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Is the cardiovascular system a therapeutic target for cannabidiol?

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Cannabidiol (CBD) has beneficial effects in disorders as wide ranging as diabetes, Huntington's disease, cancer and colitis. Accumulating evidence now also suggests that CBD is beneficial in the cardiovascular system. CBD has direct actions on isolated arteries, causing both acute and time-dependent vasorelaxation. *In vitro* incubation with CBD enhances the vasorelaxant responses in animal models of impaired endothelium-dependent vasorelaxation. CBD protects against the vascular damage caused by a high glucose environment, inflammation or the induction of type 2 diabetes in animal models and reduces the vascular hyperpermeability associated with such environments. A common theme throughout these studies is the anti-inflammatory and anti-oxidant effect of CBD. In the heart, *in vivo* CBD treatment protects against ischaemia-reperfusion damage and against cardiomyopathy associated with diabetes. Similarly, in a different model of ischaemia-reperfusion, CBD has been shown to reduce infarct size and increase blood flow in animal models of stroke, sensitive to $5HT_{1A}$ receptor antagonism. Although acute or chronic CBD treatment seems to have little effect on haemodynamics, CBD reduces the cardiovascular response to models of stress, applied either systemically or intracranially, inhibited by a $5HT_{1A}$ receptor antagonist. In blood, CBD influences the survival and death of white blood cells, white blood cell migration and platelet aggregation. Taken together, these preclinical data appear to support a positive role for CBD treatment in the heart, and in peripheral and cerebral vasculature. However, further work is required to strengthen this hypothesis, establish mechanisms of action and whether similar responses to CBD would be observed in humans.

Introduction

Cannabidiol (CBD) is an abundant, non psychoactive, plant derived cannabinoid (phytocannabinoid) whose stereochemistry was first described in 1963 by Mechoulam and colleagues [1]. Isolation of the chemical structure of CBD revealed it to be a classical cannabinoid closely related to cannabinol and Δ^{-9}-tetrahydrocannabinol (THC). Since its isolation, a range of synthetic analogues have been synthesized based on the classic cannabinoid dibenzopyran structure, including abnormal CBD (Abn-CBD), O-1918 and O-1602 [2, 3]. CBD is reported to have a diverse pharmacology which is reviewed in depth elsewhere [4]. In brief, CBD shows antagonism of the classical cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) receptors in the low nanomolar range, yet has agonist/inverse agonist actions at micromolar concentrations. Other receptor sites implicated in the action of CBD include the orphan G protein coupled receptor GPR55, the putative Abn-CBD receptor, the transient receptor potential vanilloid 1 (TRPV1) receptor, α_1-adrenoreceptors, μ opiod receptors and $5HT_{1A}$ receptors [4]. It has also been shown that CBD activates and has physiological responses mediated by peroxisome proliferator activated receptor γ (PPARγ) [5–7]. As well as a rich pharmacology, CBD is suggested to have therapeutic potential in a vast range of disorders including inflammation, oxidative stress, cancer, diabetes, gastrointestinal disturbances, neurodegenerative disorders and nociception [8–12]. Evidence is also now accumulating that there are positive effects of CBD in the vasculature. It is the aim of this review to examine this evidence and establish whether or not the cardiovascular system is a potential therapeutic target for CBD. A recent review of the safety and side effects of CBD concluded that CBD appears to be well tolerated at high doses and with chronic use in humans [13], and thus has the potential to be taken safely into the clinic. Indeed, CBD is one of the active ingredients of the currently licensed medication, Sativex®.

Vascular effects of cannabinoids

The acute vascular effects of cannabinoid compounds have been well studied in a range of models. In a variety of *in vivo* and *in vitro* models, phytocannabinoids and endogenous cannabinoids (endocannabinoids) have been shown to cause vasorelaxation. However, the potency, efficacy and mechanisms of action often differ. For example, early work in rabbit cerebral arteries showed that THC and the endocannabinoid anandamide (AEA) caused vasorelaxation that was dependent on cyclooxygenase (COX) activity [14]. Later, Randall *et al*. [15] showed AEA-induced vasorelaxation in the perfused rat mesenteric bed that was inhibited by antagonism of the CB_1 receptor and inhibition of potassium hyperpolarization. The vasorelaxant effects of AEA in rat arteries are also dependent on the vessel size in that the maximal response to AEA is greater in small resistance vessels and includes an endothelial-dependent component that is not observed in larger arteries [16]. In rat aortae, the vasorelaxant response to AEA is not sensitive to CB_1 antagonism or TRPV1 desensitization, but is sensitive to $G_{i/o}$ protein inhibition using pertussis toxin (PTX) [17]. Further differences in cannabinoid effects can be found when comparing the same arterial bed of differing species. In rabbit aortae, AEA causes greater maximal relaxation than observed in rat aortae through a SR141716A (1 μM) sensitive pathway which is dependent on the endothelium [18]. It has also been shown that cannabinoid responses are dependent on the cannabinoid compound used. For example, the endocannabinoids AEA and *N*-arachidonoyl-dopamine (NADA) cause similar degrees of vasorelaxation in rat aortae, but by different mechanisms [17]. These studies highlight the complexity of acute vasodilator actions of cannabinoids on the vasculature (for a full review see [19]).

In addition to the direct vascular effects of cannabinoids, a large number of studies now suggest that endocannabinoids are mediators of myocardial infarction and ischaemic/reperfusion injury, cardiovascular risk factors and atherosclerosis [20–22]. The potential therapeutic uses of cannabinoids other than CBD in cardiovascular diseases, including cardioprotection, stroke, arrhythmias and atherosclerosis, have been reviewed elsewhere [22–24].

