

Effect of intragastric pH on antral gastrin and somatostatin release in anaesthetised, atropinised duodenal ulcer patients and controls

S L JENSEN, J J HOLST, L A CHRISTIANSEN, M H SHOKOUH-AMIRI, M LORENTSEN, H BECK, AND H-E JENSEN

From the Department of Surgery I, Kommunehospitalet, Copenhagen, the Institute of Medical Physiology C, Panum Institute, University of Copenhagen, Copenhagen, and the Department of Surgical Gastroenterology C, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

SUMMARY The synchronous change in the antral release of gastrin and somatostatin into a vein draining the stomach was studied during acidic and alkaline intragastric pH in six anaesthetised duodenal ulcer patients and six controls after atropinisation. No differences in the basal secretion of gastrin and somatostatin were observed among the two groups. Alkaline as well as acidic intragastric pH had no effect on the antral release of somatostatin in duodenal ulcer patients and controls. In contrast, alkaline intragastric pH was associated with a significantly higher antral gastrin release in duodenal ulcer patients than in controls. Acidic intragastric pH was associated with a significantly smaller inhibition of antral gastrin release in duodenal ulcer patients than in controls. These results suggest that atropinised anaesthetised duodenal patients release gastrin abnormally in the presence of acidic or alkaline intragastric pH and that any inverse relationship between antral gastrin and somatostatin release is uncoupled under these conditions.

Somatostatin-producing D cells are found in great number in the gastric fundus and antrum of many species.¹⁻³ Many of the D cells send out cytoplasmatic processes which seem to establish direct contact with the putative target cells – for example, parietal cells in fundic mucosa and gastrin cells in antral mucosa. These findings indicate that somatostatin exerts its effects locally on the target cells as a paracrine substance.³ Experimental data point in the same way: exogenously administered somatostatin inhibits gastric acid secretion and gastrin secretion.⁴⁻⁷ Because of this information, obtained in animals, it is a generally accepted theory that endogenous somatostatin influences gastrin release in a paracrine mode.

The following questions then arise: in man is secretion of somatostatin and gastrin, by local regulation, mutually dependent? Do patients with duodenal ulcer disease have a disturbed secretion of somatostatin from the antrum compared with controls?

To clarify this we studied the changes in somatostatin and gastrin release associated with changing intragastric pH, in anaesthetised patients. The patients were studied during either parietal cell vagotomy, or cholecystectomy.

Methods

SUBJECTS

Six patients with active uncomplicated duodenal ulcer disease and six patients with uncomplicated gall stone disease (controls) participated in the study. Gall stone patients had normal gastric function judged by history, radiograph examination, oesophagogastroduodenoscopy and pentagastrin test. The table shows that duodenal ulcer patients had significantly higher peak acid output (PAO) than controls ($p < 0.01$). Age and sex distribution were similar. All duodenal ulcer patients were submitted to parietal cell vagotomy because of several relapses of their duodenal ulcer despite treatment with cimetidine. Gall stone patients were submitted to cholecystectomy. None of the patients was taking any drugs, including anti-ulcer drugs, for at least one week before surgery.

Address for correspondence: Steen Lindkær Jensen, MD, PhD, Department of Surgical Gastroent. C, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.

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Table Age, sex, BAO and PAO distribution in relation to patients with duodenal ulcer disease (DU) and controls

	DU	Controls
Age (yr)	42±2.1	44.5±3.7 ns
Female:male	3:3	4:2 ns
BAO (mmol H ⁺ /h)	4.2±0.9	4.4±1.1 ns
PAO (mmol H ⁺ /h)	48.1±5.1	16.9±3.2 p<0.01

BAO=basal acid output. PAO=peak acid output.

None of the subjects had undergone any form of gastrointestinal surgery previously and none had a history of pancreatitis, diabetes mellitus, or other endocrine disease.

Informed consent was obtained from each subject before entering the study. The study design was approved by the local ethical committee.

