Differential symptomatic and electrogastrographic effects of distal and proximal human gastric distension

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Ladabaum, Uri, Sherin S. Koshy, Michelle L. Woods, Forrest G. Hooper, Chung Owyang, and William L. Hasler. Differential symptomatic and electrogastrographic effects of distal and proximal human gastric distension. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G418-G424, 1998.—Nausea and gastric dysrhythmias occur in conditions associated with gastric distension. The roles of distal and proximal gastric mechanoreceptors in these responses are unexplored. Because antral distension induces vomiting in animals and antral and fundic vagal afferent discharges differ, we hypothesized that distal gastric distension in humans leads to greater symptomatic and dysrhythmic responses than proximal distension. Symptoms and electrogastrograms were recorded in healthy humans during distal and proximal gastric distension with a barostat. Distal but not proximal distension induced nausea and a 747 ± 250% increase in dysrhythmic power (P < 0.05), responses not affected by granisetron, indomethacin, or atropine, agents that block dysrhythmias in other settings. In the distal stomach, bloating and pain developed at lower pressures (P < 0.05) not modified by granisetron, and compliance was significantly lower (P < 0.05). In conclusion, gastric mechanoreceptor activation in the less-compliant distal stomach produces nausea and dysrhythmias via non-5-hydroxytryptamine3 (5-HT3), non-prostaglandin-dependent, and noncholinergic pathways. Distal mechanoreceptor activation induces greater bloating and pain than proximal mechanoreceptor activation via 5-HT3-independent pathways.

electrophysiology; nausea; 5-hydroxytryptamine3; mechanoreceptors; barostat

Disruption of the rhythmic electrical activity of the stomach, termed the slow wave, has been described in numerous conditions associated with nausea, including unexplained nausea and vomiting (7), gastroparesis (5), nausea of pregnancy (15), motion sickness (22), hyperglycemia (12), and supraphysiological duodenal nutrient perfusion (17). Gastric distension may be accompanied by nausea in a variety of clinical conditions, including gastric outlet obstruction and diabetic, postsurgical, or idiopathic gastroparesis (14). The mediators of gastric dysrhythmias have been elucidated in several conditions and include central cholinergic and α-adrenergic pathways in motion sickness (11), prostaglandin-dependent pathways with hyperglycemia (12), and 5-hydroxytryptamines (5-HT3) and muscarinic pathways with intestinal nutrient perfusion (17). 5-HT3 antagonists are powerful antiemetic agents used with cancer chemotherapy (20), which have also received attention in the study of visceral sensitivity (4).

The differences in mechanical and myoelectrical properties between the proximal and distal human stomach have been well described (13). Studies in animals have explored the effects of distension of these two anatomic regions. In dogs, distension of distal gastric pouches invariably produced vomiting, whereas vomiting could not be induced by comparable distension of fundic pouches (10). In the ferret, the patterns of vagal afferent discharge at rest and during distension are different for the antrum and fundus (1). No studies in humans have compared the effects of proximal and distal gastric distension on induction of symptoms and gastric dysrhythmias.

We hypothesized that in humans distal gastric distension produces more nausea and disruptions of the slow wave than proximal distension and that distension-induced nausea and dysrhythmias may be mediated by 5-HT3 serotonergic, prostaglandin-dependent, or cholinergic pathways. To test this hypothesis, we compared nausea induction and electrogastrogram (EGG) recordings during distal and proximal gastric distension with a barostat balloon in healthy subjects in the absence and presence of the 5-HT3 serotonergic receptor antagonist granisetron, the inhibitor of prostaglandin synthesis indomethacin, and the cholinergic receptor antagonist atropine. To ascertain whether regional differences in the induction of nausea are symptom specific and whether they are associated with differences in the properties of the distal and proximal gastric wall, we studied the development of bloating and pain and measured compliance in the distal and proximal stomach. Because of the proposed role of 5-HT3 serotonergic pathways in visceral perception, the development of bloating and pain and compliance were compared with and without granisetron. Through these investigations, we sought to better define the anatomic regions and pathways responsible for symptoms and EGG changes induced by gastric distension.

