenzel et al., 2013). The reason why AEA acts so differently in isolated pulmonary vessels and in perfused lungs is unclear, and the potential role of eCBs in PAH should be further investigated.

Portal hypertension (PH) is one of the most severe complications of liver cirrhosis, which in turn is a leading cause of death and liver transplantation. In this haemodynamic disturbance, mesenteric splanchnic vasodilation and hepatic vascular resistance play an essential role (see Baldassarre et al., 2013; Yang and Lin, 2015). The ECS is up-regulated in human and experimental cirrhosis, as a higher plasma AEA level was found in patients (also increased PEA and oleamide levels; Caraceni et al., 2010) and in rats with experimental cirrhosis (see Baldassarre et al., 2013; Yang and Lin, 2015). AEA caused a stronger CB1 and TRPV1 receptor-dependent vasodilatation of mesenteric, but not femoral, arteries isolated from cirrhotic rats, in comparison with their controls (Domenicali et al., 2005). On the other hand, AEA caused vasoconstriction in the isolated perfused liver, which was more marked for rats with cirrhosis induced by bile duct ligation than for their controls. The increased intrahepatic resistance was correlated with the release of TXA2 (Yang and Lin, 2015). Blockade of CB1 receptors by acute or chronic rimonabant administration and/or CB1 receptor deficiency increased the splanchnic vascular resistance in cirrhotic animals, leading to a concomitant decrease in the mesenteric arterial blood flow, reduced liver fibrosis and finally decreased PH and/or improved survival in different models of chronic liver damage. Opposing effects were found in CB2 receptor-deficient mice with experimental cirrhosis or in patients with the Q63R variant of the CB2 receptor that impairs its immunomodulating function (see Baldassarre et al., 2013). Accordingly, the CB2 receptor agonist JWH015 reduced PH, superior mesenteric arterial blood flow, hepatic angiogenesis, portosystemic shunting and hepatic fibrosis in biliary cirrhotic rats. The vascular effects in this model were, at least in part, connected with COX and NOS down-regulation (Huang et al., 2012). In the study by Reichenbach et al. (2012), the CB2 receptor agonist AM1241 led to similar beneficial effects on rats with CCl4-induced liver fibrosis (Figure 2).

A beneficial effect on cirrhotic disturbances might also be achieved by reduction of eCBs levels. Thus, the administration of the antibiotic ciprofloxacin resulted not only in a decrease in endotoxemia but also in a fall in the hepatic...
Table 3
Changes of the endocannabinoid system in hypertension (in comparison with respective normotensive groups)

| Model of hypertension         | Age          | eCB levels       | Receptor expression (or coupling efficiency) | Enzyme expression or activity and AEA transporter activity* | References                                                                 |
|-------------------------------|--------------|------------------|---------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------|
| Hypertensive patients         | 48–65 years  | Plasma: ↑ AEA    | –                                           | ↓ AEA transporter activity                                  | Li et al. (2009)                                                          |
| SHR                           | 16 weeks     | Plasma: ↑ AEA    | –                                           | ↓ AEA transporter activity                                  | Li et al. (2009) and Shi et al. (2012)                                     |
|                               | 32–40 weeks  | Heart: ↓ AEA and ↔ 2-AG | Heart: ↑ CB1                                 | Heart: ↑ FAAH expression                                    | Bátkai et al. (2004)                                                     |
|                               | 12–16 weeks  | Brain: ↔ AEA and ↔ 2-AG | Brain: ↑ CB1 (coupling efficiency)          | Brain: ↔ FAAH activity                                       | Godlewski et al. (2010)                                                  |
|                               | 10–12 weeks  | –                | Heart (LV): ↔ CB1 and ↔ CB2                | Heart (LV): ↓ FAAH expression                                | Pedzińska-Betiuk et al. (2017)                                           |
|                               | 10–12 weeks  | Kidney: ↑ AEA and ↑ 2-AG | Mesenteric artery: ↑ CB1                  | –                                                           | Kloza et al. (2017a)                                                     |
|                               |              | Kidney: ↑ AEA and ↑ 2-AG | Kidneys: ↑ CB1, ↑ CB2 and ↓ TRPV1          | Kidney: ↑ FAAH activity and ↑ MAGL activity                 | Biernacki et al. (2017)                                                  |
| DOCA-salt                     | 13–14 weeks  | –                | Aorta: ↔ CB1 and ↔ TRPV1                  | Aorta: ↔ FAAH expression                                     | Baranowska-Kuczkó et al. (2016a,b)                                       |
|                               |              |                  | Mesenteric artery: ↑ CB1 and ↔ TRPV1       | Mesenteric artery: ↔ FAAH expression                        |                                                                           |
|                               | 11–12 weeks  | Liver: ↑ AEA and ↑ 2-AG | Liver: ↑ CB1, ↔ CB2 and ↔ TRPV1           | Heart (LV): ↓ FAAH expression                                | Pedzińska-Betiuk et al. (2016)                                           |
|                               |              | Kidneys: ↑ AEA and ↑ 2-AG | Kidneys: ↑ CB1, ↑ CB2 and ↓ TRPV1         | Liver: ↔ FAAH activity and ↑ MAGL activity                  | Biernacki et al. (2016)                                                  |
|                               | 9 weeks      | Plasma: ↑ AEA    | Mesenteric artery: ↑ TRPV1                 | –                                                           | Wang et al. (2007)                                                       |
| High-salt intake              | 2K1C         | 10–11 weeks      | Mesenteric artery: ↑ TRPV1                 | ↔ AEA transporter activity                                   | Li et al. (2009)                                                         |

