Cholecystokinin pathways modulate sensations induced by gastric distension in humans

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Lal, Simon, John McLaughlin, Josephine Barlow, Massimo D’Amato, Giampaolo Giacovelli, Andrea Varro, Graham J. Dockray, and David G. Thompson. Cholecystokinin pathways modulate sensations induced by gastric distension in humans. Am J Physiol Gastrointest Liver Physiol 287: G72–G79, 2004. First published February 5, 2004; 10.1152/ajpgi.00351.2003.—Ingested fat releases CCK, causes gastric relaxation, delays gastric emptying, and limits meal size; however, the mechanistic link among these actions has not been established. Fatty acid release of CCK is chain-length sensitive; dodecanoic acid (C12) induces greater CCK release than decanoic acid (C10). The effect of C12 or C10 on tolerance to subsequent intragastric infusion of liquid was determined in healthy subjects, with and without the CCK1 receptor antagonist dexloxiglumide. Gastric wall relaxation after either fatty acid was assessed by graded volume distension and by barostat; gastric emptying was measured by gastric aspiration and by [13C]octanoic acid breath technique. C12 released more CCK (mean plasma CCK after vehicle, 4.7 ± 0.8 pM; C10, 4.8 ± 0.3 pM; C12, 8 ± 1.2 pM; P < 0.05 C12 vs. C10 or vehicle) and reduced the volume of water (and of 5 and 25% glucose solutions) delivered at maximum tolerance compared with C10 or vehicle (volume of water tolerated after vehicle, 1.535 ± 164 ml; C10, 1.335 ± 160 ml; C12, 842 ± 103 ml; P < 0.05 C12 vs. C10 or vehicle); this effect was abolished by dexloxiglumide. Intragastric volumes were always similar at the limit of tolerance, and, whereas gastric relaxation occurred to similar degrees after the fatty acids, its duration was longer after C12, which also induced a longer delay in half-gastric emptying (1/2 (min) after vehicle, 53 ± 2; C10, 67 ± 3; C12, 88 ± 7; P < 0.05 C12 vs. C10 or vehicle). In conclusion, ingestion of a CCK-releasing fatty acid reduces the tolerated volume of liquid delivered into the stomach, primarily via a CCK1 receptor-mediated delay in gastric emptying.

delaying gastric emptying (26), but it is unknown whether the same is true in humans.

In an attempt to clarify these uncertainties, we performed a series of studies in healthy volunteers: 1) to explore how endogenous CCK released in response to fatty acid modulates tolerance to liquids delivered into the stomach and 2) to determine the relationship between gastric emptying and gastric relaxation in modulating tolerance. We now provide evidence that endogenous CCK reduces the volume of a liquid that can be tolerated in the upper gastrointestinal tract via a CCK1 receptor-mediated effect and that it does so primarily by delaying gastric emptying so that the sensation of maximum fullness is achieved at a lower volume delivered.

MATERIALS AND METHODS

Subjects

Eighteen healthy volunteers (6 females; mean age 33, range 22–55; mean body mass index 23.3, range 19.5–31.6 kg/m2) were recruited from the staff of Hope Hospital and its local population. No volunteer had a history of digestive system disease, and none were taking medication that might affect gastric motility or sensation. Thirteen subjects participated in the first study, and subsets of the 18 participated in subsequent studies. Subject inclusion in any one protocol was solely determined by subject availability with no a priori selection bias introduced. All were studied in the morning after an overnight fast, and studies on a particular subject were separated by at least 3 days. Studies were performed in a quiet room while the subject reclined on a bed at an angle of 45 degrees. All gave written consent for each study protocol, approval for which had been obtained from the Salford and Trafford Local Research Ethics Committee.

Materials

Decanoic acid (C10), dodecanoic acid (C12), [13C]octanoic acid, and phenol red were purchased from Sigma-Aldrich (Gillingham, England). Tween 80 (food grade) was a gift of Quest Industries (Zwijndrecht, The Netherlands). Sep-Pak C18 cartridges were purchased from Waters (Milwaukee, WI). Dexloxiglumide (11) was supplied by Rotta Research Laboratorium (Monza, Italy).

