ACTIVATION OF EP_1 RECEPTORS BY LUBIPROSTONE IN RAT ISOLATED FORESTOMACH LONGITUDINAL MUSCLE

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Lubiprostone, a ClC-2 channel opener derived from prostaglandin E_1 (PGE_1) and indicated for the treatment of constipation, increases chloride ion transport into the intestinal lumen and thereby enhances fluid secretion. However, in healthy volunteers, lubiprostone may increase fasting gastric volume and retard gastric emptying, as well as accelerate intestinal transit (Camilleri *et al*., 2006). Nausea (31%) is the most frequently reported adverse event (Hussar, 2006). A weak ability of lubiprostone to activate prostanoid receptors has been reported in various tissues (Perentesis *et al*., 2005). We re-examined this activity of lubiprostone in rat isolated stomach, an area of the gut not previously studied. METHODS: Longitudinal muscle preparations of rat forestomach were used (male, Sprague-Dawley, 250-300 g). Muscle strips (~2 x 8 mm) were suspended in Krebs solution (5% CO_2/ 95% O_2; pH 7.4; 37^{o}C) under 10 mN tension for isometric recording; experiments were conducted in the presence of indomethacin (3 μM, at least 20 min preincubation). After obtaining contraction to PGE_2 (1 μM; previously determined as maximally-effective) and subsequent wash-off, a cumulative concentration response curve to lubiprostone was generated (0.1 nM – 10 μM, ~3 min intervals) in the presence of antagonists at the prostaglandin EP_1 (3-Pyridinecarboxylic acid, 6-[[[5-bromo-2-(phenylmethoxy)phenyl]methyl]ethylamino], EP_3 (Thiophene-2-sulfonic acid {3-[2-2-(4-methylsulfonylbenzyl)-phenyl]-acryloyl}-amide; L-798,106) or EP_4 ((N-{2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetyl}benzene sulphonamide)); GW627368X) receptors (Breault *et al.,* 1996, Juteau *et al.,* 2001 and Wilson RJ *et al.,* 2006, respectively; 20 min pre-incubation) or vehicle (0.1 % DMSO). The resultant contractile responses were quantified as a % of the 1 μM PGE_2-induced contraction (mean ± sem) and statistical analysis was performed using a Student's unpaired t-test. RESULTS: Lubiprostone 3 nM – 10 μM caused a concentration-dependent contraction of the forestomach (pEC_{50} = 7.01 ± 0.04; n=4) which was TTX (1 μM)- and scopolamine (10 μM)-insensitive (n=6; P>0.05). The maximum effect was 95 ± 3 % of that evoked by 1 μM PGE_2. Lubiprostone-induced contractions were unchanged in the presence of the EP_3 or EP_4 receptor antagonists (both 1μM; pEC_{50} = 7.10 ± 0.10 and 7.01 ± 0.09, respectively; n=4; P>0.05) but were concentration dependently antagonised by the EP_1 receptor antagonist (e.g. 300 nM pEC_{50} = 6.19 ± 0.19, apparent pK_B of 7.59, n=6), without significant suppression of the maximum response. CONCLUSIONS: Lubiprostone activates EP_1 receptors to contract rat isolated forestomach longitudinal muscle with similar efficacy to PGE_2. Since emesis may be induced by EP_1 receptor activation (Kan *et al.,* 2002), this action may at least partly explain the nausea experienced by patients taking this drug.

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