Modulation of gastric distension-induced sensations by small intestinal receptors

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Feinle, Christine, David Grundy, and Michael Fried. Modulation of gastric distension-induced sensations by small intestinal receptors. Am J Physiol Gastrointest Liver Physiol 280: G51–G57, 2001.—Duodenal lipid exacerbates gastrointestinal sensations during gastric distension. Using luminal application of the local anesthetic benzocaine, we investigated the role of intestinal receptors in the induction of these sensations. Nine healthy subjects were studied on five occasions, during which isotonic saline or 20% lipid (2 kcal/min), combined with (duodenal or jejunal) 0.75% benzocaine or vehicle at 2.5 ml/min, was infused intraduodenally before and during gastric distension. Intragastric pressures and volumes, gastrointestinal sensations, and plasma CCK levels were determined. Duodenal lipid combined with vehicle increased gastric volume (in ml: saline, −10 ± 18; lipid/vehicle, 237 ± 30) and plasma CCK [mean levels (pmol/l): saline, 2.0 ± 0.2; lipid/vehicle, 8.0 ± 1.6] and, during distensions, induced nausea (scores: saline, 3 ± 2; lipid/vehicle, 58 ± 19) and decreased pressures at which fullness and discomfort occurred. Duodenal but not jejunal benzocaine attenuated the effect of lipid on gastric volume, plasma CCK, and nausea during distension (135 ± 38 and 216 ± 40 ml, 4.6 ± 0.6 pmol/l and not assessed, and 37 ± 12 and 64 ± 21 for lipid + duodenal benzocaine and lipid + jejunal benzocaine, respectively) and on pressures for sensations. In conclusion, intestinal receptors modulate gastrointestinal sensations associated with duodenal lipid and gastric distension. There is also the potential for local neural mechanisms to regulate CCK release and thereby reduce afferent activation indirectly.

duodenal lipid; nausea; cholecystokinin; intestinal receptors; benzocaine

The mechanisms by which nutrients, and in particular fat, modulate gastrointestinal sensations and symptoms induced by gastric distension remain unclear. CCK-A and serotonin (5-HT3) receptors are involved in the effects of duodenal lipid on gastrointestinal sensations during gastric distension (5, 7), suggesting a modulatory role for small intestinal receptors responsive to CCK and 5-HT. The involvement of small intestinal mucosal receptors can be investigated by transiently blocking their activation with a local anesthetic. Previously, blockade of mucosal receptors by local anesthesia was used in the esophagus and the rectum to increase thresholds for perception and discomfort during distension of the respective organs (4, 15, 22). In the rat, application of local anesthetics to the small intestinal mucosa was shown to block the responsiveness of vagal afferent fibers to CCK (18) and CCK secretion in response to luminal peptone (16). In the present study, we therefore sought to investigate the role of intestinal receptors in the modulation of sensations induced by gastric distension and duodenal lipid in humans. This was achieved by topically applying anesthetic to the intestinal mucosa. We hypothesized that the local anesthetic benzocaine would reduce the symptomatic response to gastric distension and duodenal lipid by reducing activation of receptors sensitive to intestinal lipid without influencing the release of CCK.

MATERIALS AND METHODS

Subjects

The experiments were carried out in nine healthy subjects (3 females and 6 males) aged 21–48 yr. The subjects were of normal weight for height [body mass index: 22.1 (range 17.9–24.9) kg/m2], were nonsmokers, were not on any medication, and were without any history of gastrointestinal dis-

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ease. The study protocol was approved by the Ethics Committee of the University Hospital Zurich, Switzerland, and all subjects gave their written informed consent to take part in the study.

