Effect of CCK on proximal gastric motor function in humans

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MATERIALS AND METHODS

Subjects

Seven healthy female volunteers (mean age 22 yr; range 18–26 yr) participated in the study. None had gastrointestinal symptoms, had previously undergone abdominal surgery, or were using medication. Informed consent was obtained from each individual. The protocol of the study was approved by the ethics committee of Leiden University Medical Center.

Gastric Barostat

An electronic barostat (visceral stimulator; Synectics Medical, Stockholm, Sweden) was used to distend the stomach. A polyethylene bag (950 ml maximum capacity) was tied to the end of a multilumen tube (19 Fr). This catheter was connected to the barostat.

The barostat is able to keep the pressure in the intragastric bag at a preselected level. When the stomach relaxes, the system injects air. When the stomach contracts, the system aspirates air. Thus the barostat measures gastric motor activity as changes in intragastric volume at a constant intragastric pressure (2, 18).

The barostat is also able to induce gastric distensions at either fixed pressures (isobaric) or fixed volumes (isovolumetric). To produce fixed pressure distensions, the barostat maintains a constant pressure level by an electronic feedback regulation of the air volume within the intragastric bag. To produce fixed volume distensions, the air pump sets the desired air volume within the intragastric bag at a controlled injection (or aspiration) pressure, and then the pump is blocked (19). Maximal air flow is 38 ml/s.

Intrabag pressure is directly measured via a separate lumen of the tube. Pressure (mmHg), volume (ml), and compliance (ml/mmHg) are constantly monitored and recorded on a personal computer connected to the barostat (Polygram for Windows SVS module; Synectics Medical).

Procedures

The experiments were started at 8:30 AM after an overnight fast of at least 10 h. The catheter with bag was introduced through the mouth and positioned in the fundus of the stomach. Correct position was checked by fluoroscopy. To unfold the bag, air (200 ml) was manually inflated under controlled pressure (<20 mmHg) and the catheter was pulled back carefully until its passage was restricted by the lower esophageal sphincter. Then the tube was introduced a further 2 cm. Thereafter the bag was deflated and connected to the barostat. The subjects were seated in a comfortable reclining chair in a semirecumbent position with the lower extremities kept at 20 and 0°.

The experiments, blood samples for measurement of plasma CCK were drawn at regular intervals at -20 and 0 min before the start of infusion and thereafter every 30 min during infusion until 140 min (end of experiment).

THE MOTOR FUNCTION OF THE proximal part of the stomach is best characterized by adaptive relaxation (2, 18, 19). This consists of the ability to distend, for instance after meal ingestion, with only minimal changes in intragastric pressure. Postprandial gastric relaxation is dependent not only on the volume of the meal but also on meal composition (1, 21). Gastric tone produces gastric emptying, which is regulated by intestinal nutrients, in particular by fat. Fat is a potent stimulus of endogenous CCK release (8). CCK may modulate the process of gastric relaxation (22, 24), but the effects in humans are unknown. CCK is an important hormonal regulator of upper gastrointestinal motility and secretion (4, 12, 16, 23). We hypothesized that CCK also influences proximal gastric function in humans. We studied the effect of CCK on proximal gastric mechanical and sensory function in a placebo-controlled study. CCK-33 was administered by continuous intravenous infusion to plasma CCK levels in the postprandial range. The function of the proximal stomach was measured with an electronic barostat.
G940 CCK AND GASTRIC COMPLIANCE

Perception of the sensations of fullness, abdominal pressure, nausea, and pain were quantified during the experiment on 100-mm visual analog scales. The following questions were asked: How full do you feel? (with end points on the scale ranging from not at all full to very full). Do you experience abdominal pressure? (not at all to very strong). Do you feel nauseated? (not at all to very nauseated). Do you experience abdominal pain? (no pain to worst pain imaginable) (6). Perception of each sensation was recorded at regular intervals during the procedures and at each step during volume and pressure distensions.

