

## Characterisation of cannabidiol-induced vasorelaxation in human mesenteric arteries

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The plant derived cannabinoid cannabidiol (CBD) is a close relative of  $\Delta^9$  tetrahydrocannabinol (THC), yet lacks the psychotropic effects associated with THC. Several works, including in human arteries, have suggested that CBD inhibits the vasorelaxant effect of other cannabinoids via antagonism of a yet unidentified cannabinoid receptor. However, in rat aortae CBD has also been shown to cause time-dependent vasorelaxation. The aim of this study was to investigate any potential vasorelaxant effects of CBD in the human mesenteric artery.

With ethical approval and written informed consent, human mesenteric arteries were taken from patients (gender: 24 male, 12 female, average age:  $66 \pm 14$  years) undergoing colorectal surgery. Arteries were dissected and mounted on a Mulvany-Halpern myograph and bathed in oxygenated physiological salt solution at  $37^\circ\text{C}$  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 CBD. Mechanisms underlying CBD-induced vasorelaxation were investigated using the following:  $\text{CB}_1$  and  $\text{CB}_2$  receptor antagonism (100 nM AM251 and AM630), endothelium denudation, nitric oxide production (300  $\mu\text{M}$  L-NAME), metabolism via cyclooxygenase (COX) (10  $\mu\text{M}$  indomethacin) and potassium channel activation (vessels contracted in high potassium physiological salt solution). Data analysed by students' *t*-test with significance taken at  $P < 0.05$ .

CBD ( $p\text{EC}_{50} = 5.1 \pm 0.3$  (mean  $\pm$  s.e.m),  $R_{\text{max}} = 36.4 \pm 6.6\%$  relaxation,  $n = 12$ ) causes vasorelaxation of pre-constricted human mesenteric arteries significantly different to vehicle control ( $P < 0.05$ ). Reduced efficacy was observed in vessels pre-treated with AM251 (control,  $R_{\text{max}} = 60.5 \pm 5.5\%$  relaxation; AM251,  $R_{\text{max}} = 21.2 \pm 14.2\%$  relaxation,  $n = 8$ ;  $P < 0.05$ ) or contracted using KPSS (control,  $R_{\text{max}} = 55.7 \pm 7.2\%$  relaxation; KPSS contracted,  $R_{\text{max}} = 10.8 \pm 4.4\%$  relaxation,  $n = 5$ ;  $P < 0.05$ ). CBD potency was also reduced in endothelial denuded vessels (control,  $p\text{EC}_{50} = 6.0 \pm 0.3$ ; endothelium denuded  $p\text{EC}_{50} = 4.9 \pm 0.3$ ,  $n = 4$ ;  $P < 0.05$ ). Incubation with L-NAME inhibited CBD-induced vasorelaxation at low concentrations ( $P < 0.01$ ), but failed to alter either efficacy or potency. Neither AM630 nor indomethacin had any effect on CBD-induced vasorelaxation.

These data show for the first time that CBD causes vasorelaxation in human mesenteric arteries. This is partially mediated by the  $\text{CB}_1$  receptor, potassium channel activation, the endothelium and nitric oxide release.

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