

Effect of Low-Dose Exogenous Secretin on Pentagastrin- and Meal-Stimulated Gastric Acid Secretion in Humans

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Intravenous infusion of secretin in a dose of 0.05 CU/kg/hr inhibited pentagastrin-stimulated (100-ng/kg/hr) acid secretion by 42% ($P < 0.05$) and meal-stimulated (10% peptone, pH 5.5) acid secretion by 33% ($P < 0.05$) in 10 healthy subjects. Median serum gastrin concentration during peptone stimulation was reduced by 24% ($P < 0.05$) during secretin infusion. Median plasma secretin concentrations were 6.0 and 5.2 pmol/liter, respectively. Since these secretin concentrations are of the same magnitude as those seen after duodenal acidification, it is concluded that secretin may participate in the physiological inhibition of gastric acid secretion.

KEY WORDS: secretin; gastric acid secretion.

It has previously been shown that exogenously administered secretin inhibits gastric acid secretion in man (1-6); whether this action of secretin has any physiological importance in the regulation of gastric acid secretion is still obscure. Not until recently, when reliable radioimmunoassays for secretin became available, were physiological plasma secretin concentrations known (7, 8).

Plasma secretin concentrations in healthy individuals following physiological stimulation of secre-

tin release, ie, meal-stimulation or acidification of the duodenum, are below 10 pmol/liter (7, 9-12). Plasma secretin concentration approaches a level of 9 pmol/liter when gastric acid secretion is maximally stimulated by insulin-induced hypoglycemia (9). Reproduction of these plasma concentrations by exogenous administration is a prerequisite for any conclusions on the possible physiological significance of the observed actions. These doses have been established in studies on the effect of secretin on pancreatic bicarbonate secretion and plasma secretin and were found to be below 0.1 CU/kg/hr (12). With doses in this range, linear correlations were found between infusion dose and plasma secretin concentration, as well as between log increment in plasma secretin concentration and pancreatic bicarbonate secretion, suggesting that these infusion doses of secretin probably reflect physiological conditions.

The aim of the present study was to investigate

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the effect of these physiological doses of secretin on meal- and pentagastrin-stimulated acid secretion in healthy subjects.

MATERIALS AND METHODS

Subjects. Ten healthy volunteers, four women and six men, ages 21–42 years, were studied. The study was approved by the regional ethical committee and informed consent was obtained from all persons.

Experimental Procedure. In each subject the effect of secretin on pentagastrin-stimulated and on meal-stimulated acid secretion was studied in randomized order on four separate days.

After an overnight fast a double-lumen tube was placed in the stomach under fluoroscopic control. Meal-stimulated acid secretion was measured for 3 hr by an intragastric titration method using an automatic titration system (Radiometer, Copenhagen, Denmark) for titration to pH 5.5 with 0.5 mol NaHCO₃. The intragastric stimulus was 300 ml 10% solution of Bacto peptone (Difco Lab., Detroit, Michigan) adjusted to pH 5.5 and circulated through the stomach via the biluminal gastric tube by a peristaltic pump with an amount sufficient to keep the titration chamber filled. The amount of acid secretion was estimated by continuous titration by the pH-stat method and was recorded on a titigraph pen writer (Titigraph, Radiometer). A sudden horizontal deflection in the titration curve was taken as an index of duodenogastric reflux, and when it occurred the study was discarded and repeated on another day.

In the pentagastrin study, pentagastrin in a dose of 100 ng/kg/hr was administered as a continuous intravenous infusion for 150 min. With this dose of pentagastrin, a secretory plateau is reached after 90 min, and no fade occurs within the next 2 hr (13).

