Does gastric acid release plasma somatostatin in man?

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SUMMARY Food and insulin hypoglycaemia raise plasma concentrations of somatostatin. Both also stimulate gastric acid secretion but it is not clear whether gastric acid itself has any effect on somatostatin secretion. We, therefore, studied the effect on plasma concentrations of somatostatin of infusion of 0.1 N HCl into the stomach and duodenum of healthy subjects. Plasma somatostatin did not rise with a small dose of HCl given intragastrically (15 mmol) or intraduodenally (4 mmol). After an intraduodenal infusion of 60 mmol HCl over 30 minutes, sufficient to reduce intraluminal pH to 2, plasma somatostatin rose moderately in five subjects from a mean value ($\pm$ SEM) of 32 ± 3 pg/ml to a peak at 10 minutes of 54 ± 11 pg/ml. It is concluded that: (a) intragastric acid infusions do not release circulating somatostatin in man; and (b) that intraduodenal acidification albeit at grossly supraphysiological doses is a moderate stimulus of plasma somatostatin release. Therefore, gastric acid is unlikely to be a major factor mediating postprandial plasma somatostatin release in man.

Somatostatin is a tetradecapeptide widely distributed in brain, gut, and pancreas of many species with the greatest abundance in stomach, duodenum and pancreas.^{1,2} When administered exogenously in pharmacological doses it has many inhibitory actions, both endocrine and non-endocrine.³ We have shown that circulating concentrations of somatostatin rise in man after oral ingestion of a meal⁴ or individual nutrients, especially fat or protein,⁵ and after insulin-induced hypoglycaemia.⁶ Both oral food and hypoglycaemia are stimuli of gastric acid secretion.⁷ It is possible that gastric acid is one factor stimulating somatostatin release. Somatostatin is a potent inhibitor of gastric acid secretion⁸ and therefore may participate in a negative feedback loop.

The present study was designed to investigate whether intragastric or intraduodenal acid can release somatostatin into peripheral plasma in normal subjects.

Methods

SUBJECTS

Fourteen male volunteers, mean age 22 years (range

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21-24 years) were within 10% of their ideal body weight and taking no medication. None had a history of endocrine, gastrointestinal or renal disease. After an overnight fast the subject was intubated by mouth with a fine bore flexible tube and its tip was positioned in the stomach or second part of duodenum under radiographic control. Two separate studies were conducted.

INTRAGASTRIC INFUSION

Six subjects each received on two separate occasions, an intragastric infusion of (a) 15 mmol 0.1 N isotonic HCl, and (b) a control intragastric infusion of 150 ml 0.15 N NaCl each given over 30 minutes. Intragastric pH was continuously monitored during the infusions and up to 110 minutes thereafter by a pH-sensitive radiotelemetry capsule tethered 5 cm beyond the distal aperture of the infusion tube.⁹ Experiments were performed in random order separated by at least one week.

INTRADUODENAL INFUSION

(a) Three subjects received on one occasion an intraduodenal infusion of 4 mmol 0.1 N isotonic HCl given over five minutes. (b) Five subjects were given 60 mmol 0.1 N isotonic HCl over 30 minutes into the second part of the duodenum.

Intraluminal pH was continuously monitored as described for intragastric infusions.

Blood was taken intermittently through an indwelling heparinised needle for estimation of plasma somatostatin, gastrin, pancreatic polypeptide, gastric inhibitory polypeptide and motilin. Samples for hormone estimation were taken into lithium heparin tubes containing 10 000 KIU aprotinin, centrifuged at 4°C and separated. The plasma was frozen immediately and stored at -20°C until assay.

ASSAYS

Plasma somatostatin,¹⁰ gastrin,¹¹ pancreatic polypeptide,¹² gastric inhibitory polypeptide¹³ and motilin¹⁴ were assayed by radioimmunoassay. Before assay somatostatin was extracted using Vycor glass; I¹²⁵ tyrosine-somatostatin (4 pg/tube) was used as a tracer together with a highly specific rabbit antisomatostatin serum (final dilution 1:150 000) which gave a sensitivity of 10 pg/ml plasma.

All subjects gave informed consent in writing. These studies were approved by the District Ethical Committee of St Bartholomew's Hospital.

STATISTICS

Results are expressed as mean $\pm$ 1 SEM. Student's *t* test for matched pairs was used and $p < 0.05$ taken as significant.

Results

INTRAGASTRIC INFUSION

The basal intragastric pH was 2 and this did not alter during or after the infusion of acid alone or saline. Basal plasma somatostatin concentrations did not significantly differ in either the acid or saline experiments and plasma somatostatin concentrations did not rise with either infusion. Similarly, neither infusion elicited a significant change in serum gastrin concentrations.

INTRADUODENAL INFUSION

(a) Three subjects each received an intraduodenal infusion of 4 mmol 0.1 N HCl in five minutes. Intraduodenal pH fell in all during the infusion to a nadir of 2. In two subjects plasma somatostatin at five minutes was slightly raised compared with basal concentrations: 12 vs 19 pg/ml; 12 vs 18 pg/ml; while concentrations were unchanged in the third. See Figure 1. Plasma somatostatin was not increased in any subject throughout the remaining period of sampling. Plasma gastrin, pancreatic polypeptide, gastric inhibitory polypeptide and motilin were unchanged throughout each experiment in all three subjects.

