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Ladabaum, Uri, Morton B. Brown, Wenqin Pan, Chung Owyang, and William L. Hasler. Effects of nutrients and serotonin 5-HT_3 antagonism on symptoms evoked by distal gastric distension in humans. *Am J Physiol Gastrointest Liver Physiol* 280: G201–G208, 2001.—Distal gastric distension may contribute to meal-related dyspeptic symptoms. This study's aims were to determine the effects of distinct nutrient classes on symptoms induced by distal gastric distension and their dependence on 5-hydroxytryptamine$_3$ (5-HT_3) receptors. Nine healthy subjects rated pain, nausea, and bloating induced by isobaric distal gastric distensions (6–24 mmHg) during duodenal lipid, carbohydrate, protein, or saline perfusion after treatment with placebo or the 5-HT_3 receptor antagonist granisetron (10 μg/kg iv). Distensions produced greater pain, nausea, and bloating with lipid at 1.5 kcal/min compared with saline ($P \leq 0.02$), primarily because of greater distal gastric volumes at each distending pressure. In contrast, carbohydrate and protein had no significant effect. At 3 kcal/min, lipid increased symptoms through a volume-independent as well as a volume-dependent effect. Granisetron did not affect symptom perception or gastric pressure-volume relationships. In conclusion, isobaric distal gastric distension produces more intense symptoms during duodenal lipid compared with saline perfusion. Symptom perception during distal gastric distension is unaffected by 5-HT_3 receptor antagonism.

barostat; duodenum; pain; nausea; bloating

DYSPEPSIA, WHICH MAY BE DEFINED as upper abdominal symptoms often related to feeding (2), is a common condition with an estimated prevalence of 2.5% to 41% and yearly incidence of 1% to 11.5% (19). In nonulcer dyspepsia (NUD), symptoms are not attributable to structural or metabolic disease (2, 20). Numerous investigations have demonstrated greater symptomatic responses to gastric distension in NUD patients compared with control subjects (4, 18, 22), and altered visceral perception has garnered great attention in functional bowel disease research.

Dyspeptic symptoms may be exacerbated by meals, especially fats. In healthy subjects, duodenal lipid perfusion has been shown to heighten symptoms during fundic distension, an effect partially reversed by the serotonin [5-hydroxytryptamine (5-HT)] 5-HT_3 receptor antagonist ondansetron (8) and by the cholecystokinin receptor antagonist loxiglumide (6, 24). Thus 5-HT_3- and cholecystokinin-dependent pathways appear to be involved in the sensitization to fundic distension produced by lipid.

Patients with NUD may exhibit abnormal intragastric meal distribution, with preferential delivery of food to the distal stomach (9, 21, 33). It has been suggested that abnormal distal gastric distension may contribute to symptoms in patients with NUD. In an investigation of healthy subjects, distal but not proximal gastric distension induced nausea and distal distension evoked bloating and pain at lower pressures than proximal distension (17). The effect of duodenal nutrient perfusion on symptoms induced by distal gastric distension has not been investigated previously.

We hypothesized that symptoms induced by distal gastric distension are exacerbated by duodenal nutrient perfusion, with lipid leading to greater sensitization than carbohydrate or protein, through 5-HT_3-dependent pathways. In the present study, our aims were to compare the effects of the three major nutrient classes on symptoms induced by distal gastric distension in healthy volunteers and to investigate the role of 5-HT_3 pathways in the nutrient effect. Our objective was to improve our understanding of the potential role of nutrients and distal gastric distension in meal-related exacerbations of dyspeptic symptoms.

MATERIALS AND METHODS

Study population. Nine healthy volunteers (7 men and 2 women, age 20–55 yr) were recruited. No volunteer had a history of gastrointestinal or psychiatric illness or diabetes or was taking medication known to alter gastrointestinal function or pain perception or used to treat nausea. No volunteer was pregnant. The University of Michigan Institutional Review Board approved the research protocol, and volunteers signed informed consent documents before participation.

Experimental preparation and apparatus. Barostat balloons with a capacity of 600 ml were fashioned from nonelastic plastic and affixed to 18-Fr Salem Sump nasogastric tubes (Sherwood Medical, St. Louis, MO). Isocaloric (0.68 kcal/ml)

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solutions of carbohydrate, protein, and lipid were prepared from 20% dextrose solution (Abbott Laboratories, Abbott Park, IL), ProMod high-protein formulation (Ross Laboratories, Columbus, OH), and Microlipid lipid emulsion (Sherwood Medical, St. Louis, MO).

Indistinguishable preparations of the 5-HT_3 receptor antagonist granisetron (Kytril; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) and placebo were provided by the Investigational Drug Service of the University of Michigan for each subject. Granisetron was given at a dose of 10 μg/kg iv, the effective dose for treating chemotherapy-induced nausea (11). This dose has been shown to blunt nausea and gastric dysrhythmias evoked by supraphysiological nutrient perfusion (16).

