Differential 5-HT3 mediation of human gastrocolonic response and colonic peristaltic reflex

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Björnsson, Einar S., William D. Chey, Uri Ladabaum, Michelle L. Woods, Forrest G. Hooper, Chung Owyang, and William L. Hasler. Differential 5-HT3 mediation of human gastrocolonic response and colonic peristaltic reflex. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G498–G505, 1998.—Colonic motor function is modulated by extended and local neural reflexes involving unknown mediators. To test the role of serotonin (5-HT3) pathways, increases in colonic tone during antral distension and duodenal lipid perfusion (gastrocolonic responses) and changes in orad and caudad colonic tone in response to local colonic distension (peristaltic reflex) were measured after double-blind granisetron (10 μg/kg) or placebo infusion in healthy human volunteers. Antral distension evoked increases in colonic tone, which were blunted by granisetron (P < 0.05) without effects on antral compliance. Intraduodenal lipid perfusion also evoked increased colonic tone, which was reduced by granisetron (P < 0.05). In contrast, orad colonic contractions and caudad relaxations and contractions during colonic distension were unaffected by granisetron. In conclusion, 5-HT3 receptor antagonism blunts both the mechano- and chemoreceptor components of the human gastrocolonic response without altering antral compliance. In contrast, 5-HT3 pathways play no role in the ascending or descending components of the colonic peristaltic reflex. These findings demonstrate different roles for 5-HT3 receptors in the control of colonic motor function by the proximal gastrointestinal tract and by local neural reflexes.

gastrointestinal motility; serotonin; granisetron; balloon distension

MATERIALS AND METHODS

Subject Population

Seventeen healthy volunteers ranging from 20 to 48 yr of age (8 women and 9 men) were recruited by campus-wide advertisement. Subjects with gastrointestinal complaints, previous abdominal surgery, or taking medications known to alter gastrointestinal motility were excluded. The studies were approved by the University of Michigan Institutional Review Board. Written informed consent was obtained from all subjects before participation.

Study Design

Isobaric determination of colonic tone was performed using a barostat with recording balloons endoscopically placed in the descending colon. The evening before the study, each subject ingested 3.8 liters of colonic lavage solution (Co-Lyte; Reed and Carnick, Jersey City, NJ). After overnight fasting the subject was positioned on his or her left side and colonoscopy was performed to the cecum after minimal sedation with intravenous midazolam (4–10 mg, Versed; Hoff-
A Teflon-coated guidewire was inserted through the biopsy channel, and the colonoscope was removed. A multilumen barostat catheter, constructed from three 14-Fr Tygon tubes, was advanced over the guidewire so that the tip reached the splenic flexure, as confirmed by fluoroscopy. Three balloons were located in series along the distal 30 cm of the catheter, each balloon communicating with a separate lumen (Fig. 1). The middle stimulus balloon, constructed of latex and 5 cm in length, served as a distending stimulus. The proximal and distal balloons were highly compliant, were constructed of polyethylene, were 8 cm in length with a maximal capacity of 400 ml, and had geometric centers 15 cm from the center of the middle balloon. The proximal and the distal balloons were connected individually to an electronic barostat (Isobar-3; G & J Electronics, Toronto, Ontario, Canada) to measure changes in colonic tone. Inflation of the recording balloons was controlled by a single 700-ml cylinder within the barostat. Pressures were recorded within the cylinder apparatus. Volume and pressure output from the barostat were recorded on a paper chart (Beckman Dynograph Recorder R611; Sensor Medics, Yorba Linda, CA) and also stored in digitized form for later analysis. After a 2-h equilibration period to allow tolerance to the balloons and recovery from sedation, subjects were positioned on their left side with knees and hips flexed, where they remained for the rest of the study.

Healthy volunteers underwent assessment of the mechanoreceptor component of the gastrocolonic response and the peristaltic reflex on the same day, beginning 30 min after double-blind intravenous infusion of granisetron hydrochloride (Kytril, 10 µg/kg; Smith-Kline Beecham Pharmaceuticals, Philadelphia, PA) or placebo vehicle on separate days in randomized order at least 3 days apart. Measurement of antral compliance was performed on separate days from measurement of the mechanoreceptor component of the gastrocolonic response. Testing of the chemoreceptor component of the gastrocolonic response was performed on separate days from the mechanoreceptor studies to eliminate the possibility of interference by retained luminal lipid on colonic motor responses to subsequent stimuli.