Direct vascular effects of CBD

Work to date investigating the vascular effects of cannabinoids has primarily concentrated on the response to endocannabinoids, THC and synthetic ligands, with only limited studies conducted using CBD. However, the effects of the CBD analogue, Abn-CBD, have been characterized. Jarai *et al*. [25] showed that Abn-Cbd caused hypotension in both $CB_1^{+/+}/CB_2^{+/+}$ and $CB_1^{-/-}/CB_2^{-/-}$ mice. The effects of Abn-CBD were inhibited by high. concentrations of SR141716A, endothelium denudation and CBD. In this paper, CBD was shown to antagonize the vasorelaxant effects of Abn-CBD and AEA. Begg *et al*. [26] showed in human umbilical vein endothelial cells (HUVECs) that Abn-CBD causes hyperpolarization through PTX-sensitive activation of large conductance calcium activated potassium channels (BK_{Ca}). Similarly, in rat isolated mesenteric arteries, Abn-CBD causes vasorelaxation that is dependent on the endothelium, SR141716A sensitive pathways and potassium channel hyperpolarization through large, intermediate and small conductance calcium activated potassium ($BK_{Ca}/IK_{Ca}/SK_{Ca}$) channels [27]. Interestingly, the previous work reported an endothelial-independent pathway that involved Abn-CBD modulation of the Ca^{2+} channels. The findings of endothelial dependent and independent components of Abn-CBD-induced vasorelaxation is in agreement with a similar study of the same year showing that in rat mesenteric arteries, vasorelaxation to Abn-CBD was inhibited by PTX incubation and incubation with another CBD anologue, O-1918, and indeed this was dependent on the endothelium [28]. More recently it has been shown that Abn-CBD causes vasorelaxation in the human pulmonary artery through similar mechanisms [29]. Taken together, these findings offer support to the presence of an endothelial bound $G_{i/o}$ protein coupled receptor that causes vasorelaxation through hyperpolarization that is activated by Abn-CBD.

Fewer studies have investigated the vascular effects of CBD. Jarai and colleagues [25] found no effect of perfusing 10 μM CBD on vascular tone in phenylephrine-constricted rat mesenteric vascular bed. However, in arterial segments taken from the rat mesenteric vascular bed that have been mounted onto a Mulvany-Halpern myograph and constricted with phenylephrine, CBD causes a concentration-dependent near-maximal vasorelaxation [28]. Unfortunately, this study did not probe the mechanisms underlying this vasorelaxant effect of CBD in rat mesenteric arteries.

In human mesenteric arteries, we have very recently shown that CBD causes vasorelaxation of U46619 and endothelin-1 pre-constricted arterial segments (Stanley & O'Sullivan, 2012, under review). In human mesenteric arteries, CBD-induced vasorelaxation has a pEC_{50} in the mid-micromolar range which is similar to that observed in rat mesenteric arteries. However, CBD-induced vasorelaxation in human arteries has a maximal response of ~40% reduction of pre-imposed tone. We went on to show that CBD-induced vasorelaxation in human mesenteric arteries is endothelium-dependent, involves CB_1 receptor activation

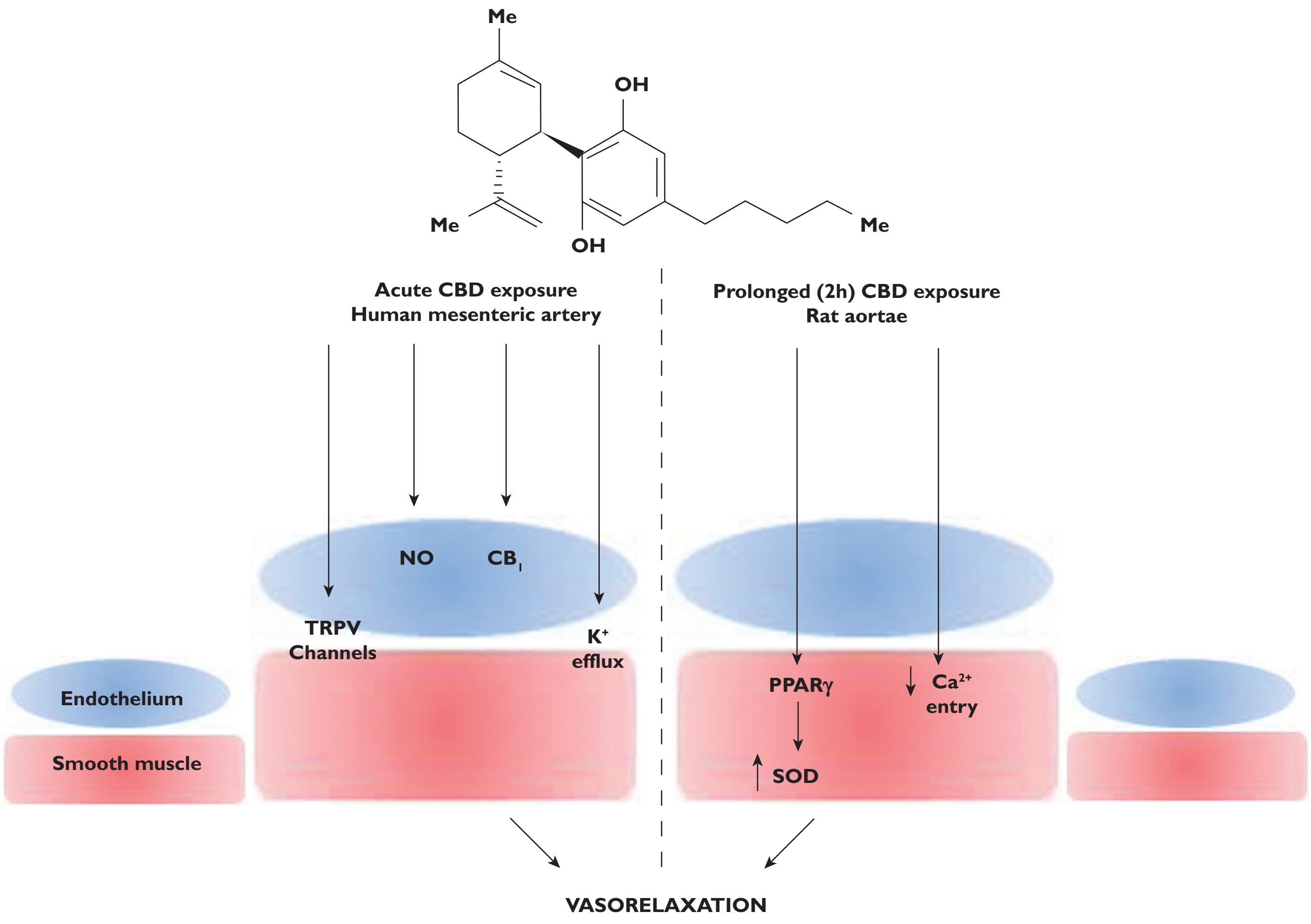

Figure 1

Direct vascular effects of CBD measured in isolated arteries. TRPV, transient receptor potential vanilloid; NO, nitric oxide; CB1, cannabinoid receptor 1; PPARγ, peroxisome proliferator activated receptor gamma; SOD, superoxide dismutase

and TRPV channel activation, nitric oxide release and potassium hyperpolarization (Figure 1) (Stanley & O'Sullivan, 2012, under review).

