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A novel motilin receptor agonist, RQ-00201894, causes prolonged facilitation of cholinergically-mediated contractions in human isolated stomach

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Motilin receptor agonists, acting as gastric prokinetics, are in clinical development for a number of conditions associated with delayed gastric emptying [1]. A key attribute is that unlike motilin, these molecules cause prolonged facilitation of gastric cholinergic activity, the main enteric excitatory nerve system. However, it is difficult to characterise such activity using recombinant receptors (which are not similarly coupled to intracellular pathways) or in animals where the receptor is absent (rodents) or differs significantly from humans (dogs) [2]. The novel, selective, motilin receptor agonist RQ-00201894 [3], effective as a prokinetic agent in animals [4, 5], has therefore been evaluated for its ability to facilitate neuronally-evoked responses in human isolated stomach.

Human gastric antrum (age 51 (25 – 60), 1:1 male:female) was obtained at surgery for obesity following informed consent. After removing the mucosa, strips (3 – 5 x 15 mm) were cut parallel to the circular muscle and suspended between platinum ring electrodes in tissue baths for isometric recording (Krebs; 5% CO_2 in O_2; 37 °C; 2 g tension). Electrical field stimulation (EFS) was applied at 5 Hz (0.5 ms pulse width, 50 V, 10 s) every 1 min, to evoke sub-maximal contractions. Drugs were applied non-cumulatively.

52 strips of antrum muscle were obtained from 8 patients undergoing sleeve gastrectomy. EFS evoked cholinergically-mediated contractions attenuated by simultaneous nitrergic activation [6]. RQ-00201894 0.1 – 30 µM concentration-dependently increased the amplitude of EFS-evoked contractions (E_{max} 1209 ± 183 %; pEC_{50} 6.0 ± 0.4, n = 4 – 6 patients, each concentration); lower concentrations had no consistent activity. At 30 µM the response faded during the continued presence of the compound. At the lower concentrations (0.1 – 10 µM) the excitation was slow in onset and after reaching maximum, was usually maintained for the remainder of the experiment (>60 min). Notably, this activity did not always occur in a regular manner, with large and small EFS-evoked contractions appearing at irregular intervals, especially at the higher concentrations.

RQ-00201894 (3 – 30 µM) also evoked a short-lasting muscle contraction (E_{max} 292 ± 76 % EFS; pEC_{50} 5.9 ± 0.5; n = 4 – 6), temporally disconnected from the increase in EFS-evoked contractions, reaching maximum more quickly and usually fading completely before the increase in EFS-evoked contraction reached maximum; the lower concentrations contracted the muscle in 2 of 5 (1 µM), 3 of 5 (0.3 µM) and 2 of 6 tissues (0.1 µM).

RQ-00201894 10 µM had no consistent ability to affect the magnitude of contractions evoked by a submaximally-effective concentration of carbachol (1 µM; contractions were 83 ± 13 % of the responses before RQ-00201894 addition; n = 4, P > 0.05 Wilcoxon signed rank test).

This study confirms the ability of motilin receptor agonists to facilitate gastric cholinergic activity in a manner which is biased towards the induction of prolonged activity. The effects of RQ-00201894 in human isolated stomach are therefore broadly consistent with the actions of other non-peptide motilin receptor agonists [6, 7].

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