Relationship between increasing duodenal lipid doses, gastric perception, and plasma hormone levels in humans

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Feinle, Christine, David Grundy, Bärbel Otto, and Michael Fried. Relationship between increasing duodenal lipid doses, gastric perception, and plasma hormone levels in humans. Am J Physiol Regulatory Integrative Comp Physiol 278: R1217–R1223, 2000.—Duodenal lipid causes gastric relaxation, CCK secretion, and nausea. Vasopressin has been implicated in motion sickness-related nausea. We hypothesized that increasing doses of lipid enhance gastric relaxation and CCK-vasopressin secretion, resulting in a dose-related exacerbation of nausea. Nine healthy subjects received isotonic saline or lipid (1, 2, or 3 kcal/min, L1, L2, L3) duodenally. Changes in gastric volume, sensations, and plasma hormone levels were assessed during infusions and isobaric gastric distensions. Lipid infusions increased gastric volume, plasma CCK (but not vasopressin) levels, and gastric compliance during distensions, compared with saline. Plasma CCK levels were related to the dose of lipid administered [CCK levels at 30 min (pmol/l), saline: 1.1 ± 0.2, L1: 1.8 ± 0.2, L2: 3.0 ± 0.2, L3: 4.3 ± 0.6]. During distensions, nausea increased in intensity with increasing doses of lipid [score (where 0 is no sensation and 100 is strongest sensation), saline: 7 ± 4, L1: 19 ± 7, L2: 44 ± 7, L3: 66 ± 8]; however, no further rise in plasma CCK occurred. Because neither lipid nor distension alone induced significant nausea, we conclude that the interaction between these stimuli together with a modulation by CCK is responsible for the effects observed. Vasopressin is not involved in lipid- and distension-induced nausea.

cholecystokinin; gastric distension; nausea; vasopressin; dose-response relationship

PATIENTS WITH FUNCTIONAL DYSEPSIA suffer from symptoms of postprandial fullness, bloating, and nausea. Symptoms frequently occur after ingestion of fatty foods. In a previous study in which two doses of duodenal lipid were given to healthy subjects, we found that nausea during gastric distension was more severe with the higher dose of lipid, indicating that the severity of nausea is enhanced when the amount of lipid administered is increased (7). Nutrient delivery to the small intestine relaxes the proximal stomach, and it is conceivable that this relaxatory response occurs in a dose-dependent fashion. Gastric relaxation is also part of the gastrointestinal correlate of nausea and vomiting (6, 23). It is therefore possible that a high degree of gastric relaxation as a result of a duodenal nutrient load may provoke nausea. Furthermore, if a relationship exists between gastric relaxation and the severity of nausea, increasing the dose of nutrients would be expected to augment gastric relaxation and, coincidentally, the severity of nausea in a dose-dependent fashion. However, the relationship between different amounts of duodenal lipid, changes in gastric relaxation, and the severity of nausea is not clear.

Hormones such as CCK and arginine-vasopressin (AVP; or antidiuretic hormone) have been implicated in the induction of nausea and vomiting (8, 10, 21). CCK is released from enteroendocrine cells into the circulation by the presence of lipid in the small intestine. Because CCK is released by lipid, but only to a minor degree by carbohydrates, and because only lipid, but not carbohydrates, increases visceral sensitivity to gastric distension and also induces nausea (7), CCK is probably involved in these changes, but we did not investigate the relationship between the amount of lipid administered and plasma CCK levels in our previous study. Intravenously administered CCK has been shown to cause dose-related gastrointestinal symptoms, including nausea and vomiting, and to simultaneously produce dose-dependent rises in plasma AVP concentrations (10), an effect abolished by the CCK-A receptor antagonist L-364,718 (11). AVP has been described as a correlate of nausea in a variety of experimental conditions, including motion sickness induced by a rotating drum (8), during vertical rotation (13), and apomorphine-induced nausea (19); hence, it has been assumed that nausea is associated with AVP secretion irrespective of the underlying cause for nausea. However, whether duodenal administration of lipid and the occurrence of nausea is also associated with a release of AVP has not been studied.