It is interesting to note that Ruiz-Valdepenas *et al*. [34] recently showed that CBD inhibited lipopolysaccharide (LPS)-induced arteriolar and venular vasodilation. LPS has been suggested to cause hypotension through activation of a novel as yet unidentified cannabinoid receptor which could be inhibited by SR141716A but not AM251 [35]. Since CBD is suggested to be an antagonist of this receptor [25], this could explain how CBD inhibits LPS-induced vasodilation.

Time-dependent vasorelaxant effects of CBD (and PPARγ agonism)

PPARγ agonists have been shown to have positive cardiovascular effects, which include increased availability of nitric oxide, reductions in blood pressure and attenuation of atherosclerosis [36, 37]. Some of the beneficial effects of PPARγ ligands are brought about by anti-inflammatory actions, including inhibition of pro-inflammatory cytokines, increasing anti-inflammatory cytokines and inhibition of inducible nitric oxide synthase (iNOS) expression (for review see [38]). Increasing evidence has indicated that cannabinoids are capable of binding to, activating and causing PPAR–mediated responses [39]. We have shown that the major active ingredient of cannabis, THC, activates PPARγ, and that THC causes time-dependent, endothelium-dependent, PPARγ-mediated vasorelaxation of the rat isolated aorta [40, 41]. Subsequently, we tested whether CBD might also activate PPARγ and that this might mediate some of the pharmacological effects of cannabidiol. In these experiments we showed that CBD is a weak/partial agonist at the PPARγ receptor which increases PPARγ transcriptional activity in PPARγ overexpressing HEK293 cells, and CBD binds to the PPARγ ligand binding domain with an $IC_{50} \approx 5\ \mu M$ [5]. Like THC, CBD (at concentrations above

100 nM) was also found to cause a time-dependent vasorelaxation of rat aortae. This time-dependent vasorelaxation was inhibited using the PPARγ antagonist GW9662 or the superoxide dismutase (SOD) inhibitor diethyldithiocarbamate (DETCA). Increased SOD activity promotes vasorelaxation through reductions in reactive oxygen species, and our data are in agreement with other work showing PPARγ ligands cause the induction of Cu/Zn-SOD [42]. However, it should be noted that recent work has suggested the use of TZDs may lead to decreases in cardiovascular function and could prompt incidents such as acute myocardial infarction, heart failure and stroke [43–45]. Side effects associated with PPARγ ligands include weight gain, oedema and increased plasma lipoproteins [46]. However, weak/partial agonists at the PPARγ receptor may be void of these detrimental side effects [46]. CBD may prove to have therapeutic utility as a low affinity agonist of PPARγ.

Haemodynamic effects of CBD

Few studies to date have examined the haemodynamic responses to CBD. One study has shown that in pentobarbitone anaesthetized rats, that CBD (50 μg kg^{-1} i.v. but not 10 μg kg^{-1}) causes a significant but transient 16 mmHg fall in mean arterial blood pressure without affecting heart rate [47]. However, other studies do not report any acute effects of *in vivo* treatment with CBD on baseline heart rate or blood pressure in animal studies [48, 49]. In a recent review, Bergamaschi *et al*. [13] concluded that CBD treatment in humans did not result in changes in blood pressure or heart rate. Thus, the majority of evidence suggests there is no effect of CBD on haemodynamics. However, as has been observed with other cannabinoid compounds, the potential hypotensive effects of CBD may need to be revealed in models of raised blood pressure. Additionally, any change in haemodynamics that might occur may be rapid [47] and therefore not observed in chronic treatment studies.

CBD is known to be anxiolytic. CBD treatment reduces anxiety related to public speaking or fearful stimuli in humans [10]. A number of studies have now also shown that CBD reduces the cardiovascular response to anxiety or stressful situations. Resstel and colleagues have shown in Wistar rats that a single dose of CBD (10 or 20 mg kg^{-1} i.p.) reduced the heart rate and blood pressure response to conditioned fear [49] or to acute restraint stress [48]. The inhibitory effect of CBD on the cardiovascular response to stress was shown to be inhibited by WAY100635, a $5HT_{1A}$ receptor antagonist. This effect appears to be mediated in the brain, as the same effect of CBD on cardiovascular responses could be mimicked when CBD was injected into the bed nucleus of the stria terminalis (a limbic structure) [50]. The potential ability of CBD treatment in humans to reduce the cardiovascular (as well as behavioural) response to stress could have significant effects on the development of atherosclerosis and hypertension, which are known to be accelerated by stress [51, 52].

Cardioprotective effects of CBD

Several studies have shown that CBD is beneficial in preventing ischaemia-reperfusion damage in the liver [53, 54] and brain [55]. In 2007, Durst and colleagues first showed that *in vivo* treatment with CBD (5 mg kg^{-1} i.p. pre-ischaemia and then for 7 days after) significantly reduced the infarct size of hearts where the left anterior descending (LAD) coronary artery had been ligated, and this was associated with a reduction in infiltrating leucocytes and circulating interleukin (IL)-6 concentrations. Furthermore, they showed that this cardioprotective effect of CBD could not be mimicked *in vitro*, and suggested that the cardioprotective effects of CBD are due to a systemic immunomodulatory effect rather than a direct effect on the heart [56]. Walsh *et al*. [47] subsequently showed that a single dose of CBD (50 μg kg^{-1} i.v.) given 10 min pre-ischaemia or 10 min pre-reperfusion could significantly reduce infarct size after LAD coronary artery ligation. This was also associated with a reduction in ventricular ectopic beats, suggesting an additional anti-arrhythmic role for CBD. Rajesh *et al*. [57] showed that 11 weeks *in vivo* treatment with CBD (20 mg kg^{-1} i.p.) significantly reduced cardiac dysfunction in diabetic mice, associated with decreased myocardial inflammation, oxidative stress, nitrative stress and fibrosis, mediated by reduced nuclear factor-κB activation (NFκB), reduced mitogen-activated protein kinase (MAPK) activation and reduced expression of adhesion molecules and tumour necrosis factor (TNF). Other studies have found that the anti-inflammatory effects of CBD via NFκB are not mediated by CB_1, CB_2 or Abn-CBD receptor activation [58].