Gastrocolonic Response Assessment

Gastric mechanoreceptor activation. Before assessment of the gastrocolonic response, each subject was intubated with a modified 18-Fr nasogastric tube, to the end of which was attached a standard latex condom for balloon distension of the stomach. The balloon, which was 9.5 cm in length, was sutured to both ends of the catheter to ensure radial, but not longitudinal, distension on inflation. After intubation, antral placement was confirmed fluoroscopically. For measurement of the gastrocolonic reflex, the proximal colonic recording

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Fig. 1. Representation of barostat balloon apparatus. A 3-balloon catheter was passed under colonoscopic guidance to the descending colon (A). The proximal colonic recording balloon was used to record the mechanoreceptor component of the gastrocolonic response. For eliciting the mechanoreceptor gastrocolonic response, a catheter with a distending balloon was fluoroscopically passed into the antrum (B). For chemoreceptor gastrocolonic response, a single-lumen lipid perfusion tube was fluoroscopically guided into the descending duodenum. The middle balloon served as the distending colonic stimulus for peristaltic reflex (C). The proximal and distal balloons served to record the orad and caudad responses to distension of the stimulus balloon during peristaltic reflex testing.
balloon was set to an operating pressure 2 mmHg above the minimal distending pressure necessary to detect respiratory variation on the volume tracing on the chart recorder. After a basal recording period of 30 min, the mechanoreceptor component of the gastrocolonic response was evoked by mechanical distension of the antral balloon with saline to volumes of 100, 200, and 300 ml at a rate of 300 ml/min in an intermittent stepwise fashion, using previously validated methods (29) (Fig. 1). The antral balloon remained filled for 5 min, during which changes in colonic tone were assessed by changes in the volume of the proximal colonic balloon. After each antral distension, a 30-min deflation period was provided to allow colonic tone to return to baseline. The magnitude of the gastrocolonic response was measured as the mean volume decrease during the inflation period compared with the 5-min period preceding inflation. The latency to the development of the mechanoreceptor-mediated response was defined as the time in seconds from the onset of gastric balloon inflation to the point at which the decrease in colonic balloon volume represented 10% of the maximal volume decrease obtained during the 5-min preinflation period. The maximal volume decrease was determined by the lowest volume level obtained from the analysis of volume values obtained in 1-s intervals in standard spreadsheet format (Lotus 1–2–3, Release 2; Lotus Development, Cambridge, MA).

To determine whether the inhibitory effects of the 5-HT3 receptor antagonist granisetron on the gastrocolonic response are mediated by relaxation of the distal stomach, barostat measurement of gastric tone was performed with and without granisetron (10 µg/kg) on separate days. Eight subjects were orally intubated with a highly compliant 6-cm polyethylene barostat balloon with a maximal volume of 550 ml, sutured on both ends to an 18-Fr nasogastric tube to ensure radial but not longitudinal inflation. The barostat balloon apparatus was placed under fluoroscopic guidance in the gastric antrum and then externally fixed to prevent movement. After a 30-min equilibration period, phasic inflation of the balloon was performed in 2-mmHg increments from 4 to 24 mmHg or until the subjects reported discomfort. Inflations were maintained for 5 min during which volume was recorded followed by 2-min deflations. Antral compliance was calculated by measuring the slope of the volume-pressure curve derived from each subject.

Duodenal chemoreceptor activation. To investigate the chemoreceptor-mediated component of the gastrocolonic response, a single-lumen intestinal feeding tube was placed under fluoroscopic guidance into the descending duodenum for intestinal lipid perfusion. After setting the operating pressure 2 mmHg above the minimal distending pressure, changes in colonic tone were measured as changes in balloon volume in the proximal barostat balloon. After a basal recording period of 30 min, duodenal perfusion (1.5 ml/min) of lipid (Microlipid; Mead Johnson, Evansville, IN) was performed at 2 kcal/min in seven volunteers and at 3 kcal/min in six volunteers for 60 min to determine the chemoreceptor component of the chemoreceptor-mediated response. This represents a total caloric delivery to the duodenum of 120 and 180 kcal, respectively. These lipid caloric perfusion rates are similar to but slightly higher than the normal rate of gastric emptying of lipids into the duodenum reported by other investigators (23). Recording of colonic tone continued for 2 h after completion of duodenal perfusion. Changes in colonic volume were calculated in 30-min segments during and after intestinal nutrient perfusion. The latency to the development of the chemoreceptor-mediated response was defined as the time in minutes from when the lipid perfusion was started to the time at which a decrease in colonic balloon volume representing 10% of the maximal volume decrease persisted for at least 15 consecutive minutes.

