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Poster presentation

Role of soluble guanylate cyclase in NO-induced effects of gastric fundus

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Nitric oxide (NO) is the most important relaxant neurotransmitter in the gastric fundus. The principal target of NO is soluble guanylate cyclase (sGC). As the $\alpha_1\beta_1$ isoform is most abundant in the gastrointestinal tract, the aim of this study was to investigate the role of sGC in NO-induced smooth muscle effects of gastric fundus using wild type (WT) and sGCα_1 knock-out (KO) mice of both sexes (8–50 weeks old). Circular muscle strips of the gastric fundus were precontracted with prostaglandin F2α (PGF2α) in the presence of atropine and guanethidine and exposed to electrical field stimulation (EFS) and exogenous NO, before and in the presence of the sGC inhibitor ODQ or the NO synthase inhibitor L-NAME. The contractile response to PGF2α did not differ between WT and KO strips. In WT strips, EFS-induced relaxations were nearly abolished by L-NAME and ODQ indicating that NO, acting at sGC, is the neurotransmitter liberated. The responses to EFS were greatly reduced in KO strips; in the presence of ODQ or L-NAME, no electrically induced relaxations were obtained. In WT strips, NO-evoked responses were not influenced by L-NAME but reduced by ODQ; the higher the concentration of NO, the less pronounced was the inhibitory effect of ODQ. In KO strips, NO-evoked responses were minimally reduced in comparison to WT strips, while the inhibitory effect of ODQ versus NO was more pronounced. The relaxant effect of 8-bromo-cGMP was not different between WT and KO strips, but the relaxant effect of BAY 41-2272 was reduced in KO strips. Cyclic guanosine monophosphate (cGMP) levels measured at maximal relaxation by EFS or NO, were increased 34–35 (male respectively female) fold by NO versus basal, but were not changed by EFS in WT strips. Basal cGMP levels were lower in KO strips, although this did not reach significance in female mice; in KO strips NO still induced a moderate increase in cGMP levels (3–5 fold versus basal) but this was significantly less pronounced. The results indicate that endogenous NO, released by EFS, mainly acts through activation of sGCα_1. The observation that the relaxant response to exogenous NO is only minimally reduced in KO strips indicates that exogenous NO is able to act mainly through sGCα_2, as the responses are still highly sensitive to ODQ. Obviously, the subcellular localization of cGMP raised by sGCα_2 in the KO strips is different from that by activation of sGCα_1 in the WT strips, as nearly the same degree of relaxation is induced by exogenous NO with a lower level of measurable cGMP.