Together, these data suggest that *in vivo* treatment with CBD has significant cardioprotective effects, which may be through a direct action on the heart or via a general anti-inflammatory, anti-oxidant mechanism (see Table 1).

Vasculoprotective effects of CBD

There is a growing body of evidence that administration of CBD can ameliorate the negative effects of conditions associated with endothelial dysfunction. The high glucose conditions associated with diabetes have been reported as a causal factor in endothelial dysfunction. High glucose promotes inhibition/uncoupling of endothelial nitric oxide, increased superoxide production, increased actions of constrictor prostanoids, decreased actions of vasorelaxant prostanoids and increased reactive oxygen species [59]. Alongside these changes, high glucose is also

Table 1

The current body of evidence supporting a therapeutic role for CBD in cardiovascular disorders

Disorder	Model	Conc/Dose of CBD	Summary of findings	Reference
	Preconstricted, Wistar rat aortae	10 μM, 2 h incubation	Vasorelaxation mediated by PPARγ receptor, ↑ SOD and ↓ Ca^{2+}entry	O'Sullivan *et al.*, 2009 [5]
	Preconstricted human mesenteric arteries	0.1–100 μM	Acute vasorelaxation mediated by CB$_1$ receptor, TRPV channels, the endothelium, and nitric oxide	Stanley & O'Sullivan, 2012 [89]
Diabetes	STZ-induced diabetic SD rats	10 mg kg^{-1} i.p. for up to 4 weeks	↓ in diabetes-induced hyperpermeability ↓ inflammation ↓ oxidative stress ↓ VEGF	El-Remessy *et al.*, 2006 [63]
	High glucose treated human coronary artery endothelial cells	0–6 μM, 48 h incubation	↓ ICAM-1 and VCAM-1 ↓ monocyte adhesion and trans-endothelial migration ↓ disruption of endothelial barrier ↓ superoxide production ↓ inflammation	Rajesh *et al.* 2007 [62]
	STZ-induced diabetic mice	20 mg kg^{-1} i.p. for 11 weeks	↓ Left ventricular dysfunction ↓ myocardial oxidative stress ↓ myocardial inflammation ↓ myocardial fibrosis ↓ myocardial nitrative stress	Rajesh *et al.*, 2010 [57]
Myocardial infarction	LAD ligation in the SD rat	5 mg kg^{-1} i.p. (pre-ischaemia and for 7 days)	↓ infarct size ↓ infiltrating leucocytes ↓ circulating IL-6	Durst *et al.*, 2007 [56]
	LAD ligation in the SD rat	50 μg kg^{-1} i.v. 10 min pre-ischaemia or 10 min pre-reperfusion	↓ infarct size ↓ ventricular ectopic beats (only when given pre-ischaemia) ↓ platelet aggregation	Walsh *et al.*, 2010 [47]
Stress	Conditioned fear, Wistar rats	10 mg kg^{-1} i.p., 30 min before testing	↓ HR and MAP response to stress	Resstel *et al.*, 2006 [49]
	Restraint stress, Wistar rats	10 or 20 mg kg^{-1} i.p., 30 min before testing	↓ HR and MAP response to stress Inhibited by a 5HT$_{1A}$ antagonist	Resstel *et al.*, 2009 [48]
Stroke	Bilateral carotid occlusion, male Mongolian gerbils	5 mg kg^{-1} i.p., 5 min after surgery	Inhibited EEG flattening Inhibited hyperlocomotion ↑ survival of CA1 hippocampal neurons	Braida *et al.*, 2003 [67]
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO	↓ infarct size ↑ CBF Independent of TRPV1 Inhibited by 5HT$_{1A}$ antagonism ↑ CBF	Mishima *et al.*, 2005 [69]
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO Repeated treatment 3 mg kg^{-1} for 14 days	↑ cerebral blood flow ↑ antioxidant power Independent of CB$_1$ Inhibited by 5HT$_{1A}$ antagonism	Hayakawa *et al.*, 2007 [70]
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO; 1, 2 or 4 h after MCAO	Inhibited neutrophil activity ↓ infarct size ↑ CBF Improved motor coordination Effective both pre- or post-ischaemia Independent of CB$_1$ or CB$_2$	Hayakawa *et al.*, 2007 [71]
Encephalitis	LPS-treated mice	3 mg kg^{-1} i.v. at the same time as LPS	↓ vasodilator effect of LPS on CBF ↓ LPS-induced BBB permeability ↓ LPS-induced expression of TNFα and COX-2	Ruiz-Valdepenas *et al.*, 2011 [34]

CBF, cerebral blood flow; EEG, electroencephalographic; HR, heart rate; ICAM, intracellular cell adhesion molecule; i.p., intraperitoneally; i.v., intravascularly; LAD, left anterior descending coronary artery; MAP, mean arterial blood pressure; MCAO, middle cerebral artery occlusion; SD, Spague Dawley; SOD, superoxide dismutase; STZ, streptozotocin; TRPV1, transient receptor potential vanilloid receptor 1; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

reported to increase leucocyte adhesion and monocyte endothelial migration [60], which has been reported to be through NFκB activity [61].

In human coronary artery endothelial cells, prolonged exposure to high glucose has been shown to cause increased levels of adhesion molecules (ICAM-1 and VCAM-1), disruption of the endothelial barrier, mitochondrial superoxide production, iNOS and NFκB expression [62]. These effects were all reduced when the cells were co-incubated with CBD compared with high glucose alone.

CBD also decreased monocyte adhesion and transendothelial migration, which are key elements in the progression of atherosclerosis. Neither the CB_1 nor CB_2 receptors were responsible for mediating the effects of CBD [62]. Using an *in vivo* model of diabetic retinopathy, El-Remessy *et al*. [63] similarly found that CBD treatment (10 mg kg^{-1}, every 2 days, i.p.) prevented vascular hyperpermeability at the blood–retinal barrier (BRB), and protected the retina against oxidative damage, inflammation and an increase in adhesion molecules. Thus, CBD-mediated protection of the vasculature in a model of diabetes may lead to a reduction in complications such as retinopathy, although this could also be driven by the neuroprotective effects of CBD.

Sepsis-related encephalitis, modelled by parenteral injection of LPS in mice, induces profound arteriolar dilation, resulting in brain hyperaemia and blood–brain barrier (BBB) disruption [34]. Administration of CBD (3 mg kg^{-1} i.v.) at the same time as LPS maintained BBB integrity, inhibited LPS-induced arteriolar and venular vasodilation, leucocyte margination, and suppressed excessive nitric oxide production. Although cerebral blood flow (CBF) was not measured directly, the results observed from various parameters led the authors to suggest that CBD had ameliorated the LPS-induced drop in CBF [34].