It is apparent that duodenal lipid potently modulates gastrointestinal function, and it is therefore conceivable that an association exists between these changes (e.g., circulating hormone levels, changes in gastric relaxation) and the severity of gastrointestinal symptoms, such as nausea. Knowledge of the physiological factors underlying nausea may provide potential therapeutic targets. The aim of our study was therefore to investigate the hypothesis that increasing doses of duodenal lipid increase gastric relaxation and CCK and

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the subjects were comfortably seated in an upright position.

**Materials and Methods**

**Subjects**

Nine healthy subjects, four females and five males, aged 22–41 yr, were included in the study. The subjects were of normal body weight for height [body mass index (kg/m²): females, 20.4 ± 1.5; males, 22.5 ± 0.9], nonsmokers, did not take any medication, and were without a history of gastrointestinal disease. The study protocol was approved by the Ethics Committee of the University Hospital Zürich. All subjects gave written informed consent before participation.

**Experimental Design**

Studies were performed in a single-blind, placebo-controlled, crossover fashion in randomized order at least 1 wk apart from each other. Each subject was studied on four occasions. The stomach was repeatedly distended while the duodenum was perfused with either isotonic saline or different doses of a lipid emulsion (Intralipid, 10, 20, or 30%, Pharmacia, Dübendorf, Switzerland; osmolality: 260, 260, or 310 mosmol/kgH₂O, energy density: 1.1, 2, or 3 kcal/ml, respectively). During lipid infusions, an energy load of ~70, 120, or 160 kcal (for the 10, 20, or 30% emulsion, respectively) was administered to each subject. Venous blood samples for CCK, AVP, neurotensin (NT), peptide YY (PYY), and pancreatic polypeptide (PP) were taken, and gastrointestinal sensations were assessed at regular intervals throughout each experiment. Each study took, including intubation procedures, ~4 h. Before entry into the study, each subject visited the laboratory once to get acquainted with the study requirements, the gastric (barostat) tube, the sensations perceived, and the symptom questionnaires. The subjects tolerated the tubes well and did not sense the empty bag in the stomach.

**Intubation**

The subjects arrived at the unit at lunchtime (1200). They were allowed a light breakfast before 0800, but no food or drinks except water afterward. A single-lumen polyvinyl tube (Merck Biomaterial, Alton, UK) was passed through the nose into the duodenum. The tube [OD 2.8 mm (8 Fr), length: 109 cm] was weighted at its end with stainless steel pins encased in a polyvinyl case and equipped by the manufacturer with a side port situated 5 cm from its tip. The tip of the tube was allowed to slowly travel into the duodenum. The position of the distal port (~15 cm distal to the pylorus) was verified fluoroscopically. Once the duodenal tube was in position, the subjects swallowed the gastric tube (OD 3.5 mm, ID 2.8 mm; Tygon Tubing, Upchurch Scientific, Oak Harbor, WA), which had an ultrathin, flaccid polyethylene bag (capacity 1,100 ml) tied to its distal end. The proximal end of the tube was connected via a three-way tap to the balloon ports of a gastric barostat (Distender Series II, G & J Electronics, Willowdale, Ontario, Canada). In the stomach, the bag was unfolded by inflating it with air, positioned in the fundus by gently pulling the tube back until its passage was restricted by the lower esophageal sphincter and then pushed back in by 3 cm. The tubes were then secured to the side of the face.

