The proximal colonic motor response to rectal mechanical and chemical stimulation

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Bampton, P. A., P. G. Dinning, M. L. Kennedy, D. Z. Lubowski, and I. J. Cook. The proximal colonic motor response to rectal mechanical and chemical stimulation. Am J Physiol Gastrointest Liver Physiol 282: G443–G449, 2002.—We aimed to determine whether rectal distension and/or infusion of bile acids stimulates propagating or non-propagating activity in the unprepared proximal colon in 10 healthy volunteers using a nasocolonic manometric catheter (16 recording sites at 7.5-cm spacing). Sensory thresholds and proximal colonic motor responses were assessed following rectal distension by balloon inflation and rectal instillation of chenodeoxycholic acid. Maximum tolerated balloon volume and the volume that stimulated a desire to defecate were both significantly (P < 0.01) reduced after rectal chenodeoxycholic acid. The frequency of colonic propagating pressure wave sequences decreased significantly in response to initial balloon inflations (P < 0.05), but the frequency doubled after subsequent chenodeoxycholic acid infusion (P < 0.002). Nonpropagating activity decreased after balloon inflation, was not influenced by acid infusion, and demonstrated a further decrease in response to repeat balloon inflation. We concluded that rectal chenodeoxycholic acid in physiological concentrations is a potent stimulus for propagating pressure waves arising in the proximal colon and reduces rectal sensory thresholds. Rectal distension inhibits all colonic motor activity.

chenodeoxycholic acid; colon; manometry; peristalsis; afferent

PROPAGATING PRESSURE WAVES contribute to the episodic flow of colonic content and to defecation (2, 9, 17, 24, 26). The factors that initiate and modulate these propagating sequences (PSs) are partially understood. Extrinsic neural pathways probably exert a modulatory effect and may be capable of activating these pressure wave patterns, because propagating sequences virtually disappear during stable sleep, whereas arousal from sleep is a potent and immediate stimulus of PSs (14, 22, 26, 31). Local colocolonic reflex pathways exist within the colon that are likely to be involved in the modulation of propagating activity, because chemical and physical stimuli may stimulate colonic propagating motor patterns and defecation (7, 20). For example, rectal glycerol stimulates myoelectrical activity in the left colon (10), and rectal bisacodyl initiates propagating pressure waves in the proximal colon that culminate in defecation (20). Rectal distension delays colonic transit time in the pig, suggesting that mechanical and chemical stimuli may have opposing effects (25).

Mechanical distension and chemoreceptor activation, perhaps acting synergistically, are two candidate mechanisms whereby colonic motor patterns might be stimulated. Intraluminal distension elicits peristaltic contractions in the esophagus and small bowel. However, a similar response to colonic distension has not been consistently demonstrated (4, 16, 25). Rectal and ascending colon distension with 500 and 750 ml of isotonic saline, respectively, have not been demonstrated to provoke a motor response (12, 30). Chenodeoxycholic acid, when administered in supraphysiological concentrations, is a recognized stimulus of colonic propagating activity (33). However, chenodeoxycholic acid infused rectally in physiological concentrations (1.9 ± 0.5 mM) (5) does not influence rectal motor activity despite the observation that these subjects reported a strong defecation urge (5, 12). The presence of this defecatory urge and subsequent defecation in a number of subjects suggested to us that chenodeoxycholic acid might be an important chemical stimulant of colonic motility. It appears that physiological concentrations of bile acids are sufficient to stimulate rectal afferents and the defecation urge, but supraphysiological concentrations might be necessary to stimulate the accompanying defecatory motor responses. Unfortunately that study did not measure motility proximal to the rectum. Hence, it remains unknown whether physiological concentrations of rectal bile acids might stimulate proximal colonic motor patterns that might facilitate defecation. A dissociation between sensory perception of defecation urge and the usual accompanying colonic motor patterns is also a possible explanation. This concept has important clinical implications. Heightened rectal sensitivity with diminished colonic contractile activity might be relevant to the pathophysiology of the syndrome of constipation with outlet delay or “obstructed defecation.” For example, these patients have a frequent

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defecation urge, frequent ineffective attempts at defecation, and may have normal or diminished colonic transit and colonic propagating sequences (8, 11, 23). We hypothesized that chemical and mechanical stimulation of the rectum interact to enhance proximal colonic propagating pressure waves and to retard non-propagating colonic activity. These responses would be predicted to enhance the transport of luminal content distally and might culminate in defecation. Our aim, therefore, was to determine the effects of rectal infusion of physiological doses of chenodeoxycholic acid and rectal distension on proximal colonic propagating activity and whether the two stimuli act synergistically.

