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Dysrhythmia Of Myogenic And Cholinergic Activity Induced By Motilin In Human Isolated Stomach

Gastric dysrhythmia precedes the sensation of nausea, and is thought to be a potential cause (1). Motilin receptor agonists can induce nausea and vomiting although at lower, therapeutically-relevant doses, nausea is inhibited (2). We have investigated an ability of motilin to promote and disrupt nerve mediated and myogenic movements of human isolated stomach.

Human gastric antrum and fundus were obtained from sleeve gastrectomies for obesity (7 male, 12 female: non diabetic; 3 female: type 2 diabetes; median age=42 (23-56)) following informed consent and ethics approval from the Health Research Authority (REC: 10/H0703/71). After removing the mucosa, circular muscle strips (3x15 mm) were suspended in tissue baths for isometric force measurements. (Krebs solution, 37°C; 5% CO_2 in O_2, 2g tension). Electrical field stimulation (EFS; 5Hz, 0.5 ms pulse width, 50V, 10s every 1min) was used to generate sub-maximal, cholinergically-mediated contractions (4). Drugs were added non-cumulatively. Data is expressed as means ± error; n = number of patients.

Motilin 10-300nM increased EFS-evoked contraction amplitudes in the antrum (e.g. by 2000±87% at 300nM; n=9) with smaller increases in the fundus (90±1% at 300nM; n=5). At the higher concentrations muscle tension also increased, fading to baseline during continued exposure. The increased EFS-evoked contractions took longer to fade and in the antrum, but not the fundus, this occurred irregularly, with alternating small and large contractions, confirming earlier observations (4). In the absence of EFS and in the presence of tetrodotoxin 1µM, atropine 1µM and L-NAME 300µM (which prevented EFS-evoked contractions; n=4), small regular spontaneous muscle contractions were observed in the antrum (6.0±0.3 cycles/ min (cpm) measured over 2 min; amplitude: 0.6±0.3 g; n=4), and fundus (in 3 of 5 patients). In the antrum, motilin 300nM increased muscle tension and greatly increased the myogenic contractions during the first 5.5±0.7 min after application (maximum increase in amplitude: 1458 ± 880%) without changing their frequency (cpm's over 2 min were, respectively 6.1±0.3 and 5.5±0.7; P>0.05 n=4). Thereafter, the contraction amplitudes became less frequent (e.g. 20 min after application the overall cpm = 2.5±0.1) and irregular. For example, in one strip from one patient 20 min after application, the contractions varied from 7.3g to 1.5g. Similar changes were observed using 100nM motilin and dysrhythmia was reached 6.0±1.5 min after application of motilin (n=3). In the fundus, motilin 300nM caused a small increase in muscle tension and amplitude of spontaneous contractions (amplitude increased by 202±256 %, n=3) but did not affect frequency (cpm: 7±0.6 to 6.5±0.6, n=4) or cause dysrhythmia.

Motilin facilitates cholinergic activity especially in the gastric antrum. Motilin can also stimulate and disrupt myogenic activity in the antrum but not the fundus, possibly via interaction with interstitial cells of Cajal, which generate slow waves to entrain muscular movements (5). The coordination of these actions enhances gastric motility yet may induce gastric dysrhythmia at higher concentrations (1).

1. Koch KL (2014). *Exp Brain Res* 232: 2553–2561.

2. Janssens et al (1990). *New England J Medicine* 322: 1028-1031

3. Broad J et al (2012). *Br J Pharmacol* 167: 763-774.

4. Xu W-D, et al (2012). *Scand J Gastroenterol* 47: 89–98.