Retardation of Gastric Emptying of Solid Food by Secretin

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The effect of secretin at nearly physiologic plasma concentrations on the gastric emptying rate of solid food was studied in 12 healthy men. A ^{99m}Tc colloid-labeled pancake was used as the test meal. The gastric emptying rate was measured during 1 h using a dual-headed γ-camera, and was expressed as the half-time of the emptying curve. To prevent endogenous secretin release, 400 mg of cimetidine was given before the meal. Subjects were studied under three conditions: (1) during infusion of saline; (2) during continuous infusion of secretin, 6.6 pmol/kg · h; and (3) during three intermittent 10-min periods of secretin infusion, 7.6 pmol/kg · h during each period. Both continuous and intermittent infusion of secretin increased half-emptying time, by 133% and 55%, respectively. The plasma secretin concentration in condition 1 was 0.8 pM; plateau concentration in condition 2 was 9.8 pM; and integrated mean concentration in condition 3 was 4.8 pM. It is concluded that secretin at approximately physiologic plasma concentrations retards gastric emptying of solid food in humans.

Secretin is a polypeptide hormone that is released by endocrine cells in the mucosa of the duodenum and upper jejunum when the intraduodenal pH falls below 3–4 (1–3). Secretin is now well recognized as a physiologic stimulant of pancreatic bicarbonate secretion (4,5). Other physiologic functions of secretin have not yet been established. Acidic solutions are known to inhibit the gastric emptying rate (6). The mediator of this inhibitory effect is not known. Secretin is a candidate for this role in view of its release by duodenal acidification. Several investigators indeed found that secretin inhibits the gastric emptying rate of liquid meals, not only at high doses (7,8), but probably also at doses that result in physiologic plasma concentrations of secretin (9,10). The effect of secretin on the gastric emptying of solid foods in humans, however, has not been studied. We therefore studied the influence of near-physiologic plasma secretin concentrations on the gastric emptying rate of a solid meal. To exclude the effect of duodenal acidification on endogenous secretin release and on gastric emptying, cimetidine was given before all tests were performed to inhibit gastric acid secretion.

Materials and Methods

Subjects

Twelve healthy male volunteers (mean age 32 yr, range 29–41 yr) were studied. All subjects gave informed consent. The study was performed according to the guidelines laid down in the declaration of Helsinki.

Test Meal

A ^{99m}Tc-labeled pancake was used as the test meal (11). The meal was made of 45 g of white flour, 10 g of Nutrilose milkpowder (Nutricia), 10 g of margarine, 5 g of sugar, and 80 ml of water and contained 7.9 g of protein, 39 g of carbohydrate, and 9.4 g of fat, corresponding to 269 kcal. About 10 MBq ^{99m}Tc colloid was added to the batter just before baking. The effective radiation dose equivalent was 0.3 mSv (= 30 mrem) per test. To measure the binding of the tracer under the influence of chewing, saliva, and gastric juice, a labeled pancake was divided into four equal portions. Three of them were chewed and spat out again. One portion was cut into small pieces. All four portions were then mixed with 75 ml of fresh pentagastrin-stimulated human gastric juice (pH 1.2) and incubated at 37°C for 4 h. The portions were then sieved. The radioactivity of the fluid obtained and that of the remaining solid material were determined. Radioactivity was equally divided over the four portions. The fluid obtained from the four portions contained only a mean of 2% (range 0%–6%) of the total activity of each of them. From these results it was concluded that the Tc colloid-labeled pancake is a

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suitable test meal for the study of the gastric emptying of solid food.

The pancake was eaten immediately after it was prepared. Having finished the pancake, each subject drank 100 ml of water, rinsing his mouth with the water. It took about 4 min to consume the meal.

Gastric Emptying Rate

The gastric emptying rate was measured using a dual-headed γ-camera (Siemens ROTA; Siemens Gammasonics, Amsterdam, the Netherlands), which was interfaced to a computer (DEC, gamma 11; Digital Equipment Corp., Marlboro, Mass.). Low-energy all purpose collimators were used. The subjects were seated between the heads of the camera leaning back slightly.

As soon as the test meal was finished digital frames were recorded for 1 h in 1-min periods. A region of interest over the stomach was chosen using the sum image of all 60 frames, certifying that the whole gastric region was included. The time-activity curves for these regions on the anterior and posterior views were then generated. The final emptying curve was obtained by calculating the geometric mean of the anterior and posterior curves. This method guarantees that the resulting emptying curve is independent of the changing depth of the meal-bound tracer due to the anatomic position of the stomach (12).

