Supplementary Material: A systematic review of the complex effects of cannabinoids on cerebral and peripheral circulation in animal models

1 SUPPLEMENTARY TABLES AND FIGURES

1.1 Figures

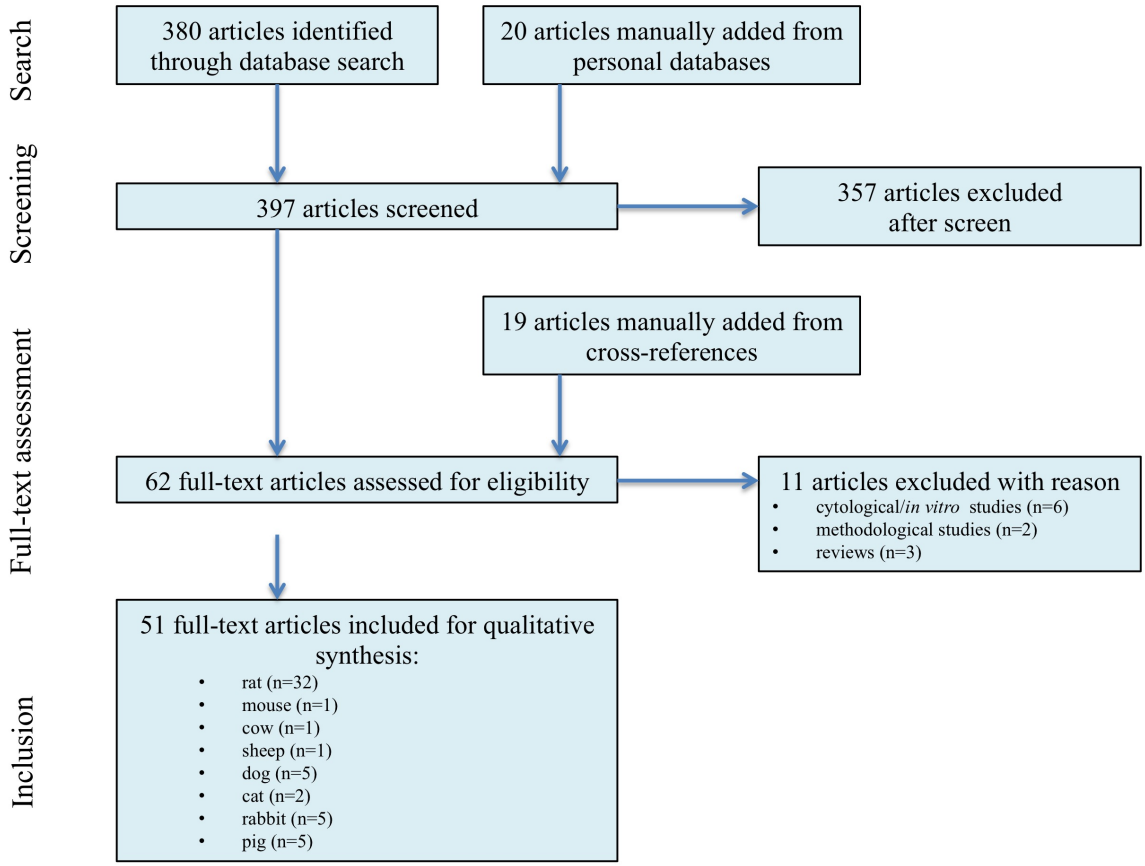

Figure S1. Article search and inclusion flow-chart

1.2 Tables

Table S1: Studies indicative of vasodilative effects of cannabinoids in animal models.