The following procedures were performed:

Minimal distending pressure. The minimal distending pressure (MDP) is the pressure needed to overcome the intra-abdominal pressure. This is defined as the first pressure level that provides an intragastric bag volume of >30 ml (2, 18). This was determined by increasing intrabag pressure in 1-mmHg steps every 2 min.

Barostat procedure. The barostat was set to maintain a pressure of 2 mmHg above the MDP. During the first 20 min (from ~20 to 0 min) the basal volume of the proximal stomach was measured. Then infusion of either saline or CCK was started. The volume was continuously measured for 45 min after the start of the infusions.

Isovolumetric distension. The bag was distended in 100-ml steps every 3 min from 0 to a maximum of 600 ml and then deflated in 100-ml steps every 3 min (until 0 ml). The procedure was stopped immediately if the maximal pressure of 25 mmHg during 5 s was reached or if the subject could not tolerate further distension. The duration of this procedure was ~30 min. After this procedure, the subject was allowed to rest for a 10-min period.

Isobaric distension. The bag was distended in 2-mmHg steps every 3 min from 0 to a maximum of 14 mmHg and thereafter deflated in 2-mmHg steps every 3 min (until 0 mmHg). The procedure was stopped immediately if the maximum bag volume of 750 ml was reached or if the subject could not tolerate further distension. The duration of this procedure was ~45 min.

Experimental Design

The experiments were performed in double-blind, randomized order. All subjects were studied during the follicular phase of the menstrual cycle. The subjects participated in three experiments with an interval of at least 7 days: 1) control experiment with saline infusion, 2) CCK infusion at 0.5 IDU·kg⁻¹·h⁻¹, and 3) CCK infusion at 1.0 IDU·kg⁻¹·h⁻¹.

CCK Infusion

CCK (porcine CCK-33; Ferring, Malmö, Sweden) was administered by continuous intravenous infusion of either 0.5 or 1.0 IDU·kg⁻¹·h⁻¹ (6 and 12 pmol·kg⁻¹·h⁻¹, respectively).

Meal Stimulation

Additional experiments were performed in the seven healthy volunteers to obtain reference values for postprandial plasma CCK levels. Plasma CCK levels were measured on two separate occasions after ingestion of a light meal (300 kcal; 10 g fat, 10 g protein, 42 g carbohydrates) and a high-calorie meal (1,016 kcal; 48 g fat, 50 g protein, 96 g carbohydrates). Blood samples were taken under fasting conditions (~20 and 0 min) and at 15, 30, 45, 60, 90, and 120 min after meal ingestion.

Data Analysis

Gastric volumes measured during the barostat procedure are given as average values over 5-min periods. Cyclic variations in bag volume, so-called “volume waves,” are defined as changes in volume of >30 ml that revert in ~2 min to a volume within 50% of the previous level (2, 21).

The pressure in the isovolumetric distensions and the volume in the isobaric distensions were measured by averaging the recordings during the last minute before the next distension. Volumes at each pressure level were already corrected for air compressibility by the computer program. Gastric fundal compliance during saline and CCK infusion was calculated based on the data of the highest volume and pressure distension at 600 ml and 14 mmHg, respectively.

The perception scores were calculated. The values obtained at ~20 min, immediately before the start of the barostat procedure, were used as the reference values.

Assay of CCK

Plasma CCK was measured by a sensitive and specific RIA using antibody T204 (9, 11). This antibody binds to all carboxy-terminal CCK peptides containing the sulfated tyrosyl region with roughly equal potency (0.65–1.65 compared with CCK-33), while there is no binding to unsulfated CCK peptide or gastrins (11). In addition, this assay is able to react with all known molecular forms of CCK present in human intestinal extracts or in human plasma after meal ingestion or bombesin stimulation (10, 11). In human plasma the main CCK peptides correspond to large CCK (CCK-58), CCK-33/CCK-39, and intermediate CCK. In the small intestine, CCK-8 was demonstrable in addition to the forms present in plasma (10, 11). The detection limit of the assay is 0.1 pmol/l plasma. The intra-assay variation ranges from 4.6% to 11.5% and the interassay variation from 11.3% to 26.1% (9).