METHODS

Subjects
Ten consecutive healthy volunteers (9 males, 1 female; mean age 29.2 ± 2.7 yr, range 23–52) with no history of gastrointestinal complaints and who reported between two bowel movements per day and one bowel movement every 2 days, were recruited by advertisement. None had taken laxatives or other medications. None had had previous abdominal surgery other than appendicectomy. Written informed consent was obtained from the participants, and the study was approved by the Human Ethics Committees of the South Eastern Area Health Service, Sydney, and the University of New South Wales.

Manometric Technique
The technique of pancolonic manometry has been described in detail previously (2). Briefly, we used a 17-channel (16 recording sideholes), 4.5-m-long extruded Silastic perfused manometric assembly (Dentsleeve, Wayville, South Australia) with an overall diameter of 3.5 mm. Each recording lumina had an internal diameter of 0.5 mm with an intersidehole distance of 7.5 cm. A latex balloon at the tip of the catheter could be inflated and deflated with air through the core channel (internal diameter 0.8 mm). The catheter was rendered radiopaque by curing strips of barium pasted to its exterior. The recording lumina were perfused with degassed, distilled water preceded by a CO2 flush to ensure removal of all air bubbles from the catheter, thus minimizing compliance (27). A low-compliance pneumohydraulic perfusion pump drove the perfusate at 0.15 ml/min (Dentsleeve, Wayville, South Australia). Pressures were measured from each sidehole with 16 external pressure transducers (Abbott Critical Care Systems, North Chicago, IL). Signals were amplified and digitized at 10 Hz by preamplifiers (AqcKnowledge III Software, BIOPAC Systems, Santa Barbara, CA). We have previously demonstrated that the rise rate characteristics afforded by a catheter of this nature are adequate for recording colonic pressure waves (2).

Experimental Protocol
Catheter placement. After an overnight fast, catheter placement commenced at 0800. The catheter tip was passed via the nose and through the pylorus under fluoroscopic control. The balloon was then inflated to a diameter of 2 cm with a volume of air according to a previously determined volume-diameter calibration curve. The catheter was manually fed through the nose in increments of ~40 cm each hour or as needed. To prevent the catheter from looping in the stomach, the position and conformation of the catheter were checked fluoroscopically every 2 h. As the tip of the catheter approached the ileocolonic junction, the balloon was progressively deflated to a diameter of 0.5 cm to avoid impaction in the distal ileum. When the catheter tip had passed through the ileocolonic junction, the balloon was reinfated to a diameter of 2 cm. Total fluoroscopy time was 30–90 s, and the maximum whole body effective radiation dose equivalent was 0.8–2.4 mSv.

At 1400 on the third day of the study, subjects were placed in the left lateral position, a polyvinylchloride rectal catheter was inserted, which incorporated two perfused recording channels 3 and 4 cm from the tip and a central core for balloon inflation. The catheter was positioned 4 cm from the internal anal verge, with the distal recording sidehole within the anal sphincter and the proximal sidehole in the rectum. A latex balloon at the tip of the catheter could be manually inflated with air.

After the rectal catheter was placed, baseline manometric recordings were made for 20 min from the pernasally placed and rectal catheters, with the subject lying in the left lateral position.

Rectal distension sensory threshold testing. The rectal balloon was then inflated with air by a hand-held syringe in a slow ramp fashion at a rate of 50 ml/min (32) on three occasions with a 5-min interval between inflations. Subjects reported 1) rectal sensory volume, defined as the volume corresponding to the onset of perception of the balloon; 2) defecation urge, defined as the onset of the desire to defecate; and 3) maximum tolerated volume, defined as the volume at which they noted the onset of discomfort.

Chenodeoxycholic acid infusion. A second single lumen polyvinylchloride rectal catheter was then inserted, and 150 ml of 1 mmol chenodeoxycholic acid (Sigma, St Louis, MO) were infused over 3 min and manometric recording continued for a further 20 min. This dose of bile acid was chosen because it approximates the measured concentration of unbound bile acid in stool water of normal subjects (1.9 ± 0.5 mM) (5). The slow ramp balloon inflations were then repeated again three times with a 5-min interval between inflations, after which recording was continued for 20 min.