Animal model	Reference	*in vitro* *in vivo*	Consc.	Bed	Molecule	Dose	Appl.	Targ.	Effect
rat	Graham and Li (1973)	*in vivo*	ur. g.a.	hindqu.	c.e.	10mg/kg	i.v.	unsp.	systemic BP↓, HR↓, resp.rate↓
						50mg/kg/day 14 days	i.p.	unsp.	develops tolerance
					Δ1-THC	0.5mg/kg	i.v.	unsp.	as for c.e.
					Δ6-THC	0.5mg/kg	i.v.	unsp.	as for c.e.
					cannabinol	1mg/kg	i.v.	unsp.	no effect
					cannabidiol	1mg/kg	i.v.	unsp.	no effect
rat	Adams et al. (1976)	*in vivo*	ur. g.a.	systemic	Δ8-/Δ9-THC	unavailable	i.v.	unsp.	transient BP↑, followed by prolonged BP↓, HR↓
				hindqu.	Δ8-/Δ9-THC	unavailable	i.a.	unsp.	vasoconstriction
rat	Kosersky (1978)	*in vivo*	consc.	systemic	Δ9-THC	25mg/kg	oral	unsp.	systolic BP↓ in spontaneously hypertensive rats
rat	Siqueira et al. (1979)	*in vivo*	ur. g.a.	systemic	Δ9-THC	2-10mg/kg	i.v.	unsp.	immediate BP↓, HR↓, BP↑ at 30", persistent BP↓ at 5' (vagal?)
rat	Varga et al. (1996)	*in vivo*	ur. g.a.	systemic	AEA	4mg/kg	i.v.	CB1r	transient BP↓, brief BP↑, prolonged BP↓
rat	Bloom et al. (1997)	*in vivo*	consc.	cerebral	Δ9-THC	0.5mg/kg 1mg/kg 4mg/kg 16mg/kg	i.v.	unsp.	increase and decrease of CBF depending on region (see text for details)
					11-OH-THC	4mg/kg	i.v.	unsp.	increase and decrease of CBF
rat	Stein et al. (1998)	*in vivo*	consc.	cerebral	AEA	3mg/kg	i.v.	CB1r	no effect on rCBF

Table S1 continued

						10mg/kg	i.v.		rCBF↓ in 7 areas (including amygdala, cingulate, frontal, prepyriform, sensorimotor, claustrocortex)
						30mg/kg	i.v.		rCBF↓ in 23 areas (including CA1 and CA3 of hippocampus, rostral core portion of nucleus accumbens, rostral caudate nucleus)
rat	White and Hiley (1998)	*in vitro*	-	mes. art.	AEA	unsp.	perf.	CB1r	relaxation in all (precontracted)
					CP 55,940			CBr	
					HU-210			CBr	
					palmytoyl-ethanolamide			CB2r	
					R-(+)-WIN 55,212-2			CB2r	
rat	Ho and Hiley (2003)	*in vitro*	-	mes. art.	AEA	1μM	perf.	CB1r	relaxation in all (precontracted)
					JWH 015	30μM		CB2r	
					R-(+)-WIN 55,212-2	60μM		CB2r	
					S-(+)-WIN 55,212-3	60μM		unsp.	
rat	Niederhoffer et al. (2003)	*in vivo*	ur. g.a.	systemic	WIN55212-2	30-1000μ/kg	i.v.	unsp.	MAP↓, HR↓, plasma NA conc.↓ dose-dependently
					CP55940	30-1000μ/kg	i.v.	unsp.	MAP↓, HR↓, plasma NA conc.↓, max. at 30μg/kg
rat	Wagner et al. (2005)	*in vitro*	-	isolated heart	AEA	1-100nmol	bolus	CB1r	coronary vasodilation