Statistical Analysis

Results are expressed as means ± SE. Data were analyzed for statistical significance using multiple ANOVA. When P < 0.05 was indicated for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which values between or within the experiments differed significantly. The significance level was set at P < 0.05.

RESULTS

Oral intubation with subsequent positioning of the intragastric bag was well tolerated. Thresholds for pain were not reached during the volume and pressure increments. The mean MDP was 7.3 ± 0.5, 7.8 ± 0.4, and 7.9 ± 0.3 mmHg at the start of the saline, 0.5 IDU·kg⁻¹·h⁻¹ CCK, and 1.0 IDU·kg⁻¹·h⁻¹ CCK infusions, respectively [not significant (NS)].

Plasma CCK

Basal plasma CCK levels before the start of infusion were not significantly different among the three experiments (Fig. 1A). During infusion of CCK at 0.5 and 1.0 IDU·kg⁻¹·h⁻¹, plasma CCK levels increased significantly from 0.3 ± 0.1 at 0 min to 2.9 ± 0.2 pmol/l at 60 min during 0.5 IDU·kg⁻¹·h⁻¹ CCK infusion (P < 0.01) and from 0.4 ± 0.2 at 0 min to 5.0 ± 0.2 pmol/l at 60 min during 1.0 IDU·kg⁻¹·h⁻¹ CCK infusion (P < 0.01). Plasma CCK levels during infusion remained significantly elevated. Plasma CCK levels during 1.0 IDU·kg⁻¹·h⁻¹ CCK infusion were not significantly different from each other.
kg\textsuperscript{-1} \cdot \text{h}^{-1} \text{CCK} were significantly higher compared with plasma CCK levels during 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK} infusion (P < 0.01). During saline infusion (control) no changes in plasma CCK were observed.

Plasma CCK levels reached after ingestion of the light and high-calorie meal are shown in Fig. 1B. After ingestion of the light meal peak plasma CCK levels of 3.6 ± 0.7 pmol/l were reached. Plasma CCK levels were significantly (P < 0.05) increased over fasting from 15 until 120 min. After ingestion of the high-calorie meal, a peak plasma CCK level of 7.3 ± 1.2 pmol/l was reached at 30 min. Plasma CCK levels were significantly (P < 0.05) increased over fasting from 15 min until 120 min. Plasma levels reached during CCK infusion (0.5 and 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1}) are comparable to peak plasma levels after ingestion of the light meal and high-calorie meal, respectively.

Basal Gastric Tone

Basal intragastric volumes before the start of infusion at 0 min were not significantly different among the three experiments (Fig. 2). During 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK} infusion, the intragastric volume gradually increased and was significantly (P < 0.01) greater compared with saline infusion starting from 15 min. At 30 min the bag volume during 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK"} was 363 ± 44 (P < 0.01) vs. 195 ± 34 ml during saline and 195 ± 14 ml during 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK (NS vs. saline).

By relaxing the proximal stomach, 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK produced a significant increase in proximal gastric compliance compared with saline infusion (P < 0.01). This effect was identical to that found in the isobaric and isovolumetric procedures. No differences were shown in the bag volume between infusion of 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK and saline.}

During the barostat procedure, continuous phasic volume waves were observed. The mean frequency of the volume waves was 1.3 ± 0.1/min before the start of infusion. During 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK infusion, the frequency of these volume waves decreased significantly (P < 0.01) from 1.3 ± 0.1 to 0.1 ± 0.06/min, whereas during saline infusion no alterations were observed (0.9 ± 0.2 vs. 1.3 ± 0.1/min). The frequency of volume waves during 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK was significantly lower than during saline (0.1 ± 0.06 vs. 0.9 ± 0.2/min; P < 0.05). During infusion of 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK, no effect on volume wave frequency was observed.