Materials and Methods

Study population. Eighteen healthy volunteers (15 men and 3 women, 20–41 yr old) were recruited. No volunteer had a history of gastrointestinal symptoms, surgery, psychiatric illness, or diabetes or was taking medication used to treat nausea or known to interfere with gastrointestinal function or pain perception. No volunteer was pregnant. The study protocols were approved by the University of Michigan Institutional Review Board, and each volunteer signed an informed consent document before participation.

Nine volunteers participated in studies of distal gastric distension with and without granisetron. Four of the volunteers who reported nausea participated in studies of distal distension with indomethacin and atropine. Twelve volunteers participated in studies of proximal gastric distension with and without granisetron.
Barostat balloon distension. Barostat balloons were fashioned from nonelastic plastic to provide near-infinite compliance and were affixed to 18-Fr Salem Sump nasogastric tubes (Sherwood Medical, St. Louis, MO). Balloon capacity was 550 ml for distal distension and 1,200 ml for proximal distension. The tube with its finely folded balloon was passed through the mouth, and the balloon was advanced into the stomach. For proximal distension, the balloon was inflated and withdrawn until resistance at the gastroesophageal junction was felt. For distal distension, the balloon was advanced to the antrum. The position of the balloon in the proximal or distal stomach was confirmed by fluoroscopy, and the tube was secured with tape at the mouth. Subjects underwent testing without and with granisetron on the same day and, after the first cycle of the distension protocol with the distal balloon, the position of the balloon in the distal stomach was confirmed by fluoroscopy. In rare cases, sudden increases in balloon volume were observed during isobaric distal distension, and proximal balloon migration was suspected and confirmed by fluoroscopy. In these instances, the balloon was repositioned and the distension cycle was repeated.

The accessory lumen of the tube was clamped and the main lumen was connected to the barostat (Isobar-3, G&J Electronics, Willowdale, ON, Canada). The barostat was connected to a chart recorder and computer for recording of pressure and volume as described below for EGG recording. A brief test inflation to 16 mmHg was performed to unfold the balloon, followed by full deflation. Isobaric distensions were performed in an intermittent step-by-step fashion in increments of 2 mmHg, from 4 to 22 mmHg. Balloon inflations were sustained for 5 min, followed by 2 min of deflation. Balloon volume, symptoms, and EGG were recorded throughout inflations and deflations as described below. The balloon was deflated if volunteers developed intolerable symptoms. The average volume during the last 4 min of each inflation was calculated after volume data were converted into spreadsheet format (Lotus 1–2–3, v. 2; Lotus Development, Cambridge, MA).

Cutaneous electrogastrography. Subjects were placed in a semirecumbent position with the head of the bed elevated to approximately 30 degrees in a quiet, darkened room without visual or auditory distraction. After gentle skin abrasion, Ag-AgCl electrodes (Accutac diaphoretic electrocardiogram electrodes; NDM, Dayton, OH) were affixed to 3 cm to the left of midline and 4 cm to the right of midline at the level of the lower costal margin. Electrodes were connected via direct nystagmus couplers (model 9859; SensorMedic, Anaheim, CA) to a chart recorder (Dynograph Recorder R611; Beckman Instruments, Palo Alto, CA). Time constants were set at 10 s and high-frequency cutoffs at 0.3 Hz to minimize interference from nongastric signals. The chart recorder was interfaced with a personal computer (model 4DX2–66V; Gateway 2000, North Sioux City, ND) via an analog-to-digital converter (model DAS-18; Metabyte, Taunton, MA). EGG traces were obtained after barostat balloon placement during a 10-min baseline period, followed by barostat distensions. Subjects remained still and used minor movements of one hand or single words to report symptom intensity.

The EGG traces were initially analyzed visually, and periods with signal artifact were excluded from further analysis. Traces were then subjected to quantitative computer analysis. Signals were digitized to 4 Hz by the analog-to-digital converter and filtered above 15 cycles per minute (cpm) and below 0.5 cpm to remove high- and low-frequency noise. Commercially available software (Fourier Perspective III; Alligator Technologies, Fountain Valley, CA) was used to perform power spectral analysis on the baseline EGG traces and on traces of the final 4 min of each balloon inflation. Data from the spectral analyses were imported into spreadsheet format (Lotus 1–2–3) to detect disturbances in the gastric slow wave rhythm.