Gastric secretion was collected for each 15 min period by intermittent mechanical suction, producing a pressure of 150 mm Hg. The volume of gastric secretion was measured and the concentration of H⁺ was determined by titration to pH 7.0 with an autotitrator (Radiometer). Osmolarity as an index of duodenogastric reflux was determined by freezing-point reduction (14). Validation studies in our laboratory have shown that reduction in gastric juice osmolarity correlated well with the degree of reflux calculated according to Faber et al (15) during approximate plateau secretion. Osmolarity as an indicator of duodenogastric reflux is in contrast to estimations based on Sodium concentration independent of the secretory rate. During the gastric acid stimulation with peptone and pentagastrin, secretin or saline (control study) were infused intravenously with a flow of 50 ml/hr in randomized order on separate days, starting at time 0. Pure natural secretin (KABI Vitrum) was infused in a dose of 0.05 CU/kg/hr. The peptide was dissolved in 0.9% NaCl with 2% human albumin added.

Plasma secretin was measured after extraction with ethanol as previously described (7, 8). Antiserum 5595-3 was used, and all samples were assayed in duplicate. The assay variation was calculated from 16 samples and included duplicate control plasmas.

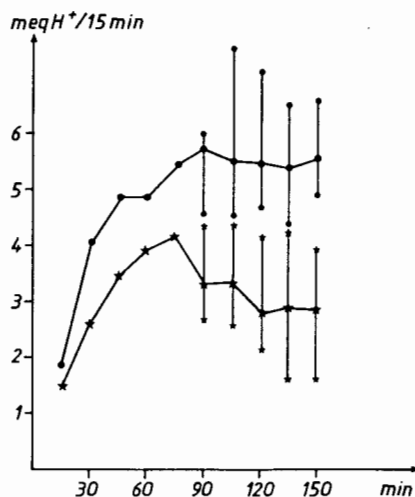


Fig 1. Gastric acid output during infusion of pentagastrin (100 ng/kg/h ●—●) and pentagastrin + secretin (0.05 CU/kg/hr, ★—★). Median and Interquartile range.

Interassay (16 assays) and intraassay variations (SD) were 0.7 and 0.4 pmol/liter, respectively, at a mean concentration of 9.8 pmol/liter. Detection limit was 0.8 pmol/liter, and ID₅₀ was 10 pmol/liter. Measurement of serum gastrin was performed as previously described (14, 15) using monoiodinated gastrin-17 tracer and Ab 2604. Component-1, gastrin-34, and gastrin-17 (sulfated as well as nonsulfated) are bound with equimolar potency to this antiserum (16, 17). The standard curves were prepared in charcoal-treated human plasma. Results are given as median and interquartile range. Differences were analyzed by the Wilcoxon test for paired differences; *P* values less than 0.05 were considered significant.

RESULTS

The effect of secretin on pentagastrin-stimulated acid secretion is shown in Figure 1. Secretin inhibited median acid output (90–150 min) from 5.4 to 3.1 meq/15 min (42%; *P* < 0.05). Plasma secretin concentrations during the combined infusion of secretin and pentagastrin were in the range 5.0–8.5 pmol/liter (Figure 2 with a median of 6.0 pmol/liter. Median osmolarity of gastric juice (90–150 min) was 287 mosm/liter (332–265) in the control study and 279 mosm/liter (324–259) in the secretin study (*P* > 0.05). Horizontal deflections of the titration curve as a sign of duodenogastric reflux occurred in two of the secretin studies and in one of the control studies. The median volume of peptone used in the secretin study to maintain the titration chamber filled was 190 ml/hr (range 118–242) and in the control study 207 ml/hr (143–280) (*P* > 0.05). Me-

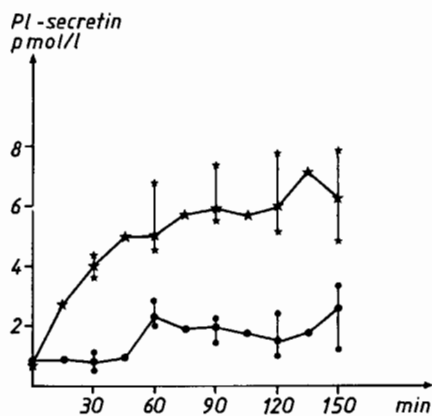


Fig 2. Plasma secretin concentration during infusion of pentagastrin (100 ng/kg/hr) + saline (★—★) and ●—● pentagastrin + secretin (0.05 CU/kg/hr, ●—●). Median and interquartile range.