**Protocol**

Once the tubes and the intravenous catheter were in place, the subjects were comfortably seated in an upright position. 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 necessary to overcome intra-abdominal pressure) was determined by increasing intragastric pressure in steps of 1 mmHg/min. Pressure was then set at MDP, and gastric volume was recorded until variations were no longer observed. MDP before the start of any duodenal infusion was 8 ± 1 mmHg and did not differ between study days. After another 10 min ("baseline"), duodenal infusion of either saline or one of the lipid emulsions commenced at a rate of 1 ml/min and was continued throughout the entire study. Thirty minutes into the infusion, the MDP was redetermined. It was unchanged after duodenal infusion of saline or 10% lipid (8 ± 1 mmHg). Infusion of 20 or 30% lipid reduced MDP to 6 ± 1 mmHg (P < 0.05). The protocol then continued with two periods of isobaric distensions, 15 min apart from each other. Stepwise increases in intrabag pressure of 1 mmHg were executed while the corresponding volumes were monitored. Each pressure level was maintained for 1 min.

**Assessment of Sensations During Infusions and Distensions**

Immediately before the start and at t = 10 and 30 min during the duodenal infusions, the subjects rated sensations of hunger, satiation, nausea, abdominal bloating, and pressure/pain on visual analog scales (VAS). The VAS consisted of a 100-mm line, with 0 mm meaning "sensation not present" and 100 mm "strongest sensation ever felt." During distensions, the subjects were asked to report when they first perceived a sensation of epigastric fullness and when they first felt epigastric discomfort. The subjects were also asked to describe the sensation of discomfort in a "sensations and symptoms questionnaire" in more detail. By checking the appropriate box, they could indicate whether "discomfort" was an uncomfortable pressure or whether they felt nauseous. If nausea was present, the subjects were also asked to rate the severity on a VAS. As soon as the subjects reported discomfort, the distension process was discontinued and the air was immediately removed from the bag. To minimize the influence of visual or auditory cues, the barostat device and the infusion pump were placed behind the subjects' backs and the barostat device was kept running continuously (i.e., even during breaks in the protocol) to maintain a constant level of noise.

**Blood Sampling**

To assess changes in plasma levels of CCK, PP, NT, PYY, and AVP, venous blood samples of 20 ml were taken immediately before the start (baseline sample) and at t = 10 and 30 min (immediately before distension 1) during the duodenal infusions, at the end of distension 1 and at the beginning and the end of distension 2. Blood samples were collected on ice, centrifuged, and then stored at −70°C until extraction. Plasma concentrations of CCK, PP, NT, PYY, and AVP were determined by sensitive and specific radioimmunoassays (1–3, 15). In the CCK assay, sulphated gastrins cross-react <1%, whereas no cross-reactivity is found with unsulphated gastrins or CCK-8. The mean detection limit of the assay is 0.3 ± 0.1 pmol/l with a confidence limit of 95%. The coefficients of variation are 5.6% at 0.67 pmol/l and 7.2% at 15.1 pmol/l for the intra-assay variation and 12.3% at 0.85 pmol/l and 15% at 14.8 pmol/l for the interassay variation. The PP assay detects changes between adjacent samples of 6 pmol/l with 95% confidence. The intra-assay coefficient of variation is 5.7%, the interassay coefficient of variation is 10.2%. The PYY assay is capable of detecting changes of plasma PYY.
between adjacent tubes of 1.5 pmol/l with 95% confidence and shows no significant cross-reaction with PP, neuropeptide Y, or NT. The NT assay is capable of detecting changes of plasma NT between adjacent tubes of 5 pmol/l with 95% confidence and shows no significant cross-reaction with gastrin, gastric inhibitory polypeptide, PP, neuropeptide Y, vasoactive intestinal polypeptide, or PYY. AVP concentrations in plasma were determined by a commercial kit (IBL, Hamburg, Germany).

In brief, after ethanol extraction of plasma samples, vasopressin is assayed by a competitive radioimmunoassay using rabbit antivasopressin antiserum and radioiodinated $^{125}$I-sin. AVP concentrations in plasma were determined by a commercial kit (IBL, Hamburg, Germany).

RESULTS

Seven of nine subjects experienced nausea, and the severity varied with the dose of lipid administered. The remaining two subjects did not report any nausea during any of the tests.