We have carried out some preliminary experiments examining the ability of CBD to modulate vasodilator responses. Using the Zucker diabetic rat model of type 2 diabetes, where endothelium-dependent vasorelaxation is known to be impaired, we showed that incubation of the aorta for 2 h with CBD (10 μM) significantly enhanced the vasorelaxant response to acetylcholine, an endothelium-dependent vasodilator [64]. We have similarly shown that incubation with CBD enhances the vasorelaxant response to acetylcholine in the spontaneously hypertensive rat (O'Sullivan, unpublished data).

Taken together these studies show that *in vitro* and *in vivo*, using cell culture, isolated tissue and animal models, CBD has been demonstrated to reduce the negative effects of high glucose, diabetes and inflammation on the vasculature and on vascular hyperpermeability. As yet, the receptor sites of action for CBD in some of these studies remain unclear, but a common theme is the reduction in inflammatory markers (see Table 1).

CBD in models of stroke

Administration of endogenous, synthetic or phytocannabinoids has been shown to provide neuroprotection using a variety of *in vivo* and *in vitro* disease models, including stroke [65]. The neuroprotective potential of CBD in ischaemic stroke was first explored by Hampson and colleagues [66], where they subjected rats to middle cerebral artery occlusion (MCAO) and demonstrated that CBD, given at onset of insult (5 mg kg^{-1}, i.v.) and 12 h after surgery (20 mg kg^{-1} i.p.), reduced infarct size and neurological impairment by 50–60%. Similarly, post ischaemic administration of CBD (1.25 to 20 mg kg^{-1}, i.p.) protected against ischaemia-induced electroencephalographic flattening, hyperlocomotion and neuronal injury in gerbils after MCAO [67]. More recently, it has been shown that CBD (3 mg kg^{-1} i.p.) reduced infarct volume following MCAO, independent of CB_1 receptor or TRPV1, but sensitive to the $5HT_{1A}$ receptor antagonist WAY100135 (10 mg kg^{-1}, i.p.) [68, 69]. Furthermore, CBD (3 mg kg^{-1} i.p.) provided neuroprotection even when administered up to 2 h post reperfusion without the development of tolerance [70, 71].

CBF is reduced or completely abolished in certain areas of the brain during ischaemic stroke, thus, restoring CBF to provide adequate perfusion is of great importance. CBD has been shown to be successful in increasing CBF, as measured by laser-Doppler flowmetry, following MCAO and after reperfusion (3 mg kg^{-1} i.p.) [69–71]. The increased CBF induced by CBD (3 mg kg^{-1} i.p.) was partially decreased by $5HT_{1A}$ receptor antagonism, suggesting that CBD may exert these beneficial effects, at least in part, via the serotonergic $5HT_{1A}$ receptor [69]. Exposing newborn piglets to hypoxia-ischaemia, Alvarez and colleagues [72] also demonstrated the ability of CBD (0.1 mg kg^{-1} i.v., post insult) to provide neuroprotection in a manner that included the preservation of cerebral circulation.

As previously discussed, administration of CBD (3 mg kg^{-1} i.v.) at the same time as LPS maintains BBB integrity [34]. Although CBF was not measured directly, the results observed from various parameters led the authors to suggest that CBD had ameliorated the LPS-induced drop in CBF [34]. BBB disruption is an important facet in the pathophysiology of ischaemic stroke [73]. Therefore, CBD-mediated preservation of this barrier, as demonstrated in other disease models could represent another mechanism of CBD-mediated protection in ischaemic stroke. Agonism of PPARγ may represent another mechanism of action for the beneficial effects of CBD in stroke. Several groups have found that synthetic PPARγ agonists, thiazolidinediones (TZDs), a class of drugs used to improve insulin sensitivity, reduced infarct size and improved functional recovery from stroke in rats [74–78]. Improvement is associated with reduced inflammation which is a probable mechanism of recovery, and, importantly, improvement is seen whether TZDs are administered before or after MCAO [75, 77]. Recently, *in vivo* CBD treatment has been shown to have neuroprotective effects in an Alzheimer's disease model which were inhibited with a PPARγ antagonist [6]. Similarly, we have shown in a cell culture model of the BBB that CBD restores the enhanced permeability induced by oxygen glucose deprivation, which could be inhibited by a PPARγ antagonist (Hind & O'Sullivan, unpublished observations).

In summary, CBD provides neuroprotection in animal and *in vitro* models of stroke. In addition to any direct neuroprotective effects of CBD, this is mediated by the ability of CBD to increase cerebral blood flow and reduce vascular hyperpermeability in the brain (see Table 1).

Haematological effects of CBD

In addition to the effects of CBD on the heart and vasculature, there is evidence that CBD also influences blood cell function. Early studies showed that CBD increases phospholipase A_2 expression and lipooxygenase products in platelets [79] and that CBD inhibits adenosine or epinephrine stimulated platelet aggregation [80], and more recently, collagen stimulated platelet aggregation [47]. 5-HT release from platelets has been shown to be decreased by CBD [81] or not affected by CBD [80].

In white blood cells, CBD induces apoptosis of fresh human monocytes [82] and human leukaemia cell lines [83, 84], which the later study showed was dependent on CB_2 activation, but not CB_1 or TRPV1. However, CBD can also prevent serum-deprived cell death of lymphoblastoid cells in serum-free medium by anti-oxidant mechanisms [85]. McHugh *et al*. [86] showed that CBD itself did not affect neutrophil migration, but that CBD inhibited formyl-Met-Leu-Phe-OH (fMLP)-stimluated neutrophil migration. CBD also inhibits monocyte adhesion and infiltration [62] and white blood cell margination in cerebral blood vessels after LPS treatment [34]. CBD significantly inhibits myeloperoxidase (which is expressed in neutrophils, monocytes and some populations of human macrophages) activity at 1 h and 20 h after reperfusion in mouse MCAO models [70, 87]. CBD also causes a dose-dependent suppression of lymphocyte proliferation in a murine collagen-induced arthritis model [88].

Together these studies show that CBD influences both the survival and death of white blood cells, white blood cell migration and platelet aggregation, which could underpin the ability of CBD to delay or prevent the development of cardiovascular disorders.

