Δ^9-TETRAHYDROCANNABINOL (THC) ANTAGONISES THE VASORELAXANT EFFECTS OF ANANDAMIDE IN RAT ISOLATED MESENTERIC ARTERIES

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Individually, both THC and anandamide cause vasorelaxation in rat mesenteric arteries. However, the interactions between exogenous and endogenous cannabinoids are still largely unknown, and evidence suggests that THC may act as an antagonist to other cannabinoid molecules (Bayewitch *et al*., 1996; Kelley & Thayer, 2004). We have therefore examined the effects of THC on vasorelaxation to anandamide.

Male Wistar rats (200-300 g) were killed by cervical dislocation. Small mesenteric resistance arteries (G3) or the superior mesenteric artery (G0) were isolated, cut into 2 mm lengths and mounted on a Mulvany-Halpern myograph. Vessels were bathed in oxygenated Krebs' solution at 37^{o}C. Vessels were set to a baseline tone of 5 mN, and U46619 was added to increase tension by at least 5 mN.

THC caused significant rightward shifts in the concentration-response curve to anandamide in G3 vessels at 1 μM (control pEC_{50} = 6.43 ± 0.22, mean ± SEM, *n*=8 cf pEC_{50} = 5.09 ± 0.57, *n*=8, *P*<0.05, ANOVA) and 10 μM (pEC_{50} = 4.49 ± 0.20, *n*=6, *P*<0.01). THC (10 μM) did not affect the concentration-response curve to the non-cannabinoid vasorelaxant, verapamil (control pEC_{50} = 7.01 ± 0.12, *n*=5; & THC 10 μM pEC_{50} = 7.22 ± 0.09, *n*=6), the vanilloid receptor agonist capsaicin (capsaicin pEC_{50} = 5.37 ± 0.11, *n*=5; & THC 10 μM pEC_{50} = 5.45 ± 0.08, *n*=4), or the CB_1 receptor agonist CP 55,940 (CP 55,940 pEC_{50} = 5.86 ± 0.09, *n*=5; & THC 10 μM pEC_{50} = 5.77 ± 0.18, *n*=5). THC (10 μM) also did not affect the actions of anandamide in the superior mesenteric artery (G0; control pEC_{50} = 5.39 ± 0.29, *n*=7; & THC 10 μM pEC_{50} = 5.44 ± 0.34, *n*=7). When THC (10 μM) was applied in combination with endothelial-denudation in G3 vessels, THC did not significantly inhibit the vasorelaxant effects of anandamide further than was seen with denudation alone (denuded vessels pEC_{50} = 5.28 ± 0.29, *n*=7; denuded vessels & THC 10 μM pEC_{50} = 4.25 ± 0.59, *n*=6). The inhibitory effect of 1 μM THC on vasorelaxation to anandamide was significantly enhanced in the presence of L-NAME (THC 1 μM pEC_{50} = 5.59 ± 0.13, *n*=8; THC 1 μM & L-NAME pEC_{50} = 3.22 ± 0.93, *n*=5, *P*<0.05). The magnitude and duration of vasorelaxation to carbachol (10 μM) in the presence of indomethacin (10 μM) and L-NAME (300 μM) (mediated by endothelium-derived hyperpolarising factor (EDHF)) was also significantly reduced in the presence of THC (10 μM or 100 μM). The effects of THC were similar in profile to the effects of the gap junction inhibitor, 18α-glycyrrhetinic acid (18α-GA, 100 μM).

In summary, THC inhibits the vasorelaxant activities of the endogenous cannabinoid anandamide in small isolated mesenteric arteries. This is not through non-specific actions, or actions at the vanilloid receptor or CB_1 receptor, but possibly through inhibition of EDHF activity via inhibition of intercellular communication.

Bayewitch *et al.* (1996). *J. Biol. Chem.,* **271**, 9902-99055.
Kelley & Thayer (2004). *Neuropharmacology.*, **46**, 709-715.

This study was funded by the British Heart Foundation (PG2001/150).