Table S1 continued

					Delta-THC	10-100nmol	bolus	unsp.	coronary vasoconstriction
rat	O'Sullivan et al. (2005b)	*in vitro*	-	aortic rings	Δ9-THC	cumulative μM range	perf.	unsp.	vasorelaxation/-constriction
					AEA			CB1r	vasorelaxation
					NADA			CB1r	vasorelaxation
rat	O'Sullivan et al. (2005a)	*in vitro*	-	aortic and mes. rings	Δ9-THC	cumulative μM range	perf.	unsp.	vasorelaxation in smaller branches, Ca^{2+}-influx block; vasoconstriction in sup. mes. art. (stem) at high concentration; antagonism to AEA-vasorelaxation
rat	O'Sullivan et al. (2005c)	*in vitro*	-	aortic and mes. rings	Δ9-THC	10μM	perf.	unsp.	time-dependent vasorelaxation mediated by PPARγ
rat	O'Sullivan et al. (2006)	*in vitro*	-	isolated aorta	Δ9-THC	10μM, 2h incubation	-	unsp.	no effect
				mes. art.	Δ9-THC		-		enhanced endothelium-dependent vasorelaxation in sup. mes. art. and potentiated contraction in resistance vessels
rat	Breyne et al. (2006)	*in vitro*	-	gastric artery	methan-andamide	100μmol/L	perf.	CB1r	dose-dependent relaxation, probable Ca^{2+}-influx$\downarrow$
rat	O'Sullivan et al. (2007)	*in vitro*	consc.	isolated mes. art.	Δ9-THC	cumulative μM range	perf.	unsp.	enhanced vasorelaxation in hypertensive rats
		in vivo		hindqu. and systemic	Δ9-THC	1mg	i.v.	CB1r	mediated vasopressor effect (long-lasting BP$\uparrow$), not enhanced by hypertension

Table S1 continued

rat	Wheal et al. (2007)	*in vivo*	consc.	systemic	AEA	3mg/kg	i.v.	CB1r	hypotension in spontaneously hypertensive rats
					R-(+)-WIN 55,212-2	150μg/kg	i.v.	CB1r	hypotension in spontaneously hypertensive rats
rat	Pakdeechote et al. (2007)	*in vitro*	-	isolated mes. art.	AEA	1μM	perf.	CB1r	CB1r-mediated attenuation of neurogenic vasoconstriction
					R-(+)-WIN 55,212-2	1μM	perf.	CB1r	non CB1r-mediated attenuation of neurogenic vasoconstriction
					CP55940	1μM	perf.	CB1r	non CB1r-mediated attenuation of neurogenic vasoconstriction
rat	Hillard et al. (2007)	*in vitro*	-	isolated MCA	2-AG	5-10000nM	perf.	CB1r	attenuation of U-46619 induced vasoconstriction
rat	O'Sullivan et al. (2009)	*in vitro*	-	aorta	cannabidiol	1μM	perf.	unsp.	time-dependent vasorelaxation, in part mediated by PPARγ
rat	Ho and Gardiner (2009)	*in vivo*	consc.	systemic	AEA	3mg/kg	i.v.	CB1r	dose-dependent MAP$\downarrow$ in hypertensive rats, no effect in normotensive rats
					R-(+)-WIN 55,212-2	150μg/kg	i.v.	CB1r	MAP$\downarrow$ in hypertensive rats, MAP$\uparrow$ in normotensive rats
rat	Gardiner et al. (2009)	*in vivo*	consc.	systemic	methan-andamide	0.5-5mg/kg	i.v.	CB1r	CB1r-mediated renal and mesenteric vasoconstriction and hindquarter vasodilation
rat	Mair et al. (2010)	*in vitro*	-	coronary artery	AEA	1nM-30μM	perf.	CB1r	concentration-dependent vasorelaxation via a sphingosine kinase-1 mechanism
rat	Tamaki et al. (2012)	*in vitro*	-	mes. art.	AEA	0.1-1nM	perf.	CB1r	vasodilation
						10nM-1μM	perf.	CB1r	vasoconstriction