After an overnight fast, subjects were intubated orally with a single-lumen 8-Fr Dobhoff feeding tube (Corpak MedSystems, Wheeling, IL) for delivery of nutrients or normal saline (Abbott Laboratories). The tip of the tube was positioned under fluoroscopy in the descending duodenum. The barostat balloon was then passed orally and was positioned under fluoroscopic guidance in the distal stomach, with the tubing along the greater curve of the stomach, the tip in the prepyloric region, and the balloon primarily in the antrum. The feeding tube was connected to a calibrated infusion pump. The barostat balloon tube was connected to a barostat machine (Isobar-3; G&J Electronics, Willowdale, ON, Canada), which was connected to a chart recorder (Dynograph Recorder R611; Beckman Instruments, Palo Alto, CA) for pressure and volume recording and interfaced with a personal computer (model 4DX2–66V; Gateway 2000, North Sioux City, ND) via an analog-to-digital converter (model DAS-16; Metrabyte, Taunton, MA).

Study protocol. Each subject was assigned randomly to a different sequence of the four duodenal solutions using an incomplete block design. Subjects underwent testing on 4 separate days over 3–6 wk. Two duodenal solutions were tested on the first and second days, and the remaining two solutions were tested on the third and fourth days. Subjects were blinded regarding the order of duodenal solutions and nature of the distension protocol. Placebo or granisetron was given on the first day in a randomized, double-blinded fashion, with crossover from one treatment to the other on the second day. Placebo and granisetron were again administered in a randomized, double-blinded, crossover fashion on the third and fourth days.

On each study day, subjects underwent placement of the feeding tube and balloon and then lay supine with the head elevated 30° in a darkened room, with the study equipment and solutions out of view. Following a 30-min acclimation period, a morning testing session began with intravenous granisetron or placebo given over 5 min (t_{-5} to t_0). Fifteen minutes after t_0, perfusion with the first duodenal solution began at 2.2 ml/min (1.5 kcal/min for nutrients). This caloric perfusion rate is similar to the normal rate of gastric emptying of lipid into the duodenum reported by other investigators (25). After 20 min of perfusion (35 min after t_0), isobaric balloon distensions were performed in an intermittent stepwise fashion in 2-mmHg increments from 6 mmHg to 24 mmHg while maintaining the duodenal perfusion rate. Balloon inflations were performed at a rate of 25 ml/s and sustained for 1 min, followed by 1 min of deflation. During and between distensions, subjects were asked to rate independently the intensity of pain, nausea, and bloating from 0 (absent symptom) to 5 (maximum tolerated symptom), with 1 representing threshold. A visual aid was displayed in front of the subjects at all times, with the numerical rating system and a corresponding color intensity representation for symptom severity. The balloon was deflated if volunteers reported intolerable symptoms.

The perfusion rate was then increased to 4.4 ml/min (3 kcal/min for nutrients). This caloric perfusion rate is slightly higher than the previously reported normal rate of gastric emptying of lipid into the duodenum (25). After 20 min at this higher perfusion rate, distensions were again performed during ongoing duodenal perfusion, and symptoms were recorded. On completion, appropriate feeding tube and balloon positions were confirmed by fluoroscopy.

A 3-h rest period followed the morning session to allow for complete clearance of any physiological effect of the first nutrient. An afternoon testing session began with a second dose of the treatment given in the morning (placebo or granisetron) to prevent loss of pharmacological effect. Perfusion and testing with a second solution were then performed in the same fashion.

Rarely, sudden steep increases in balloon volume of ~200–300 ml were observed during distension, and proximal balloon migration was suspected and demonstrated by fluoroscopy. The balloon was then repositioned and the distension cycle was repeated. We have performed distal gastric barostat balloon inflations under direct fluoroscopic visualization and have confirmed that, barring unexpected volume changes, the balloon remains in the distal stomach during inflation and deflation and primarily distends the antrum.

Statistical analysis. Average pain, nausea, and bloating scores were plotted against distending pressure for each experimental condition. Mixed-effects models accounting for repeated measures within subjects were fitted to each symptom using pressure, $(\text{pressure})^2$, and nutrient as the independent variables to examine the overall effect of each nutrient on symptom intensity, adjusted for pressure, throughout the entire range of distending pressures. If a statistically significant difference among all nutrients was detected, individual nutrients were compared. These models test the hypothesis that the curves of symptom score as a function of pressure differ among the various duodenal perfusions.

Average volumes during the last 40 s of each inflation were calculated for each subject after importing volume data into a spreadsheet (Lotus 1-2-3, release 2; Lotus Development, Cambridge, MA). Average distal gastric volume for all subjects was plotted against distending pressure for each experimental condition. Mixed-effects models analogous to those for symptoms were fitted to compare distal gastric pressure-volume relationships during perfusion with the different duodenal solutions.

Because symptoms as well as distal gastric pressure-volume relationships varied depending on the nature of the duodenal solution, mixed models with volume replacing pressure as an independent variable were fitted to each symptom. These models were used to test the hypothesis that the effects of nutrient on symptoms could be explained by changes in the distal gastric pressure-volume relationship induced by nutrient.

Finally, to test the effects of granisetron, treatment with granisetron or placebo replaced nutrient as an independent variable, and a mixed model was fitted separately for each nutrient. Statistical significance was set at $\alpha \leq 0.05$.

Symptom scores increased during the higher (4.4 ml/min) compared with the lower (2.2 ml/min) rate of perfusion for all duodenal solutions. The magnitude of this difference in symptoms between the higher and lower rate was comparable for all solutions. The results for the lower rate of perfusion are presented in detail. For the higher rate of perfusion, results that differed compared with the lower rate of perfusion are emphasized.