Preparation of Fatty Acid Emulsions

Test emulsions were made as reported in our previous studies (23): 1.5% (vol/vol) Tween 80 was added to 250 ml PBS (pH 7.3, 350 mosmol/kgH2O) to form the vehicle solution. The fatty acids were warmed above their melting point and added to the vehicle solution in liquid phase, the two being vigorously mixed while cooling to 37°C to form stable emulsions of 0.1 M and with similar caloric values [156

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kCal/l (C10) and 180 kCal/l (C12)). Fatty acid (0.1 M) was administered in each study (i.e., 4.3 and 5 g of C10 and C12, respectively, in 250 ml of vehicle solution) via a naso- or orogastric tube during 2 min.

CCK Radioimmunoassay

Venous blood samples were taken from a cannula in an antecubital vein (Venflon, 18 gauge; BOC Ohmeda AB, Helsingborg, Sweden) placed in heparinized glass tubes, and centrifuged at 3,000 rpm for 5 min. Plasma was frozen and stored at minus 20°C until assayed. Plasma CCK was determined after concentrating samples by Sep-Pak C18 cartridges as described previously (6). The assay used antibody Dino (1:1,500,000), kindly provided by the late Prof. John Calam, which is specific for the sulfated COOH terminus of CCK-8 and for CCK-33 and does not react with gastrin. Bolton-Hunter ([125I]CCK-8 (Amersham, Little Chalfont, England) was used as label.

Measurement of Tolerance to Intragastric Liquid

Fatty acid (C10 or C12) or vehicle was administered into the stomach during 2 min by oro- or nasogastric infusion on three separate occasions in a single-blind, randomized order via a 12-gauge feeding tube (Penneine Healthcare, Derby, UK). After 20 min (the time at which plasma CCK levels are maximal) (23), either water or glucose (5 and 25% wt/vol, equivalent to 200 and 1,000 kCal/l, respectively) was infused via the feeding tube at a rate of 200 ml/min using a peristaltic pump (Ole Dich Instruments, Hvidovre, Denmark) and continued either until subjects reported that their limit of tolerance was reached or when 2,400 ml had been delivered. Sensations were recorded (see Assessment of Sensations) before administration, 15-min after the fatty acid, at the limit of tolerance to water delivery, and thereafter at 15-min intervals until symptoms disappeared. Plasma CCK measurements were made before and at 15 min after fatty acid or vehicle administration.

Effect of Dexloxiglumide on C12-Induced Reduction in Tolerated Volume

Dexloxiglumide, a specific CCK₁ receptor antagonist (11), was infused through an intravenous catheter sited in an antecubital vein at a rate of 15 mg·kg⁻¹·h⁻¹ for 10 min and then at a rate of 5 mg·kg⁻¹·h⁻¹ until the end of the study. This dose regimen was based on previous data using the related compound loxiglumide, which is approximately half as potent and has been shown to produce maximal blockade of CCK₁ receptors in humans at the infusion rate of 10 mg·kg⁻¹·h⁻¹ (28). The dexloxiglumide solution was indistinguishable in appearance from the control solution, and both were prepared under an independent pharmacist to ensure that neither the subject nor the researcher were aware of the nature of the infusion. Subjects were randomized according to a four-treatment, four-period, complete crossover (Latin square) design to receive either dexloxiglumide or control (0.9% saline) by intravenous infusion, followed by either intragastric vehicle or C12. Twenty minutes later in all treatment arms, water was infused into the stomach (200 ml/min) to the limit of tolerance. The intravenous infusion (dexloxiglumide or placebo) began 20 min before the intragastric delivery of the fatty acid and continued until maximum tolerated volume was reached or until 2.4 liters had been delivered without reaching the limit of tolerance.

Measurement of Tolerance to Direct Gastric Distension

A 2-liter capacity polythene bag (1) was advanced through the esophagus and into the stomach, unfolded by inflation with 400 ml of air, and then withdrawn until resistance was met, indicating that its proximal end was at the lower esophageal sphincter. The bag was advanced 2 cm and then fully deflated, and the catheter was affixed to the subjects’ cheek with adhesive tape to prevent bag displacement. After 10 min, one of the fatty acid solutions was instilled into the stomach, then after 20 min, the bag was inflated with air at 200 ml/min until the limit of tolerance was reached.