↔ no change; ↑ increase; ↓ decrease; 2K1C, two-kidney one-clip; CB1, cannabinoid CB1; CB2 receptor; LV, left ventricle.

*AEA transporter activity was determined in lymphocytes.
Changes in the endocannabinoid system in hypertension

The following changes in components of ECS demonstrated that it plays a protective role in hypertension (see Table 3). Firstly, the plasma level of AEA was higher in hypertensive patients and in three models of hypertensive rats (SHR, high-salt diet and two-kidney one-clip) when compared with the respective normotensive controls. Secondly, the expression of CB1 and TRPV1 receptors, activation of which leads to vasodilatation (CB1 and TRPV1 receptors) and a decrease in cardiac contractility (CB1 receptors), was higher in the heart of SHR, aorta of SHR and mesenteric artery of SHR, DOCA-salt rats and rats fed a high-salt diet. These changes were dependent on the hypertension model and the tissue. Thus, unlike in the plasma, the AEA level was decreased in hearts from SHR. In DOCA-salt hypertensive rats, expression of CB1 receptors was increased in G3 vessels but not in the aorta. The higher level of CB1 receptors in the total heart of SHR (Batkai et al., 2004) but not in their left ventricles (Pedzinska-Betiuik et al., 2017) might result from the different age or from regional differences within the heart. One should keep in mind that cardiac CB1 receptors are known to exert pro-inflammatory, pro-oxidative and pro-fibrogenic effects, whereas the CB2 receptors diminish the above actions (see Ho and Kelly, 2017); TRPV1 receptors attenuated the high-salt-induced cardiac hypertrophy (Lang et al., 2015).

The question arises as to which mechanism is responsible for the enhancement of eCB levels in hypertension. One possibility is the decrease in activity and/or expression of the enzymes responsible for their degradation. Accordingly, the decrease in myocardial AEA level in SHR was connected with an increase in FAAH expression in this tissue, whereas the CB2 receptors diminish the above actions (see Ho and Kelly, 2017); TRPV1 receptors attenuated the high-salt-induced cardiac hypertrophy (Lang et al., 2015).

The central hypotensive effect of the FAAH inhibitor AM3506 was associated with an increase in brain CB1 receptor coupling. Another mechanism might be the attenuation of AEA transporter activity, which may explain the higher plasma AEA level in hypertensive patients and SHR, but not in renal hypertensive rats (for details see Table 3).

Conclusions

In conclusion, the ECS is overactivated in arterial, pulmonary and portal hypertension. It is not clear, however, whether these changes are protective or detrimental, as cannabinoids exert pleiotropic effects on the cardiovascular system via numerous central and peripheral mechanisms, in both normotension and in hypertension. In addition, vasodilatation of the mesenteric vascular bed is protective in arterial, and detrimental in portal hypertension. Thus, as shown in Figure 2, the activation of central and peripheral CB1 receptors leads mainly to an increase and decrease in arterial BP respectively. Effects on BP might be connected with a central and peripheral modification of sympathetic tone, cardiac contractility and vascular diameter. One should keep in mind that eCBs can cause vasodilatation directly and vasoconstriction via formation of metabolites (PGs). This is one of the reasons for the different results obtained in vitro in isolated vessels and in perfused vascular beds (e.g. in lungs). The final results are additionally dependent on the model of hypertension, age, sex and the cannabinoid ligands used. Importantly, chronic experiments have cast doubt on the promising suggestion derived from acute experiments that targeting the ECS offers novel therapeutic strategies in the treatment of hypertension. Additional factors responsible for the modification of BP in chronic experiments include the increase and decrease of inflammatory, oxidative and fibrogenic effects mediated by CB1 receptors and CB2 receptors respectively. Interestingly, there is evidence that the ECS is influenced by some dietary factors such as β-caryophyllene and particular flavonoids (see Sharma et al., 2016). Thus, more experimental and clinical studies are needed to clarify the role of eCBs in different types of hypertension. Further therapeutic research should focus on the investigation of chronic effects of non-psychoactive cannabinoids, such as CBD, peripherally restricted CB receptor ligands and their interaction with food or antihypertensive drugs targeting the RAS. This is important not only with respect to the search for new therapeutic strategies, but also in the context of cardiovascular effects of cannabinoids and the steadily increasing legalization of cannabis use for recreational and medical purposes.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017a,b,c).

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Conflict of interest

The authors declare no conflicts of interest.

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