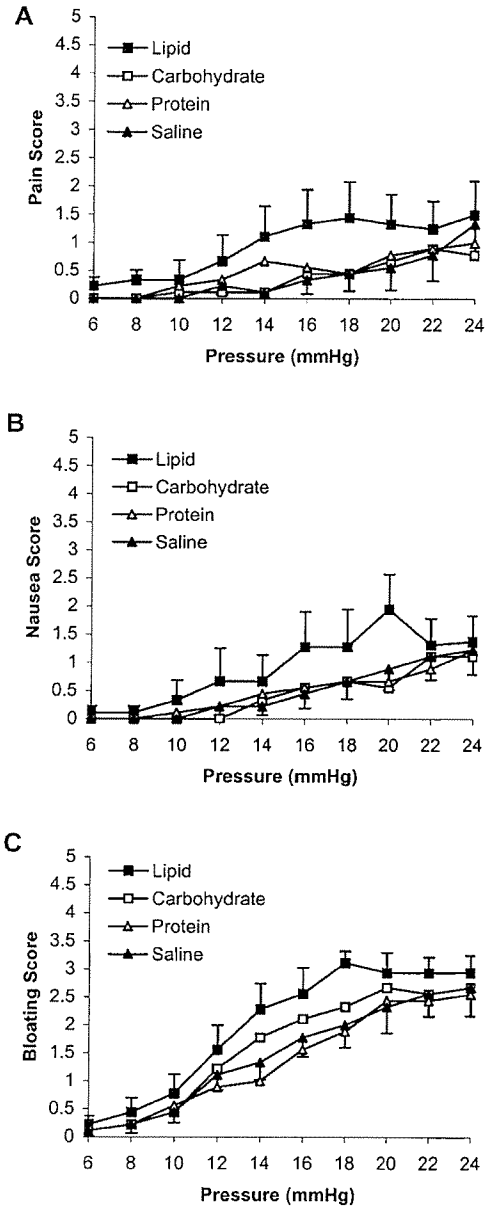


Fig. 1. Nutrient-specific increases in symptoms induced by distal gastric distension during duodenal nutrient perfusion at 1.5 kcal/min. Mean symptom scores are shown as a function of pressure during duodenal perfusion with lipid, carbohydrate, protein, and saline (2.2 ml/min). Only lipid led to greater distension-induced symptom scores than saline for pain (*A*; $P = 0.0034$), nausea (*B*; $P = 0.020$), and bloating (*C*; $P = 0.018$). Standard error bars are shown for lipid and saline scores. For clarity, standard errors for carbohydrate and protein are omitted.

RESULTS

Effects of nutrients on distension-induced symptoms and pressure-volume relationship. Figure 1 shows the average symptom scores at each distending pressure for the four duodenal perfusion solutions at 2.2 ml/min (1.5 kcal/min for nutrients) during intravenous placebo treatment. The intensity of pain, nausea, and bloating rose as a function of distending pressure under all conditions. During nearly all deflations, symptom scores returned to baseline (data not shown), suggesting that symptoms were induced primarily by distal gastric distention and not nutrient perfusion alone. Rarely, nausea lingered into the deflation period, whereas pain and bloating tended to abate promptly with balloon deflation.

As shown in Fig. 1, distension-induced symptom scores differed among duodenal solutions for all three symptoms: pain ($P = 0.0079$), nausea ($P = 0.036$), and bloating ($P = 0.036$). When comparing individual solutions, distensions during duodenal lipid perfusion led to more intense pain ($P = 0.0034$), nausea ($P = 0.020$), and bloating ($P = 0.018$) than during saline perfusion. In contrast to the effect of lipid, no significant differences in symptoms induced by distal gastric distension were found during carbohydrate or protein perfusion compared with saline perfusion.

As shown by the curves in Fig. 2*A*, distal gastric pressure-volume relationships during duodenal perfusion differed among perfusing solutions at 2.2 ml/min ($P = 0.0015$). Although the volumes achieved by isobaric distension were higher during all nutrient perfusions compared with saline perfusion, only lipid dem-