Assessment of Sensations

Subjects were asked both to describe the nature of the sensations that led to the limitation of tolerance to the liquid delivered and also to rate any sensations of nausea and fullness on visual analog scales (scaled 0–100, with 0 indicating the absence of the sensation and 100 indicating the maximal imaginable sensation) (14).

Determination of Gastric Secrecion

C12 was infused into the stomach, and 20 min later, gastric contents were aspirated to dryness. Water containing a nonabsorbable dye (phenol red 15 mg/l) was then infused at 200 ml/min to the limit of tolerance, and the gastric contents were aspirated rapidly. Phenol red concentration in aliquots of the infused and aspirated water was measured spectrophotometrically at an alkaline pH from the absorbance at 560 nm to determine the degree of dilution that had occurred, providing an estimate of gastric secretion (7).

Measurement of Gastric Emptying

Fatty acid or vehicle solution was infused into the stomach, and 20 min later water labeled with [13C]octanoic acid (200 mg/l) was infused at 200 ml/min. To reliably compare gastric emptying rates after each of the test solutions, the same amount of [13C]octanoic acid-labeled water was infused for a given individual. This volume was chosen to be identical to the maximum amount tolerated after C12 for each subject (as determined in earlier studies). Exhaled breath specimens were collected 1 min before and at 15, 30, 45, 60, 90, and 120 min after the water infusion. On each occasion, the subject exhaled completely through a straw inserted into a 10-ml glass test tube, which was then sealed with a rubber cap. Breath samples were analyzed by using an isotope ratio mass spectrometer method. This allowed the determination of the isotopic composition of carbon in expired CO₂ by determination of the 13C-to-12C ratio in the sample (21). By convention, this is expressed relative to the 13C-to-12C ratio (R) in standard CO₂ [Pee Dee Belemnite (PDB)] to produce a δ 13C value (10): δ 13C = [(Rsample / Rstd) × 1,000], where R = 13C/12C ratio and Rstd = 0.112372. The half-gastric emptying time (t½) of 13C to be recovered was then determined for each subject using the cumulative 13C (with respect to 12C) recovery from the breath over time (10).

Measurement of Gastric Wall Stiffness

Proximal gastric wall stiffness was measured by using a previously developed and validated technique (1, 23, 24, 33). In summary, the method involves serial measurements of intragastric pressure during stepwise volume inflation of a 1-liter capacity, thin-walled polyethylene bag sited in the proximal stomach. The subject swallowed a 12-gauge feeding tube for orogastric infusion of the fatty acid or vehicle solution with the bag attached to a separate tube to allow its intragastric inflation. After 10 min, the bag was progressively inflated in 50 ml increments at intervals of 1 min until 600 ml was reached. Because it is known that the first distension induces an initial relaxatory response but that subsequent distensions produce a consistent pressure-volume relationship (1), data from the second inflation were used for analysis. After the second inflation, either fatty acid or vehicle solution alone was instilled into the stomach and bag inflation was repeated 20 min later. The gastric pressure-volume relationships were then derived for each subject for the two distensions. When gastric distension is induced by fixed volume steps, the term elastance is most appropriately used. This is the reciprocal value of compliance (the term used to describe pressure-volume relationships when distension is induced in fixed pressure steps), and the slope of the pressure-volume curve is a measure of the stiffness of the gastric wall. As in previous studies, a simple index of the average gastric wall stiffness (mmHg) under each condition was obtained by adding the
values of intragastric pressure recorded for all the inflation volume steps from 50 to 600 ml during each series and then dividing this value by the number of inflation steps (1, 23, 24, 33).