Table S1 continued

rat	Iring et al. (2013)	*in vivo*	ur. g.a	cerebral	AM-251	10mg/kg	i.v.	unsp.	no effect on CoBF
					AM-404	10mg/kg	i.v.	unsp.	initial CoBF↑, systemic BP↑, followed by CoBF↓ and BP↓
rat	Sánchez-Pastor et al. (2014)	*in vitro*	-	aortic rings	ACPA	0.1-50μM	perf.	CB1r	vasorelaxation involving activation of K_{Ca}1.1- and inhibition of Ca_V1.2-channels
rat	MacIntyre et al. (2014)	*in vitro*	-	isolated retinal arterioles	Abn-CBD	10μM	GPR18 CB_E	perf.	inhibition of endothelin-induced vasoconstriction, endothelium-dependent, involving SK_{Ca} channels
rat	Al Suleimani et al. (2015)	*in vitro*	-	sup. mes. art.	O-1601	10nM-100μM	perf.	CB1r	vasorelaxation partly endothelium-mediated in third order branch
rat	Baranowska-Kuczko et al. (2016)	*in vitro*	-	aortic and mes. art. rings	methan-andamide	0.01-30μM	perf.	CB1r	vasorelaxation of pre-constricted vessels
mouse	Zhang et al. (2008)	*in vivo*	ket-xy g.a.	cerebral	O-1966	1mg/kg	i.v. i.p.	CB2r	rCBF↑
rabbit	Ellis et al. (1995)	*in vitro*	-	cerebral	Δ9-THC	$10^{-13}$to 10^{-3}M	perf.	unsp.	dose-dependent vasodilation
rabbit	Fleming et al. (1999)	*in vitro*	-	mes. art. rings	HU 210	μM range	perf.	CB1r	relaxation
					Δ9-THC	μM range	perf.	CB1r CB1r	relaxation
					AEA	0.03-30μM	perf.	CB1r	slowly developing relaxation involvement of EDHF, activated by CB1r

Table S1 continued

				carotid art. rings	HU 210	μM range	perf.	CB1r	no effect
					Δ9-THC	μM range	perf.	CB1r	no effect
					AEA	0.03-30μM	perf.	CB1r	no effect
dog	Cavero et al. (1972)	*in vivo*	s-p g.a.	systemic	Δ9-THC	2.5mg/kg	i.v.	unsp.	BP↓, HR↓, cardiac output↓, splanchnic vasoconstriction
dog	Cavero et al. (1973)	*in vivo*	s-p g.a.	systemic	Δ9-THC	39μg/kg 312.5μg/kg 2.5mg/kg	i.v.	unsp.	aortic BP↓, cardiac output↓, left ventricular peak pressure↓, left ventricular and diastolic pressure↓, no effect on cerebral stroke volume
dog	Cavero et al. (1974)	*in vivo*	s-p g.a.	systemic	Δ9-THC	2.5mg/kg	i.v.	unsp.	dose-dependent BP↓, HR↓, cardiac output↓, right ventricular contractile force↓, total peripheral vascular resistance↓
cat	Graham and Li (1973)	*in vivo*	ur. g.a.	hindqu.	c.e.	10mg/kg	i.v.	unsp.	systemic BP↓
					Δ1-THC	0.2mg/kg	i.v.	unsp.	pulse↓, resp. rate↓ hindlimb PP↓
					AEA	$10^{-13}$to 10^{-3}M	perf.	CB1r	dose-dependent vasodilation
cat	Gebremedhin et al. (1999)	*in vitro*	-	isolated cerebral arteries	R-(+)-WIN 55,212-2	10 to100nM	perf.	CB1r	L-type Ca^{2+}-current↓
					AEA	10 to 300nM	perf.	CB1r	L-type Ca^{2+}-current↓
cow	Pratt et al. (1998)	*in vitro*	-	coronary art. rings	AEA	cumulative μM range	perf.	CB1r	non CB1r-mediated vasodilation

Table S1 continued

sheep	Grainger and Boachie-Ansah (2001)	*in vitro*	-	coronary art. rings	AEA	0.01-30μM	perf.	CB1r	concentration-dependent relaxation, in part endothelium-dependent, in part K^+-channel mediated
pig	Su et al. (2015)	*in vitro*	-	retinal arterioles	Abn-CBD	$10^{-10}$to 10^{-4}M	perf.	GPR, CB_E	vasorelaxation in pre-contracted vessels, action on endothelium