Duodenal Infusions Without Gastric Distension

Gastric volume changes. All lipid emulsions significantly increased intrabag volume compared with isotonic saline, but no differences existed between the different lipid doses (Fig. 1).

Symptom scores. During the first 30 min, the different duodenal infusions had no effect on the scores for hunger, satiety, bloating, pressure/pain, or nausea, except for an increase of the score for nausea (baseline: $2 \pm 1$, at 30 min: $25 \pm 9$) during infusion of 30% lipid ($P < 0.05$).

Duodenal Infusions Combined with Gastric Distension

Pressure/volume profiles. During saline infusion, distension of the proximal stomach led to a steady rise in intragastric volume. All lipid infusions increased intragastric volume at a given pressure compared with saline, but there were no differences between the three lipid doses or between the subjects that developed nausea and those who did not (Fig. 2, A and B).

Gastric perception during distension. During 10% lipid, sensations of both fullness and discomfort occurred at significantly higher intragastric volumes and similar pressures compared with saline. During infusion of 20 and 30% lipid, however, fullness and discomfort were not significantly increased gastric volumes (i.e., reduced intragastric tone) compared with isotonic saline. Data are means $\pm$ SE, $n = 9$ subjects. *Significantly different from saline, $P < 0.05$. 

![Fig. 1. Gastric volume responses to duodenal infusions. All 3 lipid emulsions (10, 20, and 30% lipid) significantly increased gastric volumes (i.e., reduced intragastric tone) compared with isotonic saline. Data are means $\pm$ SE, n = 9 subjects. *Significantly different from saline, P < 0.05.](http://ajpregu.physiology.org/)

Statistical Analysis

Data were analyzed by ANOVA. If statistically significant differences were obtained, Student's t-test was used to carry out pairwise comparisons. Multiple comparisons were accounted for by applying a Bonferroni correction to the P values obtained. Data are presented as means $\pm$ SE. Probability values of $P < 0.05$ were regarded as statistically significant.
fort were reported at significantly lower intragastric pressures compared with saline and 10% lipid, but at volumes that were not different from those during saline (Fig. 3, Table 1).

Quality of the sensation of discomfort. During duodenal saline infusion, discomfort was described during 92% of distensions as a pressure in the epigastrium and in 8% as nausea. The nausea score on the VAS was 7 ± 4. Increasing doses of lipid resulted in an increased incidence of nausea during distensions (22, 61, and 78% of distensions during 10, 20, and 30% lipid, respectively) and an increased intensity of nausea at the end of distensions (VAS scores: 19 ± 7, 44 ± 7, and 66 ± 8, during 10, 20, and 30% lipid, respectively), which was correlated with the dose of lipid ($r^2 = 0.69, P < 0.05$).

Correlation between nausea and pressure/volume thresholds for discomfort. Negative correlations were found between the intensity of nausea and volumes or pressures at which discomfort arose during distensions (Fig. 4).

**Plasma Hormone Responses**

Duodenal lipid (without gastric distension) led to rises in plasma levels of CCK, NT, PYY, and PP, but not of AVP (Fig. 5). For CCK and NT, the rise was related to the dose of lipid administered (CCK: $r^2 = 0.57$, NT: $r^2 = 0.62, P < 0.05$). During 30% lipid, a further rise of plasma PYY levels was observed during gastric distensions. This rise was probably due to the continuing

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**Fig. 2.** Intragastric pressure-volume relationships during isobaric gastric distensions and duodenal infusion of isotonic saline or lipid emulsions in subjects ($n = 7$) experiencing nausea (A) and as a comparison between subjects experiencing nausea (solid lines) and those who did not (dashed lines; $n = 2$) (B). Data are means ± SE. MDP, minimal distending pressure.

