CANNABINOID INHIBITION OF PHARMACOLOGICALLY EVOKED ELECTROGENIC SECRETORY FUNCTION OF THE RAT PROXIMAL COLON

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Extracts of cannabis have been widely used historically to treat a variety of gastrointestinal disorders including secretory diarrhoea. Cannabinoid CB_1 receptors expressed on submucosal cholinergic and non-cholinergic neurons in the intestine have been shown to be involved in neural regulation of epithelial transport functions by modulating secretory transmitter release MacNaughton *et al*., (2004). Using the Ussing chamber technique and short circuit current (SCC) as a measure of electrogenic ion transport, Tyler *et al.*, (2000) demonstrated that electric field stimulated (EFS) secretion in the rat ileum was inhibited by the cannabinoid receptor agonist WIN 55212-2 acting at presynaptic CB_1 receptors. In the guinea pig ileum the same agonist inhibited both EFS and capsaicin stimulated ion transport via activation of CB_1 receptors (MacNaughton *et al*., 2004). The aim of the present study was to examine the effects of cannabinoids on pharmacologically evoked ion transport in the rat proximal colon using capsaicin (which stimulates vanniloid VR_1 receptors on sensory intrinsic primary afferent neurones), veratridine (which opens voltage dependent neuronal Na^+ channels) and nicotine.

Muscle-stripped epithelial sheets devoid of the myenteric plexus of the proximal colon from rats (male, Wistar, 350-550g) were voltage clamped in Ussing chambers for monitoring of transmural SCC as described by Yarrow *et al*., (1991). Basolateral single additions of capsaicin (1μM), nicotine (100μM) produced transient increases in SCC whereas veratridine (30μM) produced a sustained increase in SCC (20.30 ± 0.49 (n=48), 56.9± 12.0 (n=6), 50.9±8.9 (n=6) respectively), over a resting basal SCC of 21.8 ± 1.2 (n=30) Values are expressed as mean change in SCC.μAcm^{-2} ± s.e.m. All drugs were dissolved in absolute ethanol with the exception of nicotine, which was dissolved in distilled water. The secretory responses to all three secretagogues were TTX (1μM) sensitive but atropine (1μM) insensitive. 30min pre-incubation with the non-selective cannabinoid receptor agonist CP 55,940 (1μM) caused a significant ($P<0.05$ unpaired t test) inhibition of the secretory response to both capsaicin and nicotine (72.2% (n=12) and 49.5% (n=7) respectively). The inhibitory effects of CP 55,940 were completely reversed by 30 min pre-treatment with the selective CB_1 antagonist SR141716 (1μM) (n=6) ($P<0.05$ unpaired t test). Another non-selective cannabinoid receptor agonist WIN 55,212-2 (1μM) also produced a SR141716 (1μM) sensitive inhibition of both capsaicin and nicotine (80.8 % (n=6) and 59.4 % (n=6) respectively, ($P<0.05$ unpaired t test) evoked increase in SCC. In contrast, the secretory response to veratridine was totally refractory to both CP 55,940 (1μM) (n=6) and WIN 55,212-2 (1μM) (n=6), a slight but non-significant potentiation being obtained with the former cannabinoid agonist.

These data show that in the rat colon, cannabinoids acting at the CB_1 receptors inhibit the secretory responses to some forms of pharmacological stimulation. These responses are nerve mediated and the transmitter(s) involved are non-cholinergic in nature.

MacNaughton *et al*., (2004) *Am J Physiol Gastrointest Liver Physiol* **286**: G863–G871
Tyler *et al*., (2000) *Eur. J. Pharmacology* **409**, 207–211
Yarrow *et al*., (1991) *Naunyn Schmiedebergs Arch Pharmacol*.**344** (5): 557-63.

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