Abbreviations: Consc. consciousness, Appl. application mode, Targ. target, ur. urethane, g.a. general anesthesia, hindqu. hindquarters, c.e. cannabis extract, i.v. intravenous, unsp. unspecified, BP blood pressure, HR heart rate, resp. respiratory , THC tetrahydrocannabinol, i.a. intraarterial, i.p. intraperitoneal, consc. conscious, AEA anandamide, CB1r cannabinoid receptor type 1, CB2r cannabinoid receptor type 2, CBF cerebral blood flow, rCBF regional cerebral blood flow, mes. mesenteric, art. artery, perf. perfusion, MAP mean arterial pressure, NA conc. noradrenaline concentration, max. maximum, CoBF cerebro-cortical blood flow, NADA N-arachnidonoyl-dopamine, MCA middle cerebral artery, Abn-CBD abnormal cannabidiol sup. superior, PPARγ Peroxisome proliferator-activated receptor gamma, ACPA arachidonylcyclopropylamide,ket-xy ketamine-xylazine, EDHF endothelium-derived hyperpolarizing factor, s-p sodium-pentobarbital, PP perfusion pressure, abnCBD abnormal cannabidiol, GPR G-protein coupled receptor 18, CB_E noncannabinoid endothelial receptor.

Table S2: Studies indicative of vasoconstrictive effects of cannabinoids in animal models.

Animal model	Reference	*in vitro* *in vivo*	Consc.	Bed	Molecule	Dose	Appl.	Targ.	Effect
rat	Adams et al. (1976)	*in vivo*	ur. g.a.	systemic	Δ8-/Δ9-THC	unavailable	i.v.	unsp.	transient BP↑, followed by prolonged BP↓, HR↓
				hindqu.	Δ8-/Δ9-THC	unavailable	i.a.	unsp.	vasoconstriction
rat	Siqueira et al. (1979)	*in vivo*	ur. g.a.	systemic	Δ9-THC	2-10mg/kg	i.v.	unsp.	immediate BP↓, HR↓, BP↑ at 30", persistent BP↓ at 5' (vagal)
rat	Kawasaki et al. (1980)	*in vivo*	ur. g.a.	systemic	Δ9-THC	1mg/kg 2mg/kg 5mg/kg	i.v.	unsp.	transient dose-related BP↑, HR↓ (vagal)
rat	Varga et al. (1996)	*in vivo*	ur. g.a.	systemic	AEA	4mg/kg	i.v.	CB1r	transient BP↓, brief BP↑, prolonged BP↓
rat	Bloom et al. (1997)	*in vivo*	consc.	cerebral	Δ9-THC	0.5mg/kg 1mg/kg 4mg/kg 16mg/kg	i.v.	unsp.	increase and decrease of CBF depending on region (see text for details)
					11-OH-THC	4mg/kg	i.v.	unsp.	increase and decrease of CBF
rat	Stein et al. (1998)	*in vivo*	consc.	cerebral	AEA	3mg/kg	i.v.	CB1r	no effect on rCBF
						10mg/kg	i.v.		rCBF↓ in 7 areas (including amygdala, cingulate, frontal, prepyriform, sensorimotor, claustrocortex)
						30mg/kg	i.v.		rCBF↓ in 23 areas (including CA1 and CA3 of hippocampus, rostral core portion of nucleus accumbens, rostral caudate nucleus)