The rate of gastric emptying was expressed as the half-emptying time ($t_{1/2}$), which is the time necessary to empty half of the activity originally present in the stomach, beginning at the start of registration, i.e., at the end of the meal. The half-emptying time was determined by fitting a power exponential curve to the emptying curve, as recommended by Elashoff et al. (13). The use of this curve gives a reasonably good description of a variety of emptying patterns of different meals. The relation between the fraction of the meal still present in the stomach (f) and the time (t) is expressed by the formula

$$f = 2^{-(t/t_{1/2})^{\beta}},$$

in which the variable power exponent β determines deviations from a monoexponential decay curve. The emptying curve for solid food often shows a lag phase, i.e., a period during which no food is emptied from the stomach (14,15). This phase probably represents the time required to grind the food into smaller particles (16). With an increasing length of the lag phase, the value of the power exponent β will be progressively larger than 1.0.

The power exponential curve was fitted to the emptying curve using a nonlinear least-squares method. The quality of the fit is represented by the parameter R^2, which should approximate 1.0 (13).

Secretin Assay

Concentrations of secretin in plasma and infusion fluids were determined by radioimmunoassay as described previously (17,18).

Tests Performed

All tests were done after an overnight fast. During each test the subjects had an intravenous needle in each arm, one for blood sampling and the other for infusion of saline with or without secretin. Twenty-five minutes before the meal, 400 mg of cimetidine (Smith Kline & French, Welwyn Garden City, U.K.) was given intravenously to inhibit gastric acid secretion and thereby prevent release of endogenous secretin, so that plasma secretin concentrations could be kept completely controlled during all tests. To test the release of secretin under these circumstances, 3 subjects were given an unlabeled pancake after cimetidine. Blood samples were taken before and at 5-min intervals after the meal for plasma secretin determination. In previous studies cimetidine has been shown not to affect the gastric emptying rate in humans (19–21). To further test this, the gastric emptying rate was determined in 6 subjects with and without the concomitant administration of cimetidine. During the tests without cimetidine, blood samples were taken at 10-min intervals.

Gastric emptying was measured during saline infusion (control) and during continuous and intermittent infusion of secretin. In the control study, as performed in all 12 subjects, 0.15 M NaCl at a rate of 30 ml/h was being infused. Six subjects were studied while secretin was infused continuously during the whole test. Highly purified natural porcine secretin (Kabi Vitrum, Stockholm, Sweden) was dissolved in 0.15 M NaCl, containing 0.25% (wt/vol) human serum albumin. Secretin was given at a dose of 6.6 ± 0.5 pmol/kg · h as measured by radioimmunoassay. The infusion, at a rate of 30 ml/h, was started just before the meal was eaten. Nine subjects were studied while secretin was infused intermittently. Secretin was given during three periods of 10 min, from 7.5 to 17.5, from 25 to 35, and from 42.5 to 52.5 min after finishing the meal. In the remaining time 0.15 M NaCl was given. The dose of secretin during each period was 7.6 ± 1.4 pmol/kg · h. The total volume infused was 30–40 ml. The tests were performed in a random order in each subject with an interval between the tests of at least 1 wk.

Blood samples were taken during the control studies and the studies with continuous infusion of secretin 15 min before and 30 and 60 min after the meal. During the intermittent administration of secretin, samples were taken before and 17.5, 25, 35, 42.5, and 52.5 min after the start of the registration. Samples were collected into ice-chilled tubes and left on ice until centrifugation immediately after the end of the test. Plasma was stored at −20°C until radioimmunoassay. The samples were coded and assayed in random order.

Statistical Analysis

Results are given as mean ± SD. The half-emptying times and the power exponents (β) during the continuous and intermittent infusion of secretin were compared with their respective paired control values by the Wilcoxon rank sum test for paired results. Differences were considered to be significant when $p < 0.05$.

Results

The plasma secretin concentrations remained at fasting levels during the whole hour after the

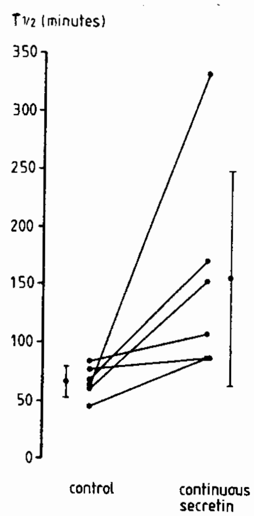

Figure 1. Gastric half-emptying times ($t_{1/2}$) of a ^{99m}Tc colloid-labeled pancake during control studies and during continuous infusion of secretin (6.6 ± 0.5 pmol/kg · h) in 6 healthy subjects (mean ± SD).