For each tracing, signal power was determined for the bradygastric range (1–2 cpm), normogastric range (2–4.5 cpm), and tachygastric range (4.5–9 cpm). Dyrrhythmic power was defined as the sum of bradygastric and tachygastric power. For each distending pressure, powers in the normogastric and dysrhythmic ranges were expressed as a percentage of the basal value. For each subject, dysrhythmic power as a percentage of the basal value was compared at all distending pressures, and the greatest value was defined as the maximal increase in dysrhythmic power.

Symptom reporting. At each distending pressure, subjects were asked to independently rate bloating, pain, and nausea as absent, mild, moderate, or severe. The proportions of subjects reporting nausea with distal and proximal balloon distension with and without granisetron were compared, and pressure thresholds for development of moderate bloating and pain were compared for distal and proximal distension with and without granisetron.

Test conditions and study design. After an overnight fast, a barostat balloon was placed in the distal or proximal stomach of each subject. If performed on the same day, distension studies without medication were followed by studies with granisetron (SmithKline Beecham Pharmaceuticals, Philadelphia, PA), separated by a 90-min rest period. Placebo saline or granisetron was administered in a single-blind fashion. Granisetron was dosed at 10 µg/kg intravenously, the effective dose for treating chemotherapy-induced nausea and the dose previously found to block dysrhythmias induced by duodenal nutrient perfusion (17). The studies with indomethacin (Geneva Pharmaceuticals, Broomfield, CO) and atropine (atropine sulfate; American Regent Laboratories, Shirley, NY) were each performed on separate days. Studies with indomethacin were performed after 3 days of oral dosing at 50 mg three times per day and a final dose of 50 mg on the morning of the study. Atropine was given as a 0.5-mg intravenous bolus followed by a constant infusion at 0.25 mg/min.

After 30 min of acclimation to the barostat balloon and an additional 20 min after medication was administered for studies with granisetron and atropine, a 10-min EGG baseline tracing was obtained, followed by distensions with the barostat. EGG, volume, and symptoms were recorded at each distending pressure.

Statistical analysis. Results for electrogastrographic parameters, distending pressures, volumes, and compliance were expressed as means ± SE and were compared using Student’s paired t-test within the same group of subjects and Student’s unpaired t-test between groups of subjects. All t-tests were two-tailed. Proportions were compared using the χ² test. Statistical significance was accepted at P ≤ 0.05.

RESULTS

Induction of nausea. As shown in Fig. 1, the proportion of subjects reporting nausea with distal gastric distension rose as a function of distending pressure, with seven of nine subjects reporting nausea at or below 20 mmHg. In contrast, none of the subjects reported nausea with fundic distension (P < 0.01). The development of nausea was not prevented in any subject by granisetron, indomethacin, or atropine administration. Thus distension of the distal, but not the proximal, stomach elicits nausea, which is not abolished by blockade of 5-HT₃ receptors, prostaglandin...
synthesis, or cholinergic receptors, suggesting these pathways are not the principal mediators of gastric distension-induced nausea.

Dysrhythmic EGG power. In subjects experiencing nausea, a significant average maximal increase in dysrhythmic power of $747 \pm 250\%$ was elicited with distal gastric distension ($P < 0.05$ compared with baseline) (Fig. 2). By visual analysis, distal gastric distension evoked dysrhythmias that were predominantly bradygastric and that replaced the normal 3 cpm activity. Upon quantitative analysis, the increase in dysrhythmic power with distal gastric distension was not associated with significant increases in power in the normogastric frequency range. Figure 3 demonstrates a normal 3 cpm slow wave activity at baseline and the development of bradygastria with a dominant frequency of 1.5 cpm with distal gastric distension in one subject who reported nausea. In contrast, the average maximal change in dysrhythmic power with proximal gastric distension was $163 \pm 74\%$ ($P > 0.05$ compared with baseline) (Fig. 2). Proximal gastric distension evoked increases in power in the normogastric frequency range (data not shown). Thus dysrhythmic power as a fraction of total power did not increase with proximal distension. The dysrhythmic power increase produced by distal distension was not prevented by granisetron, with an average maximal increase in dysrhythmic power of $647 \pm 269\%$ ($P < 0.05$ compared with baseline) (Fig. 2). Indomethacin and atropine also failed to prevent dysrhythmias with distal distension, with respective maximal increases in dysrhythmic power of $477 \pm 120\%$ and $537 \pm 94\%$ ($P < 0.05$ compared with baseline) (Fig. 2).

