Serotonergic mediation of postprandial colonic tonic and phasic responses in humans

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Abstract

This study examined the hypothesis that 5HT₃ mechanisms mediate the postprandial gastrocolonic response in humans. Fasting and postprandial colonic tone and motility were studied in 12 healthy volunteers and the effects of a selective 5HT₃ antagonist, ondansetron assessed in a double blind, randomised, placebo controlled fashion. A manometry barostat assembly was positioned in the transverse or descending colon to quantitate contractile activity fasting, after drug infusion and postprandially after a 1000 kcal meal. Fasting colonic tone and motility indices were similar in the placebo and ondansetron groups; ondansetron did not affect fasting motility. The placebo group showed a significant reduction in barostat balloon volume (signifying increased tone) from 232 ml (median, interquartile range (IQR) 179-261) during fasting to 181 ml (median, IQR 128-208) (postprandially) ($p=0.02$). In contrast, the ondansetron group did not have a tonic colonic response (median 248 ml (IQR 199-300) fasting to median, 226 ml (IQR 185-290) postprandially) after the meal. Phasic volume events measured by the barostat increased postprandially in both groups. Postprandial motor activity measured by manometry increased significantly in the placebo group, but not in the ondansetron group. In conclusion, a 5HT₃ mechanism participates in the physiological contractile responses in the human transverse and descending colon after ingestion of a high energy meal.

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Since the turn of the century, there has been an indefatigable interest in the colonic response to the ingestion of a meal. In his radiological studies in cats, Cannon¹ noted that passage of food through the ileocaecal valve stimulated colonic activity. Hurst wrote 'On comparing the appearance of the colon every hour through the day, I was stuck by the fact that it only changed materially after those hours in which a meal had been taken'.² Subsequently, Misiewicz *et al*³ and Snape *et al*⁴ performed quantitative studies showing increased colonic pressure activity, particularly in distal rather than proximal colon,³ and increased colonic spike (myoelectric) activity. These studies led to an interest in the mechanisms mediating this response: cholinergic pathways,^{3,5} gastrin,⁴ cholecystokinin,⁶ and prostaglandin E₁⁷ were implicated. These studies were based chiefly on concomitant plasma measurements of putative mediators and effects of pharmacological agents. Subsequent studies reported repeated postprandial gastro-

colonic responses during prolonged manometric studies⁸ and radioisotopic colonic transit studies,⁹ and a regional variation in the time course of the colonic contractile response was suggested.¹⁰

The availability of more specific pharmacological antagonists in recent years has led to further approaches to understand the mechanism of the gastrocolonic response. For example, loxiglumide, cholecystokinin A receptor antagonist, did not inhibit the gastrocolonic response in health or patients with irritable bowel syndrome,¹¹ in whom an exaggerated response is often associated with postprandial gain and diarrhoea.¹²

By applying an electronic barostat to the colon, recent studies show that there is a prominent tonic component in the gastrocolonic response.^{13,14} In humans, postprandial colonic tone could be inhibited by atropine¹⁵ suggesting muscarinic cholinergic control. Serotonin exerts profound effects on proximal colonic function in humans¹⁶ and on ileocolonic transit in an experimental animal model.¹⁷ As myenteric cholinergic neurons have 5HT₃ receptors,¹⁸ we wished to test the hypothesis that 5HT₃ mechanisms may mediate the gastrocolonic response in humans.

Our aim was to study fasting and postprandial motility and tone with particular interest in the effect of a 5HT₃ antagonist, ondansetron, which was given in a randomised, double blind, placebo controlled fashion.

Methods

SUBJECTS

Twelve healthy subjects (seven male, five female; age range: 22-45 years, mean: 31) were recruited by public advertisement. Informed written consent was obtained from all participants before the study. The protocol had been approved by the Mayo Clinic Institutional Review Board.