Measurement of Proximal Gastric Volume Changes at a Fixed Intragastric Pressure

Subjects swallowed two 12-gauge feeding tubes in the morning after an overnight fast on separate occasions. One of the tubes was for orogastric infusion of fatty acid or vehicle solution, and the other was attached to a 1-liter capacity, thin-walled polyethylene bag for subsequent inflation. The bag was positioned in the proximal stomach (as described above) and connected to a barostat (Synectics Medical, Stockholm, Sweden). After a 10-min adaptation period, the minimal distending pressure (MDP) was determined by increasing intrabag pressure by 1 mmHg every 3 min until a volume of at least 30 ml was reached. The bag was then completely deflated, and the pressure level was set at MDP + 2 mmHg. After a further 30 min, either fatty acid or vehicle alone was administered and intrabag volume was then measured for 45 min (31).

Effect of Fatty Acid on Maximum Volume Tolerated by Drinking

To investigate whether the mode of delivery of liquid load might affect the reduction in tolerance, vehicle or C12 was administered to subjects on separate occasions as in previous experiments, and 20 min later, subjects drank water from a cup at a rate of 200 ml/min until the maximum tolerated volume was reached.

Data Analysis

Results are shown in the text as means ± SE. Estimation of probability of difference among paired data was undertaken by Student’s paired t-test for parametric data or by Wilcoxon matched pair signed-rank test for nonparametric data, as appropriate. Multiple comparisons (e.g., among the effects of C10, C12, and vehicle) were made by one-way repeated-measures ANOVA for parametric data (on ranks for nonparametric data) followed by Student-Newman-Keuls post hoc test to determine which conditions differed significantly. Multiple pair-wise post hoc comparisons in the dexloxiglumide study were made by using the Tukey honestly significantly different post hoc test after one-way ANOVA for Latin square design. Pearson product moment correlation was used to compare plasma CCK responses with sensation score ratings and t1/2 with volumes tolerated.

RESULTS

Effect of Fatty Acid on Tolerance to Intragastric Water Infusion

Thirteen subjects received either vehicle, C10, or C12, followed by the intragastric infusion of water to maximum tolerance.

Maximum tolerated volumes. Subjects tolerated a lower volume of water delivered at maximum tolerance after C12 (842 ± 103 ml) compared with either C10 (1,335 ± 160 ml; P < 0.05 vs. C12) or vehicle (1,535 ± 164 ml; P < 0.05 vs. C12).

CCK levels. There was no difference in the fasted plasma CCK values on any of the study days (mean fasted plasma CCK concentration prevehicle: 2.4 ± 0.4 pM; pre-C10: 2.6 ± 0.7 pM; pre-C12: 2.5 ± 0.3 pM), C12, C10, and vehicle alone induced a rise in plasma CCK levels compared with fasted levels (P < 0.05 for all conditions), but importantly, only C12 and not C10 induced a rise in plasma CCK compared with the effect of vehicle solution (mean plasma CCK concentration 15 min after vehicle, 4.7 ± 0.8 pM; C10, 4.8 ± 0.3 pM; C12, 8 ± 1.2 pM; P < 0.05 C12 vs. C10 or vehicle).

Sensations experienced. There was no difference in the sensation scores recorded before administration of the solutions (Fig. 1). The 2.4 liters of water was infused into two subjects after vehicle and in one subject after C10 without reaching the limit of tolerance. In all of the other subjects, fullness was the limiting sensation. In addition, nausea was also reported at the maximum tolerated volume more frequently (8 subjects after C12, 6 subjects after C10, and 0 subjects after vehicle) and intensively (Fig. 1) after either of the fatty acids than after vehicle. All sensations returned to baseline levels by 45 min, although the speed of their disappearance was slower after C12 than either C10 or vehicle (Fig. 1). There was no relationship between plasma CCK levels and sensation intensity at maximum tolerated volume (P > 0.05, Pearson product moment correlation).