To further characterize the effect of granisetron on dysrhythmia induction, the threshold distal distending pressure required for doubling of dysrhythmic power and the distending pressure at maximal dysrhythmic power were compared with and without granisetron. As shown in Fig. 4, the threshold distal distending pressure required for doubling of dysrhythmic power without medication was $10.9 \pm 1.6$ mmHg, which was not significantly different from the value of $10.6 \pm 1.7$ mmHg with granisetron ($P > 0.05$). Similarly, as shown in Fig. 5, the distending pressure at maximal dysrhythmic power without medication was $13.4 \pm 1.8$ mmHg, which was not significantly different from the value of $12.9 \pm 2.0$ mmHg with granisetron ($P > 0.05$).

Thus, in addition to inducing nausea, distal gastric distension leads to a significant increase in dysrhythmic power, characterized primarily by bradygastria, which, similar to distension-induced nausea, is not prevented by blockade of 5-HT3 serotonergic, prostaglandin-dependent, or cholinergic pathways. In contrast,
proximal gastric distension, which does not induce nausea, does not lead to significant increases in dysrhythmic power.

Induction of bloating and pain. In contrast to the exclusive induction of nausea by distal gastric distension, bloating and pain were elicited by both distal and proximal gastric distension. However, these symptoms developed at lower pressures in the distal compared with the proximal stomach. Although no fixed sequence was observed in all subjects for the development of the three symptoms, bloating tended to precede nausea and pain. The average distal gastric distending pressure that elicited moderate bloating was 10.4 ± 0.8 mmHg, significantly lower than the average proximal distending pressure of 15.0 ± 0.7 mmHg required to elicit moderate bloating (P < 0.05) (Fig. 6). The pressures evoking moderate bloating were unaffected by granisetron in both the distal and proximal stomach (11.4 ± 1.2 and 13.1 ± 1.1 mmHg, respectively, both P > 0.05 compared with no medication) (Fig. 6). Moderate pain was elicited at an average distal gastric distending pressure of 16.7 ± 1.6 mmHg, which was also significantly lower than the pressure of 20 mmHg required to elicit moderate pain in the five subjects who reported pain with proximal distension (P < 0.05) (Fig. 7). One of

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Fig. 4. Threshold pressure for doubling of dysrhythmic power with distal gastric balloon distension in subjects developing nausea. The pressure at which doubling of dysrhythmic power occurred was unaffected by granisetron (P > 0.05; NS, not significantly different). Values are means ± SE.

Fig. 5. Distending pressure at maximal dysrhythmic power with distal gastric balloon distension in subjects developing nausea. The pressure at which maximal dysrhythmic power was observed was unchanged with granisetron (P > 0.05). Values are means ± SE.

Fig. 6. Pressure eliciting moderate bloating. Moderate bloating was elicited at a lower pressure with distal gastric compared with proximal gastric balloon distension (P < 0.05). The pressures eliciting moderate bloating were unaffected by granisetron (P > 0.05 for comparisons between control and granisetron). Values are means ± SE.

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Fig. 7. Pressure eliciting moderate pain. Moderate pain was elicited at a lower pressure with distal gastric compared with proximal gastric balloon distension (P < 0.05). The pressure eliciting moderate pain was unaffected by granisetron (P > 0.05). Proximal gastric relaxation produced by granisetron precluded the development of pressures high enough (>18 mmHg) to elicit pain. Values are means ± SE.
the six subjects never experienced pain with proximal distension. With granisetron, the distal distending pressure required to elicit moderate pain was 17.4 ± 1.9 mmHg (P > 0.05 compared with no medication) (Fig. 7). Proximal gastric relaxation induced by granisetron (see below) precluded the development of pressures high enough to induce moderate pain in the majority of subjects. Thus bloating and pain, the perception of which is not affected by 5-HT3 receptor blockade, are elicited at lower pressures in the distal compared with the proximal stomach. Unlike nausea, however, which is elicited exclusively by distal distension, both distal and proximal distension evoke bloating and pain, symptoms not associated with disruptions of slow wave rhythmity.

