Facilitation of murine enteric cholinergic neurotransmission by 5-HT₄ receptor activation: control by phosphodiesterases

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1. INTRODUCTION
Activation of 5-HT₄ receptors present on porcine enteric cholinergic neurons enhances ongoing cholinergic activity and smooth muscle contraction; the signaling pathway of the 5-HT₄ receptors in the cholinergic neurons is controlled by phosphodiesterase 4 (PDE). The presence of 5-HT₄ receptors on murine cholinergic neurons innervating the enteric smooth muscle layer and the possible control by PDEs was now investigated.

2. METHODS
Circular smooth muscle strips from fundus, jejunum and colon were mounted in organ baths with oxygenated Krebs solution for isometric registration. In the presence of guanethidine (4 µM), L-NAME (300 µM) and for colon also MRS 2500 (1 µM), submaximal cholinergic on-contractions were induced by electrical field stimulation (EFS). The influence of the selective 5-HT₄ receptor agonist prucalopride (0.003 to 0.03 µM), the non-selective PDE inhibitor, 3-isobutyl-1-methylxanthine (IBMX; 0.1 to 10 µM), and their combination on the EFS-induced contractions was studied.

3. RESULTS
Prucalopride concentration-dependently increased EFS-induced submaximal cholinergic contractions in the 3 tissues. The increase by 0.03 µM prucalopride was 104 ± 11 % in the fundus, 38 ± 5 % in the jejunum and 52 ± 10 % in the colon (n = 7-9). The effect of 0.03 µM prucalopride was abolished by the selective 5-HT₄ receptor antagonist GR113808 (0.3 µM). IBMX concentration-dependently reduced the cholinergic contractions; a concentration reducing the EFS-induced contractions by maximally 20 % was selected for the interaction study with prucalopride (3 µM in fundus, 0.3 µM in jejunum and 1 µM in colon). In the fundus, the mild not significant facilitating effect of 0.003 µM prucalopride on cholinergic activity (38 ± 6 %, n = 9) became significant in the presence of 3 µM IBMX (63 ± 14 %, n = 9; p < 0.001). In jejunum and colon, the facilitating effect of 0.003 µM prucalopride was not enhanced in the presence of IBMX.

4. CONCLUSION
In murine fundus, jejunum and colon, 5-HT₄ receptors are present on the cholinergic neurons towards the circular smooth muscle layer. PDEs are present in the circular smooth muscle cells, their inhibition with IBMX increasing the cyclic nucleotide amount leading to a relaxing effect. In the fundus, the 5-HT₄ receptors on the cholinergic neurons seem controlled by PDEs. The lower concentrations of IBMX that had to be used in the jejunum and colon might not inhibit the PDEs in the cholinergic neurons sufficiently. The absence of potentiation of prucalopride with IBMX in the colon and jejunum needs thus further investigation with PDE subtype selective inhibitors.