Manometric Definitions
We used the same method of analysis of the manometric trace as described in our previous papers (2). To recap briefly, once pressure waves had been identified, a propagating sequence was defined as an array of three or more pressure waves recorded from adjacent recording sites in which the conduction velocity between wave onset within that sequence lay between 0.2 and 12 cm/s. Propagating sequences were further qualified by the terms antegrade or retrograde, depending on the direction of propagation.

Propagating sequences were subclassified as high-amplitude propagating sequences if the amplitude of at least one component propagating pressure waves was >116 mmHg (representing the mean amplitude plus 2 standard deviations of colonic propagating sequences).

The area under the pressure curve (AUC) was used as an overall measure of colonic motor activity and as an appropriate index of nonpropagating activity, because this was by far the most prevalent pressure pattern seen. Cough- or strain-induced artefacts occurring during an epoch in which the AUC was to be calculated were removed from the trace. A value equivalent to the average for the remainder of the epoch was then assigned to the removed segment.
Data Analysis

The colon, for the purposes of analysis, was divided into 16 regions, with region 1 being the cecum, region 4 the hepatic flexure, region 8 the splenic flexure, and region 16 the rectum. Propagating sequence site of origin and extent of propagation was referenced to these regions. The colon was divided into three segments for the purpose of analysis of regional responses in nonpropagating activity: segment cecoascending colon (regions 1–4), transverse colon (regions 5–8), and descending colon (regions 9–12).

The manometric trace was examined for propagating sequences in $4 \times 15$-min epochs. These epochs were the 15 min before the first set of balloon inflations, the 15 min during and immediately following the first set of inflations, the 15 min after the chenodeoxycholic acid infusion, and the 15 min during the final set of balloon inflations. The AUC was measured in 5-min epochs during these times.

Volume within the rectal balloon corresponding to each of the three rectal sensory thresholds was compared before and after chenodeoxycholic acid infusion using a paired t-test. Inferences among propagating sequence frequency, amplitude, and velocity at baseline, after balloon inflation, and after chenodeoxycholic acid infusion were made again based on a paired t-test with Bonferroni correction factor for repeated measures. Inferences regarding regional variability of motor activity were made using a repeated-measures ANOVA. All data are expressed as means ± SE unless stated otherwise.

RESULTS

Catheter Placement

In all 10 subjects, the tip of the catheter lay distal to the splenic flexure at the time of stimulation studies. It was located at the distal descending colon in five, proximal sigmoid colon in two, and distal sigmoid colon in three. We did not analyze data from the sigmoid colon, because the number of sideholes in the sigmoid colon was too small to give meaningful results.

Rectal Sensory Thresholds

No time-dependent effect of distension volume was noted. Hence data for the three inflations were averaged. Chenodeoxycholic acid did not significantly influence the rectal sensory threshold, but it did reduce significantly the defecatory urge threshold from $81 \pm 9$ to $56 \pm 7$ mls ($P < 0.01$) and the maximum tolerated rectal volume from $144 \pm 21$ to $103 \pm 15$ ml ($P < 0.01$; Fig. 1).

Colonic Motor Responses

Propagating pressure wave sequences. When compared with the baseline frequency of propagating sequences in all regions of the proximal colon ($0.7 \pm 0.2/15$ min), PS frequency was significantly reduced to $0.29 \pm 0.15$ during the initial set of balloon inflations ($P < 0.045$). In response to the second set of balloon inflations, PS frequency was reduced to $0.2 \pm 0.2$ per 15 mins, which was also significantly lower than baseline frequency ($P < 0.05$; Fig. 2). Indeed, repeat balloon stimulation following chenodeoxycholic acid instillation appeared to "switch off" the increased propagating activity stimulated by the chenodeoxycholic acid.

Chenodeoxycholic acid had a relatively prompt stimulatory effect on proximal colonic propagating pressure waves (Fig. 3). When compared with baseline, propagating sequence frequency more than doubled to $1.5 \pm 0.2$ per 15 min after chenodeoxycholic acid infusion ($P < 0.002$; Fig. 2). The preferential site of origin of PSs changed in response to chemical rectal stimulation. During the baseline period, 67% of PSs originated in the cecoascending colon. This proportion increased to 72% following chenodeoxycholic acid infusion. Only 50% of the few propagating sequences occurring after balloon inflation arose from the cecoascending colon, suggesting that propagating sequences arising from this site may have been inhibited by rectal distension.