Peristaltic Reflex Assessment

The orad component of the peristaltic reflex was assessed by the proximal balloon, whereas the distal balloon assessed the caudad response, in both cases after inflation of the middle stimulus balloon. Each recording balloon was inflated to an operating pressure 2 mmHg above the minimal distending pressure. The peristaltic reflex was evoked by inflation of the middle stimulus balloon with air at a rate of 30 ml/s to volumes of 30, 60, and 90 ml. Stimulus inflations were maintained for 30 s and were followed by 5-min intervening periods of deflation to allow colonic tone to return to baseline. The magnitude of the contractile or relaxant response was measured by the difference between the minimal or maximal volume during the inflation period compared with a 30-s preinflation baseline period. A positive ascending or descending contraction was defined as a recording balloon volume decrease of at least 1 ml occurring during the 30 s of stimulus balloon inflation. The latency of the ascending or descending contraction was defined as the time from the onset of stimulus inflation to the point at which the decrease in proximal or distal balloon volume represented 10% of the maximal decrease. A positive descending relaxation was defined as a recording balloon volume increase of at least 1 ml in the first 15 s of stimulus balloon inflation. The latency of the descending relaxation was defined as the time from onset of stimulus inflation to the point at which the increase in distal balloon volume represented 10% of the maximal volume increase. Minimal and maximal volume values were obtained with spreadsheet analysis of data acquired in 1-s intervals.

Statistical Analysis

Results are expressed as means ± SE. Basal colonic tone, gastrocolonic response latencies, the magnitude of the chemoreceptor-mediated gastrocolonic response, antral compliance, and peristaltic reflex latencies were compared using the paired two-tailed Student's t-test. The magnitudes of the mechanoreceptor-mediated gastrocolonic response and the peristaltic reflex were compared using two-way ANOVA for repeated measures. P < 0.05 defined statistical significance.

RESULTS

Basal Colonic Tone

All volunteers tolerated placement of the barostat catheter well and did not perceive the inflation of the recording balloons in the colon. The mean operating pressure was 11.7 ± 0.9 mmHg with minimal interindividual differences. Under control conditions, the mean basal colon balloon volumes were similar after placebo (143 ± 17 ml) and granisetron infusion [138 ± 16 ml; P = not significant (NS)].

Gastrocolonic Response Assessment

Gastric mechanoreceptor activation. Inflation of the antral balloon with saline produced reproducible decreases in colonic recording balloon volume with latencies of 60–90 s, indicative of increased colonic tone in all healthy volunteers (Fig. 2). After placebo infusion,
antral distension evoked volume-dependent increases in colonic tone with a maximal effect at an antral inflation volume of 300 ml, which resulted in a 37 ± 6 ml decrease in colon balloon volume (Fig. 3). After granisetron (10 µg/kg) infusion, colonic tone changes in response to antral distension were markedly blunted, reflected by only a 5 ± 14 ml decrease in colonic recording balloon volume with an antral balloon volume of 300 ml (Fig. 3; P < 0.05).

To determine if the inhibitory effects of granisetron on the mechanoreceptor-mediated gastrocolonic response stem from induction of gastric relaxation, measurement of antral compliance was performed after double-blind infusion of granisetron on separate days. Isobaric antral balloon inflation from 4 to 24 mmHg produced pressure-dependent increases in antral volume after placebo and granisetron (Fig. 4). Compliance values calculated from the slopes of the volume-pressure curves were similar for placebo (27 ± 2 ml/mmHg) and granisetron (28 ± 1 ml/mmHg; NS).

Duodenal chemoreceptor activation. Intraduodenal perfusion of lipids evoked reproducible increases in colonic tone which were much delayed compared with the mechanoreceptor-mediated gastrocolonic response. Lipid perfusion at 2 kcal/min evoked decreases in colonic recording balloon volumes with latencies of 97 ± 20 min, whereas perfusions at 3 kcal/min reduced colonic balloon volumes with latencies of 48 ± 15 min (P < 0.05). After placebo infusion maximal recording balloon volume decreases with duodenal perfusions at 2 and 3 kcal/min were 64 ± 28 and 90 ± 20 ml, respectively (Table 1). After granisetron (10 µg/kg) infusion,

Table 1. Effects of granisetron on duodenal lipid-evoked colonic tone increases in individual healthy volunteers

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the decreases in colonic balloon volume with duodenal lipid perfusion rates of 2 and 3 kcal/min were significantly blunted (Table 1; \( P < 0.05 \)).