Isovolumetric Distensions

Gradual volume distension of the stomach resulted in increasing intragastric pressures and perception scores during both intravenous saline and CCK infusion (Figs. 3 and 4). Compared at the same volume step, the intragastric pressures were lower when the stomach was relaxed by infusion of CCK at 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1}. The pressure at the highest volume distension (600 ml) was significantly lower during 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK infusion (14.8 ± 1.3 mmHg) compared with saline (18.1 ± 0.7 mmHg) (P < 0.05; Fig. 3). No significant differences were shown between 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK and saline (17.3 ± 0.6 vs. 18.1 ± 0.7 mmHg at 600 ml).

Gastric fundal compliance at 600 ml was also greater during 1.0 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK infusion (42 ± 4 ml/mmHg) compared with saline (34 ± 1 ml/mmHg; P < 0.05). The compliance between 0.5 IDU \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \text{CCK
(35 ± 1 ml/mmHg) and saline was not significantly different.

The volume increments resulted in increasing perception scores during both saline and CCK infusion. Compared with saline, perception scores during 0.5 IDU·kg⁻¹·h⁻¹ CCK were not significantly different. However, during 1.0 IDU·kg⁻¹·h⁻¹ CCK the perception scores of abdominal pressure and fullness were significantly (P < 0.05) lower when the stomach was relaxed by CCK. In other words, 1.0 IDU·kg⁻¹·h⁻¹ CCK decreased both the pressure and perception at the same distending volume levels (Fig. 4).

Isobaric Distensions

Distensions of the stomach with progressively higher intragastric pressures produced increasing intragastric volumes and perception scores in all experiments (Figs. 4 and 5). The volume at the maximum pressure distension of 14 mmHg was significantly greater during 1.0 IDU·kg⁻¹·h⁻¹ CCK infusion (634 ± 46 ml) compared with saline (442 ± 30 ml) (P < 0.01). The volume was also significantly different between 1.0 IDU·kg⁻¹·h⁻¹ CCK and saline from the distension of 10–14 mmHg and during deflation until the step of 8 mmHg (Fig. 5). No significant differences in intragastric volume between infusion of 0.5 IDU·kg⁻¹·h⁻¹ CCK and saline were found.

The compliance at the maximum pressure distension was significantly (P < 0.01) increased during infusion of 1.0 IDU·kg⁻¹·h⁻¹ CCK (44 ± 3 ml/mmHg) compared with saline (31 ± 2 ml/mmHg), but not during infusion of 0.5 IDU·kg⁻¹·h⁻¹ CCK (36 ± 4 ml/mmHg; NS vs. saline).

The pressure-volume curve during stepwise deflation from 14 to 2 mmHg showed a significantly larger
volume than during inflation from 2 to 14 mmHg with 1.0 IDU·kg\(^{-1}·h^{-1}\) CCK (P < 0.05 at 6, 8, and 10 mmHg), creating a hysteresis loop (Fig. 6). This was also observed during saline (NS).

The pressure increments produced increasing perception scores during infusion of saline and both doses of CCK. Comparison between 1.0 IDU·kg\(^{-1}·h^{-1}\) CCK and saline did not show a difference in perception (Fig. 4D). Although at identical pressure levels intragastric volumes were larger during 1.0 IDU·kg\(^{-1}·h^{-1}\) CCK infusion, the perception scores were in the same range as during saline infusion.

