Acute colitis alters the effects of cannabinoid and opioid receptor agonists on colonic nociception

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Background/Aim: Abdominal pain is a debilitating symptom of inflammatory bowel disease. We have shown that the combination of sub-analgesic concentrations of cannabinoid 1 receptor (CB1R) and mu-opioid receptor (MOR) agonists inhibit colonic pain signalling in non-inflamed mice and is devoid of side effects. This study investigated the effect of cannabinoid and MOR agonists alone or in combination on colonic nociception during acute colitis.

Methods: Dextran sulfate sodium administration induced colitis in male and female C57BL/6 mice. Colonic pain signalling was assessed by measuring the visceromotor response (VMR) to colorectal distension (20-80 μL) *in vivo* and mechanosensitivity of single colonic afferent axons in *ex vivo* extracellular afferent nerve recordings. Data were analyzed using a one- or two-way ANOVA with Bonferroni test. N= number of mice; n=number of single axons.

Results: ACEA (CB1R agonist; 3 mg/kg), effective in healthy mice, did not inhibit VMR in mice with colitis ($p=0.55$, N=6). Conversely, HU-308 (CB2R agonist; 3 mg/kg), which had no effect in healthy mice, inhibited VMR in colitis compared to vehicle (32% reduction, $p<0.05$, N=6). While morphine (MOR agonist; 0.3 mg/kg) had no effect in healthy mice, it inhibited VMR during colitis (34% reduction, $p<0.01$, N = 8). Interestingly, the effect of combining low dose ACEA (0.3 mg/kg) and morphine (0.3mg/kg) was larger than that of morphine alone (62% vs. 34% reduction; $p=0.06$, N=5-8). While ACEA (1μM) inhibited colonic mechanosensitivity in healthy mice, ACEA (10 μM) was required in colitis (15.2 vs. 11.6 Hz; $p<0.05$, n=11, N=6). However, combining sub-analgesic concentrations of ACEA (100 nM) and DAMGO (MOR agonist;1 nM) still significantly reduced mechanosensitivity (18.4 vs. 12.0 Hz; $p<0.05$, n=7, N=5).

Conclusions: During colitis, the effectiveness of CB1R, CB2 and MOR agonists on pain signaling is altered. However, combining sub-analgesic CB1R and MOR agonists is still more effective than the MOR agonist alone.