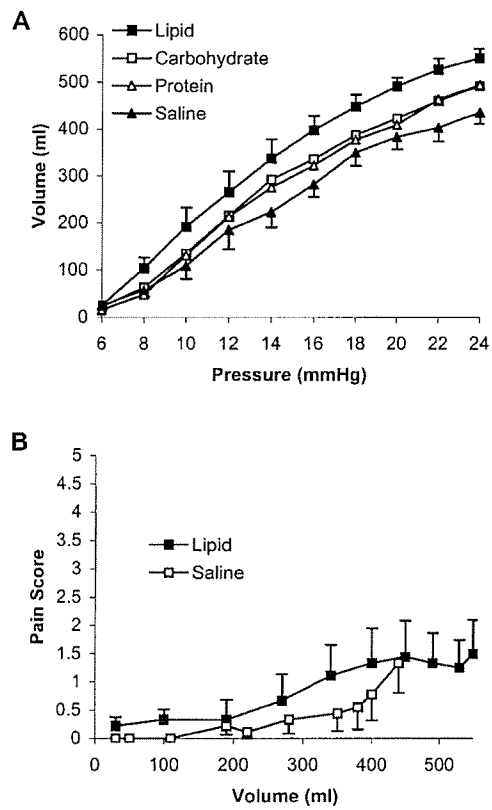
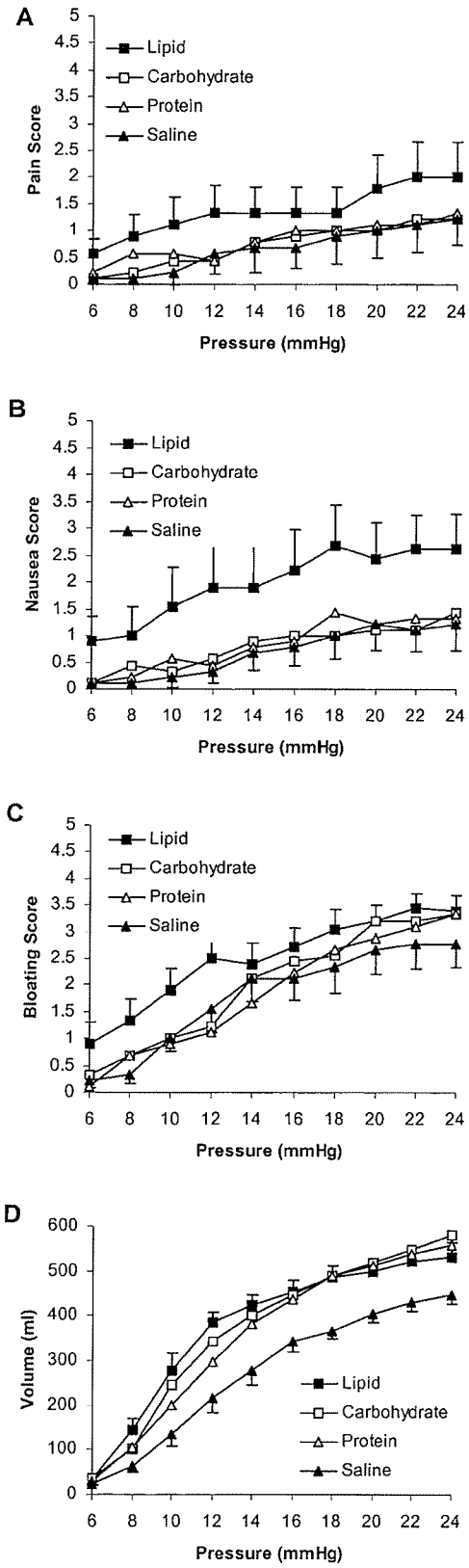


Fig. 2. Effect of duodenal nutrient perfusion on distal gastric pressure-volume relationship. *A*: distal gastric volume is shown as a function of pressure during duodenal perfusion with lipid, carbohydrate, and protein at 1.5 kcal/min and saline (2.2 ml/min). Only lipid increased distension-induced volume compared with saline ($P = 0.0001$). *B*: mean pain scores as a function of volume are higher during lipid perfusion at 1.5 kcal/min compared with saline (2.2 ml/min), but the difference is not statistically significant ($P = 0.088$). Standard error bars are shown for lipid and saline scores. For clarity, standard errors for carbohydrate and protein are omitted.



onstrated a significant effect (P = 0.0001). Therefore, symptoms as well as distal gastric volume during isobaric distension were increased significantly by duodenal lipid perfusion, but not by carbohydrate or protein, at 1.5 kcal/min.

To investigate whether the effect of lipid perfusion at 1.5 kcal/min on symptoms could be explained by lipid's effect on the distal gastric pressure-volume relationship, symptoms were assessed as a function of distal gastric volume rather than distending pressure. With volume as a predictor, differences in symptom scores among the perfusing solutions were no longer significant for nausea or bloating, and differences in pain scores approached but did not reach statistical significance (P = 0.088). This is illustrated in Fig. 2*B*, which shows pain scores as a function of distending volume for lipid and saline. Although pain scores were higher for lipid, the difference between lipid and saline was less marked than when symptoms were analyzed as a function of pressure (Fig. 1*A*) and was not statistically significant. Therefore, the principal factor accounting for increases in distension-induced symptoms with lipid at 1.5 kcal/min is the increased distal gastric volume achieved at each distending pressure during lipid compared with saline perfusion.

As with the lower perfusion rate of 2.2 ml/min, distension-induced symptom scores differed among duodenal solutions at the higher rate of 4.4 ml/min (3 kcal/min for nutrients) for all three symptoms when analyzed as a function of distending pressure (Fig. 3, *A–C*): pain (P = 0.020), nausea (P = 0.0073), and bloating (P = 0.013). When comparing individual solutions, distensions during duodenal lipid perfusion led to more intense pain (P = 0.0051), nausea (P = 0.0023), and bloating (P = 0.0030) than during saline perfusion.