There were no significant differences in the extent of propagation by the propagating sequences among the experimental conditions. The mean amplitude of propagating pressure waves was lower in propagating sequences that occurred following chenodeoxycholic acid infusion ($34 \pm 5$ mmHg) than in those during baseline recording ($55 \pm 8$ mmHg, $P < 0.03$). The propagating sequences occurring after balloon inflation were of a similar amplitude ($36 \pm 6$ mmHg) to those occurring after chenodeoxycholic acid infusion.

Responses to either stimulus were not immediate. Propagating sequences occurred a mean of $6.3 \pm 1.4$ min (range 1–14 min) after commencement of chenodeoxycholic acid infusion, compared with $9.1 \pm 1.7$ min after commencement of balloon inflation (not significant).

AUC

When compared with a baseline value of $2,779 \pm 149$ mmHg/s, the AUC in the cecoascending colon de-
increased significantly in response to rectal balloon inflation to 2,270 ± 199 mmHg/s (P < 0.001). No significant alterations in AUC were observed in the transverse or descending colon after the first set of inflations; however, in response to the second set of inflations, the AUC in the cecoascending colon decreased further to 1,706 ± 127 mmHg/s (P = 0.0003), and on this occasion, there was a significant decrease in the transverse colon compared with the baseline 1,783 ± 145 (P < 0.002). In contrast, there were no statistically significant alterations in the AUC in response to balloon inflations in the descending colon, and the infusion of chenodeoxycholic acid appeared to have no effect on the AUC in any part of the colon. (Fig. 4).

**Symptoms**

No patients experienced an urge to defecate after the initial set of balloon inflations. Five of the ten subjects experienced an urge to defecate within 10 min of commencement of the chenodeoxycholic acid instillation, and this urge was associated with a proximal colonic propagating sequence in three subjects. One subject experienced successive urges associated with propagating sequences and defecated 8 min after infusion. A further four patients defecated within the hour after the completion of the study. Hence, in all, five patients defecated 8–60 min after the rectal chenodeoxycholic acid infusion.

**DISCUSSION**

We have demonstrated that chenodeoxycholic acid in physiological concentrations reduces sensory thresholds to rectal balloon distension. This study demonstrates that the stimulation of rectal afferents can elicit both inhibitory and excitatory responses from the unprepared proximal human colon. In contrast to this synergism in effects on rectal sensation between chemical and mechanical stimuli, these stimuli had opposing effects in terms of colonic motor responses. Rectal instillation of a physiological concentration of chenodeoxycholic acid initiates propagating sequences in the proximal unprepared colon. Balloon distension of the rectum inhibits all types of proximal colonic activity. These responses are presumed to be mediated by long colocolonic pathways. These observations are consistent with the hypothesis that a combination of chemical and mechanical rectal stimulation enhances proximal colonic propagating activity while retarding nonpropagating activity and that such a combination of responses is likely to facilitate colonic transit and defecation.

The colon is responsive to stretch in vivo and in vitro (4, 28). We found that rectal balloon distension suppressed both propagating and nonpropagating activity and that this response was most pronounced in the cecoascending colon. The reported observations to date are conflicting with some (16) showing colonic distension to have little or no effect on the elicitation of colonic propagating events in the human colon, whereas others (4) found balloon distension to elicit...
propulsive activity in 53% of subjects. Rectal balloon distension in the dog does not elicit giant migrating contractions that are the manometric correlate of defecation (21). On the other hand, rectal distension in pigs prolongs colonic transit time (25) and decreases colonic myoelectrical activity in humans (13). Our findings, in the context of these previous studies, suggest that rectal distension activates inhibitory pathways, thereby reducing proximal colonic motor activity, with the net effect of delaying colonic transit. It is likely that such a response to rectal distension prevents further passage of stool to a loaded rectum, which might further challenge continence mechanisms. This hypothetical extrinsic pathway is supported by studies on isolated canine colonic loops in which extrinsic adrenergic neural pathways appear to mediate the colocolonic inhibitory reflex (18).

Bile acids are well known to cause diarrhea by stimulating motility and, at higher doses, by promoting secretion (6, 12, 15, 29, 33). The rectal infusion of chenodeoxycholic acid, both in supraphysiological and physiological concentrations, decreases rectal sensory thresholds to balloon inflation (12, 19, 30). In supraphysiological but not physiological concentrations, rectal chenodeoxycholic acid has been associated with initiation of a colonic motor response despite the observation that physiological concentrations did induce a defecatory urge in the majority (6, 12, 15, 19, 22, 29, 30, 33). However, those studies may have overlooked proximal colonic motor responses to lower doses of chenodeoxycholic acid, because only distal colonic activity was measured. Indeed many of the propagating motor patterns that culminate in a defecatory urge originate in the proximal colon (2). From our data, it is not possible to determine whether the affects on rectal afferents are direct, via chemoreceptor activation, or indirect, via chemical-induced alterations in colonic wall tone or compliance.