**Experimental Design**

Each subject was studied on five separate occasions. The studies were performed in a single-blind, placebo-controlled cross-over fashion in randomized order and at least 1 wk apart from each other. On four of the five occasions, the stomach was distended while the duodenum was perfused with either isotonic saline or a lipid emulsion (20% Intralipid, 2 kcal/ml, 350 mosmol/kg; Pharmacia, Dübendorf, Switzerland) and either the local anesthetic benzocaine (Subcutin N, benzocaine 0.75% dissolved in 9.25% polyoxy1-40-hydrogenated castor oil, 20% propylene glycol, 70% purified water; Ritsert, Eberbach, Germany) or vehicle alone. Benzocaine is highly bioactive and acts primarily on terminal nerve endings and intraepithelial receptors but has no significant effect on subepithelial structures or nerve trunks. Once absorbed, benzocaine is degraded immediately, and systemic effects are rare (1). According to a previous study (4), detectable plasma levels occurred no earlier than 10 min after commencement of the benzocaine administration (into the esophagus). Levels were reported to increase over the infusion period but were not related to the benzocaine dose administered. The maximum plasma concentration found was 41.3 ng/ml in one subject, with a high interindividual variability. Plasma benzocaine levels were not measured in our study. Venous blood samples for CCK were taken, and gastrointestinal sensations were assessed at regular intervals throughout the experiments. On the fifth occasion, the lipid emulsion was infused into the duodenum while benzocaine was administered through a second lumen 30 cm distal to the duodenal orifice (i.e., into the jejunum). This experimental condition was introduced to investigate whether the effects of benzocaine were local or could be obtained by delivering benzocaine distant to the site of the lipid infusion. No blood was taken on this occasion. Each study took ~4 h. During the lipid infusion, an energy load of ~150 kcal was administered to each subject. Before inclusion in the study, each subject was required to visit the laboratory once. The purpose of this visit was to familiarize the subjects with the requirements of the study, the gastric (barostat) tube, the sensations perceived during gastric distensions, and the symptom questionnaires. All subjects tolerated the tube well and were included in the study.

**Gastric and Duodenal Tubes**

The subjects were allowed a light breakfast (a cup of tea or coffee, 2 slices of toast, 20 g of margarine, and 30 g of jam) before 8:00 AM but no food or drinks except water thereafter, and they arrived at the unit at lunch time (12:00 PM). A single-lumen polyvinyl tube [OD 2.8 mm (8 Fr), length 109 cm; Merck Biomaterial, Alton, UK] was introduced through the nose into the duodenum. The infusion port of the tube was situated 5 cm from its tip. The position of the port, ~15 cm distal to the pylorus, was verified fluoroscopically. For the fifth study condition, an intestinal tube was purpose built. A commercially available enteral feeding tube (for jejunal administration of benzocaine) was attached to the polyvinyl tube used for the duodenal infusion (see above). The first tube was 30 cm longer than the latter tube. Once the respective tube was in position, the subjects swallowed a flexible single-lumen gastric tube (OD 3.5 mm, ID 2.8 mm; Tygon Tubing, Upchurch Scientific, Oak Harbor, WA). The tube had an ultrathin flaccid polyethylene bag (capacity 1,100 ml) tied onto its distal end. Immediately outside the subject’s body, the proximal end of the tube was connected via a three-way tap to the measurement and balloon ports of a gastric barostat (Distender Series II; G & J Electronics, Willowdale, ON, Canada). Once the tube was in the stomach, the bag was unfolded by inflating it with air and positioned in the fundus of the stomach by gently pulling the tube back until its passage was restricted by the lower esophageal sphincter and then pushing back in by 3 cm. To prevent the tubes from moving during the study, they were taped to the side of the face. The functioning of the barostat was previously described in detail (2). In brief, the barostat is capable of measuring changes in gastric volume at a fixed pressure. Thus if the gastric wall relaxes air is injected into the gastric bag to maintain the pressure, whereas air is withdrawn if the stomach contracts. In addition, distensions of the stomach can be carried out.

