Activation of cannabinoid receptors reduces inflammation and motility disturbances in an animal model of inflammatory bowel disease (IBD)

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Cannabinoid receptor agonists can reduce inflammation and tissue damage in different animal models of colitis (Kimball et al., 2006). Gastrointestinal inflammation is associated with profound changes in smooth muscle contractility (Wells et al., 2004) and alterations in the enteric nervous system (ENS) (Poli et al., 2001). We have used the 2,4,6-trinitro-benzenesulfonic acid (TNBS) - model of colitis to characterize the motility disturbances in acute inflammation and the ability of CP55,940 and dexamethasone to reduce them.

Colitis was evoked in male Wistar rats (210-290g) by intra-colonic administration of 6.7mg TNBS in 0.25ml 25% ethanol. The degree of inflammation was quantified using macroscopic damage score (MDS, 0-13 scale) and myeloperoxidase (MPO) activity (U/g wet tissue weight) as an index of neutrophil infiltration. Longitudinal muscle strips were used for the motility studies. Spontaneous activity (amplitude of low frequency contractions, ALF), carbachol evoked contractions and % relaxation to veratridine ($5x10^{-6}$ M) were evaluated. Frequency-response curves to electrical field stimulation were constructed (1-15Hz, at voltage supramaximal at 5Hz, 0.2ms pulse width). Amplitude of contraction was calculated per g tissue (dry weight). Drugs were administered i.p., CP 55,940 (in Tween 80 in saline) at 0.4mg/kg and dexamethasone phosphate (in saline) at 1.3mg/kg (0.5hour before TNBS administration, 24 and 48 hours after). Animals were sacrificed 72 hours post colitis-induction. The control group received Tween 80 in saline. Results are expressed as mean±SEM and compared using unpaired *t*-test.

In TNBS treated animals all the motility responses were significantly depressed, whereas MDS and MPO activity increased. CP 55,940 (C) and dexamethasone (D) reduced TNBS-induced neutrophil infiltration (MPO: 45.03±6.89 and 8.25±4.78, respectively, $P<0.05$ versus vehicle, V, 91.51±2.96). However the MDS was not influenced significantly (C:2.83±1.08, D:2.00±0.68, V:3.40±0.68). CP 55,940 partially reversed the TNBS-induced reduction in ALF (C:84.47±13.94, V:57.32±9.21), whereas dexamethasone markedly improved this parameter (154.03±22.12, $P<0.05$ versus V). The TNBS-induced reduction in the response to carbachol was reversed by both drug treatments, but this was only significant for dexamethasone. The % relaxation to veratridine was significantly larger in the drug treated groups in comparison to vehicle treated group (C:72.02±6.86, D: 74.08±7.75 and V:49.24±4.85). The EFS evoked rebound contractions were significantly improved by both drug treatments for frequencies from 3 to 15Hz.

This study demonstrates that CP 55,940 reduces the inflammation and functional disturbances in an animal model of colitis, although at the dose studied it was not as effective as dexamethasone.

Kimball et al. (2006) *Am J Physiol Gastrointest Liver Physiol* **291**(2): G364-71
Poli et al. (2001) *Neurochem Res* **26**(8-9): 1085-93
Wells et al. (2004) *Pfluegers Arch* **448**(5): 515-24