Fig. 1 Plasma somatostatin in three subjects given an intraduodenal infusion of 4 mmol HCl.

(b) Five subjects each received an intraduodenal infusion of 60 mmol 0.1 N HCl over 30 minutes. See Figures 2a, 2b. Intraluminal pH fell immediately from a mean pre-infusion concentration of 6.9 ± 0.4 to a nadir of 2.0 ± 0.1 at two minutes and remained low throughout the infusion. Intraluminal pH rapidly returned to its pre-infusion level when the infusion had been completed. Plasma somatostatin rose from a basal concentration 32 ± 3 pg/ml to a peak of 54 ± 11 pg/ml at 10 minutes ($p < 0.05$ vs basal); and was significantly raised at 20 minutes 46 ± 5 pg/ml ($p < 0.01$) and 30 minutes 45 ± 5 pg/ml ($p < 0.01$). Plasma somatostatin returned to basal concentrations by 40 minutes and gradually declined below basal concentrations thereafter.

Plasma gastrin, gastric inhibitory polypeptide and pancreatic polypeptide concentrations did not change during this infusion. Plasma motilin fell moderately during the acid infusion although this reduction reached significance at one time point only; basal 317 ± 59 pg/ml, 247 ± 57 pg/ml at 20 minutes ($p < 0.05$). Plasma motilin returned to pre-infusion levels by 60 minutes after which it declined below basal concentrations.

Discussion

The present study was designed to investigate the potential role of gastric acid as a factor mediating the release of circulating somatostatin in man. Intra-gastric and intraduodenal infusion of HCl in dogs raises portal and peripheral plasma somatostatin and intraluminal somatostatin concentrations.^{15 16 17} Somatostatin released into the local draining veins after intragastric instillation of a protein meal in dogs is enhanced by prior adjustment of the meal to a pH of 2.¹⁸

In the present study plasma somatostatin concentrations were not significantly altered by either an intragastric infusion of 15 mmol 0.1 N HCl given over 30 minutes, a dose which mimics the estimated maximal postprandial gastric acid output¹⁹ or intraduodenal infusion of 4 mmol 0.1 N HCl over five minutes, a stimulus reported to raise plasma concen-

Fig. 2 (a) Intraduodenal pH, plasma gastrin and plasma somatostatin in five subjects given an intraduodenal infusion of 60 mmol HCl. (b) Plasma motilin, pancreatic polypeptide, and gastric inhibitory polypeptide in five subjects given an intraduodenal infusion of 60 mmol HCl.

trations of other putative gut hormones.^{20 21 22 23} During an intraduodenal infusion of 60 mmol 0.1 N HCl over 30 minutes, a grossly supraphysiological dose which caused a sustained reduction in intraduodenal pH not found distal to the duodenal bulb in healthy subjects,^{24 25} there was a moderate rise in plasma somatostatin concentrations from 32 ± 3 pg/ml to a peak of 54 ± 11 pg/ml. This response should be compared with the effect of a 30 minute infusion into the second part of the duodenum of 100 calories of fat emulsion in normal subjects in which plasma somatostatin rose from a basal concentration of 30 ± 3 pg/ml to a peak of 101 ± 11 pg/ml.²⁶ Thus we conclude that even grossly unphysiological duodenal acidification is a submaximal stimulus of plasma somatostatin. The failure to reproduce in man the effects on plasma somatostatin of intragastric and intraduodenal acidification found in dogs may be because of species variation and differences in assay technique. Furthermore, the increases in plasma somatostatin in dogs were most marked in local draining veins. Our studies are confined to the systemic circulation. The effects of acid on local somatostatin release in man may not be reflected in peripheral blood measurements. Nor do our studies gainsay the possibility that gastric acid has a permissive effect on somatostatin release to other stimuli such as food.

As intraduodenal acidification has been widely

reported to stimulate the release of many other putative gut hormones in man, plasma gastric inhibitory polypeptide, pancreatic polypeptide and motilin were measured in addition to somatostatin and gastrin during the intraduodenal acidification experiments. Plasma gastric inhibitory polypeptide concentrations have been reported to be significantly increased after intraduodenal infusion of 5 mmol 0.1 N HCl. Similar small doses of intraduodenal acid have been reported to raise plasma gastric inhibitory polypeptide, polypeptide and motilin concentrations in man.^{20 21 22} It is surprising, therefore, that neither plasma gastric inhibitory polypeptide nor polypeptide were significantly raised by either 4 mmol or 60 mmol 0.1 N HCl infused into the duodenum. Furthermore, motilin concentrations showed a small but significant decrease during the infusion of the higher dose with a rebound to baseline concentrations when the intraduodenal pH had returned to 7. The reasons for these discrepant results are not clear. The reported rise in pancreatic polypeptide with a small dose of intraduodenal acid was of very short duration.²² The gastric inhibitory polypeptide and motilin response previously described, however, were sustained.^{20 21} It may be significant that other workers have also failed to show an effect of intraduodenal infusion of HCl on plasma gastric inhibitory polypeptide in normal subjects.²⁷ They attributed this divergence

to different antibody specificities. There can be no doubt that an adequate stimulus to lower intraluminal pH was given. The sustained albeit submaximal somatostatin response suggests that intraduodenal acidification did not simply damage the mucosa and thereby prevent all regulatory peptide responses.

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