**Protocol**

At 1:30 PM, the subjects were comfortably seated in an upright position on a hospital bed, and the study began. The experimental protocol is shown in Fig. 1. At first, the minimal distending pressure (MDP, defined as the intrabag pressure that first results in a bag volume of 30 ml of air and is necessary to overcome intra-abdominal pressure) was determined by gradually increasing intragastric pressure in steps of 1 mmHg/min. Intrabag pressure was then set at MDP, and
the corresponding volume (~30 ml) was recorded. Once a stable recording had been obtained for 10 min, duodenal infusion of either benzocaine or the vehicle solution was introduced (infusion period 1) as a single bolus of 10 ml and continued at a rate of 2.5 ml/min for the remainder of the study. A similar protocol was followed during the fifth experimental condition, when benzocaine was infused into the jejunum. Thirty minutes after the start of this infusion, administration of either lipid or saline commenced at a rate of 1 ml/min (infusion period 2) and was also continued for the duration of the study. During jejunal infusion of benzocaine, only lipid, but not saline, was infused intraduodenally. Thirty minutes after the start of the second (saline or lipid) infusion, an isobaric distension was carried out. For this purpose, 1-mmHg stepwise increases in intrabag pressure (starting at MDP) were executed while the volumes at the different pressure steps were monitored. Each step was maintained for 1 min. We chose a stepwise increasing distension protocol for three main reasons. First, this protocol most closely mimics gastric distension during food ingestion. Second, because the subjects were not explicitly told that their stomachs would be distended but were informed that during the study gastric pressures and volumes would be assessed or manipulated, the subjects were not able to anticipate when or if a distension was carried out. In addition, we used this distension protocol previously (6) and showed that perception data from repeated distensions were reproducible. Third, we feared that random exposure of patients to painfully high distension stimuli (as may be the case with random distension protocols) might lead to anxiety and hypervigilance, resulting in a reduction in sensory thresholds (11).

Assessment Of Sensations During Infusions and Distensions

Immediately before the start of the (duodenal or jejunal) benzocaine or vehicle infusion and at t = 0, 15, and 30 min during the lipid or saline infusion, the subjects rated sensations of hunger, fullness, nausea, and abdominal bloating on visual analog scales (VAS). The VAS consisted of a 10-cm line, with 0 meaning “sensation not present” and 10 “strongest sensation ever felt.” During the distension, the subjects were asked to report when they first perceived a sensation of epigastric fullness and when they first perceived epigastric discomfort. The sensations were shown in previous studies to be reported reproducibly during gastric distensions (6, 14). In addition, the subjects rated the severity of nausea at the end of the distension on VAS. As soon as the subjects reported discomfort, the distension process was discontinued and the air was removed from the bag.

Blood Samples

To assess changes in plasma levels of CCK, venous blood samples were collected from a catheter inserted in a forearm vein immediately before the start of the duodenal benzocaine or vehicle infusion (baseline sample), at t = 0, 15, and 30 min during the lipid or saline infusion, and at the beginning and the end of the distension (Fig. 1) in iced EDTA tubes, centrifuged immediately after the experiment at 2°C for 20 min, and then stored at −20°C until extraction. Plasma CCK was measured by a sensitive and specific radioimmunoassay as previously described (12, 13). The antibody used (T204) binds to all biologically active CCK peptides containing sulfated tyrosine with almost equal affinity. On a molar basis, sulfated gastrins cross-react <2% in the assay, whereas no cross-reactivity is found with unsulfated gastrins or structurally unrelated peptides. The detection limit of the assay is 0.5 pmol/l plasma. The intra-assay variation ranges from 4.6 to 11.5% in the steep part of the standard curve, and the inter-assay variation ranges from 11.3 to 26.1%.

Data Analysis

Gastric volume changes. As an index for the changes in gastric relaxation during the different duodenal infusions, the volume readings at MDP obtained during the baseline recording (10 min) and during the last 15 min of infusion periods 1 (benzocaine or vehicle) and 2 (lipid or saline) were each averaged. Changes in gastric volume between baseline and the different infusions were obtained by calculating the difference in mean volumes between infusion period 1 and baseline and between infusion period 2 and infusion period 1.