As shown by the curves in Fig. 3*D*, distal gastric pressure-volume relationships during duodenal perfusion differed among perfusing solutions at 4.4 ml/min (P = 0.0001). Volumes during saline perfusion were lower than during lipid (P = 0.0001), carbohydrate (P = 0.0001), and protein (P = 0.0003) perfusion. In contrast to the results at the lower perfusion rate, however, significant differences among solutions at 4.4 ml/min were found when symptoms were modeled as a function of volume: pain (P = 0.045), nausea (P = 0.0001), and bloating (P = 0.044). These differences were smaller than with symptoms analyzed as a function of pressure. With volume as a predictor, symptom scores during lipid compared with saline perfusion were higher for pain (P = 0.030) and nausea (P =

Fig. 3. Increases in symptoms and volumes induced by distal gastric distension during duodenal nutrient perfusion at 3 kcal/min. Mean symptom scores and distal gastric volumes are shown as a function of pressure during duodenal perfusion with lipid, carbohydrate, protein, and saline (4.4 ml/min). Lipid led to greater distension-induced symptom scores than saline for pain (*A*; P = 0.0051), nausea (*B*; P = 0.0023), and bloating (*C*; P = 0.0030). Volumes during saline perfusion were lower than during lipid (P = 0.0001), carbohydrate (P = 0.0001), and protein (P = 0.0003) perfusion (*D*). Standard error bars are shown for lipid and saline scores and volumes. For clarity, standard errors for carbohydrate and protein are omitted.

0.0001), but the difference for bloating was not significant. However, bloating scores for lipid were higher than those for protein (P = 0.018) and carbohydrate (P = 0.031). Therefore, at 3 kcal/min following 1.5 kcal/min, lipid has an effect on distal gastric perception that is independent of its effect on the distal gastric pressure-volume relationship. This can be appreciated by noting the very similar effect of all three nutrients at the higher perfusion rate on the distal gastric pressure-volume relationship (Fig. 3*D*) and the unique effect of lipid on symptoms (Fig. 3, *A–C*).

Effect of granisetron on nutrient-induced sensitization and pressure-volume relationship. For all perfusing solutions, symptoms during distal gastric distension were not blunted by granisetron treatment compared with placebo. Figure 4 shows the intensity of symptoms during duodenal lipid or saline perfusion at 2.2 ml/min, each following treatment with either granisetron or placebo. During lipid perfusion, neither pain, nausea, nor bloating scores differed between granisetron and placebo treatments. Similarly, no symptom was affected by granisetron compared with placebo during saline perfusion. Thus the increased symptomatic response to isobaric distal gastric distension induced by duodenal lipid is not modified by granisetron treatment, suggesting that the lipid effect is not dependent on 5-HT_3 receptors. Furthermore, the lack of effect of granisetron during perfusion with saline as well as the three nutrients implies that perception of distal gastric distension does not rely on 5-HT_3-dependent pathways.

To determine whether the lack of effect of granisetron on symptoms could be due to changes in distal gastric wall properties (with an analgesic effect counteracted by increased volume at a given pressure), pressure-volume relationships were compared for each perfusing solution after granisetron or placebo treatment. As illustrated in Fig. 5, granisetron had no effect on distal gastric distending volume during lipid or saline perfusion at 2.2 ml/min. Similarly, granisetron did not alter distending volume during carbohydrate or protein perfusion. This lack of effect of granisetron suggests that its failure to alter perceptual responses is not due to granisetron-induced changes in distal gastric wall properties.

As with the lower perfusion rate of 2.2 ml/min, granisetron had no effect on distension-induced symptoms or distal gastric volumes during perfusions at 4.4 ml/min (data not shown).

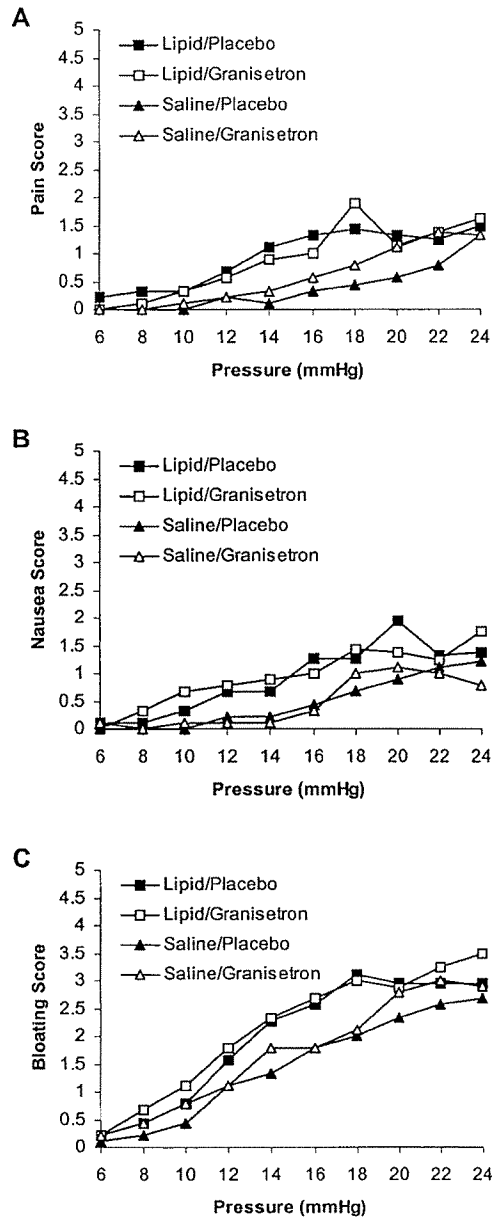


Fig. 4. Lack of effect of granisetron on symptoms induced by distal gastric distension and duodenal nutrient perfusion. Mean symptom scores are shown as a function of distending pressure during duodenal lipid perfusion at 1.5 kcal/min and saline perfusion (2.2 ml/min) after intravenous administration of granisetron at 10 μg/kg or placebo. Pain scores (*A*), nausea scores (*B*), and bloating scores (*C*) did not differ with granisetron or placebo during lipid or saline perfusion. For clarity, standard error bars are omitted.