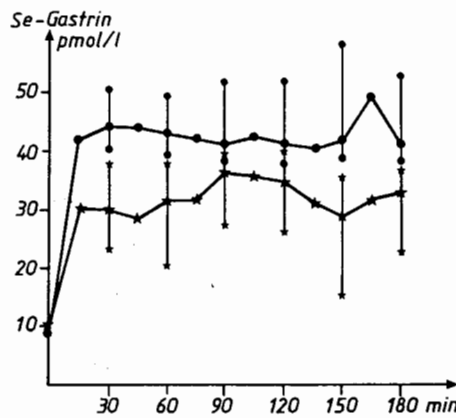


Fig 4. Plasma gastrin concentration during meal stimulation and infusion of saline (●—●) and infusion of secretin (0.05 CU/kg/hr, ★—★).

dian cumulative meal-stimulated acid secretion was inhibited from 45 to 31 meq H⁺ (33%; *P* < 0.05) (Figure 3), and median serum gastrin concentrations (15–180 min) from 42 to 31 pmol/liter (*P* < 0.05) (Figure 4). Plasma secretin concentrations during the combined meal stimulation and secretin infusion was in the range of 3.2–7.1 pmol/liter, (Figure 5) with a median of 5.2 pmol/liter.

In none of the control studies, ie, during infusion of pentagastrin + saline or during meal stimulation + saline infusion did plasma secretin change significantly. Pentagastrin infusion, however, resulted in a modest increase in plasma secretin concentration and meal stimulation in a decrease (*P* > 0.05).

DISCUSSION

The present study shows that secretin in a dose resulting in plasma concentrations in the same range as seen after duodenal acidification inhibits meal- and pentagastrin-stimulated acid secretion and meal-stimulated serum gastrin concentration. This observation corresponds well with the findings by Chey et al that elimination of meal-induced endogenous secretin by anti-secretin antiserum increased acid secretion in dogs with an innervated gastric pouch (18).

In a previous study, in which the effect of duodenal acidification and injection of secretin were compared, no effect of secretin injection on acid secretion could be demonstrated, although plasma

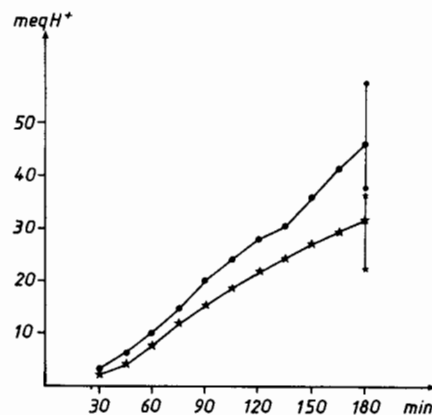


Fig 3. Cumulative meal-stimulated gastric acid secretion during saline infusion (●—●) and during infusion of secretin (0.05 CU/kg/hr, ★—★). Median and interquartile range.

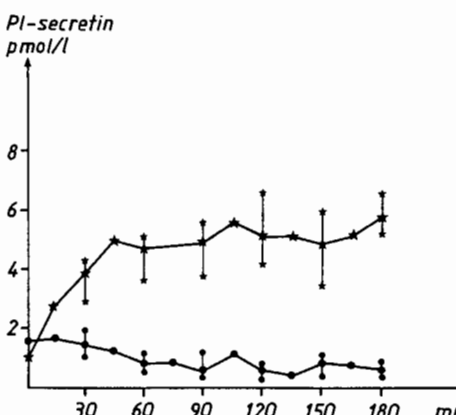


Fig 5. Plasma secretin concentration during meal stimulation and infusion of saline (●—●) and infusion of secretin (0.05 CU/kg/hr, ★—★).

secretin concentrations greatly exceeded those found after duodenal acidification which inhibited acid secretion significantly (19). The lack of effect of secretin injection could be due to the fact that acid secretion was stimulated with a supramaximal dose of pentagastrin (6 μ /kg/hr). This does of course not explain the dissociation between the effect of duodenal acidification and secretin injection, which must be explained either by release of some additional substance with acid inhibitory properties, by duodenal acidification, or by insufficient biological activity of the secretin preparation used.