**Peristaltic Reflex Assessment**

Inflation of the stimulus balloon in the descending colon resulted in reproducible increases in colonic tone orad to the stimulus (ascending contraction; Fig. 5A) and a biphasic response caudad to the stimulus consisting of an initial decrease in tone followed by an increase in tone (descending responses; Fig. 5B).

Ascending contraction. Inflation of the colonic stimulus balloon produced increases in colonic tone orad to the stimulus with latencies of \( 8 \, \pm \, 2 \, \text{s} \) in all healthy volunteers. After placebo infusion, stimulus balloon inflation produced volume-dependent volume decreases in the orad recording balloon of \( 44 \, \pm \, 14 \), \( 66 \, \pm \, 19 \), and \( 69 \, \pm \, 21 \) ml with stimulus volumes of 30, 60, and 90 ml, respectively (Fig. 6). After granisetron (10 µg/kg) infusion, orad colonic volume responses with stimulus balloon inflation were unchanged compared with placebo (Fig. 6; NS).

Descending responses. Inflation of the colonic stimulus balloon produced biphasic responses in the caudad recording balloon with initial relaxations (latencies \( 5 \, \pm \, 2 \, \text{s} \)) followed by contractile phases (latencies \( 17 \, \pm \, 3 \, \text{s} \)). After placebo infusion the maximal descending relaxation was observed after 30-ml inflation of the stimulus balloon, which produced volume increases in the caudad recording balloon of \( 7 \, \pm \, 2 \, \text{ml} \) (Fig. 7). Stimulus balloon inflation produced volume-dependent descending contractions occurring after the relaxation phase with maximal caudad recording balloon volume decreases of \( 112 \, \pm \, 17 \, \text{ml} \) with 90-ml stimulus inflations (Fig. 8). After granisetron infusion the magnitudes of the increases and subsequent decreases in caudad recording balloon volumes after stimulus balloon inflation were unchanged compared with placebo (NS).

**DISCUSSION**

Colonic motor activity is characterized by a number of intrinsic stereotypical contractile patterns which are responsible for the mixing and propulsion of feces (27, 28). There are well-described external factors that can influence these motor complexes. The gastrocolonic

**Fig. 5.** Representative tracings of the ascending (A) contraction and descending (B) response components of the peristaltic reflex are shown. A: inflation of stimulus balloon evoked a decrease in volume of orad colonic recording balloon. B: inflation of the stimulus balloon induced an initial relaxation followed by contraction of the caudal colonic recording balloon.
Serotonin (5-hydroxytryptamine, 5-HT) plays a significant role in the physiological modulation of colonic motor activity. In the gut, serotonin is released both by enteric neurons and enterochromaffin cells (36). 5-HT receptors are present on enteric neurons, enterochromaffin cells, gastrointestinal smooth muscle, and possibly enterocytes and immune tissues as well (12). Once released, serotonin increases small intestinal motility by activation of intramural cholinergic neurons (26). 5-HT₁A, 5-HT₃, and 5-HT₄ receptors are detected on enteric neurons (1, 7, 10, 11, 13). 5-HT₃ pathways are proposed as mediators of both the gastrocolonic response and the peristaltic reflex. In recent human studies, the 5-HT₃ receptor antagonist ondansetron was shown to blunt the increase in colonic tone after meal ingestion (37). Serotonin is released into the intestinal vasculature when the peristaltic reflex is evoked by colonic or intestinal mucosal stimulation or by increased intraluminal pressure (2, 3, 9, 25). Serotonin is proposed to act on 5-HT₃/5-HT₁P receptors on enteric sensory neurons containing calcitonin gene-related peptide to initiate the peristaltic reflex in isolated human small intestine; however, 5-HT₃ receptors have been implicated in initiating the peristaltic reflex in guinea pig colon (9, 17, 25). Other peptides that modulate the peristaltic reflex include γ-aminobutyric acid and pituitary adenylate cyclase-activating peptide (16, 20). The roles of 5-HT₃ pathways in the mechanoreceptor- and chemoreceptor-mediated gastrocolonic responses and in the in vivo human colonic peristaltic reflex have been unexplored and were the subjects of this study.