COLONIC INTUBATION

On the evening before the study, subjects ingested an oral colonic lavage solution (composed of polyethylene glycol and electrolytes (OLS, Abbott Laboratories, Chicago, IL) until the faecal effluent was clear liquid, free of particulate matter. At 800 am the next day, colonoscopy to the caecum was performed by one investigator (MC) with the subjects consciously sedated under the minimum dose (2-4 mg) of intravenous midazolam (Versed, Roche Laboratories, Nutley, NJ) necessary to maintain acceptable comfort. No endoscopic abnormalities were seen and no solid matter was retained in

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the colon of any subject. A 4 metre, soft tipped, Teflon coated guide wire (Microvasive, Hobbs Medical Inc, Stafford Springs, CT) was inserted under fluoroscopic control into the caecum, and the colonoscope was withdrawn. A combined assembly consisting of four manometric catheters with a barostat balloon (described below) was then guided into the colon over the guide wire with the aid of fluoroscopy. In six subjects, the tube was inserted with the barostat balloon positioned in the transverse colon; in six subjects, the balloon was left in the proximal descending colon, just distal to the splenic flexure. Participants rested in a bed throughout the study; they recovered rapidly from the sedation and were alert at the start of experiments four hours after the tube was placed in the colon. At the end of the experiments, gentle traction on the catheter assembly with the balloon deflated permitted its removal without discomfort or complications.

RECORDING ASSEMBLY

The multilumen catheter comprised several lumens (Fig 1): one lumen of 4.8 mm in outer diameter and 3.2 mm in inner diameter served to operate the barostat balloon; a lumen for the guide wire; and four side hole capillary lumens (inner diameter; 0.78 mm each) for pneumo-

hydraulic, low compliance perfusion manometry. The perfusion pressure was 69 kPa and flow rates averaged 0.1 ml/min. The side holes were 2 cm proximal, and 2 cm, 7 cm, and 12 cm distal to the barostat balloon. The barostat balloon was 10 cm long and was tied at both ends to metal rings incorporated in the catheter assembly. As reported previously,¹⁴ the polyethylene bags are infinitely compliant in the volume range 0 to 500 ml.

The intra-balloon pressure (operating pressure) was individually selected for each subject during the fasting period and was kept constant during the entire experimental period. The pressure that recorded the first signs of changes in intra-abdominal pressure induced by respiratory movements in each subject was identified, and was then clamped 2 mm Hg above this minimal pressure. In this pressure clamped system, changes in the volume of the balloon reflect changes in wall tone of the viscus¹⁹ and increased intraluminal pressure.

DATA STORAGE

Pressures and volumes in the barostat balloon, phasic pressure fluctuations recorded by manometry, respiratory movements recorded by a pneumobelt, and experimental interventions were all recorded as analogue signals on Honeywell paper recorders. The analogue signals were sampled at 4 Hz, digitised, entered into a computer (Microvax System; Digital Equipment Corporation, Boston, MA) and stored for later analysis on magnetic hard disk and paper. All analyses were performed by computer. The stored digitised data were scaled to match the experimental calibration and were then processed sequentially from the start of the recording.

EXPERIMENTAL DESIGN (FIG 2)

Four hours after placement of the colonic catheter assembly, all subjects were positioned on a bed in a 30° head up, supine position. Fluctuations in balloon volumes, intra-balloon pressures, and intraluminal pressures were recorded during fasting for 60 minutes: 30 minutes before, and 30 minutes after intravenous infusion of ondansetron (Zofran, Glaxo Inc, Research Triangle, NC; dose: 0.15 mg/kg, which is the route and highest single dose permitted in humans by the Food and Drug Administration of the United States) or saline as placebo. There were six volunteers in each group. The infusion period lasted five minutes. All participants then consumed a standardised 750 ml, 1000 kcal chocolate malt (53% fat, 35% carbohydrate, 12% protein). The meal, which has been used in previous studies^{4-6,9,10,14,15} to induce the gastrocolonic response, was ingested within a period of five minutes. Balloon volume, intra-balloon pressure, and intraluminal manometric pressures were recorded for 120 minutes postprandially. Subjects were awake during the entire study period.

DATA ANALYSIS

Initial filtering – Using a modified VAX LAB

Figure 1: Multilumen catheter assembly showing 10 cm long barostat balloon, and manometric sideholes, 2 cm proximal and 2, 7, and 12 cm distal to it. Note guidewire passing through distal end of assembly.

Figure 2: Scheme showing measurements performed on the barostat tracings with the aid of a computer analysis.

filtering program (Digital Equipment Corporation, Boston, MA), barostat balloon volumes were cleared of respiratory artifacts (frequency >10/min) recorded simultaneously by the pneumobelt. Manometric data were cleared of movement artifact by computerised deletion of small pressure fluctuations (<3 mm Hg in magnitude, or <4 seconds in duration) that occurred simultaneously over all four manometric recording sites. The manometric data were then passed through a polynomial filter to remove minimal pressure variations (up to 6 mm Hg) occurring with larger pressure waves.