Conclusion

In summary, this review has presented evidence of the positive effects of CBD in the cardiovascular system, summarised in Table 1. In isolated arteries, direct application of CBD causes both acute and time-dependent vasorelaxation of preconstricted arteries and enhances endothelium-dependent vasorelaxation in models of endothelial dysfunction. *In vivo*, CBD treatment does not appear to have any effect on resting blood pressure or heart rate, but does reduce the cardiovascular response to various types of stress. *In vivo*, CBD treatment has a protective role in reducing the effects of cardiac ischaemia and reperfusion, or in reducing cardiac dysfunction associated with diabetes. Similarly, CBD has a protective role in reducing the ischaemic damage in models of stroke, partly due to maintaining cerebral blood flow. In models of altered vascular permeability, CBD reduces the hyperpermeability of the BRB in diabetes and BBB hyperpermeability after LPS injection. Similarly, CBD ameliorates the negative effects of a high glucose environment on cell adhesion molecules and barrier function. Together, these data suggest that the cardiovascular system is indeed a valid therapeutic target for CBD. However, the target sites of action for CBD remain to be established for most of these responses. Whether these responses to CBD will translate into the human cardiovascular system also remains to be established.

Competing Interests

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REFERENCES

1 Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006; 147: S163–S71.

2 Pertwee RG. Pharmacological actions of cannabinoids. Cannabinoids 2005. p. 1–51.

3 Razdan RK. Structure-activity relationship of classical cannabinoids. In: The Cannabinoid Receptors, ed. Reggio PH. New York: Humana Press, 2009; 3–19.

4 Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br J Pharmacol 2008; 153: 199–215.

5 O'Sullivan SE, Sun Y, Bennett AJ, Randall MD, Kendall DA. Time-dependent vascular actions of cannabidiol in the rat aorta. Eur J Pharmacol 2009; 612: 61–8.

6 Esposito G, Scuderi C, Valenza M, Togna GI, Latina V, De Filippis D, Cipriano M, Carratu MR, Iuvone T, Steardo L. Cannabidiol reduces Abeta-induced neuroinflammation and promotes hippocampal neurogenesis through PPARgamma involvement. PLoS ONE 2011; 6: e28668.

7 De Filippis D, Esposito G, Cirillo C, Cipriano M, De Winter BY, Scuderi C, Sarnelli G, Cuomo R, Steardo L, De Man JG, Iuvone T. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS ONE 2011; 6: e28159.

8 Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses 2006; 66: 234–46.

9 Capasso R, Borrelli F, Aviello G, Romano B, Scalisi C, Capasso F, Izzo AA. Cannabidiol, extracted from *Cannabis sativa*, selectively inhibits inflammatory hypermotility in mice. Br J Pharmacol 2008; 154: 1001–8.

10 Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr 2008; 30: 271–80.

11 Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders? CNS Neurosci Ther 2009; 15: 65–75.

12 Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. Free Radic Biol Med 2011; 51: 1054–61.

13 Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. Curr Drug Saf 2011; 6: 237–49.

14 Ellis EF, Moore SF, Willoughby KA. Anandamide and delta 9-THC dilation of cerebral arterioles is blocked by indomethacin. Am J Physiol Heart Circ Physiol 1995; 269: H1859–64.

15 Randall MD, Alexander SPH, Bennett T, Boyd EA, Fry JR, Gardiner SM, Kemp PA, McCulloch AI, Kendall DA. An endogenous cannabinoid as an endothelium-derived vasorelaxant. Biochem Biophys Res Commun 1996; 229: 114–20.

16 O'Sullivan S, David AK, Michael DR. Heterogeneity in the mechanisms of vasorelaxation to anandamide in resistance and conduit rat mesenteric arteries. Br J Pharmacol 2004; 142: 435–42.

17 O'Sullivan SE, Kendall DA, Randall MD. Vascular effects of [Delta]9-tetrahydrocannabinol (THC), anandamide and N-arachidonoyldopamine (NADA) in the rat isolated aorta. Eur J Pharmacol 2005; 507: 211–21.

18 Mukhopadhyay S, Chapnick BM, Howlett AC. Anandamide-induced vasorelaxation in rabbit aortic rings has two components: G protein dependent and independent. Am J Physiol Heart Circ Physiol 2002; 282: H2046–54.

19 Randall DM, Kendall AD, O'Sullivan SE. The complexities of the cardiovascular actions of cannabinoids. Br J Pharmacol 2004; 142: 20–6.

20 Batkai S, Pacher P. Endocannabinoids and cardiac contractile function: pathophysiological implications. Pharmacol Res 2009; 60: 99–106.

21 Montecucco F, Di Marzo V. At the heart of the matter: the endocannabinoid system in cardiovascular function and dysfunction. Trends Pharmacol Sci 2012; 33: 331–40.

22 Tuma RF, Steffens S. Targeting the endocannabinod system to limit myocardial and cerebral ischemic and reperfusion injury. Curr Pharm Biotechnol 2012; 13: 46–58.

23 Durst R, Lotan C. The potential for clinical use of cannabinoids in treatment of cardiovascular diseases. Cardiovasc Ther 2011; 29: 17–22.

24 Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. Clin Cardiol 2012; 35: 329–35.

25 Jarai Z, Wagner JA, Varga K, Lake KD, Compton DR, Martin BR, Zimmer AM, Bonner TI, Buckley NE, Mezey E, Razdan RK, Zimmer A, Kunos G . Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci U S A 1999; 96: 14136–41.

26 Begg M, Mo F-M, OffertÃ¡ler L, BÃ¡tkai S, Pacher P, Razdan RK, Lovinger DM, Kunos G. G protein-coupled endothelial receptor for atypical cannabinoid ligands modulates a Ca2+-dependent K+ current. J Biol Chem 2003; 278: 46188–94.

27 Ho WS, Hiley CR. Vasodilator actions of abnormal-cannabidiol in rat isolated small mesenteric artery. Br J Pharmacol 2003; 138: 1320–32.

28 Offertaler L, Mo F-M, BÃ¡tkai S, Liu J, Begg M, Razdan RK, Martin BR, Bukoski RD, Kunos G. Selective ligands and cellular effectors of a G protein-coupled endothelial cannabinoid receptor. Mol Pharmacol 2003; 63: 699–705.