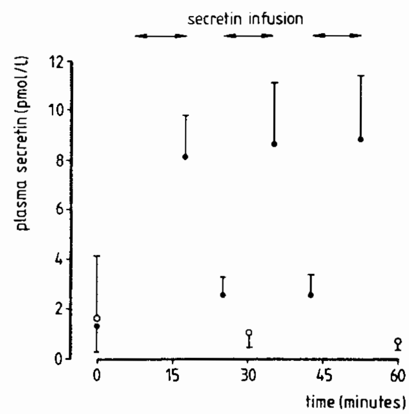

Figure 3. Plasma secretin concentrations (mean ± SD) during intermittent infusion of secretin (●) (7.6 ± 1.4 pmol/kg · h) and during control studies (○) in 9 healthy subjects.

ingestion of the unlabeled pancake in the 3 subjects from whom samples were taken at 5-min intervals (mean concentration before the meal 0.8 ± 0.4 pmol/L, postprandially 0.8 ± 0.5 pmol/L).

During the tests without concomitant administration of cimetidine, basal plasma secretin concentration was 1.5 ± 1.5 pmol/L, increasing only minimally during the hour studied (integrated mean concentration = 2.0 ± 0.9 pmol/L; n = 4). No effect of cimetidine on gastric emptying could be shown. The mean half-emptying time was 59 ± 13 min without cimetidine and 62 ± 10 min with cimetidine, whereas the power exponents were 1.3 ± 0.3 and 1.2 ± 0.2, respectively (n = 6).

The fasting secretin level after cimetidine administration in the 12 subjects was 1.2 ± 1.8 pmol/L. The concentration did not increase during control studies. During continuous infusion of secretin, plasma concentrations were 10.2 ± 3.5 pmol/L at 30 min and 9.4 ± 3.4 pmol/L at 60 min. Continuous infusion of secretin increased the half-emptying time significantly from 67 ± 13 min to 156 ± 92 min (Figures 1 and 2). The power exponent was not significantly affected by secretin; β = 0.9 ± 0.3 during secretin infusion versus 1.2 ± 0.3 during control studies.

During intermittent infusion of secretin, plasma concentrations reached peak levels around 8.5 pmol/L and fell to 2.5 pmol/L between infusion periods (Figure 3). Assuming that plasma secretin

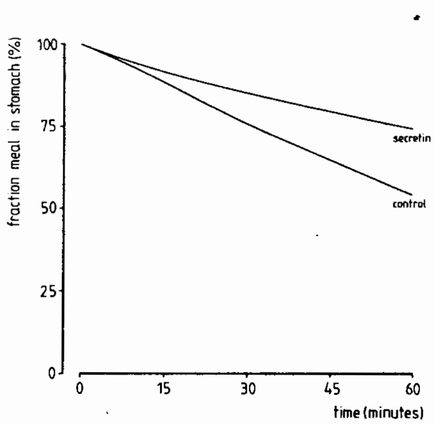

Figure 2. Mean gastric emptying curves of a ^{99m}Tc colloid-labeled pancake during control studies ($t_{1/2}$ = 67 min, power exponent = 1.2) and during continuous infusion of secretin (6.6 ± 0.5 pmol/kg · h) ($t_{1/2}$ = 156 min, power exponent = 0.9) in 6 healthy subjects.

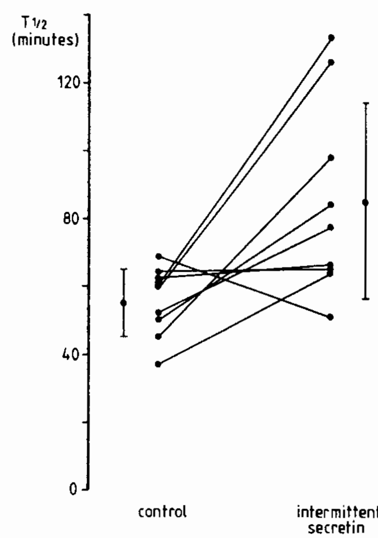

Figure 4. Gastric half-emptying times ($t_{1/2}$) of a ^{99m}Tc colloid-labeled pancake during control studies and during intermittent infusion of secretin (7.6 ± 1.4 pmol/kg · h) in 9 healthy subjects (mean ± SD).