In the present study, we demonstrate a twofold increase in proximal colonic propagating sequence frequency after rectal instillation of 1 mmol chenodeoxycholic acid. The propagating sequences initiated by chenodeoxycholic acid in our study travelled a relatively short distance (~18% of the length of the colon) and were of a relatively low amplitude. These motor patterns do not fit within the definition of “high amplitude propagating contractions,” previously described as occurring before spontaneous defecation and defecation stimulated by bisacodyl (2, 17, 20). Nevertheless, we and others (17) have shown some propagating sequences that do not extend all the way to the rectum do occur before spontaneous defecation. Furthermore, propagating pressure waves of comparable amplitude to those induced in response to chenodeoxycholic acid in the present study have been shown previously to have the capacity to move colonic content (9, 24) and do occur with increasing frequency in the hour before defecation (2).

Randomization of the stimuli administration would have been desirable. However, due to the persistence of the bile acid within the rectum after infusion and the indeterminate nature of the duration of its effect, it was not possible to randomize the stimuli as well as examine the hypothesis that bile acids sensitize the rectum to subsequent distension. However, it is unlikely that the lack of such randomization biased the results. Existing colonic motility studies have not observed a sudden fall followed abruptly by a fourfold increase in propagated sequence frequency (1, 3, 14, 22, 26). Furthermore, it is difficult to comprehend poten-

Fig. 4. Effect of balloon inflation and chenodeoxycholic acid on the area under the pressure curve (AUC). The 3 graphs represent averaged data from all regions within cecoascending (A), transverse (B), and descending colon (C). All effects were more pronounced in the proximal colonic regions than were in the distal colon. Initial balloon inflation of the rectum induced a significant reduction in AUC that was confined to the cecoascending colon (P < 0.001), whereas subsequent inflation induced further significant reductions in cecoascending (P < 0.0003) and transverse colon (P < 0.002). Infusion of chenodeoxycholic acid did not affect the AUC.
tial bias, which might account for both a decrease then an increase in propagating activity as seen in the present study. Alternatively, the effect attributed to chenodeoxycholic acid infusion in the present study could represent a late response to the balloon inflation rather than a response to the chenodeoxycholic acid infusion per se. However, the response to distension is unlikely to account for the massive stimulatory effect of chenodeoxycholic acid, because the response to distension has been shown, convincingly, to be inhibitory in nature. Any effect of the distension would have served only to attenuate the response to chenodeoxycholic acid.

Although measurement of colonic tone was beyond the scope of this study, one might speculate that increased colonic tone following chenodeoxycholic acid infusion or decreased tone in response to rectal distension might enhance and attenuate, respectively, the ability of the catheters to detect phasic colonic wall motion and thereby account, in part, for our observations. On the basis of an earlier study by Von der Ohe et al. (34), we think this is unlikely. In that study, they compared the detection of phasic events by a colonic barostat with perfusion manometry and found that phasic events were recorded with similar fidelity, although once the colonic barostat balloon was inflated beyond 5.6 cm in that study, the frequency of phasic events detected by perfusion manometry was less than that detected by the barostat. However, a colonic diameter as great as 5.6 cm is quite nonphysiological and would not be expected in normal volunteers. Furthermore, if changes in tone alone were responsible for our observation, then we would expect the detection of both propagating and nonpropagating waves to be increased after chenodeoxycholic acid infusion. In contrast, we observed only an increase in propagating pressure waves after this stimulus. Hence, we feel that the regional activation and the actual frequency of phasic events, and certainly the prevalence of propagating sequences, were unlikely to have been affected substantially by any changes in wall tone. The possibility remains, however, that the actual amplitude of phasic pressure waves and AUC may have been influenced by changes in tone.

We conclude that rectal chemoreceptor stimulation may play an important physiological role in the initiation of proximal colonic propagating sequences. Rectal mechanoreceptor stimulation is inhibitory to the unprepared proximal human colon. These findings support the hypothesis that long colocolonic reflexes exist and may well be important in modulating colonic flow and defecation.

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REFERENCES