DISCUSSION

We have found that symptoms induced by isobaric distal gastric distension in healthy humans are intensified by duodenal nutrient perfusion in a nutrient-specific fashion, with lipid increasing pain, nausea, and bloating and carbohydrate and protein producing no significant effect. Lipid-induced distal gastric relaxation allows larger volumes to be achieved by distension at each fixed pressure. The increase in distension-induced symptoms during lipid perfusion is explained primarily by the effect of lipid on the distal gastric pressure-volume relationship. However, at the higher caloric perfusion rate, lipid displays a volume-independent as well as a volume-dependent effect. The lack of effect of granisetron on symptoms and on the distal gastric pressure-volume relationship during all perfusions suggests that pathways mediating perception of distal gastric distension, as well as the effects of lipid, are not dependent on 5-HT_3 receptors.

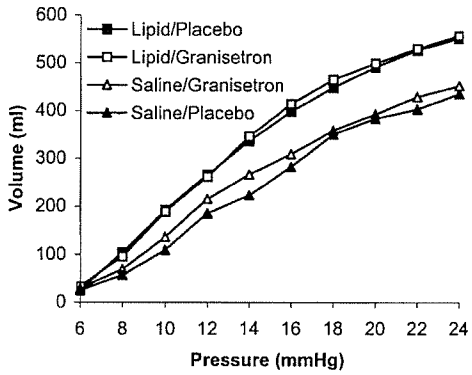


Fig. 5. Effect of granisetron on distal gastric pressure-volume relationship. Volume is shown as a function of pressure during duodenal lipid perfusion at 1.5 kcal/min and saline perfusion (2.2 ml/min) after intravenous administration of granisetron (10 μg/kg) or placebo. Volume did not differ with granisetron or placebo during either perfusion. For clarity, standard error bars are omitted.

Most studies of gastric perception have concentrated on the proximal stomach, including investigations reporting visceral hypersensitivity in NUD (4, 15, 18, 22, 23, 29, 32). Some meal-related dyspeptic symptoms may originate in the proximal stomach, such as early satiety in NUD patients with impaired proximal accommodation to a meal (30). However, patients with NUD may exhibit abnormal meal distribution to the distal stomach (9, 21, 33), healthy subjects experience more intense symptoms during distal compared with proximal gastric distension (17), and postprandial fullness is related to antral distension in normal subjects (12). Therefore, we sought to investigate the effect of nutrients on symptoms induced by distal gastric distension.

The increase in distal gastric volume with isobaric distension seen during lipid perfusion in our study reflects a decrease in tone, or relaxation, that can be explained by enterogastric reflexes that inhibit distal gastric motor activity (10). Isobaric gastric distension has been shown to produce greater symptoms, as well as larger volumes, during glucagon-induced gastric relaxation compared with saline treatment, pointing to the importance of gastric tone in determining symptom intensity during isobaric distension (26). A recent investigation by Distrutti et al. (5) with a novel tensostat, which produces isotonic distensions, demonstrated that gastric wall tension is the primary determinant of perception of nonnociceptive distension. Although we did not control tension during distensions, the higher distending volumes during lipid perfusion would result in higher wall tension compared with the lower distending volumes during saline perfusion at the same distending pressure ($T = P \cdot R/2$ for a sphere, where T = wall tension, P = pressure, and R = radius, which is determined by volume). This higher wall tension could contribute to the higher symptom scores reported during lipid perfusion, including the noxious sensations of pain and nausea.

By not finding differences among duodenal solutions at 2.2 ml/min in our analysis of symptoms as a function of distending volume, we have failed to show a sensitizing effect of nutrient on the distal stomach that is independent of the change in the pressure-volume relationship. Feinle et al. (7) have shown that duodenal perfusion with lipid at 2 kcal/min leads to symptoms at lower proximal gastric distending pressures without volume increases compared with saline perfusion, which can be interpreted as sensitization of the proximal stomach by lipid. In contrast, lipid at 1 kcal/min leads to symptoms at lower pressures but also higher volumes (7), making it difficult to distinguish sensitization from effects on tone. In our study, the 1.5 kcal/min perfusion rate falls between the rates used by Feinle et al. and may not be high enough to demonstrate sensitization. The higher perfusion rate of 3 kcal/min in our study did demonstrate higher pain and nausea scores for lipid compared with saline after accounting for changes in the pressure-volume relationship. This must be interpreted in light of the fact that each solution was perfused at 4.4 ml/min following perfusion at 2.2 ml/min and sensory testing, so that lipid at 4.4 ml/min (following lipid at 2.2 ml/min) may not be strictly comparable to saline at 4.4 ml/min (following saline at 2.2 ml/min). Nonetheless, the differences at the higher dose reflect overall differences among the solutions in the context of escalating perfusion rates. Thus lipid increases symptoms induced by isobaric distal gastric distension by two mechanisms: modification of the distal gastric pressure-volume relationship at the lower and higher perfusion rates and a nutrient effect independent of this modification at the higher perfusion rate.