Manometric activity – Phasic pressure activity quantitated in the manometric tracings, 2 cm proximal, and 2 cm and 7 cm distal to the barostat bag was averaged for the before and after drug fasting periods, and for the two hour postprandial periods. The computer program calculated the mean amplitude, area under the contractions, and frequency expressed/hour.

Barostat tracings – A modified VAX LAB program was used to separate baseline volume for phasic volume events recorded by the barostat balloon. Phasic volume events were defined as changes ≥10% comparative with the baseline volume, and occurring at a frequency of 1–4/minute. This was the frequency of volume waves previously recorded in the human colon.^{14 15} Baseline volumes were calculated by computer-

ised exclusion of phasic volume events from the barostat tracings and were then averaged over each minute (minute baseline volumes). Mean of minute barostat volumes during the fasting (before and after drug) and postprandial periods were calculated. To correct for interindividual variations of fasting barostat volumes reflecting anatomical variations in colonic diameter, postprandial change in colonic tone was also expressed as a percentage of change from mean fasting barostat volumes. The maximum response of colonic tone to the meal was determined as the minimum postprandial volume that persisted for at least 10 consecutive minutes. The time from the start of the meal until the onset of this maximum response was calculated, and termed ‘latency’. The duration of this maximum response was defined as the time (at least 10 minutes, according to the definition above) during which this response was not changed by more than 10%. In summary, the following parameters were measured in the barostat tracings (Fig 2): fasting tone (ml), postprandial tone (ml), phasic volume events (number, mean amplitude, and area under the curve, all expressed/hour), and maximum tone (volume, latency, and duration).

STATISTICAL ANALYSIS

Two tailed unpaired *t* test was used to compare fasting measurements and the percentage reduction in tone postprandially in the ondansetron and placebo groups (*p*<0.05 being significant). Paired Student’s *t* test was used to compare baseline barostat volume (estimate of tone) during the fasting and postprandial periods, using both mean and minimum postprandial volumes. To compensate for two comparisons, we accepted *p*<0.025 as statistically significant. In analysing the phasic pressure or volume events, we restricted the statistical comparisons to the area under the curve (as calculated by the computer analysis) to avoid detecting differences by chance. Thus, comparison of fasting *v* after drug ingestion, and fasting *v* postprandial were performed separately for the placebo and ondansetron groups using paired *t* test, and Bonferroni’s correction was again applied (*p*<0.025 being significant). All data are reported as median and interquartile range (IQR) because some of the data (for example, frequency and mean amplitude, but not area under the contractions) were not normally distributed.

Results

FASTING COLONIC TONE, BEFORE AND AFTER DRUG INGESTION

Representative examples of colonic barostat/manometry tracings are given for two volunteers (Fig 3A: placebo; Fig 3B: ondansetron). There was no significant difference in the barostat operating pressures in the two groups (placebo median 14, range 12–17 mm Hg; ondansetron median 15, range 13–17 mm Hg). The fasting barostat volumes in the two groups before (placebo median 232 ml (IQR 179–261),

Figure 3: Original barostat/manometry tracings in two volunteers: (A)=placebo and (B)=ondansetron. Note placebo treatment is associated with postprandial reduction in baseline barostat volume; in contrast, ondansetron treatment inhibits postprandial change in baseline barostat volume. Note increased postprandial frequency of contractions detected on manometric recordings 2, 7, and 12 cm distal to the barostat balloon.

Figure 4: Effect of ondansetron and placebo on tone in the colon after a 1000 kcal meal (PP= postprandial; data show both mean and minimum postprandial volume, indicating mean and maximum postprandial tone) *: $p<0.025$ v fasting in the placebo or ondansetron group. Note the appreciable reduction in barostat balloon volume with placebo (left panel), and the lack of effect of the meal on mean PP volume with ondansetron treatment (right panel). The minimum PP barostat volume with ondansetron treatment is also significantly different from fasting.

ondansetron median 248 ml (IQR 199–300)) and after (placebo median 230 ml (IQR 164–262), ondansetron median 255 ml (IQR 206–302)) administration of placebo or the drug were very similar.

