BMC Pharmacology

Poster presentation

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NO-induced motility effects in gastric fundus and pylorus of sGCβ1his105phe mutant mice

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from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):P15 doi:10.1186/1471-2210-7-S1-P15

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/P15

Nitric oxide (NO) is the most important relaxant neurotransmitter in the stomach. The principal target of NO is soluble guanylate cyclase (sGC), of which two physiologically prevailing isoforms exist, namely α1β1 and α2β1. The aim of this study was to investigate the role of sGC in NO-induced smooth muscle effects of gastric fundus and pylorus, and in gastric emptying, using wild type (WT) and sGCβ1his105phe mutant mice (7–14 weeks old).

In vitro precontracted gastric fundus circular muscle strips and pyloric rings of female mice were exposed to electrical field stimulation (EFS) and exogenous NO in the presence of atropine and guanethidine, before and after addition of the sGC inhibitor ODQ. In vivo, a phenol red meal was gavaged in male mice for determination of gastric emptying and intestinal transit.

The body weight of the mutant mice was significantly lower than that of the WT mice (17.1 ± 1.1 g, mean ± s.e.m., n = 12 versus 22.5 ± 0.7 g, n = 15, p = 0.0002). The weight of the emptied stomach and of the gastric fundus circular muscle strips was significantly higher in the mutant mice versus WT mice (stomach: 486 ± 74 mg, n = 5 versus 210 ± 10 mg, n = 6, p = 0.0028; strips: 17.55 ± 2.92 mg, n = 10 versus 7.60 ± 0.67 mg, n = 12, p = 0.0017). In WT strips, EFS-induced relaxations were abolished by ODQ. The responses to EFS were greatly reduced in the mutant strips, but some relaxation occurred at the higher stimulation frequencies. In WT strips, NO-evoked responses were 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 nearly abolished. Relaxations induced by EFS as well as NO were abolished in mutant pyloric rings. Gastric emptying was significantly reduced in mutant mice compared to WT mice (51 ± 10%, n = 10 versus 74 ± 3%, n = 12, p = 0.0254), whereas intestinal transit did not differ between mutant and WT mice (geometric center: 2.82 ± 0.19, n = 10 versus 3.04 ± 0.21, n = 12, p = 0.4462).

sGCβ1 mutation nearly abolishes relaxations by endogenous and exogenous NO in gastric fundus and pylorus. The increased resistance at the pylorus probably explains the delay in gastric emptying.