Gastric distensions. During the distension, intragastric volumes during consecutive pressure steps were calculated by averaging the volume readings obtained during the last 30 s of each pressure step. These data were then used to construct pressure-volume profiles for the different experimental conditions. Differences in profiles between experimental conditions were evaluated by comparing intragastric volumes at a certain intragastric pressure. Because the end points of the curves varied from subject to subject, the highest common pressure tolerated by an individual during all five conditions was chosen, and the volumes at this pressure were taken for analysis. The outcome of the statistical analysis was not influenced by using different end points in individual subjects because each subject acted as his or her own control. In addition, areas under the curves (AUCs) of the pressure-volume profiles were calculated. We have used AUCs, volumes at a certain pressure, or slopes of the curves previously to characterize the pressure-volume curves during gastric distensions (Refs. 5–7; unpublished data). The slopes of the pressure-volume curve rely on the linearity of the curve. If the curve is linear only over a short distance, and if this does not occur on the same region of the curve during all experimental conditions, the results are difficult to interpret. On the other hand, volumes at a certain pressure reflect how much individual curves are separated from each other, given that the curves do not cross each other with increasing pressure, which was never the case in our study. We therefore prefer to use AUCs or volumes at certain pressures to characterize our pressure-volume profiles.

Sensory responses. Differences between VAS scores obtained at t = 30 min and t = 0 min and at baseline were used to compare the effects of the different infusions on sensations in the absence of gastric distension. During gastric distension, volumes and pressures required to induce fullness and discomfort were calculated for the five experimental conditions, and the intensity of nausea as rated by the subjects on VAS was evaluated.

Statistical Analysis

Data were analyzed by ANOVA followed by post hoc analysis and are presented as means ± SE. Probability values of P < 0.05 were regarded as statistically significant.

RESULTS

Responses to Duodenal Infusions

Gastric volume changes. Duodenal or jejunal administration of vehicle or benzocaine alone did not change gastric volume compared with baseline (Fig. 2). After duodenal infusion of vehicle, duodenal lipid increased gastric volume compared with saline (P < 0.05), indicating a decrease in gastric tone. Administration of
benzocaine into the duodenum before lipid infusion reduced the relaxatory effect of lipid by ~50% (P < 0.05). Administration of benzocaine into the jejunum did not alter the effects of duodenal lipid on gastric volume.

Scores for sensations. No effect of the different duodenal infusions on the scores for hunger, fullness, bloating, or nausea before gastric distensions commenced was noted.

Responses to Duodenal Infusions Combined With Gastric Distension

Gastric pressure/volume responses. No differences were observed between saline given with vehicle or benzocaine, as indicated by AUCs and the volumes at the highest common pressure (Table 1). Duodenal lipid infusion, whether given with vehicle or duodenal or jejunal benzocaine, increased intragastric volume at a given pressure to a similar degree compared with duodenal saline infusion (P < 0.05).

Gastric perception of distension. Benzocaine itself did not have an effect on gastric perception, because there were no differences between duodenal vehicle and benzocaine during saline infusion (Table 1). When duodenal lipid was given with vehicle, fullness and discomfort occurred at lower intragastric pressures but at volumes similar to those during saline infusion. When lipid was given with duodenal benzocaine, sensations were reported at higher intragastric pressures and volumes than during lipid administration with vehicle (P < 0.05). Jejunal administration of benzocaine did not alter the effects of lipid on gastric perception during distension.

Intensity of nausea during distension. When saline was given with vehicle or benzocaine, nausea scores on the VAS were very low (Fig. 3). During infusion of lipid with vehicle or jejunal benzocaine, however, the intensity of nausea was significantly increased (P < 0.05). Duodenal benzocaine reduced the severity of nausea by 36% (P < 0.05).

Plasma CCK Response

Duodenal infusion of vehicle or benzocaine with or without isotonic saline did not increase plasma CCK levels (Fig. 4). When given with vehicle, lipid significantly raised plasma CCK levels (P < 0.05). Prior administration of benzocaine into the duodenum prevented the initial peak of plasma CCK and, overall, reduced plasma CCK levels during the lipid infusion period. Gastric distension did not cause a further rise in plasma CCK during any experimental condition. Although plasma CCK levels appeared markedly lower during distension, these levels were not significantly different from those during saline infusion.