Table S2 continued

rat	Wagner et al. (2005)	*in vitro*	-	isolated heart	AEA	1-100nmol	bolus	CB1r	coronary vasodilation
					Delta-THC	10-100nmol	bolus	unsp.	coronary vasoconstriction
rat	O'Sullivan et al. (2005b)	*in vitro*	-	aortic rings	Δ9-THC	cumulative μM range	perf.	unsp.	vasorelaxation/-constriction
					AEA			CB1r	vasorelaxation
					NADA			CB1r	vasorelaxation
rat	O'Sullivan et al. (2005a)	*in vitro*	-	aortic and mes. rings	Δ9-THC	cumulative μM range	perf.	unsp.	vasorelaxation in smaller branches, Ca^{2+}-influx block; vasoconstriction in sup. mes. art. (stem) at high concentration; antagonism to AEA-vasorelaxation
rat	O'Sullivan et al. (2006)	*in vitro*	-	isolated aorta	Δ9-THC	10μM, 2h incubation	-	unsp.	no effect
				mes. art.	Δ9-THC		-		enhanced endothelium-dependent vasorelaxation in sup. mes. art. and potentiated contraction in resistance vessels
rat	Gardiner et al. (2009)	*in vivo*	consc.	systemic	methan-andamide	0.5-5mg/kg	i.v.	CB1r	CB1r-mediated renal and mesenteric vasoconstriction and hindquarter vasodilation
rat	Tamaki et al. (2012)	*in vitro*	-	mes. art.	AEA	0.1-1nM	perf.	CB1r	vasodilation
						10nM-1μM	perf.	CB1r	vasoconstriction
rat	Wenzel et al. (2013)	*in vitro*	-	isolated perf. lung	AEA	10μM	perf.	CB1r	pulmonary vasoconstriction

Table S2 continued

rat	Iring et al. (2013)	*in vivo*	ur. g.a	cerebral	AM-251	10mg/kg	i.v.	unsp.	no effect on CoBF
					AM-404	10mg/kg	i.v.	unsp.	initial CoBF↑, systemic BP↑, followed by CoBF↓ and BP↓
rabbit	Barbosa et al. (1981)	*in vitro*	-	central ear art.	Δ9-THC	15-30mM	perf.	unsp.	sustained contractions by NA release
rabbit	Wahn et al. (2005)	*in vitro*	-	isolated lung	AEA	5μM	perf.	CB1r	pulmonary artery pressure↑
					2-AG	0.4μ	perf.	CB1r	pulmonary artery pressure↑ (via COX-2 metabolites)
					R-methan-andamide	unsp.	perf.	CB1r	no effect
					Δ9-THC	unsp.	perf.	unsp.	no effect
					HU 210	unsp.	perf.	CB1r	no effect
dog	Cavero et al. (1972)	*in vivo*	s-p g.a.	systemic	Δ9-THC	2.5mg/kg	i.v.	unsp.	BP↓, HR↓, cardiac output↓, splanchnic vasoconstriction
dog	Cavero et al. (1974)	*in vivo*	s-p g.a.	systemic	Δ9-THC	2.5mg/kg	i.v.	unsp.	dose-dependent BP↓, HR↓, cardiac output↓, right ventricular contractile force↓, total peripheral vascular resistance↓
dog	Jandhyala et al. (1976)	*in vivo*	s-p g.a.	systemic	Δ9-THC	2.5mg/kg	i.v.	unsp.	HR↓, pulmonary blood flow↓, pulmonary artery pressure↑, pulmonary vascular resistance↑
pig	Vaddady et al. (2011)	*in vivo*	g.a.	hemor. shock model	Δ9-THC	0.5mg/kg 1mg/kg 4mg/kg	i.v.	unsp.	selective vasoconstriction in liver microvasculature

Abbreviations: Consc. consciousness, Appl. application mode, Targ. target, ur. urethane, g.a. general anesthesia, THC tetrahydrocannabinol, i.v. intravenous, unsp. unspecified, BP blood pressure, HR heart rate, hindqu. hindquarters, i.a. intraarterial, AEA anandamide, CB1r cannabinoid receptor type 1, CB2r cannabinoid receptor type 2, consc. conscious, CBF cerebral blood flow, rCBF regional cerebral blood flow, perf. perfusion, NADA N-arachnidonoyl-dopamine,mes. mesenteric, art. artery, CoBF cerebrocortical blood flow, NA noradrenaline, s-p sodium-pentobarbital, hem. hemorrhagic.

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