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COMMENTARY

The cardiovascular actions of anandamide: more targets?

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Abbreviations: CB, cannabinoid; ICI 118551, erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol); MK-801, (5R, 10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen; NADA, *N*-arachidonoyl dopamine; SR141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamidehydrochloride; $TRPV_1$, Transient receptor potential vanilloid receptor

The cardiovascular actions of endogenous cannabinoids such as anandamide are complex and confused (see Randall *et al*., 2004). Previously, in anaesthetised rats Malinowska and colleagues have reported that anandamide causes a triphasic response. This is made up of an initial bradycardia and depressor action (phase I) due to the activation of vanilloid receptors, followed by a transient pressor effect (phase II) and a longer lasting hypotensive phase (phase III), which is sensitive to the cannabinoid CB_1 receptor antagonist SR141716A (Malinowska *et al*., 2001). In the current edition, Kwolek *et al*. (2005) have characterised the pressor mechanisms underlying the transient phase II in anaesthetised rats. In doing so they have added to the list of non-CB targets at which anandamide acts.

Kwolek *et al*. (2005) have now reported that the phase II pressor actions are independent of cannabinoid CB_1 receptors and vanilloid $TRPV_1$ receptors but sensitive to propranolol, the β_2-adrenoceptor antagonist ICI 118551 and the NMDA receptor antagonist MK-801 in anaesthetised but not pithed rats. The conclusion from these findings is that there are central actions *via* β_2-adrenoceptors and NMDA receptors. In contrast to these observations, Gardiner *et al*. (2002) reported that, in the conscious rat, ICI 118551 actually enhanced the pressor actions and vasoconstrictor responses to anandamide.

Although these findings complete the characterisation of the triphasic response in the urethane-anaesthetised rat, they also raise further issues within this complicated and confused area. To date, much of the controversy arises from the finding in anaesthetised rats that anandamide causes the well-documented triphasic response, while in the conscious state there are pressor actions and vasoconstriction (Stein *et al*., 1996; Lake *et al*., 1997; Gardiner *et al*., 2002). In the current paper by Kwolek *et al*. (2005), it is reported that the phase II transient pressor response is present in the urethane-anaesthetised rats but not under pentobarbitone anaesthesia. This may certainly suggest that the cardiovascular actions of anandamide are dependent on the experimental conditions under which they are studied. The current study raises a question over the choice of general anaesthetic, does pentobarbitone inhibit phase II pressor actions or does urethane uncover phase II? Alternatively, could it be that in the whole animal general anaesthesia suppresses these apparent pressor actions to an extent that hypotension is uncovered in phase III when opposing vasoconstriction (seen in the conscious state) is lost? This uncovering under general anaesthesia might suggest that phase III is artefactual and would resolve the controversy as to why hypotension is not seen in the conscious state, despite anandamide being a vasodilator in isolated blood vessels. Aside from these speculations, it is also noteworthy that the hypotension in phase III was sensitive to destruction of the nervous system by pithing under both general anaesthetics. Does this imply a role for an intact autonomic nervous system in these responses? Indeed it would be helpful to know more about the effects of the various treatments on phase III.

Aside from the issue of experimental conditions, the pharmacological characterisation of the phase II pressor responses has led the authors to propose that it involves central glutamatergic pathways. Since the pressor response was unaffected by bilateral vagotomy, the authors have argued against a reflex mediated *via* afferent or efferent vagal fibres due to the hypotension in phase I. The proposed effects of anandamide on these central glutamatergic pathways clearly require further characterisation; do they represent central actions of the cannabinoid or are they secondary, for example, due to the hypotension in phase I leading to cerebral hypoperfusion and the activation of NMDA receptors? It would be interesting to know what happens to the cardiovascular system when anandamide is administered directly into the central nervous system. In this regard, Seagard *et al*. (2004) have already reported that injection of anandamide into the nucleus tractus solitarius increased baroreceptor sensitivity in the rat. From these observations, it was suggested that anandamide caused cannabinoid CB_1 receptor-dependent modulation of glumatergic or GABAergic pathways. In addition, Padley *et al*. (2003) have reported that injection of synthetic cannabinoids into the rostral ventrolateral medulla oblongata of urethane-anaesthetised rats leads to sympathetically mediated hypertension.

The present study implies yet another non-CB target for anandamide and what we now need to know is the generality of this observation. Hence, it would seem important to establish whether synthetic or plant-derived cannabinoids also act in this way and similarly whether it is a property shared by

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other endogenous cannabinoids such as *N*-arachidonoyl dopamine (NADA).

The next question to be raised for further research is what is the precise mechanism of the peripheral, calcium-dependent pressor actions? Certainly, anandamide is a vasorelaxant of isolated blood vessels; so might the peripheral pressor actions represent a feature of the integrated system? What we do know is that they do not involve α-adrenoceptors, purinoceptors, 5-HT_{2A} receptors, neuropeptide Y_1 receptors, vasopressin V_{1a} receptors, endothelins or the renin–angiotensin system.

In summary, the authors in the present paper have now fully characterised the triphasic cardiovascular profile in the urethane-anaesthetised rat and identified novel targets for anandamide. In doing so, they have also further underscored the view that anandamide's cardiovascular actions are dependent on the conditions under which they are studied.

References

GARDINER, S.M., MARCH, J.E., KEMP, P.A. & BENNETT, T. (2002). Complex regional haemodynamic effects of anandamide in conscious rats. *Br. J. Pharmacol.,* **135,** 1889–1896.

KWOLEK, G., ZAKRZESKA, A., SCHLICKER, E., GOTHERT, M., GODLEWSKI, G. & MALINOWSKA, B. (2005). Central and peripheral components of the pressor effect of anandamide in urethane-anaesthetized rats. *Br. J. Pharmacol.,* **145,** 567–575 (this issue).

LAKE, K.D., MARTIN, B.R., KUNOS, G. & VARGA, K. (1997). Cardiovascular effects of anandamide in anaesthetized and conscious normotensive rats. *Hypertension,* **29,** 1204–1210.

MALINOWSKA, B., KWOLEK, G. & GOTHERT, M. (2001). Anandamide and methanandamide induce both vanilloid VR1- and cannabinoid CB1 receptor mediated changes in heart rate and blood pressure in anaesthetized rats. *Nauyn-Schmiedeberg's Arch. Pharmacol.,* **364,** 562–569.

PADLEY, J.R., LI, Q., PILOWSKY, P.M. & GOODCHILD, A.K. (2003). Cannabinoid receptor activation in the rostral ventrolateral medulla oblongata evokes cardiorespiratory effects in anaesthetised rats. *Br. J. Pharmacol.,* **140,** 384–394.

RANDALL, M.D., KENDALL, D.A. & O'SULLIVAN, S.E. (2004). The complexities of the cardiovascular actions of cannabinoids. *Br. J. Pharmacol.,* **142,** 20–26.

SEAGARD, J.L., DEAN, C., PATEL, S., RADEMACHER, D.J., HOPP, F.A., SCMELING, W.T. & HILLIARD, C.J. (2004). Anandamide content and interaction of endocannabinoid/GABA modulatory effects in the NTS on baroreceptor-evoked sympathoinhibition. *Am. J. Physiol.,* **286,** H992–H1000.

STEIN, E.A., FULLER, S.A., EDGEMOND, W.S. & CAMPBELL, W.B. (1996). Physiological and behavioural effects of the endogenous cannabinoid, arachidonylethanolamine (anandamide), in the rat. *Br J Pharmacol.,* **119,** 107–114.

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