In contrast, Londong et al (6) found a correlation between plasma secretin concentrations after different doses of secretin and gastric acid inhibition. The concentrations were, however, greatly above physiological levels, the lowest dose administered being 0.5 μ g/kg/hr. There was, however, no proportionality between plasma secretin concentration and acid inhibition (a fourfold increase in secretin dose only increased acid inhibition by 20%), which explains why Londong et al found 55% inhibition of acid secretion compared to 22% in our study although the secretin dose was 10 times higher.

Kleibeuker et al (20) found that meals of low pH inhibited gastric production of acid by 30–50% and produced secretin levels of 3.2–3.9 pmol/liter. In contrast, exogenous secretin producing plasma levels of 3.5 pmol/liter did not inhibit gastrin release and acid secretion during a meal of pH 5.5. The authors concluded that factors other than secretin are the mediators of acid-induced inhibition of gastric secretion. This discrepancy with the present results can hardly be explained by the slightly higher, but still physiological, secretin concentrations in our study; only a dissociation between the bio- and immunoactivity of the secretin preparation used by Kleibeuker et al might provide a reasonable explanation. Furthermore, the two antisera may react differently with human and porcine secretin, and porcine secretin is used for standards in both assays. Hence, the levels of endogenous secretin may be underestimated by Kleibeuker et al and the infusion rate of porcine secretin therefore too low (or too high in the present study).

In a previous study from this institution (13) 0.5 CU/kg/hr of secretin inhibited acid secretion stimulated by 150 ng/kg/hr of pentagastrin by only 12%. This discrepancy with the present study may be due to the fact that no albumin was added to the secretin infusion, so that an unknown and possibly variable amount of secretin reached the blood stream. This

may also explain why the same amount of secretin exerted an increased acid inhibition when higher doses of pentagastrin were used (1 and 6 μ g/kg/hr). In this study secretin induced reflux in two of five studies during 150 ng/kg/hr of pentagastrin and in 0 of 3 studies when 6 μ g/kg/hr of pentagastrin was used.

In a recent study using the same dose of secretin as in the present study, inhibition of spontaneous acid secretion was demonstrated (21). Decrease of acid output could, however, only be demonstrated in one of four 30-min periods during secretin infusion. The authors point to the problem of duodenogastric reflux when studying the effect of secretin on acid secretion, since the same study performed with secretin in a dose of 0.25 μ g/kg/hr was uninterpretable due to massive reflux. Their criteria for duodenogastric reflux was an increase in pH over 2 units from one gastric sample to another. In our study, reduction in osmolarity due to dilution when NaHCO_3 reacts with HCl, measured by freezing-point reduction, was taken as an indicator of reflux; this is a sensitive technique which, in cases with reduced gastric secretory volume, tends to overestimate rather than underestimate reflux (14). The fact that no significant difference in osmolarity was found during the interval 90–150 min between control and secretin study indicates that reflux is unlikely to be responsible for the observed acid inhibition. Furthermore, during meal stimulation, reflux could not explain the observed difference in acid secretion. The fact that plasma secretin increased moderately during pentagastrin stimulation and decreased during meal stimulation is probably due to the higher pH of the lumen, but unknown, amount of gastric content which empties into the duodenum during stimulation with peptone (pH 5.5) rather than during pentagastrin stimulation, where pH is between 1 and 2.

In conclusion, this study has shown that an amount of secretin which may be released from the duodenum under physiological circumstances is sufficient to inhibit stimulated gastric acid secretion. Consequently, secretin may participate in the physiological regulation of gastric acid secretion.

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