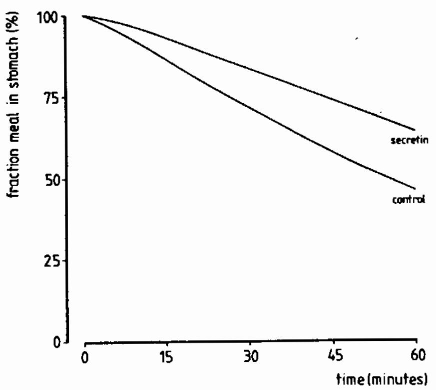

Figure 5. Mean gastric emptying curves of a ^{99m}Tc colloid-labeled pancake during control studies ($t_{1/2}$ = 55 min, power exponent = 1.2) and during intermittent infusion of secretin (7.6 ± 1.4 pmol/kg · h) ($t_{1/2}$ = 85 min, power exponent = 1.3) in 9 healthy subjects.

started to rise from fasting level when the secretin infusion was first begun, and that at 60 min the plasma concentration was similar to those at 25 and 42.5 min, an integrated mean concentration could be calculated for each subject. This mean integrated concentration was 4.8 ± 0.9 pmol/L. Intermittent infusion of secretin significantly increased half-emptying time from 55 ± 10 min to 85 ± 29 min (Figures 4 and 5). The power exponent was not affected by intermittent secretin administration; β = 1.3 ± 0.5 during secretin infusion versus 1.2 ± 0.2 during control studies. The power exponential curve fit well to the emptying curves; the median R^2 was 0.97 (range 0.69–0.99; $R^2 \leq 0.90$ in 3 of 33 tests).

Discussion

Secretin mediates stimulation of pancreatic fluid and bicarbonate secretion in response to acidification of the duodenum. It has been hypothesized that in addition to this effect secretin may also have a role in the prevention of duodenal acidification by inhibition of gastric acid secretion and the gastric emptying rate. Although secretin is indeed a potent inhibitor of gastric acid secretion and gastrin release (22,23), there is recent evidence that secretin does not have a physiologic role in the regulation of these in humans (9).

In respect to gastric emptying, two studies (9,10) suggest that secretin may be a physiologically important inhibitor of the emptying rate of liquids in humans. In this study we now show that secretin is also a potent inhibitor of the gastric emptying of solids. The question is whether this capacity has any impact for the regulation of gastric motility. Physiologic postprandial plasma concentrations of secretin, as measured by the assay used in this study, are ≤ 7 pmol/L (24). During the continuous infusion of secretin described above, the concentrations were therefore slightly above the physiologic range. During the intermittent infusion, the peak plasma secretin concentrations of about 8.5 pmol/L were still somewhat above the upper limit of postprandial concentrations (24), but the estimated integrated mean concentration of 4.8 pmol/L approximated those seen in the normal postprandial situation. In addition, intermittent infusion resulted in fluctuating plasma secretin concentrations, which is also seen under physiologic conditions (2,3,24). The marked retardation of the gastric emptying during the intermittent infusion, namely an increase by 55% of the half-emptying time, is therefore a strong indication that secretin is also able to inhibit the emptying rate of solid food at slightly lower plasma concentrations, which are in the physiologic range.

The finding that cimetidine did not affect gastric emptying does not disagree with the above conclusion. Plasma secretin concentration hardly increased after the meal without cimetidine, and any effect of this minimal increase on gastric emptying would be undetectably small. The minimal stimulating effect of the test meal on plasma secretin during the hour studied is probably due to two factors. First, the meal has a low protein content and is thus a poor stimulant of acid secretion. Second, intragastric pH is often increased during the first 30 min after a meal, due to its buffering capacity, and duodenal contents are therefore not acidified (2).

There was a large interindividual variation in the responses of the gastric emptying rate to the secretin administration. This was not explained by differences in plasma secretin concentrations, as there was no correlation between these concentrations and the increase of the half-emptying times ($r = 0.51$, $p > 0.05$). The observed variation seems therefore to be due to differences in gastric sensitivity to secretin.

The mechanism through which secretin influences gastric emptying is not elucidated by this study. In previous studies in humans it has been shown that high doses of secretin induce contraction of the pylorus (25,26) and possibly reduce the intracavitary pressure of the stomach (26), thereby slowing the gastric emptying. Secretin may elicit these effects through direct action on the gastric smooth muscle similar to the action of the neuropeptide vasoactive intestinal peptide (27), which is structurally related to secretin, or it may elicit the release of local substances like prostaglandins or enkephalins, which are present in the wall of the stomach and whose actions result in retardation of gastric emptying (28,29).

Secretin is not the only intestinal hormone with an inhibitory effect on gastric motility. Neurotensin (30), peptide YY (31), and the neuropeptide bombesin (32,33) have all been shown to retard gastric emptying in humans. The physiologic impact of all of these effects has not yet been elucidated. Two recent studies (34,35) indicate that cholecystokinin is a physiologic hormonal mediator of fat-induced inhibition of gastric emptying in humans. From this study and previous studies it can be concluded that secretin may be considered to be of physiologic importance in the regulation of the gastric emptying rate of liquids as well as solid food in humans.

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