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Modulation of the nonadrenergic noncholinergic relaxation of the rat gastric fundus by K_{Ca}1.1 channels

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Introduction: Ca^{2+}-activated K^+ channels type 1.1 (K_{Ca}1.1 channels) are widely expressed in mammalian cells, including neurons and smooth muscle cells, in which they are important regulators of neurotransmitter release and smooth muscle contractility, respectively (1). The aim of this study was to investigate the effects of K_{Ca}1.1 channel blockers on the nonadrenergic noncholinergic (NANC) relaxation of the proximal stomach.

Method: Longitudinal muscle strips from the gastric fundus of Wistar rats were mounted inside 5-ml organ baths containing Krebs solution maintained at 37° C and bubbled with carbogen under isotonic (1-g load) and NANC (1 µM atropine + 5 µM guanethidine) conditions. NANC relaxations of U46619 (0.1 µM)-precontracted strips were induced by low (2 Hz)- and high (13 Hz)-frequency electrical field stimulation (EFS); the amplitude of the first relaxation and the AUC of the second one are largely due to nitric oxide and vasoactive intestinal polypeptide, respectively (2). All responses were normalized by dividing them for the maximal relaxation induced by papaverine (300 µM). The results were evaluated by means of paired Student's test.

Results: The selective K_{Ca} 1.1 channel blocker iberiotoxin (50 nM) and the K_{Ca} 1.1 and 3.1 channel blocker charybdotoxin (100 nM) increased EFS (2 Hz)-induced relaxation amplitude by 23.1±5.5 % (n=9, P<0.01) and 22.9±3.0 % (n=7, P<0.01) of controls, respectively. The selective K_{Ca} 3.1 channel blocker TRAM-34 (1 µM) and a low concentration (60 nM) of the selective K_{Ca} 1.1 channel blocker paxilline did not significantly affect the EFS (2 Hz)-induced relaxation amplitude, which, on the contrary, was increased to 111.6±3.6 % of controls (P<0.05, n=8) by a high concentration (10 µM) of paxilline. Iberiotoxin increased EFS (13 Hz)-induced relaxation AUC by 12.1±2.6 % (P<0.01) of controls, whereas charybdotoxin (100 nM) and paxilline (60 nM and 10 µM) did not significantly affect it. Iberiotoxin (50 nM), charybdotoxin (100 nM) and paxilline (60 nM and 10 µM) further contracted the U46619 (0.1 µM)-precontracted strips (by 16.4±3.0 %, 12.5±1.5 %, 1.0±0.7 % and 1.9±0.7 %, respectively).

Conclusions: These data suggest that K_{Ca} 1.1 channels modulate the induced tone of the gastric smooth muscle and the nitrergic component of the NANC relaxation. The possible role of K_{Ca} 1.1 channels in the regulation of the peptidergic component of the NANC relaxation needs further investigation.

References: 1. Contreras *et al.* (2013). *Channels (Austin)* **7**: 442-58. 2. Currò *et al.* (2008). *Eur Rev Med Pharmacol Sci* **12 Suppl 1**: 53-62.