**Fig. 3.** Scatter plots of pressures (A) and volumes (B) at which discomfort occurred during gastric distensions and duodenal infusions in individual subjects who experienced nausea, especially during infusion of 20 and 30% lipid ($n = 7$, ■) and those who did not ($n = 2$, □).
infusion of lipid, because PYY levels continued to rise between the two distension periods. No changes during distensions were found for the other hormones. Overall, levels of CCK, NT, PP, and PYY, but not of AVP, were significantly higher during infusions of 20 and 30% lipid than during saline. No correlations were observed between plasma hormone concentrations and the pressures or volumes at which discomfort occurred. A weak correlation was found between nausea scores and plasma NT levels at the end of distensions ($r^2 = 0.47$, $P < 0.05$). No such relationships were found for CCK, PP, PYY, or AVP.

**DISCUSSION**

In this study, we demonstrated that both the severity of nausea and gastric sensitivity during distensions of the proximal stomach increase in relation to the dose of duodenal lipid administered. Duodenal lipid infusion without gastric distension profoundly raised plasma levels of gastrointestinal hormones without profoundly changing gastrointestinal sensations.

In a previous study (7), we found that both lipid and carbohydrate increased gastric pressure-volume relationship, compared with the saline control infusion. In contrast to carbohydrate, however, only lipid enhanced visceral sensitivity to gastric distension and also induced nausea. As CCK is released by lipid, but not by carbohydrate, we hypothesized that CCK plays an important role in these changes. Plasma CCK levels were raised during duodenal infusion of lipid in the present study, and the rise was related to the dose of lipid administered, suggesting that the observed change of gastric volume (tone) in response to duodenal lipid was, at least in part, mediated by the action of CCK. However, the rise in plasma CCK during duodenal lipid was not accompanied by major changes in gastrointestinal sensations. Because it has been demonstrated in food intake studies that intestinal lipid or intravenous CCK infusions potently induce early satiety (9, 18, 20, 22), the lack of effect on conscious sensation during the first 30 min of infusion in our study is probably due to the missing gastric distension stimulus.

Plasma AVP levels were not affected by the duodenal lipid infusion. Previously, it has been shown that intravenously administered CCK increases plasma levels of AVP (10). In addition, AVP secretion has been associated with motion sickness-related nausea, as plasma levels of AVP rise soon after the nauseating stimulus is applied (14). However, although duodenal lipid released CCK, this was not accompanied by a rise in plasma AVP in our study. Therefore, it appears that AVP does not play a role in lipid-induced changes of gastric function and sensations during gastric distension, confirming the data of a study showing that AVP levels were not increased after a very large meal (10).

The increase in intragastric volume in response to the duodenal lipid infusions did not elicit conscious sensations in our subjects. This is in keeping with a recent report (5) that showed that although increasing doses of duodenal nutrients cause increased gastric relaxation and hence increased intragastric volumes, conscious perception of these processes was not enhanced. This observation indicates that gastric relaxation per se does not activate receptors mediating conscious sensation. In contrast, active distension of

<table>
<thead>
<tr>
<th>Volumes, ml</th>
<th>Saline</th>
<th>10% Lipid</th>
<th>20% Lipid</th>
<th>30% Lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullness</td>
<td>328 ± 34</td>
<td>484 ± 33*</td>
<td>350 ± 43</td>
<td>285 ± 46</td>
</tr>
<tr>
<td>Discomfort</td>
<td>497 ± 35</td>
<td>700 ± 32*</td>
<td>522 ± 47</td>
<td>468 ± 71</td>
</tr>
<tr>
<td>Pressures, mmHg above MDP</td>
<td></td>
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<td></td>
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<tr>
<td>Fullness</td>
<td>6.3 ± 0.8</td>
<td>6.0 ± 0.4</td>
<td>3.8 ± 0.4*</td>
<td>3.2 ± 0.5†</td>
</tr>
<tr>
<td>Discomfort</td>
<td>9.0 ± 0.7</td>
<td>8.7 ± 0.6</td>
<td>5.7 ± 0.6*</td>
<td>5.1 ± 0.6†</td>
</tr>
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Data are means ± SE; n = 9 subjects. MDP, minimal distending pressure. Significantly different from *saline, †10% lipid, $P < 0.05$.

