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The Vasorelaxant Effects of Anandamide in the Human Mesenteric Artery

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In animals, it has been shown in several vascular beds that the endogenous cannabinoid anandamide (AEA) causes potent, near maximal vasorelaxation. However, in human mesenteric arteries, we have shown that the effects of AEA are less pronounced than has been reported in animals (Stanley & O'Sullivan, BPS winter meeting 2010). The aim of this research was to attempt to unmask potential limiting factors preventing AEA-induced vasorelaxation, and also to characterise the mechanisms underlying AEA-induced vasorelaxation.

With ethical approval and written informed consent, human mesenteric arteries were taken from patients (21 male, 5 female, 68 ± 2.5 [mean ± S.E.M] years) undergoing colorectal surgery. Arteries were dissected and mounted on a Mulvany-Halpern myograph and bathed in oxygenated physiological salt solution at 37°C under a set pressure of 90% of 100 mmHg. U46619 and endothelin-1 were added to increase tension by a minimum of 5 mN. Once a stable contraction had been achieved, concentration-responses curves were carried out to AEA. The potential role for metabolism of AEA was probed by incubation with the non-selective cyclooxygenase (COX) inhibitor indomethacin (10 μM), the fatty acid hydrolase inhibitor (FAAH) URB597 (1 μM), or by endothelium denudation. Potential mechanisms of action were characterised by antagonism of CB_1 (AM251, 100 nM), CB_2 (AM630, 100 nM) or desentisation of the TRPV1 receptor (capsaicin, 10 μM).

AEA (1–30 μM) caused concentration-dependent vasorelaxation of pre-constricted human mesenteric arteries that was significantly different to vehicle control (AEA 1 μM, 13.3 ± 2.3 % relaxation vs EtOH 0.01%, 5.9 ± 2.3 % relaxation, $P<0.05$; AEA 30 μM, 27.6 ± 3.9 % relaxation vs EtOH 0.3%, 11.2 ± 3.0 % relaxation, $n=12$; $P<0.001$, Student's paired *t*-test). Inhibition of COX ($n=5$) or FAAH ($n=4$) did not affect AEA-induced vasorelaxation. However, removal of the endothelium reduced vasorelaxant responses to AEA ($n=5$, $P<0.01$, 2-way ANOVA). Antagonism of CB_1 also reduced the vasorelaxant responses to AEA ($n=5$, $P<0.01$, 2-way ANOVA comparison of whole data set). Antagonism of CB_2 ($n=4$) or desensitisation of the TRPV1 receptor ($n=6$) had no effect on responses to AEA.

These data show for the first time that AEA relaxes human mesenteric arteries, which is partially mediated by the endothelium and the CB_1 receptor. The vasorelaxation seen to AEA was considerably smaller compared to that previously observed in the same vascular bed in animal studies.

Stanley CP *et al.* (2010). BPS Winter meeting poster presentation (CP018).