The present investigation provides novel information on the role of 5-HT₃ receptors in the modulation of the in vivo gastrocolonic response and peristaltic reflex in healthy human volunteers. We evaluated both the mechanoreceptor and the chemoreceptor components of the gastrocolonic response, using methods similar to those previously described to determine if the extrinsic sensory pathways employed by each might be similar to each other and to the response observed after ingestion of a mixed caloric meal (39). For the nutrient perfusion studies, we chose a lipofluid rate that has been demonstrated not to activate small intestinal mechanoreceptors (24). Furthermore, in contrast to other studies that employed markedly supraphysiological perfusion rates (6 kcal/min) (39), lipid delivery in our study more closely approximated the rate of gastric emptying of fats into the duodenum reported by others (23). As was shown after ingestion of a caloric meal, 5-HT₃ receptor antagonism blunted the increase in colonic tone after antral distension and duodenal lipid perfusion (37). The 5-HT₃ receptor antagonist granisetron had no effect on antral compliance during isobaric distension, consistent with previous investigations showing that the 5-HT₃ receptor antagonist ondansetron increases rectal compliance but has no effect on gastric compliance (40). Specifically, the lack of effect of...
granisetron on antral compliance demonstrates that the blunting of the mechanoreceptor gastrocolonic response by the 5-HT₃ receptor antagonist does not result from induction of distal gastric relaxation. Taken together, these findings indicate that 5-HT₃ pathways play mediator roles in both the mechanoreceptor and chemoreceptor components of the gastrocolonic response. As was observed with atropine, the inhibition of the colonic motor response to antral distension by granisetron was somewhat more prominent than that observed after duodenal lipid perfusion (39). The presence of 5-HT₃ receptors on the cholinergic innervation to the gut and their ability to facilitate acetylcholine release might provide an explanation for the similar relative inhibitory effects of atropine and granisetron on the mechanoreceptor- and chemoreceptor-mediated components of the gastrocolonic response (10, 22).

In contrast to its effects on the gastrocolonic response, the 5-HT₃ receptor antagonist granisetron had no effect on either the ascending contraction or on the descending relaxation and contraction components of the in vivo human colonic peristaltic reflex. Our results are in accordance with the observations by Grider and colleagues (17) and suggest that 5-HT₃ pathways play little role by themselves in the human peristaltic reflex. This does not exclude the possibilities that 5-HT₃ pathways may be important in other species or that they play small modulatory roles which can be detected only with blockade of other more significant mediators. Nonetheless, these observations are consistent with a differential 5-HT₃ regulation of extended and local neural reflexes which modulate human colonic motor activity. Our in vivo model of the peristaltic reflex is obviously different from the in vitro studies of isolated gastrointestinal tissues. The biphasic descending response to contractile phase after the relaxation phase has not been observed under in vitro conditions, and its physiological relevance is uncertain, although it has been noted previously in the same human model employed in the present investigation (29). It is conceivable that the contraction caudad to the distending stimulus may represent a propagation of the orad peristaltic contraction.

The findings of this investigation provide insight into responses observed with clinical use of the 5-HT₃ receptor antagonists. A common side effect of the 5-HT₃ receptor antagonist class is the slowing of colonic transit with induction of constipation in healthy volunteers and patients (14, 33, 35). Our observations suggest that the 5-HT₃ receptor antagonists likely evoke this symptom via inhibition of extended neural reflexes such as the gastrocolonic response without significantly affecting basal colonic tone or neural reflexes intrinsic to the colon wall.

In conclusion, 5-HT₃ receptor antagonism strongly inhibits the in vivo antral mechanoreceptor-mediated gastrocolonic response in healthy human volunteers without altering the antral compliance, indicating mediation by serotonergic pathways. Furthermore, the gastrocolonic response to duodenal lipid perfusion is also blunted by the 5-HT₃ receptor antagonist granisetron, showing at least partial mediation of the chemoreceptor component of the response by 5-HT₃ neural pathways. In contrast, 5-HT₃ receptor pathways play no role in the ascending or descending components of the in vivo colonic peristaltic reflex. These observations suggest differential regulation of extended and local neural reflex arcs that modulate human colonic motility and provide a possible mechanism for the inhibitory effects of 5-HT₃ receptor antagonists on colonic transit.

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