Effect of Dexloxiglumide on C12-Induced Reduction in Tolerated Volume

Eight subjects participated in this study. Dexloxiglumide reversed the effect of C12 in reducing the volume of water tolerated (Fig. 2). Maximum tolerance in all conditions was again characterized by the sensation of fullness, and more subjects again reported nausea after C12 than vehicle (Table 1). Dexloxiglumide did not alter the character of the sensation reported at the maximum tolerated volume.
Effect of Fatty Acid on Intragastric Volume at the Limit of Tolerance

Because we had found that there was a reduction in the volume of water delivered at maximum tolerance after C12 compared with either C10 or vehicle, we determined whether the observed differences in volume delivered were related to differences in intragastric volume at maximum tolerance. Tolerance to water infusion after fatty acid or vehicle was reassessed in eight subjects, and on this occasion the contents of the stomach were rapidly aspirated immediately after maximum tolerance had been reached and the volume retrieved was noted. There was no difference in the volumes aspirated from the stomach at maximum tolerance after any of the test solutions, despite a reduction of 560 ± 75 ml in the volume delivered to the stomach after C12 compared with C10 or vehicle (Fig. 3, A and B), indicating that intragastric volume was a major factor in limiting tolerance.

Because the volume retrieved at maximum tolerance would have consisted of the volume of infusate (water) remaining in the stomach, together with the volume of any residual fatty acid or vehicle remaining in the stomach and any gastric secretion occurring during the infusion, the effect of C12 on gastric dilution was also determined in a further six subjects using phenol red, to determine the extent to which gastric secretion after C12 could have contributed to any differences in the gastric volumes measured at maximum tolerance. From analysis of phenol red concentrations in the aspirate, the mean dilution after C12 was 15.7 ± 5%, indicating that gastric secretion could not have accounted for the C12-induced reduction in volume at the limit of tolerance.

Effect of Fatty Acid on Gastric Emptying

Because under the experimental circumstances used the rate of water delivery was constant and the amount of gastric secretion was small, we predicted that the differences in the volume of water required to achieve maximum tolerance should be related to its rate of gastric emptying. We therefore determined the effect of C10, C12, or vehicle on the subsequent gastric emptying rate of a water load using a [13C]octanoic acid breath technique in six subjects. C12 delayed gastric emptying more than either C10 or vehicle (Fig. 3C). Moreover, $t_{1/2}$ was negatively correlated with the maximum tolerated volume ($r = -0.5, P < 0.02$), indicating that the slower the gastric emptying, the smaller the volume tolerated.

Effect of Fatty Acid on Tolerance to Direct Gastric Distension

Similar gastric bag distension volumes were recorded at the limit of tolerance after C10 or C12 in six subjects, whereas for each of these individuals, the volumes of water delivered to achieve the limit of tolerance in the previous studies were consistently different (Fig. 4).

Effect of Fatty Acids on Gastric Wall Stiffness

We measured gastric wall stiffness after C12, C10, or vehicle on three separate occasions in five subjects. In all subjects, C12 and C10 induced a greater downward shift in the pressure-volume relationship during distension compared with vehicle, indicating gastric relaxation (mean reduction in wall stiffness after C12 fatty acid, $2 ± 0.53$ mmHg; after C10 fatty acid, $2 ± 0.47$ mmHg; Fig. 5). In these subjects, the maximum volume of water delivered at maximum tolerance in previous studies was $1,185 ± 220$ ml after C12, compared with $1,710 ± 240$ ml after C10 and $1,860 ± 240$ ml after vehicle ($P < 0.05$ C12 vs. C10 or vehicle).

Proximal Gastric Volume Changes at Fixed Intragastric Pressure after Fatty Acid

The effect of C12 on gastric relaxation was assessed in five subjects. There was no difference in the MDP recorded before the infusion of either vehicle ($7.6 ± 1.6$ mmHg) or C12 ($7.6 ± 0.7$ mmHg). As in previous studies (4), fluctuations in intrabag volumes were seen with the passage of time before fatty acid or vehicle delivery (mean frequency 1.6 per min). Both C12 and vehicle induced an increase in intrabag volume at constant pressure (Fig. 6) together with loss of fluctuation in volume, the effect being consistently more prolonged after C12. At 20 min after vehicle solution (the time at which the water was

Table 1. Sensations reported and scored (0–100) at maximum tolerance to gastric water infusion after dodecanoic acid or vehicle during intravenous dexloxiglumide (5 mg·kg⁻¹·h⁻¹) or saline infusion