Compliance of distal and proximal stomach. To determine whether differences in the induction of symptoms are associated with regional differences in the properties of the gastric wall, proximal and distal gastric compliance were measured. Figure 8 demonstrates the higher overall compliance of the proximal compared with the distal stomach (47 ± 4 vs. 27 ± 1 ml/mmHg; P < 0.001). Granisetron induced significant proximal gastric relaxation, increasing proximal compliance to 106 ± 6 ml/mmHg (P < 0.001 compared with no medication), whereas it had no effect on distal gastric compliance (27 ± 1 ml/mmHg, P > 0.05 compared with no medication) (Fig. 8). Thus the distal stomach, in which distension leads to dysrhythmias and greater symptoms, also exhibits less compliance than the proximal stomach. Furthermore, 5-HT3-receptor blockade significantly increases proximal but not distal gastric compliance, suggesting that 5-HT3 serotonergic pathways participate in the maintenance of proximal gastric tone and highlighting further the different properties of the gastric wall in these two regions.

**DISCUSSION**

The contrasting properties of the proximal and distal stomach are well recognized (13). The proximal stomach, which exhibits tonic contraction with superimposed phasic contractions, is capable of receptor relaxation and accommodation and functions as a reservoir and the main determinant of liquid emptying. The distal stomach exhibits strong phasic contractions and functions to contain, triturate, and regulate the emptying of solids. Pacesetter potentials or slow waves originating in the orad gastric body propagate distally but are not found in the proximal stomach.

Studies in animals have explored the different effects of distal and proximal gastric distension. In dogs, distension of distal gastric pouches created surgically, termed isolated pyloric pouches, invariably produced vomiting when distended with pressures of 30–35 mmHg; this vomiting reflex was completely abolished by vagotomy (10). Despite numerous attempts, vomiting could not be induced by comparable distension of surgically created fundic pouches (10). In the ferret, the patterns of vagal afferent discharge are different for the antrum and fundus (1). Fibers arising in the antrum exhibit spontaneous firing in phase with spontaneous contractions, and with distension discharges increase in correlation with enhanced antral motility. Fibers arising in the body or fundus show irregular spontaneous discharges unrelated to intragastric pressure, and with distension these discharges increase. It has been suggested that tension receptors in the proximal stomach signal the degree of distension and those in the antrum encode information about contractions (1).

Whether dogs experience anything similar to the complex human symptom of nausea before distension-induced vomiting is not known. Although nausea is often associated with vomiting, this is not invariable, and we do not know whether vomiting could be induced in humans as in the dog with higher distal gastric distending pressures than we achieved in this study. Notably, several volunteers complained of severe nausea and imminent vomiting with distal distension, prompting immediate balloon deflation. It is possible that sustained distension would have produced vomiting. Although vagotomy abolished the vomiting reflex in dogs and vagal firing patterns are different during distension of the antrum or fundus in the ferret, it is not clear whether nausea induced by gastric distension in humans is mediated by vagal pathways. The inability of granisetron, indomethacin, or atropine to block induction of nausea suggests that the relevant pathways are not 5-HT3 serotonergic, prostaglandin-dependent, or cholinergic.

Disruption of the gastric slow wave has been described in various clinical and experimental conditions associated with nausea, including unexplained nausea and vomiting (7), gastroparesis (5), nausea of pregnancy (15), motion sickness (22), hyperglycemia (12), and supraphysiological duodenal nutrient perfusion (17). The pathways mediating dysrhythmias have been elucidated in several conditions, including central cho-
linergic and α-adrenergic pathways in motion sickness (11), prostaglandins with hyperglycemia and transfer-
al nicotine in nonsmokers (12, 16), and 5-HT₃ and muscarinic pathways with intestinal nutrient perfu-
sion (17). In addition to not preventing nausea, we were unable to block the dysrhythmic response induced by distal gastric distension with granisetron, indometha-
cin, or atropine, suggesting that the pathways involved in generation of these dysrhythmias are not 5-HT₃ serotonergic, prostaglandin dependent, or cholinergic. It remains to be established whether the induction of dysrhythmias is due to a local effect of distension on the myoelectric properties of the distal stomach or due to feedback mechanisms affecting the gastric pacemaker, including unidentified neurohumoral mediators.

Gastric balloon distension has been used to explore differences in visceral sensitivity between healthy controls and patients with functional dyspepsia, a condition in which symptoms such as epigastric discomfort, bloating, nausea, and early satiety are often related to feeding but are not attributable to structural or meta-

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