DISCUSSION

Our data indicate that CCK at postprandial plasma concentrations decreases basal gastric tone and increases compliance as shown during isobaric and isovolumetric distensions. The effect of CCK on the mechanics of the proximal stomach was present only during infusion of 1.0 IDU·kg\(^{-1}·h^{-1}\) CCK-33 when plasma CCK levels of ~5 pmol/l were reached. These levels are comparable to peak plasma levels seen after ingestion of a high-calorie meal. During infusion of 1.0 IDU·kg\(^{-1}·h^{-1}\) CCK-33, gallbladder contraction is almost complete (5, 16). During infusion of 0.5 IDU·kg\(^{-1}·h^{-1}\) CCK, when plasma levels comparable to those after ingestion of a light meal were reached, no significant effect of CCK on proximal gastric mechanics could be demonstrated. However, during infusion of 0.5 IDU·kg\(^{-1}·h^{-1}\) CCK gallbladder contraction occurs and the gallbladder empties by 50% (5, 16). It has to be noted that because of the heterogeneity of CCK in postprandial plasma, it is impossible to exactly mimic the plasma CCK pattern by infusion of CCK. In this study, porcine CCK-33 was infused because this CCK peptide has bioactivity similar to that of human CCK and is registered for administration to humans in The Netherlands.

Of the macronutrients, fat is especially capable of relaxing the stomach (1, 21). The postprandial relaxation is dependent on the fat content of the meal; that is, the higher the fat content, the more pronounced the gastric relaxation (21). Both orally ingested and duodenal fat increase gastric relaxation, pointing to intestinal control over gastric fundal tone (3, 21). It is not known whether the effect of intestinal fat on proximal gastric mechanics is mediated by endogenous CCK. No studies have been performed evaluating the effect of intestinal fat on proximal gastric mechanics during concomitant CCK receptor blockade. Our results indicate that in humans gastric fundal relaxation may be a physiological action of CCK. This finding is in agreement with the results from animal experiments (20, 22, 24).

Fat-rich meals are emptied from the stomach more slowly than meals low in fat content. Fat stimulates endogenous CCK secretion. At physiological plasma concentrations CCK inhibits gastric emptying. CCK receptor blockade on the other hand may accelerate gastric emptying, depending on the composition of the meal (13, 17). The present finding that CCK induces gastric fundal relaxation and increases the compliance of the gastric wall is in line with previous observations that CCK delays gastric emptying (12, 14).

The mechanism of action of CCK on the proximal stomach is less clear. Although the effect of CCK on the proximal stomach is related to the plasma levels of circulating CCK, our results do not provide strict evidence that CCK influences proximal gastric mechanics directly by acting as a circulating hormone. It has been suggested in animal experiments that CCK decreases intragastric pressure by neural pathways involving vagal and splanchnic nerves (20).

Afferent (vagal) pathways convey information on intragastric pressure or volume signaled by muscle or serosal mechanoreceptors. Distension of the proximal stomach with progressively higher intragastric pressures or volumes resulted in increased perception scores during both saline and CCK infusion. Only during isovolumetric distensions were perception scores significantly different between CCK and saline. It should be noted that at the same volumes intragastric pressure was lower during CCK compared with saline. However, during isobaric distensions at identical pressures no differences in perception scores between CCK and saline were observed. These findings indicate that sensory receptors in the proximal stomach are more sensitive to pressure than to volume variations. This is in line with the recent observation by Distrutti et al. (7) that perception of gastric distension in humans is mediated by tension and not volume receptors.

It is remarkable that the pressure-volume curves during deflation were different from those during inflation. This phenomenon, called hysteresis, results from a “latency” of the fundic wall to regain its original shape and is related to the displacement of viscera surrounding the stomach. During CCK infusion the hysteresis effect was more pronounced than during control. However, the hysteresis effect by CCK was significant only during pressure distension, when intrabag volume was larger and more viscera had to be displaced.
During the barostat procedure (constant pressure at MDP plus 2 mmHg) cyclic fluctuations in volume from the baseline were observed. These fluctuations are considered as continuous phasic contractions and are registered as volume waves. During CCK infusion the frequency of these volume waves decreased significantly. Similar observations have been made during intraduodenal lip infusion when phasic contractility is reduced (3). It is well known that also in the antrum the frequency and amplitude of phasic contractions decrease during CCK infusion (15).

In summary, our results suggest that in humans CCK may have a physiological role in regulating proximal gastric mechanics by inducing relaxation and increasing gastric wall compliance. Consequently, CCK reduces the perception of fullness and abdominal pressure during distension.

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