

ROLE OF 5-HT RECEPTORS IN MODULATING PROPULSIVE ACTIVITY AND ACCOMMODATION IN THE GUINEA PIG DISTAL COLON

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Background: Serotonin (5-HT) modulates gastrointestinal motility by activating several receptor types (5-HT_{1,2,3,4,7}). **Aims:** To determine the presence of 5-HT_{2B}, 5-HT₃, 5-HT₄ and 5-HT₇ receptor mRNAs by classical RT-PCR, evaluate their relative expression by quantitative real time RT-PCR, and define their role in propulsive activity in isolated distal colon segments. **Methods:** Male albino guinea pigs (350-500 g) were used. Total RNA was isolated by the RNeasy Protect Mini Kit. First-strand cDNA was synthesized from the total RNA by the ThermoScript RT-PCR system. Real time RT-PCR experiments were performed by the FastStart SYBR Green Master kit. In functional studies, propulsion was elicited by distending intraluminally a thin rubber balloon (0.05-0.1 ml). The velocity of balloon propulsion (mm/s) was considered as the main parameter of peristaltic activity. Selective antagonists at 5-HT_{2B} (SB 204741: 10-100 nM), 5-HT₃ (ondansetron: 1 μM), 5-HT₄ (RS-39604: 1 μM), and 5-HT₇ (SB-269970: 1-1000 nM) receptors were used to determine the involvement of the four receptor types in propulsive activity. In a separate set of experiments, the effect of SB 269970 (100 nM) was evaluated as change in intraluminal pressure to a given change in intraluminal volume on colonic wall accommodation in 1-cm long segments after slow intraluminal fluid infusion. **Results:** PCR products corresponding to 5-HT_{2B}, 5-HT₃, 5-HT₄ and 5-HT₇ mRNA were all present in the distal colon and real time RT-PCR showed comparable levels of 5-HT_{2B} (6.8 10⁻³ fg), 5-HT₃ (7.7 10⁻³ fg) and 5-HT₇ (8 10⁻³ fg) receptor mRNAs, which were higher in density compared to the 5-HT₄ (3.5 10⁻³ fg) mRNA. In functional studies, receptor blockade resulted in a reduction of propulsive activity by 65% (5-HT₃), 85% (5-HT₄), and 30% (5-HT₇), while 5-HT_{2B} receptor blockade was ineffective. Peristaltic activity was invariably blocked by the simultaneous administration of the first three antagonists. Intraluminal infusion (1 min duration) of short colonic segments with 0.1-0.3 ml/min caused a slight increase of intraluminal pressure in the range 500-1300 Pa. This effect was reduced by 30-40% by 100nM SB 269970. **Conclusions:** 5-HT₃, 5-HT₄ and to a lesser extent 5-HT₇, but not 5-HT_{2B}, receptors participate in the regulation of colonic propulsive activity. In addition, 5-HT₇ receptors activated by endogenous 5-HT are involved in circular muscle accommodation without affecting propulsive activity. Since 5-HT₇ receptors have been previously shown to mediate accommodation also in the ileum, these receptors may emerge as a novel therapeutic target for the development of drugs affecting functional bowel disorders.