Table 1. Parameters characterizing pressure-volume profiles and sensory thresholds during isobaric gastric distension

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<th>V-S</th>
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<td>AUC, ml-mmHg</td>
<td>739±83</td>
<td>713±97</td>
<td>1,534±146*</td>
<td>1,364±129†</td>
<td>1,405±123</td>
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| Volume at highest common pressure, ml | 340±38 | 294±31 | 494±49* | 458±39† | 451±37
| Volumes at fullness and discomfort, ml | 324±39 | 343±38 | 352±43 | 473±44‡ | 339±34
| Fullness       | 432±37 | 466±40 | 501±45 | 600±46‡ | 460±32
| Discomfort     | 6.5±0.6 | 6.1±0.7 | 2.4±0.4* | 4.6±0.5‡ | 2.7±0.4
| Pressures at fullness and discomfort, mmHg above MDP | 8.3±0.9 | 8.3±0.8 | 5.2±0.8* | 6.9±0.7‡ | 5.0±0.6

Data are means ± SE. S, saline; L, lipid; V, vehicle; B, benzocaine; JB, jejunal benzocaine. AUC, area under the curve, MDP, minimal distending pressure. Statistically significant differences (P < 0.05): *V-L vs. V-S, †B-L vs. B-S, ‡B-L vs. V-L.
during gastric distension when lipid was combined with benzocaine compared with vehicle, the differences just failed to reach statistical significance ($P = 0.06$).

DISCUSSION

In this study, we demonstrated that benzocaine, infused into the small intestine at the site of the lipid infusion, reduced nausea and gastric sensitivity to distension. The data support our hypothesis (5–7) that small intestinal afferents play an important role in the modulation of gastrointestinal sensations and visceral perception. However, plasma CCK levels in response to the lipid infusion were also decreased after luminal anesthesia, suggesting that local reflexes may play a role in the regulation of CCK release, which in turn could have secondary influences on visceral sensations.

Mucosal receptors have been shown to modulate visceral perception in other parts of the gastrointestinal tract, such as the esophagus (4, 15) and the rectum (22). In these previous studies, the anesthetic was applied at the location of the distension stimulus, and therefore inhibition of mucosal mechanoreceptors was probably responsible for the decrease in perception. In the present study, benzocaine inhibited activation of receptors at a site distant from the distension stimulus. In this way, we were able to demonstrate modulation of gastric perception during gastric distension through activation of intestinal chemoreceptors by lipid. That benzocaine exerted its action locally on intestinal receptors rather than on the stomach after absorption is demonstrated in two ways. First, benzocaine infusion did not affect gastric perception during duodenal saline infusion. Second, intrajejunal administration of benzocaine, i.e., distal to the site of the lipid infusion, did not affect gastric perception and symptoms induced by duodenal lipid. The modulatory effect of lipid on sensations and symptoms induced by gastric distension was also reduced by benzocaine, inasmuch as the severity of nausea was attenuated. Thus our data provide evidence that stimulation of small intestinal receptors can modulate processing and perception of gastric sensation.

Benzocaine did not completely abolish the effects of lipid on gastric volume and on gastric compliance during distensions. Initially, the increase of gastric volume at baseline pressure induced by the lipid infusion was partially blocked by benzocaine. During distensions, however, gastric pressure-volume relationships were not different whether the lipid infusion was given with benzocaine or vehicle. This may indicate that the dose of benzocaine administered was insufficient to block all receptors affected by duodenal lipid, hence leading to increased recruitment of small intestinal receptors by fat over time. The striking finding in this context is that despite very similar gastric volume responses to distension during these two experimental conditions, the symptomatic responses differed: although benzocaine did not inhibit gastric relaxation, it improved the occurrence and intensity of nausea during duodenal lipid infusion and gastric distension. Our data, therefore, indicate a dissociation between gastric relaxatory changes and the induction of gastrointestinal symptoms. Furthermore, they indicate a direct input from the small intestine to the central nervous system. In contrast, impaired gastric relaxation and reduced compliance have been discussed as factors underlying functional dyspepsia (9, 19–21). Although we have not assessed gastric accommodation in our present study, we investigated gastric relaxation in response to duodenal lipid infusion. Because gastric accommodation is the relaxatory response of the stomach to meal ingestion, we can hypothesize that if gastric relaxation is impaired, the accommodation response to a meal may also be compromised. Our data would therefore suggest that the concept of impaired gastric relaxation as a factor underlying gastrointestinal symptoms may be only partially valid, because during benzocaine infusion gastric relaxation in response to lipid was reduced, which did not coincide with a deterioration of symptoms. During gastric distensions, on the other hand, no differences in gastric compliance were found whether or not the subjects were symptomatic.