29 Kozlowska H, Baranowska M, Schlicker E, Kozlowski M, Laudanski J, Malinowska B. Identification of the vasodilatory endothelial cannabinoid receptor in the human pulmonary artery. J Hypertens 2007; 25: 2240–8.

30 Deutsch DG, Goligorsky MS, Schmid PC, Krebsbach RJ, Schmid HH, Das SK, Dey SK, Arreaza G, Thorup C, Stefano G, Moore LC. Production and physiological actions of anandamide in the vasculature of the rat kidney. J Clin Invest 1997; 100: 1538–46.

31 O'Sullivan SE, Kendall DA, Randall MD. Characterisation of the vasorelaxant properties of the novel endocannabinoid *N*-arachidonoyl-dopamine (NADA). Br J Pharmacol 2004; 141: 803–12.

32 Zygmunt PM, Petersson J, Andersson DA, H-h C, Sorgard M, Di Marzo V, Julius D, Hogestatt ED. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 1999; 400: 452–7.

33 Zygmunt PM, Andersson DA, Hogestatt ED. Delta 9-tetrahydrocannabinol and cannabinol activate capsaicin-sensitive sensory nerves via a CB1 and CB2 cannabinoid receptor-independent mechanism. J Neurosci 2002; 22: 4720–7.

34 Ruiz-Valdepenas L, Martinez-Orgado JA, Benito C, Millan A, Tolon RM, Romero J. Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study. J Neuroinflammation 2011; 8: 5. doi: 10.1186/1742-2094-8-5

35 Batkai S, Pacher P, Jarai Z, Wagner JA, Kunos G. Cannabinoid antagonist SR-141716 inhibits endotoxic hypotension by a cardiac mechanism not involving CB1 or CB2 receptors. Am J Physiol Heart Circ Physiol 2004; 287: H595–600.

36 Bishop-Bailey D. Peroxisome proliferator-activated receptors in the cardiovascular system. Br J Pharmacol 2000; 129: 823–34.

37 Hsueh WA, Bruemmer D. Peroxisome proliferator-activated receptor gamma: implications for cardiovascular disease. Hypertension 2004; 43: 297–305.

38 Szeles L, Torocsik D, Nagy L. PPARgamma in immunity and inflammation: cell types and diseases. Biochim Biophys Acta 2007; 1771: 1014–30.

39 O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. Br J Pharmacol 2007; 152: 576–82.

40 O'Sullivan SE, Tarling EJ, Bennett AJ, Kendall DA, Randall MD. Novel time-dependent vascular actions of [Delta]9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. Biochem Biophys Res Commun 2005; 337: 824–31.

41 O'Sullivan SE, Kendall DA, Randall MD. Further characterization of the time-dependent vascular effects of Δ^{-9}tetrahydrocannabinol. J Pharmacol Exp Ther 2006; 317: 428–38.

42 Hwang J, Kleinhenz DJ, Lassegue B, Griendling KK, Dikalov S, Hart CM. Peroxisome proliferator-activated receptor-gamma ligands regulate endothelial membrane superoxide production. Am J Physiol Cell Physiol 2005; 288: C899–905.

43 Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ 2009; 339: b2942.

44 Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304: 411–8.

45 Filion KB, Joseph L, Boivin JF, Suissa S, Brophy JM. Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus. Pharmacoepidemiol Drug Saf 2011; 20: 785–96.

46 Gelman L, Feige JN, Desvergne B. Molecular basis of selective PPARgamma modulation for the treatment of Type 2 diabetes. Biochim Biophys Acta 2007; 1771: 1094–107.

47 Walsh SK, Hepburn CY, Kane KA, Wainwright CL. Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion. Br J Pharmacol 2010; 160: 1234–42.

48 Resstel LB, Tavares RF, Lisboa SF, Joca SR, Correa FM, Guimaraes FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. Br J Pharmacol 2009; 156: 181–8.

49 Resstel LB, Joca SR, Moreira FA, Correa FM, Guimaraes FS. Effects of cannabidiol and diazepam on behavioral and cardiovascular responses induced by contextual conditioned fear in rats. Behav Brain Res 2006; 172: 294–8.

50 Gomes FV, Resstel LB, Guimaraes FS. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology 2011; 213: 465–73.

51 Kumari M, Grahame-Clarke C, Shanks N, Marmot M, Lightman S, Vallance P. Chronic stress accelerates atherosclerosis in the apolipoprotein E deficient mouse. Stress 2003; 6: 297–9.

52 Toot JD, Reho JJ, Novak J, Dunphy G, Ely DL, Ramirez RJ. Colony social stress differentially alters blood pressure and resistance-sized mesenteric artery reactivity in SHR/y and WKY male rats. Stress 2011; 14: 33–41.

53 Fouad AA, Jresat I. Therapeutic potential of cannabidiol against ischemia/reperfusion liver injury in rats. Eur J Pharmacol 2011; 670: 216–23.

54 Mukhopadhyay P, Rajesh M, Horvath B, Batkai S, Park O, Tanchian G, Gao RY, Patel V, Wink DA, Liaudet L, Hasko G, Mechoulam R, Pacher P. Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating inflammatory signaling and response, oxidative/nitrative stress, and cell death. Free Radic Biol Med 2011; 50: 1368–81.

55 Lafuente H, Alvarez FJ, Pazos MR, Alvarez A, Rey-Santano MC, Mielgo V, Murgia-Esteve X, Hilario E, Martinez-Orgado J. Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. Pediatr Res 2011; 70: 272–7.

56 Durst R, Danenberg H, Gallily R, Mechoulam R, Meir K, Grad, E, Beeri R, Pugatsch T, Tarsish E, Lotan C. Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. Am J Physiol Heart Circ Physiol 2007; 293: H3602–7.

57 Rajesh M, Mukhopadhyay P, Batkai S, Patel V, Saito K, Matsumoto S, Kashiwaya Y, Horvath B, Mukhopadhyay B, Becker L, Hasko G, Liaudet L, Wink DA, Veves A, Mechoulam R, Pacher P. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J Am Coll Cardiol 2010; 56: 2115–25.

58 Kozela E, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z. Cannabinoids Delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells. J Biol Chem 2010; 285: 1616–26.

59 Vanhoutte PM, Shimokawa H, Tang EHC, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiol 2009; 196: 193–222.

60 Tsao PS, Niebauer J, Buitrago R, Lin PS, Wang BY, Cooke, JP, Chen YD, Reaven GM. Interaction of diabetes and hypertension on determinants of endothelial adhesiveness. Arterioscler Thromb Vasc Biol 1998; 18: 947–53.

