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MEETING ABSTRACT

A4.2

Effects of Ca^{2+}-activated K^+ channel modulators on the contractility of the rat gastric fundus

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Background: Ca^{2+}-activated K^+ (K_{Ca}) channels are important regulators of excitability of the gastrointestinal smooth muscle cells. $K_{Ca}1.1$ and 2 channels (also called large- and small-conductance Ca^{2+}-activated K^+ [BK and SK] channels, respectively) regulate Ca^{2+} entry from the extracellular fluid. In addition, the opening of $K_{Ca}2$ channels mediates the effects of some inhibitory neurotransmitters. The aim of our study was to investigate the effects of K_{Ca} channel modulators on the contractility of the proximal stomach.

Methods: Longitudinal muscle strips were prepared from the rat gastric fundus and were suspended under isotonic conditions (9.8 mN load) in Krebs solution maintained at 37°C, bubbled with carbogen and containing atropine (1 µM) and guanethidine (5 µM) (to obtain nonadrenergic, noncholinergic [NANC] conditions) inside 5-ml organ baths. The relaxations were studied in strips precontracted by the TP receptor agonist U46619 (0.1 µM). The effects of iberiotoxin (IBTX), UCL1684 and TRAM-34 (selective blockers of $K_{Ca}1.1$, 2 and 3.1 channels, respectively) and NS1619 and NS309 (activators of $K_{Ca}1.1$, 4 and 5.1 channels, and 2 and 3.1 channels, respectively) were investigated. Responses are expressed as percentages of maximal strip relaxations induced by papaverine (300 µM).

Results: IBTX (50 nM), UCL1684 (0.3 µM) and TRAM-34 (1 µM) did not affect basal muscle contractility ($n = 4$ each). When their effects were evaluated on U46619 (0.1 µM)-precontracted strips, UCL1684 (0.3 µM) and IBTX (50 nM) further contracted the strips by 3.8 ± 2.2% ($n = 6$) and 16.1 ± 3.0% ($n = 9$), respectively. NS1619 (30 and 60 µM) relaxed the strips by 9.1 ± 1.0% ($n = 11$) and 25.3 ± 3.6% ($n = 5$), respectively. NS309 (0.3–30 µM) induced concentration-dependent relaxations with pD_2 and E_{max} of 5.32 ± 0.53 and 90.5 ± 2.6% ($n = 8$), respectively. TRAM-34 (1 µM) did not significantly affect NS309 (0.3–30 µM)-induced relaxations ($n = 4$). On the contrary, the relaxations induced by NS309 (10 µM) were greatly reduced by UCL1684 (1 µM) (71.4 ± 2.1%, $n = 12$, and 17.6 ± 2.5%, $n = 4$, $p < 0.001$, without and with UCL1684, respectively).

Discussion: The results of our study suggest that K_{Ca} channels have no role in controlling resting membrane potential of smooth muscle cells of rat gastric fundus. A small number of $K_{Ca}1.1$ and 2 seems to open in response to U46619-induced effects. The activation of $K_{Ca}2$ channels produces significant relaxations of the proximal stomach, suggesting that $K_{Ca}2$ channel openers could be considered as useful relaxant agents of the gastric smooth muscle.

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