Δ^9-Tetrahydrocannabinol inhibits electrically-evoked calcitonin gene-related peptide release from capsaicin-sensitive nerves

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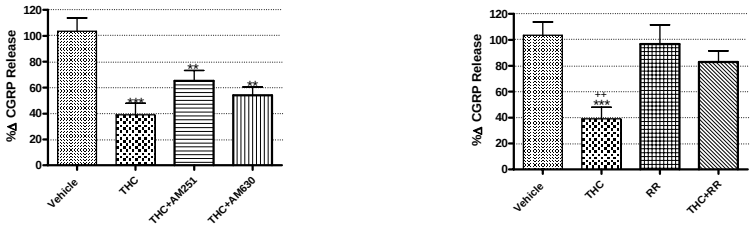
Cannabinoids have wide-ranging effects on the cardiovascular system not all of which are mediated through the cannabinoid receptors CB_1 and CB_2. Zygmunt *et al* (2002) have shown that Δ^9-tetrahydrocannabinol (THC) causes the release of calcitonin gene-related peptide (CGRP) from capsaicin-sensitive sensory nerves in rat isolated mesenteric arteries, resulting in a potent vasodilation that can not be blocked by CB_1/ CB_2 antagonists, and is likely to involve a TRP type ion channel. It has also been shown that THC attenuates sensory neurotransmission in the rat isolated mesenteric arterial bed (Duncan *et al*, 2004). This was observed as an inhibition of vasorelaxation following electric field stimulation (EFS) of capsaicin-sensitive sensory nerves, and was unaffected by CB_1/CB_2 antagonists. In the present study we investigated directly the effect of THC on EFS-induced release of CGRP from sensory nerves, by assaying perfusate levels of CGRP, and investigated the possible involvement of cannabinoid receptors and TRP channels.

Mesenteric arterial beds from male Wistar rats were cannulated via the superior mesenteric artery, removed and perfused with Krebs' solution (5 ml min^{-1}, 37^{o}C). Sympathetic neurotransmission was blocked (5 μM guanethidine) and preparations preconstricted with methoxamine (30-50 mmHg above baseline). Perfusate was collected prior to and during EFS (8 Hz, 0.1 ms, 60 V, 30 s). CGRP was isolated from the perfusate by solid phase extraction and measured by EIA (Rat CGRP Kit #A05482, SPIBio, France).

THC (1 μM) had no significant effect on the tone of the preparations, but significantly inhibited the EFS-induced release of CGRP from sensory nerves in the mesenteric arterial beds (Fig. 1). This effect was unaffected by the CB_1 and CB_2 antagonists AM251 and AM630 (1 μM) respectively. However, THC in the presence of ruthenium red (RR) (1 μM) did not significantly inhibit the release of CGRP.

Figure 1. Inhibitory effect of Δ^9- THC on electrically evoked CGRP release.



Analysed by 1way ANOVA & Newman-Keuls multiple comparisons. p<0.001, **p<0.01, Significance to Vehicle control. ++ P<0.01, Significance to RR + THC***

We show for the first time that THC inhibits the EFS-induced release of CGRP from perivascular capsaicin-sensitive sensory nerves by directly measuring CGRP release; this evoked release can not be blocked by CB_1/CB_2 antagonists but is abolished by ruthenium red, suggesting the involvement of a TRP ion channel.

Duncan M *et al,* (2004) *J Pharmacol Exp Ther* **331**, 411-419
Zygmunt PM *et al,* (2002) *J Neurosci* **22**, 4720-4727