61 Hamuro M, Polan J, Natarajan M, Mohan S. High glucose induced nuclear factor kappa B mediated inhibition of endothelial cell migration. Atherosclerosis 2002; 162: 277–87.

62 Rajesh M, Mukhopadhyay P, Batkai S, Hasko G, Liaudet L, Drel VR, Obrosova IG, Pacher P. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. Am J Physiol Heart Circ Physiol 2007; 293: H610–9.

63 El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai N-T, Caldwell RB, Liou GI. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. Am J Pathol 2006; 168: 235–44.

64 Stanley CP, O'Sullivan SE. Characterisation of cannabidiol-induced vasorelaxation in human mesenteric arteries. Proceedings of the British Pharmacological Society. 2011. Available at http://www.pA2online.org/abstracts/vol9issue3abst098p.pdf (last accessed 11 July 2012).

65 Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006; 58: 389–462.

66 Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. Ann N Y Acad Sci 2000; 899: 274–82.

67 Braida D, Pegorini S, Arcidiacono MV, Consalez GG, Croci L, Sala M. Post-ischemic treatment with cannabidiol prevents electroencephalographic flattening, hyperlocomotion and neuronal injury in gerbils. Neurosci Lett 2003; 346: 61–4.

68 Hayakawa K, Mishima K, Abe K, Hasebe N, Takamatsu F, Yasuda H, Ikeda T, Inui K, Egashira N, Iwasaki K, Fujiwara M. Cannabidiol prevents infarction via the non-CB1 cannabinoid receptor mechanism. Neuroreport 2004; 15: 2381–5.

69 Mishima K, Hayakawa K, Abe K, Ikeda T, Egashira N, Iwasaki K, Fujiwara M. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. Stroke 2005; 36: 1077–82.

70 Hayakawa K, Mishima K, Nozako M, Hazekawa M, Irie K, Fujioka M, Orito K, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism. J Neurochem 2007; 102: 1488–96.

71 Hayakawa K, Mishima K, Nozako M, Ogata A, Hazekawa M, Liu AX, Fujioka M, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. Repeated treatment with cannabidiol but not delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance. Neuropharmacology 2007; 52: 1079–87.

72 Alvarez FJ, Lafuente H, Rey-Santano MC, Mielgo VE, Gastiasoro E, Rueda M, Pertwee RG, Castillo AI, Romero J, Martinez-Orgado J. Neuroprotective effects of the nonpsychoactive cannabinoid cannabidiol in hypoxic-ischemic newborn piglets. Pediatr Res 2008; 64: 653–8.

73 Yang Y, Rosenberg GA. Blood-brain barrier breakdown in acute and chronic cerebrovascular disease. Stroke 2011; 42: 3323–8.

74 Shimazu T, Inoue I, Araki N, Asano Y, Sawada M, Furuya D, Nagoya H, Greenberg JH. A peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not in permanent ischemia. Stroke 2005; 36: 353–9.

75 Sundararajan S, Gamboa JL, Victor NA, Wanderi EW, Lust WD, Landreth GE. Peroxisome proliferator-activated receptor-gamma ligands reduce inflammation and infarction size in transient focal ischemia. Neuroscience 2005; 130: 685–96.

76 Zhao X, Zhang Y, Strong R, Grotta JC, Aronowski J. 15d-Prostaglandin J2 activates peroxisome proliferator-activated receptor-gamma, promotes expression of catalase, and reduces inflammation, behavioral dysfunction, and neuronal loss after intracerebral hemorrhage in rats. J Cereb Blood Flow Metab 2006; 26: 811–20.

77 Luo Y, Yin W, Signore AP, Zhang F, Hong Z, Wang S, Graham SH, Chen J. Neuroprotection against focal ischemic brain injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. J Neurochem 2006; 97: 435–48.

78 Lee J, Reding M. Effects of thiazolidinediones on stroke recovery: a case-matched controlled study. Neurochem Res 2007; 32: 635–8.

79 White HL, Tansik RL. Effects of delta 9-tetrahydrocannabinol and cannabidiol on phospholipase and other enzymes regulating arachidonate metabolism. Prostaglandins Med 1980; 4: 409–17.

80 Formukong EA, Evans AT, Evans FJ. The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa* L. on human and rabbit platelet aggregation. J Pharm Pharmacol 1989; 41: 705–9.

81 Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. Int J Clin Pharmacol Res 1985; 5: 243–6.

82 Wu HY, Chang AC, Wang CC, Kuo FH, Lee CY, Liu DZ, Jan TR. Cannabidiol induced a contrasting pro-apoptotic effect between freshly isolated and precultured human monocytes. Toxicol Appl Pharmacol 2010; 246: 141–7.

83 Gallily R, Even-Chena T, Katzavian G, Lehmann D, Dagan A, Mechoulam R. Gamma-irradiation enhances apoptosis induced by cannabidiol, a non-psychotropic cannabinoid, in cultured HL-60 myeloblastic leukemia cells. Leuk Lymphoma 2003; 44: 1767–73.

84 McKallip RJ, Jia W, Schlomer J, Warren JW, Nagarkatti PS, Nagarkatti M. Cannabidiol-induced apoptosis in human leukemia cells: a novel role of cannabidiol in the regulation of p22phox and Nox4 expression. Mol Pharmacol 2006; 70: 897–908.

85 Chen Y, Buck J. Cannabinoids protect cells from oxidative cell death: a receptor-independent mechanism. J Pharmacol Exp Ther 2000; 293: 807–12.

86 McHugh D, Tanner C, Mechoulam R, Pertwee RG, Ross RA. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: evidence for a site distinct from CB1 and CB2. Mol Pharmacol 2008; 73: 441–50.

87 Hayakawa K, Mishima K, Irie K, Hazekawa M, Mishima S, Fujioka M, Orito K, Egashira N, Katsurabayashi S, Takasaki K, Iwasaki K, Fujiwara M. Cannabidiol prevents a post-ischemic injury progressively induced by cerebral ischemia via a high-mobility group box1-inhibiting mechanism. Neuropharmacology 2008; 55: 1280–6.

88 Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A 2000; 97: 9561–6.

89 Stanely CP, O'Sullivan SE. CB1, TRPV1 and the endothelium mediate vasorelaxation to cannabidiol in human mesenteric arteries. 2012 Under review.