Although a change in the distal gastric pressure-volume relationship is primarily responsible for the greater distension-induced symptoms we observed during lipid perfusion, the independent nutrient effect seen at 3 kcal/min suggests possible interactions between visceral afferent signals from duodenal chemoreceptors and gastric mechanoreceptors. This type of interacting input to the central nervous system has been recognized in animals, for example, in convergence onto brain stem neurons of inputs from gastric distension and portal vein glucose infusion in rats (1) and convergent esophageal and gastric mechanoreceptor inputs onto vagal motor neurons in ferrets (3). The precise site of interaction between duodenal and gastric afferents in humans remains to be determined.

We found no effect of granisetron on pressure-volume relationships or on symptoms induced by distal gastric distension during duodenal perfusion with nutrients or saline. Ondansetron, another 5-HT_3 receptor antagonist, has been reported to blunt symptoms induced by duodenal lipid perfusion and proximal gastric distension (8). The reasons for these different results may relate to differences between the proximal and distal stomach and to details of experimental design but remain to be clarified. We are not aware of studies exploring differences in 5-HT_3 receptor distribution between the proximal and distal human stomach. Given the well-recognized contrasting physiological properties of the proximal and distal stomach (13), it is

conceivable that receptors involved in visceral perception or nociception, which may include 5-HT receptors, may be differentially distributed in the two regions or their afferent pathways. Animal studies of gastric 5-HT_3 receptors center on motor phenomena but highlight differences between the proximal and distal stomach (27, 28, 31). If 5-HT release participates in mediating sensation and nociception during gastric distension and duodenal nutrient perfusion, region-specific differences in afferent pathways, analogous to region-specific differences in motor responses to 5-HT, may explain the contrasting effects of 5-HT_3 antagonists on symptom perception in the proximal and distal stomach. Although we cannot rule out an effect of granisetron at higher doses, dose seems an unlikely explanation for the lack of pharmacological effect, given that we administered a dose shown to treat chemotherapy-induced nausea (11) as well as blunt nausea and gastric dysrhythmias evoked by supraphysiological nutrient perfusion (16). Notably, the previous study with ondansetron also used a standard clinical dose (8).

An important difference between our study and the investigation of ondansetron and fundic sensitivity to distension and lipid concerns the methods used for gastric distension. In contrast to sustained progressive distensions at 100 ml/min (8), we performed minute-long intermittent isobaric distensions at increasing pressures with an inflation rate of 25 ml/s, separated by complete deflations. The symptomatic responses to ramp compared with rapid intermittent distensions may differ (14), and the apparent differences in the roles of 5-HT_3 receptors as mediators of symptoms in the two studies may relate to stimulation of different mechanoreceptors or sensory pathways with the two modes of distension.

In conclusion, among the major nutrient classes, only lipid increases the pain, nausea, and bloating induced by distal gastric isobaric distension. At the lower caloric perfusion rate, this effect is explained by lipid-induced distal gastric relaxation. At the higher rate, the effect is explained in part by lipid-induced relaxation, but an additional volume-independent effect becomes evident. In addition, perception of distal gastric distension during duodenal saline or nutrient perfusion does not rely on 5-HT_3-dependent pathways. These findings contribute to our understanding of meal-related functional gastrointestinal symptoms.