We found a decreased release of CCK in response to benzocaine administration, a finding that has not, to the best of our knowledge, been described in humans previously. In the rat, it was shown that application of lidocaine to the small intestinal mucosa abolished the stimulatory action of peptone on plasma CCK levels (16). In addition, pretreatment of small intestinal mucosa with lignocaine caused a reduction in discharge of mesenteric afferent fibers in response to CCK (18). Hence, in addition to an anesthetic effect that would generally reduce activation of afferent endings located in the small intestinal mucosa and therefore would explain the reduced sensitivity to lipid observed in our
study, our data suggest that benzocaine may also exert its effect on nausea and gastric sensitivity by blocking release of CCK. In this way, benzocaine would indirectly decrease stimulation of intestinal afferents responsive to CCK, resulting in a reduced modulation of sensitivity to distension and generation of nausea. Activation of small intestinal mucosal receptors directly by nutrients or via release of neuromodulators such as CCK would therefore provide a pathway not only for the modulation of gastrointestinal motor, secretory, and digestive function but also for the induction of postprandial sensations and symptoms. Involvement of CCK-A receptors in the induction of nausea induced by duodenal lipid and gastric distension was previously demonstrated in healthy subjects (5).

The data from this study may have implications for the treatment of patients suffering from gastrointestinal symptoms. Exaggerated visceral perceptual abnormalities are frequent in patients with functional dyspepsia (3, 17, 20); hence, drugs that reduce perception of mechanical and chemical luminal stimulation may contribute to the improvement of symptoms. Therefore, the observation of a beneficial effect of topical (peripheral) analgesia suggests that future compounds with peripheral visceral analgesic properties hold promise for the treatment of functional bowel disorders, including functional dyspepsia.

The distension protocols used in studies investigating visceral perception are still a matter of considerable debate. Random protocols have been suggested to be superior over ramp distensions because they minimize response bias. Response bias is a well-known phenomenon in the psychophysics of perception (10) but appears to be more frequent in patients with functional dyspepsia than in healthy subjects (17). In these patients, reports of pain during gastric sham distension occur significantly more frequently than in healthy subjects (17). In our present study we used healthy subjects, and we showed previously (5–7) that the symptomatic responses to sham distension are negligible. Alternatively, random distension protocols have been suggested, yet recent studies have indicated that randomly exposing patients to painfully high distension stimuli (as is the case with these protocols) might lead to anxiety and hypervigilance, resulting in a reduction in sensory thresholds (11). The induction of nausea in our studies may be caused to a degree by interoceptive aversive conditioning. However, if this were an important contributing factor, an increase in the occurrence and/or intensity of nausea during distensions would be expected between consecutive study days. This was, however, not the case. Moreover, the first four study conditions were carried out in randomized order, and nausea was consistently and most severely induced in the condition involving infusion of the lipid emulsion with duodenal vehicle. Previously and also in the present study, we used stepwise increases in volume or pressure to elicit gastrointestinal sensations because this study protocol most closely reflects gastric distension during food ingestion. Because there is as yet no gold standard for distension protocols and each of the protocols has its advantages and disadvantages, the data gained from these studies must be interpreted with care.

In summary, our study demonstrates the importance of small intestinal receptors in the modulation of visceral perception and sensitivity. Our data indicate a potential benefit of substances that reduce stimulation of small intestinal receptors for the treatment of gastrointestinal symptoms. The therapeutic relevance of these findings in the treatment of functional dyspepsia requires further investigation.

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