POSTPRANDIAL COLONIC TONE

Ingestion of a meal resulted in an immediate significant reduction of minute barostat volumes in the placebo group. This reduction (median 25 (IQR 21–45)% comparative with fasting) persisted throughout the two hour postprandial study period (Fig 3A, Fig 4). Ondansetron inhibited this overall postprandial increase in colonic tone (Fig 3B, Fig 4) with a reduction of volume of median 8 (IQR 3–16)% ($p\leq0.01$ v placebo). Ondansetron did not completely abolish the maximum increase in colonic tone to the meal, shown by the lowest volume of the barostat postprandially (Fig 4). The time between the ingestion of the meal and onset of this maximum response (latency) was not different in the placebo (median five minutes, IQR 0–33 minutes) and ondansetron (median eight minutes, IQR 4–12 minutes). Similarly the duration of these maximum responses was not different in the two groups (placebo median 20 minutes (IQR 15–50), ondansetron median 13 minutes (IQR 11–19)).

COLONIC MANOMETRIC ACTIVITY AND PHASIC VOLUME EVENTS (TABLE)

The fasting data in the ondansetron and placebo groups were not statistically different. Neither placebo nor ondansetron significantly affected phasic events during fasting. In the postprandial

period, placebo treated subjects had a significant ($p<0.025$) increase in both manometric activity and phasic volume events. In the ondansetron group, postprandial phasic activity detected by manometry was not significantly different from fasting ($p=0.18$). Postprandial phasic volume events were, however, increased comparative with fasting in this group ($p=0.02$).

Discussion

Our study clearly shows that tonic colonic responses after ingestion of a high fat meal are inhibited by the 5HT₃ antagonist, ondansetron. Serotonin is known to stimulate proximal colonic function.¹⁶ Our results suggest that ondansetron inhibited a component of the gastrocolonic response.^{3,4,20} This inhibition of both tonic activity measured by the barostat and the phasic component of the gastrocolonic response measured by manometry is similar to that seen with atropine.¹⁵ We are unaware of any data in published works that would suggest interaction between 5HT₃ receptors and other putative mediators of the gastrocolonic response, such as gastrin, cholecystokinin, and prostaglandin E₁.^{4,6,7} Serotonin type 3 receptors have not been described on gastrointestinal smooth muscle, but are located in cholinergic interneurons.¹⁸ Our data suggest the hypothesis that the effects of ondansetron may be exerted through cholinergic neurons. Further studies are needed to evaluate whether ondansetron acts through cholinergic neurons or separately.

Colonic phasic volume events measured by the barostat were similar in the placebo and ondansetron groups. Thus, in contrast with the manometric data, the ondansetron group showed a significant increase in phasic volume events postprandially. This contrasts with the lack of any significant change in manometric phasic activity in the ondansetron group postprandially. One possible explanation for this apparent discrepancy is the comparative insensitivity of manometry in the colon when it has an internal diameter greater than 5.6 cm.²¹ In a previous study, we noted that a change in luminal diameter from 5.2 cm to 5.8 cm resulted in a reduction of phasic events measured by manometry from 100 to 33% comparative with the number recorded by means of the barostat balloon. Because ondansetron inhibited the postprandial decrease in baseline volume seen with placebo, the colonic volume was greater with ondansetron, rendering manometry less sensitive to detect colonic wall motion, compared

Colonic motility by manometry and barostat. Median data (interquartile range in parentheses)

	Placebo			Ondansetron		
	Fasting	After drug	Postprandial	Fasting	After drug	Postprandial
Manometry						
No peaks/hour	81 (69–106)	72 (67–102)	114 (98–122)	42 (36–73)	65 (47–80)	57 (43–66)
Mean amplitude (mm Hg)	11.9 (10.2–13)	12.7 (11.7–13.6)	14 (12.9–14.3)	11.5 (10.0–14.0)	12.5 (11.4–15.8)	11 (10.5–12.5)
Area under curve/hour $\times 10^3$ (mm Hg/min)	13 (8.8–14.7)	12.6 (9.1–14.0)	15.5 (13.5–19.8)*	7.5 (4.5–8.2)	9.9 (8.2–11.9)	9.4 (8.4–10.6)
Barostat						
No peaks/hour	121 (84–142)	109 (90–134)	139 (112–152)	104 (63–134)	96 (71–125)	114 (84–144)
Mean amplitude (ml)	38 (35–46)	40 (39–47)	48 (43–52)	34 (29–40)	37 (33–58)	47 (38–72)
Area under curve/hour $\times 10^3$ (ml/min)	55.2 (37.1–72.7)	57.2 (45.3–75.3)	81.9 (59.9–89.4)*	37 (19–58.1)	47.6 (34.5–89.2)	71.1 (48.1–96.9)*