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<tr>
<td>Nausea</td>
<td>2</td>
<td>33±9</td>
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<td>Fullness</td>
<td>8</td>
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Values are means ± SE. Sensn., sensation.
delivered in the other protocols), the intragastric volume fluctuations had returned and the intrabag volume had almost recovered to its basal value, whereas 20 min after C12 the increased intrabag volume persisted (mean increase in intrabag volume 20 min after C12, 461 ± 168 ml; after vehicle, 123 ± 35 ml). In these subjects, the volume of water delivered at maximum tolerance in previous studies was 1,090 ± 270 ml after C12 compared with 1,975 ± 270 ml after vehicle (P < 0.05 vs. C12).

**Effect of Fatty Acid on Tolerance to Intragastric Glucose Infusion**

C12 reduced the volume of both water and glucose (5 or 25% wt/vol) delivered at maximum tolerance in seven subjects (Fig. 7). The volumes of gastric aspirate at maximum tolerance were similar, indicating that the major factor limiting tolerance was intragastric volume rather than the nutrient or caloric content of the liquid load. The calorie content of the 5% glucose solution tolerated after C12 was 175 ± 45 kCal delivered in previous studies (*P < 0.05).
compared with 268 ± 40 kCal after vehicle, and the calorie content of the 25% glucose solution tolerated after C12 was 784 ± 184 kCal compared with 1,150 ± 166 kCal after vehicle.

**Effect of Fatty Acid on Maximum Volume Tolerated by Drinking**

Eight subjects participated in this study. Subjects drank less water after C12 (800 ± 170 ml) than vehicle (1,020 ± 210; \( P < 0.05 \) vs. C12) before reaching the limit of tolerance.

**DISCUSSION**

The multiple, interlinked experiments we used to study the role of endogenous CCK in the regulation of gastrointestinal sensations, gastric emptying, and gastric relaxation now demonstrate that the CCK-releasing fatty acid C12 reduces the volume of liquid delivered into the upper gastrointestinal tract to achieve maximum tolerance more than C10 or vehicle and that this effect probably occurs via a CCK₁ receptor-mediated delay in gastric emptying. Moreover, it appears that it is the volume of gastric contents (i.e., the degree of gastric distension) that is the principal factor that limits tolerance to gastric filling.

Studies in animals (5, 26) have suggested that CCK might limit the amount of meal ingested by at least two mechanisms: either by a direct signal to the central nervous system independently of gastric distension (5) probably via CCK₁ receptors expressed on vagal afferent nerve terminals (8 27) and/or indirectly by delaying gastric emptying (26), which would result in greater gastric distension for a given volume delivered. We now provide several lines of evidence to show that in humans the mechanism whereby C12 limits the volume delivered into the upper gastrointestinal tract is by delaying gastric emptying. We showed that the volume of gastric contents aspirated at the limit of tolerance was similar despite a clear difference in the volume of water or glucose delivered after C12, C10, or vehicle. These findings suggest that it is the volume of liquid within the stomach (which is the result of the rate at which it empties from the stomach given that its rate of delivery was constant and gastric secretion was minimal) that determines the amount tolerated. Furthermore, we showed that C12 delayed gastric emptying more than C10, consistent with the single, earlier observation made 30 years ago by Hunt and Knox (17), and we also showed that the slower the rate of gastric emptying the smaller the volume delivered at maximum tolerance. In addition, it is noteworthy that the sensation of fullness lasted longer after C12 than C10 or vehicle, consistent with delayed gastric emptying after C12.

