5-HT_7 RECEPTOR ACTIVATION INHIBITS SUBSTANCE-P-INDUCED BUT NOT CARBACHOL-INDUCED CONTRACTIONS IN GUINEA-PIG ILEUM: A POSSIBLE CROSS-TALK BETWEEN 5-HT_7 AND NK RECEPTORS?

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5-HT_7 receptor activation is known to mediate relaxation of gastrointestinal smooth muscle. Previous studies have demonstrated that activation of 5-HT_7 receptors inhibits contractions induced by substance-P in the guinea-pig ileum (Carter *et al*., 1995), carbachol in the human colon (Prins *et al*., 1999) and prostaglandin-$F_{2\alpha}$ in dog stomach (Janssen *et al*., 2005). We have investigated the effect of a non-selective 5-HT receptor agonist 5-carboxamidotryptamine (5-CT) on substance-P and carbachol-induced contractions in the guinea-pig ileum, in the absence or presence of a cocktail of non-5-HT_7 receptor antagonists, in order to elucidate whether or not the relaxation response in this particular tissue is due to direct activation of the 5-HT_7 receptor.

Whole guinea pig ileal segments (~10 mm) were dissected from adult male Dunkin Hartley guinea pigs (300-350g) 10 cm distal to the ileocaecal junction and suspended in 5 ml tissue baths containing Krebs' buffer (NaCl 121.5, $CaCl_2$ 2.5, KH_2PO_4 1.2, KCl 4.7, $MgSO_4$ 1.2, $NaHCO_3$ 25.0, glucose 5.6 mM) at 37°C, oxygenated with 5% CO_2 in O_2 under 1g tension for isometric recording. The tissues were contracted either with carbachol (300 nM; $EC_{80;}$ 1.9±0.2 g) or substance-P (100 nM; EC_{80}; 2.1±0.2 g) in the absence or presence of an antagonist cocktail (WAY100635 [0.1 µM; 5-HT_{1A} receptor antagonist], GR127935 [1 µM; 5-HT_{1B} and 5-HT_{1D} receptor antagonist], ketanserin [1 µM; 5-HT_{2A} receptor antagonist], SB204741 [1 µM; 5-HT_{2B} receptor antagonist], ondansetron [1 µM; 5-HT_3 receptor antagonist], SB204070A [0.1 µM; 5-HT_4 receptor antagonist] and scopolamine [10µM only for substance-P experiments]).

5-CT (0.01-100 µM) inhibited substance-P-induced contractions (maximum inhibition of 26.9±8.4% (n=7) and 39.4±6.6% (n=8) at 3 µM 5-CT in the absence or presence of antagonist cocktail respectively) but had no effect on carbachol-induced contractions (3.1±1.7% vs 7.8±3.9% inhibition, vehicle vs 5-CT at 10µM respectively, n=4). The inhibitory effect of 5-CT on substance-P-induced contractions was fully reversed by the selective 5-HT_7 receptor antagonist SB269970 (1 µM).

These results suggest that, at least in the guinea-pig ileum, the inhibitory action of 5-HT_7 receptor activation is specific to the receptor or pathways involved in mediating substance-P-induced contraction and further suggest a possible cross-talk between 5-HT_7 and NK receptors.

Carter D. *et al.* (1995) *Eur. J. Pharmacol.*, **280,** 243-250.
Janssen P. *et al.* (2005) *Am. J. Physiol.*, **289,** G108-G115.
Prins N.H. *et al.* (1999) *Br. J. Pharmacol.*, **128,** 849-852.