Fig. 4. Correlations between volume thresholds (A) or pressure (B) for discomfort and nausea intensity. All data from all infusions are plotted.
the stomach, during which no further increase in plasma hormone levels occurred, induced sensations of fullness and discomfort. Moreover, without causing any differences in gastric wall compliance, the three doses of lipid modulated conscious sensation in a differential way. The lowest lipid dose caused a desensitization, in as much as discomfort, experienced as an uncomfortable pressure or pain, occurred at higher volumes than during the saline condition. This observation indicates that duodenal lipid may be able to modulate visceral pain perception, supporting the concept that vagal stimulation (with duodenal lipid activating small intestinal receptors connected to vagal afferents) decreases perception of pain by modulating spinal pain pathways (12) that are thought to be responsible for the mediation of conscious sensation. Indeed, a study in humans showed that ingestion of a high-fat meal decreased perception of cold-induced pain compared with a low-fat meal (24). Therefore, our own and other studies indicate that lipid in the small intestine may be capable of modulating pain perception. However, further studies are required to investigate modulation of visceral pain by nutrients in detail. Increasing the dose of lipid increased the sensitivity of the stomach to gastric distension, and sensations occurred at similar volumes but lower pressures than during saline infusion. Moreover, nausea was reported as the main sensation during distensions. Stimulation of gastric mechanoreceptors was probably comparable between the various experimental conditions, because gastric pressure-volume relationships during the different doses of lipid were similar. Therefore, the induction of nausea was most likely due to input to the central nervous system from small intestinal chemoreceptors stimulated by lipid. Our data show that while gastric distension is important for the induction of conscious sensation, the nature of these sensations and the threshold level for their induction can be modulated by duodenal lipid in a dose-dependent manner.

An understanding of where between the gut and the brain the afferent information from different sites (gastric distension, duodenal lipid, circulating hormones) is integrated to result in reflex and behavioral and symptomatic changes has potentially important clinical implications. A synergistic effect of CCK and gastric loads on gastric vagal afferent activity has been described previously. Combining close arterial injection of CCK with a gastric saline load caused a stronger vagal afferent response than either stimulus alone. Moreover, CCK sensitized vagal afferent fibers to subsequent gastric distension loads (16, 17). However, plasma levels of CCK are not likely to be as high as the doses used in these studies (100 pmol), and, therefore, activation of gastric vagal afferents by CCK was probably not a major mechanism accounting for the effects observed in our study. At smaller CCK doses, more closely mimicking circulating levels, gastric vagal afferents do not respond to CCK, whereas intestinal afferents do (4). Therefore, and also because CCK concentrations at the location of the release were probably far higher than plasma levels, it is more likely that intestinal receptors responsive to CCK were involved. If this were the case, integration of afferent signals from the stomach and small intestine would not take place at a gastric level but more likely within the central nervous system where the two inputs converge.

We have identified a number of factors that may be involved in the induction of postprandial symptoms, such as nausea, and therefore may have potential therapeutic implications. Because the severity of nausea is increased with increasing doses of lipid, dietary modifications consisting of a decrease in the amount of fat in the diet may improve dyspeptic symptoms. Moreover, pharmacological manipulation could include substances that decrease or slow fat digestion to reduce CCK secretion or substances that inhibit the effect of CCK.

In summary, duodenal lipid increases gastric relaxation and dose dependently increases plasma levels of gastrointestinal hormones but does not induce remarkable conscious sensations in the absence of gastric distension. In contrast, whereas duodenal nutrients and circulating hormones may not be capable of actively inducing sensations, they potently modulate the quality of distension-induced sensations and gastric sensitivity. Therefore, our data demonstrate an interaction between mechanical and chemical stimuli in the upper gastrointestinal tract in the induction of postprandial sensations and symptoms in humans.
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