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REFERENCES

1. **Appia F, Ewart WR, Pittam BS, and Wingate DL.** Convergence of sensory information from abdominal viscera in the rat brain stem. *Am J Physiol Gastrointest Liver Physiol* 251: G169–G175, 1986.
2. **Barbara L, Camilleri M, Corinaldesi R, Crean GP, Heading RC, Johnson AG, Malagelada JR, Stanghellini V, and Wienbeck M.** Definition and investigation of dyspepsia. Consensus of an international ad hoc working party. *Dig Dis Sci* 34: 1272–1276, 1989.
3. **Blackshaw LA.** Gastro-oesophageal afferent and serotonergic inputs to vagal efferent neurones. *J Auton Nerv Syst* 49: 93–103, 1994.
4. **Bradette M, Pare P, Douville P, and Morin A.** Visceral perception in health and functional dyspepsia. Crossover study of gastric distension with placebo and domperidone. *Dig Dis Sci* 36: 52–58, 1991.
5. **Distrutti E, Azpiroz F, Soldevilla A, and Malagelada JR.** Gastric wall tension determines perception of gastric distention. *Gastroenterology* 116: 1035–1042, 1999.
6. **Feinle C, D'Amato M, and Read NW.** Cholecystokinin-A receptors modulate gastric sensory and motor responses to gastric distension and duodenal lipid. *Gastroenterology* 110: 1379–1385, 1996.
7. **Feinle C, Grundy D, and Read NW.** Effects of duodenal nutrients on sensory and motor responses of the human stomach to distension. *Am J Physiol Gastrointest Liver Physiol* 273: G721–G726, 1997.
8. **Feinle C and Read NW.** Ondansetron reduces nausea induced by gastroduodenal stimulation without changing gastric motility. *Am J Physiol Gastrointest Liver Physiol* 271: G591–G597, 1996.
9. **Gilja OH, Hausken T, Wilhelmsen I, and Berstad A.** Impaired accommodation of proximal stomach to a meal in functional dyspepsia. *Dig Dis Sci* 41: 689–696, 1996.
10. **Hasler WL.** The physiology of gastric motility and gastric emptying. In: *Textbook of Gastroenterology*, edited by Yamada T. Philadelphia: Lippincott, Williams and Wilkins, 1999, p. 188–215.
11. **Jantunen IT, Kataja VV, and Muhonen TT.** An overview of randomised studies comparing 5-HT_3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. *Eur J Cancer* 33: 66–74, 1997.
12. **Jones KL, Doran SM, Hveem K, Bartholomeusz FD, Morley JE, Sun WM, Chatterton BE, and Horowitz M.** Relation between postprandial satiation and antral area in normal subjects. *Am J Clin Nutr* 66: 127–132, 1997.
13. **Kelly KA.** Gastric emptying of liquids and solids: roles of proximal and distal stomach. *Am J Physiol Gastrointest Liver Physiol* 239: G71–G76, 1980.
14. **Khan MI, Read NW, and Grundy D.** Effect of varying the rate and pattern of gastric distension on its sensory perception and motor activity. *Am J Physiol Gastrointest Liver Physiol* 264: G824–G827, 1993.
15. **Klatt S, Beock W, Rentschler J, Beckh K, and Adler G.** Effects of tropisetron, a 5-HT_3 receptor antagonist, on proximal gastric motor and sensory function in nonulcer dyspepsia. *Digestion* 60: 147–152, 1999.
16. **Koshy S, Bennett T, Hooper F, Woods M, Owyang C, and Hasler W.** Intestinal nutrient chemoreceptor-evoked gastric slow wave dysrhythmias: mediation by serotonergic and muscarinic pathways (Abstract). *Dig Dis Sci* 41: 1880, 1996.
17. **Ladabaum U, Koshy SS, Woods ML, Hooper FG, Owyang C, and Hasler WL.** Differential symptomatic and electrogastrographic effects of distal and proximal human gastric distension. *Am J Physiol Gastrointest Liver Physiol* 275: G418–G424, 1998.
18. **Lemann M, Dederding JP, Flourie B, Franchisseur C, Rambaud JC, and Jian R.** Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. *Dig Dis Sci* 36: 1249–1254, 1991.
19. **Locke GR III.** The epidemiology of functional gastrointestinal disorders in North America. *Gastroenterol Clin North Am* 25: 1–19, 1996.
20. **Malagelada JR.** Functional dyspepsia. Insights on mechanisms and management strategies. *Gastroenterol Clin North Am* 25: 103–112, 1996.
21. **Marzio L, Falcucci M, Grossi L, Ciccaglione FA, Malatesta MG, Castellano A, and Ballone E.** Proximal and distal gastric distension in normal subjects and *H. pylori*-positive and -negative dyspeptic patients and correlation with symptoms. *Dig Dis Sci* 43: 2757–2763, 1998.

22. **Mearin F, Cucala M, Azpiroz F, and Malagelada JR.** The origin of symptoms on the brain-gut axis in functional dyspepsia. *Gastroenterology* 101: 999–1006, 1991.
23. **Mertz H, Walsh JH, Sytnik B, and Mayer EA.** The effect of octreotide on human gastric compliance and sensory perception. *Neurogastroenterol Motil* 7: 175–185, 1995.
24. **Mesquita MA, Thompson DG, Troncon LE, D'Amato M, Rovati LC, and Barlow J.** Effect of cholecystokinin-A receptor blockade on lipid-induced gastric relaxation in humans. *Am J Physiol Gastrointest Liver Physiol* 273: G118–G123, 1997.
25. **Meyer JH, Hlinka M, Kao D, Lake R, MacLaughlin E, Graham LS, and Elashoff JD.** Gastric emptying of oil from solid and liquid meals. Effect of human pancreatic insufficiency. *Dig Dis Sci* 41: 1691–1699, 1996.
26. **Notivol R, Coffin B, Azpiroz F, Mearin F, Serra J, and Malagelada JR.** Gastric tone determines the sensitivity of the stomach to distention. *Gastroenterology* 108: 330–336, 1995.
27. **Plaza MA, Arruebo MP, and Murillo MD.** 5-Hydroxytryptamine induces forestomach hypomotility in sheep through 5-HT_4 receptors. *Exp Physiol* 81: 781–790, 1996.
28. **Plaza MA, Arruebo MP, and Murillo MD.** Effects of 5-hydroxytryptamine agonists on myoelectric activity of the forestomach and antroduodenal area in sheep. *J Pharm Pharmacol* 48: 1302–1308, 1996.
29. **Salet GA, Samsom M, Roelofs JM, van Berge Henegouwen GP, Smout AJ, and Akkermans LM.** Responses to gastric distension in functional dyspepsia. *Gut* 42: 823–829, 1998.
30. **Tack J, Piessevaux H, Coulie B, Caenepeel P, and Janssens J.** Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 115: 1346–1352, 1998.
31. **Tamura T, Sano I, Satoh M, Mizumoto A, and Itoh Z.** Pharmacological characterization of 5-hydroxytryptamine-induced motor activity (in vitro) in the guinea pig gastric antrum and corpus. *Eur J Pharmacol* 308: 315–324, 1996.
32. **Thumshirn M, Camilleri M, Choi MG, and Zinsmeister AR.** Modulation of gastric sensory and motor functions by nitrergic and α_2-adrenergic agents in humans. *Gastroenterology* 116: 573–585, 1999.
33. **Troncon LE, Bennett RJ, Ahluwalia NK, and Thompson DG.** Abnormal intragastric distribution of food during gastric emptying in functional dyspepsia patients. *Gut* 35: 327–332, 1994.