Δ⁹-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 CB₁ and CB₂. Zygmunt et al (2002) have shown that Δ⁹-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 CB₁/CB₂ 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 CB₁/CB₂ 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°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 CB₁ and CB₂ 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.

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 CB₁/CB₂ antagonists but is abolished by ruthenium red, suggesting the involvement of a TRP ion channel.