Possible mechanisms for the inhibition of gastric emptying by C12 include reduced proximal gastric tone, reduced antral peristalsis, and/or increased pyloric or intestinal tone. Our demonstration that C12 reduces gastric wall stiffness and induces prolonged gastric relaxation suggests that more prolonged residence of liquid within the fundus is one of the likely factors influencing emptying. It seems unlikely, however, that the degree of gastric relaxation can solely explain the effect of C12 on gastric emptying, because C10 and C12 relaxed the stomach to comparable degrees, despite having different effects on gastric emptying. In keeping with this, it has been reported previously that the rate of emptying of a liquid meal

![Fig. 6. Mean intrabag volume at constant pressure before and after administration of vehicle (●) or C12 (○). Both vehicle and C12 induced a rapid increase in intragastric volume indicating gastric relaxation, the effect being more prolonged after C12.](image-url)

![Fig. 7. A: C12 reduced the volume of both water and glucose delivered at the limit of tolerance (*\( P < 0.05 \) C12 vs. vehicle). B: there were no differences in the volume of gastric contents aspirated after any infusion.](image-url)
from the stomach correlates poorly with any change in proximal gastric relaxation (29). Indeed, it is also possible that the delaying effect of C12 could be via an action on the distal stomach, possibly by suppressing the contribution that peristaltic antral contractions make to the process of gastric emptying (12 23) and/or via a pyloric or postpyloric effect to reduce efflux through the duodenum (2, 32).

In considering the genesis of fullness (at maximum volume tolerance), it is important to consider both the proximal and the distal stomach. We have shown that the volume of liquid within the stomach is the major determinant of tolerance, but we have not specifically addressed the relative contribution of proximal vs. distal gastric distension in inducing fullness. It has previously been shown that proximal gastric distension induces fullness (15, 16), and it has also been suggested that gastric relaxation should lead to an increase rather than a decrease in meal ingestation (31). However, we showed that C12 limited the volume of liquid delivered at maximum tolerance despite inducing prolonged gastric relaxation, suggesting that CCK limits tolerance to a liquid by prolonging its residence in the proximal stomach, and so delaying its emptying and leading to increased gastric distension for a given volume delivered. Gastric distension by a liquid also, of course, involves distension of the distal stomach, and it is equally important to consider an additional role of the distal stomach in the genesis of fullness, because it has recently been shown that the perception of postprandial fullness is closely related to the antral area in healthy subjects (18, 30).

It has previously been suggested that the major mechanism limiting tolerance to gastric distension is gastric wall tension (13), which is a function of both gastric wall stretch (a function of intragastric volume) and gastric tone (a function of intragastric volume and pressure). Because we found no difference in the intragastric volume at maximal tolerance, despite different intragastric pressures after vehicle and fatty acid, our data strongly suggest that fullness is determined primarily by gastric stretch rather than gastric tone. This suggests that activation of stretch-responsive gastric mechanoreceptors determine sensation intensity during gastric filling and thereby limit ingested volume.

Our results also indicate that although the release of CCK limited the volume tolerated by delaying gastric emptying, it had no independent effect on the quality of sensation experienced, because both C10 and C12 produced similar sensations compared with vehicle alone. It is noteworthy that subjects felt more nausea after either of the fatty acids than after vehicle. This implies that, whereas gastric wall stretch can induce the sensation of fullness, an additional fatty acid-related stimulation induces nausea. A CCK-mediated effect has been implicated previously in the induction of nausea (25), so it is interesting to see that nausea did not appear to be solely dependent on CCK release in our studies, because not only did both fatty acids evoke similar degrees of nausea, but also the nausea induced by C12 was not abolished by dexloxiglumide. Therefore, it seems that fatty-acid responsive, yet CCK-independent, pathways appear to contribute to the induction of nausea, perhaps via a direct effect on vagal afferents, because we have recently found in rats that fatty acids delivered into the upper intestine can directly activate vagal afferent nerves (20).

To interpret our findings in a broader context of food intake regulation, it must be remembered that eating behavior is a complex process combining physiological, psychological, and social cues to govern the initiation of eating, the amount consumed, and the duration of the intermeal period. Our results, for example, do not allow us to comment on the regulatory processes that lead to the initiation of meal consumption. It is also important to note that CCK is only one of a number of peptides produced from the mucosa of the upper gastrointestinal tract in response to food that may be involved in the regulation of gastrointestinal responses and the genesis of sensations after a meal. Peptides, such as ghrelin (3) and orexin-A (19), are also produced by the gastrointestinal epithelium, act on the vagus (9), and increase food intake. The interplay among those factors that increase and those that limit meal consumption for a given degree of gastric distension now needs to be explored.

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