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Cinaciguat in the gastrointestinal tract of apo-sGC mice.

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In apo-sGC mice (His105Phe mutation in sGCβ_1), both sGC isoforms ($\alpha_1\beta_1$ and $\alpha_2\beta_1$) are heme-deficient and can no longer be activated by NO; these mice can be considered as a model for oxidized/heme-free sGC. Gastrointestinal consequences of lacking NO-sensitive sGC are most pronounced at the level of the stomach; apo-sGC mice show an enlarged stomach, hypertrophy of the smooth muscle layers of fundus and pylorus and delayed gastric emptying (1). Cinaciguat is a NO- and heme-independent activator of sGC; its vascular relaxing effect is increased when sGC is oxidized, losing its heme group. The aim of this study was to investigate the influence of cinaciguat on in vitro muscle tone of fundus and pylorus, and on gastric emptying in apo-sGC mice.

Circular smooth muscle fundus strips from apo-sGC mice and WT controls (mixed 129/SvJ-C57BL/6J) were mounted in organ baths with aerated Krebs solution and incubated with the sGC inhibitor ODQ (10 μM) or its solvent (ethanol) for 30 min. Strips were then pre-contracted with $PGF_{2\alpha}$ (300 nM) and the relaxant effect of cumulatively administered cinaciguat (1-10-100 nM) was examined. Pyloric rings were mounted and the influence of cinaciguat (100 nM) was studied on spontaneous tone. In 16h fasting apo-sGC and WT mice, cinaciguat or its solvent (60% PBS, 20% DGME, 20% Cremophor) were administered intraperitoneally (IP; 300 µg/kg) or intravenously (IV; 300, 100 or 30 µg/kg) and 15 min (IP injections) or 5 min (IV injections) later 250 µl of a liquid phenol red meal was gavaged. Fifteen min after gavage, mice were sacrificed by cervical dislocation and the stomach and small bowel were excised. Gastric emptying was calculated as the amount of phenol red that left the stomach as % of the total amount of phenol red recovered; phenol red was assayed by spectrophotometry.

In fundus strips, cinaciguat (from 1 nM on) induced a sustained relaxation, which was more pronounced in apo-sGC mice ($P<0.05$ for 1 nM; a trend is observed for 10 and 100 nM; n=6-8). ODQ increased the relaxant effect of cinaciguat in WT fundus strips ($P<0.05$ for 10 and 100 nM; n=6-8), but it had no influence on the relaxant effect of cinaciguat in fundus strips of apo-sGC mice (n=6-8). In pyloric rings, cinaciguat induced relaxation in WT rings (12 ± 4% of the spontaneous tone present in the pyloric rings at a load of 0.25 g; n=7), but did not relax apo-sGC pyloric rings (n=7).

Gastric emptying was significantly delayed in apo-sGC mice compared to WT mice (16 ± 5 % versus 63 ± 3%, n=6, $P<0.001$ after IP administration of solvent; 29 ± 7 % versus 68 ± 7%, n=4-6, $P<0.01$ after IV administration of solvent). Cinaciguat (IP; 300 µg/kg; n=6) did not improve the delayed gastric emptying in apo-sGC mice. IV injection of cinaciguat (300 µg/kg and 100 µg/kg; n=4-6) delayed gastric emptying significantly in WT mice ($P<0.05$), but had no influence on gastric emptying in apo-sGC mice. IV injection of a lower dose of cinaciguat (30 µg/kg; n=6) did not have this inhibitory effect on gastric emptying in the WT mice, but it was also not able to improve the delayed gastric emptying in apo-sGC mice.
The data show that cinaciguat more efficiently relaxes fundus muscle when sGC is in the heme-free condition, but it is unable to relax the pylorus of apo-sGC mice. This might explain its unability to improve delayed gastric emptying in apo-sGC mice.

(1) Cosyns SMR et al, Neurogastroenterol Motil 25, e339, 2013