Statistical analysis was restricted to area under the curve to avoid detection of differences by chance. Comparisons between fasting and after drug ingestion were not significant. * $p\leq0.025$ v fasting.

with the inflated barostat balloon, which is apposed to the internal colonic surface. Hence, the amplitude or frequency of phasic events detected by manometry may not necessarily be accurate measures, and the barostat may record phasic contractile responses in the postprandial period with greater fidelity than manometry. Despite this discrepancy in the effects of ondansetron on phasic activity, the drug's inhibition of overall postprandial colonic tone is unequivocal. Data in this study show that a 5HT₃ mechanism participates in mediating the physiological contractile response of the human transverse and descending colon to the ingestion of food. Two interpretations may be considered. Firstly, ondansetron may inhibit visceral afferents,²² preventing the stimulation of vagal cholinergic efferents participating in the gastrocolonic response. Alternatively, ondansetron may inhibit the enteric nerves in the final pathway of the gastrocolonic reflex, by inhibiting 5HT₃ receptors on cholinergic S type interneurons. Ondansetron probably did not inhibit non-adrenergic, non-cholinergic AH type neurones,²³ which are typically inhibitory, as this would have enhanced contraction of the colon, contrary with our findings in response to ondansetron. Ondansetron has very weak affinity for 5HT_{1C}, α_1 , and μ opioid receptors (pK_b 5.43–5.49). As the selectivity ratio for 5HT₃ receptors is about 100-fold greater, however, we believe it is probable that the effects we saw are indeed mediated through 5HT₃ receptors.^{24,25} In a separate study using a scintigraphic method to estimate ascending colon volume, we have recently shown that ondansetron also inhibits the reduction of ascending colon volume seen 30–120 minutes after ingestion of a 1000 kcal meal.²⁶ These complementary data confirm an important role for 5HT₃ mechanisms in the physiological control of colonic motor function.

Ondansetron has previously been shown to inhibit colonic transit in health.^{27,28} The methods used in these studies were not sufficiently sensitive to discover if this was a result of a change in fasting or postprandial colonic transit. As meal induced colonic contractility is one of the main components resulting in mass movements or aboral transit,^{1,3} however, we hypothesise that ondansetron's effects are predominantly seen postprandially.

Antagonists to 5HT₃ receptors have been used clinically as anti-emetics, particularly in patients with cisplatin induced emesis.²² They may also have useful motor effects, however, in view of the location of 5HT₃ receptors on cholinergic¹⁸ and non-adrenergic, non-cholinergic²³ interneurons. Their main potential role in the colon may be in inhibiting motor dysfunctions associated with excessive contractility. The most common example of increased colonic phasic pressure activity met in clinical practice is irritable bowel syndrome^{3,5,12}; a less common example of rapid colonic transit associated with colonic hypertonicity but normal phasic pressure activity is carcinoid diarrhoea.²⁹ These disorders may potentially be ameliorated with specific 5HT₃ receptor antagonists. In fact, Steadman *et al* reported a moderate, though statistically insignificant, effect of ondansetron on colonic

transit in irritable bowel syndrome patients selected on the basis of a predominant symptom of diarrhoea.³⁰ In the future, it is conceivable that more potent 5HT₃ antagonists may provide more effective means to inhibit the prominent colonic motor responses to ingestion of a meal, and possibly the postprandial diarrhoea associated with meal evoked colonic propulsion.

In summary, our studies show that 5HT₃ mechanisms participate in mediating the gastrocolonic response. Although the site of action of the 5HT₃ antagonist cannot be ascertained by out studies, our data suggest that the effect of 5HT₃ antagonists should be tested in patients with irritable bowel syndrome or other disorders associated with exaggerated colonic motility.

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