Triphasic cardiovascular response to cannabinoids – Focus on underlying mechanisms

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The endocannabinoid anandamide exerts complex effects on the cardiovascular system [Malinowska et al., Br J Pharmacol, 2011]. Thus, rapid intravenous injection of anandamide and its stable analogue methanandamide in anaesthetized rats and mice induces typical triphasic changes. Phase I, the so-called Bezold-Jarisch reflex, is characterized by a rapid bradycardia and hypotension associated with a decrease in cardiac contractility and an increase in total peripheral resistance. Phase II is a brief pressor response associated with an increase in cardiac contractility and blood flow in the mesenteric and renal arteries. Phase III comprises a prolonged (lasting up to 10 min) and marked decrease in blood pressure, mesenteric and renal blood flow, a marked decrease in cardiac contractility and a slight decrease in heart rate and total peripheral resistance.

Phase I is mediated via vanilloid TRPV1 receptors since it was induced also by the TRPV1 receptor agonist capsaicin (but not by the CB1 receptor agonist CP55940), blocked by the TRPV1 receptor antagonists capsazepine and ruthenium red (but not by the CB1 receptor antagonist rimonabant) and absent in TRPV1−/− mice.

Phase II consists of a peripheral component that is most probably located in blood vessels, is sensitive to nifedipine, ruthenium red and pentobarbitone and, hence, probably represents a Ca2+-dependent mode of action and a central component. The paraventricular nucleus of the hypothalamus (PVN) may present a Ca2+-dependent mode of action and a central component. This effect only occurred when the peripheral CB1 receptors were blocked by administration of CB1 receptor antagonists, including AM6545 that does not reach the brain. It was sensitive to adrenalectomy and counteracted by antagonists of CB1, NMDA, thromboxane A2 and β2-adrenergic receptors [AM251 (directly into the PVN), MK-801, SQ29548 and IC118551, respectively] suggesting that the latter four receptors are involved in the events ultimately leading to the anandamide-induced adrenal secretion of catecholamines. Importantly, the hypotensive effect of intravenously administered CP55940 was reversed into a hypertensive one in the presence of AM6545 and both responses were abolished by chemical lesion of the PVN by kainic acid.

Phase III is mediated mainly by presynaptic inhibitory CB1 receptors located on the postganglionic (although a preganglionic localization cannot be excluded) sympathetic nerve endings innervating resistance vessels and heart. The CB1 receptor antagonist-sensitive inhibitory effect of these receptors was detected after electrical stimulation of the preganglionic sympathetic nerve fibres in pithed rabbits or rats or following injection of nicotine but not phenylephrine/noradrenaline or isoprenaline (increasing blood pressure and heart rate, respectively). The prolonged hypotension might also be related to the activation of CB1 and/or vanilloid TRPV1 receptors in the spinal cord or to a direct vasodilatation via O-1918 sensitive cove receptors.

In conscious rats anandamide and methanandamide induced a brief pressor (phase II) response connected with renal and mesenteric vasoconstriction and hindquarters vasodilatation. In addition, higher doses of anandamide elicited an initial bradycardia, hypotension and hindquarters vasoconstriction (phase I). However, unlike in anaesthetized rats, none of the cannabinoids led to a prolonged hypotension (phase III). Cardiovascular effects of anandamide are changed under pathophysiological conditions. Thus, in anaesthetized rats myocardial ischemia enhanced phase I and reduced phase III whereas hypertension enhanced phase III.

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Cannabinoids and antiepileptic drugs

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The existing evidence indicates that synthetic agonists of cannabinoid receptors exert anticonvulsant activity in various models of experimental epilepsy in rodents. Specifically, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinyl)-pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate (WIN 55,212-2 mesylate – non-selective CB1 and CB2 receptor agonist) inhibited pilocarpine-induced seizures in rats [Wallace et al., Eur J Pharmacol, 2001] and cocaine- or N-methyl-D-aspartate-induced convulsions in mice [Hayase et al., J Pharm Pharmacol, 2001]. Arachidonyl-2'-chloroethylamide (ACEA—a selective CB1 receptor agonist co-administered with a fatty-acid amide hydrolase, phenylmethylsulfonyl fluoride [PMSF]), raised the threshold for electroconvulsions in mice [Luszczki et al., Eur J Pharmacol, 2006] and attenuated pentyleneterazol-induced clonic seizure activity in mice [Bahremand et al., Epilepsy Res, 2008, 2009]. Although cannabidiol has been already tried in epileptic patients in the form of an add-on therapy and was well tolerated, due to the low number of cases no reliable conclusions on its antiepileptic efficacy can be drawn so far [Miller, Epilepsy Curr, 2013]. The reviewed below experimental data on the interaction between cannabinoid agonists and antiepileptic drugs may provide some clues for the expected clinical trials on this issue.

ACEA at a subthreshold dose of 2.5 mg/kg (combined with PMSF at 30 mg/kg) significantly enhanced the protective activity of valproate against maximal electroshock-induced seizures in mice, the adverse effects of valproate, evaluated in the chimney test (motor coordination), passive avoidance task (long-term memory) and grip-strength test (neuromuscular strength), being not potentiated. However, the increased anticonvulsant potential of valproate was associated with a significant elevation of its brain total concentration by 49% [Luszczki et al., Eur J Pharmacol, 2006]. When combined with phenobarbital, ACEA (at 2.5 mg/kg) significantly potentiated its anticonvulsant action against maximal electroshock in mice and the total brain concentration of phenobarbital was not affected. The adverse potential of this antiepileptic was not enhanced and moreover, its protective index was increased. However, the protective activity of carbamazepine, lamotrigin, oxcarbazepine, phenytoin, or topiramate was not affected by ACEA [Luszczki et al., Prog Neuropsychopharmacol Biol Psychiat, 2010]. In another model of experimental epilepsy, pentetrazol-induced clonic convulsions in mice, ACEA at a higher dose of 10 mg/kg (co-administered with PMSF at 30 mg/kg) potentiated the protective activity of ethosuximide, phenobarbital, and valproate, the respective median effective doses being reduced