EXPERIMENTAL PROTOCOL

All subjects were premedicated with morphine (15 mg) and atropine (0.6 mg) intramuscularly 30 minutes before admission to the theatre. They were anaesthetised after an overnight fast with halothane-nitrous oxide-oxygen and ventilated manually. They were prepared with intragastric tubes, one for monitoring of pH and one for instillation of hydrochloric acid (HCl) or bicarbonate (HCO₃⁻). After abdominal incision the position of the gastric tubes in the antrum was checked by palpation. Polyethylene catheters were inserted into the right gastroepiploic artery and vein just above pylorus for blood sampling.

The experimental protocol consisted of instillation of (1) 100 ml 0.1 M HCl for 7.5 minutes and (2) instillation of 200 ml 0.1 M NaHCO₃⁻ for 10 minutes into the antrum. Intragastric pH was monitored continuously and averaged 5 before instillation of HCl, 1.5 during instillation of HCl and 7.4 during instillation of HCO₃⁻. Venous and arterial blood samples were taken from the catheters inserted into the right gastroepiploic vessels which were opened for one minute at each blood sampling time.

The venous blood was allowed to drain freely into graded tubes for one minute periods, allowing determination of venous blood flow. Blood samples were collected simultaneously from the vein and the artery at -5, 0, 2.5, 5, 7.5, 10, 12.5, 15, and 17.5 minutes; zero time being the moment of instillation of HCl, and 7.5 being the moment of instillation of HCO₃⁻.

LABORATORY PROCEDURES

The venous and arterial effluents from the right gastroepiploic vessels were collected in chilled tubes (Minisorp, NUNC, Roskilde, Denmark) containing heparin and centrifuged for 10 minutes at 4°C. The supernatant was decanted and frozen immediately

until radioimmunoassay for somatostatin⁸ and gastrin.⁹ Somatostatin was assayed using antiserum R213 against sequence 5–10.⁸ Detection limit of the assay was 1 pmol/l, and the coefficient of variation was better than 10% in the working range. The gastrin antiserum (2609) was directed against the C-terminals of gastrin-17. It binds all the four gastrin components in circulation with equal potency.⁹

STATISTICAL ANALYSIS

Student's *t* tests were used for the evaluation of data. All values are given as mean±SEM. *p*-Values of less than 0.05 were considered significant.

Results

The mean blood flow in controls did not differ significantly from that of duodenal ulcer patients in the basal period as well as in the experimental period (Fig. 1). In both groups of subjects the mean blood flows were increased significantly above the basal levels throughout the experimental period (*p*<0.05). The blood flows during the experimental period did not differ from each other in either of the two groups of subjects.

Neither in arterial nor venous antral plasma were differences observed in basal gastrin concentrations between duodenal ulcer patients and controls (Fig. 1). The arterial gastrin concentrations were significantly lower than the venous concentrations during the basal period (*p*<0.01 at -5 and 0 min.).

The mean somatostatin concentrations in arterial or venous plasma in the basal period in duodenal ulcer patients did not differ significantly from those of controls (Fig. 2). No differences in arterial and venous somatostatin concentrations were observed in the basal or the experimental periods.

After HCl instillation venous gastrin concentrations decreased significantly below the basal levels in controls as well as in duodenal ulcer patients (*p*<0.01 at 5 and 7.5 minutes in each group of subjects). The decrease in gastrin release was significantly lower in duodenal ulcer patients than in controls (*p*<0.01 at 5, and 7.5 minutes). After HCO₃⁻ instillation venous gastrin concentrations immediately returned back to basal levels and increased significantly above these at 12.5, 15, and 17.5 minutes (*p*<0.01 at each time). The increase in gastrin concentrations was significantly higher in duodenal ulcer patients than in controls (*p*<0.05 at 12.5 minutes; *p*<0.01 at 15, and 17.5 minutes) (Fig. 1). The arterial gastrin concentrations were unchanged and significantly below the venous concentrations during the entire experimental period in both groups of subjects.

Neither HCl nor HCO₃⁻ instillation caused significant changes in venous or arterial concentrations of

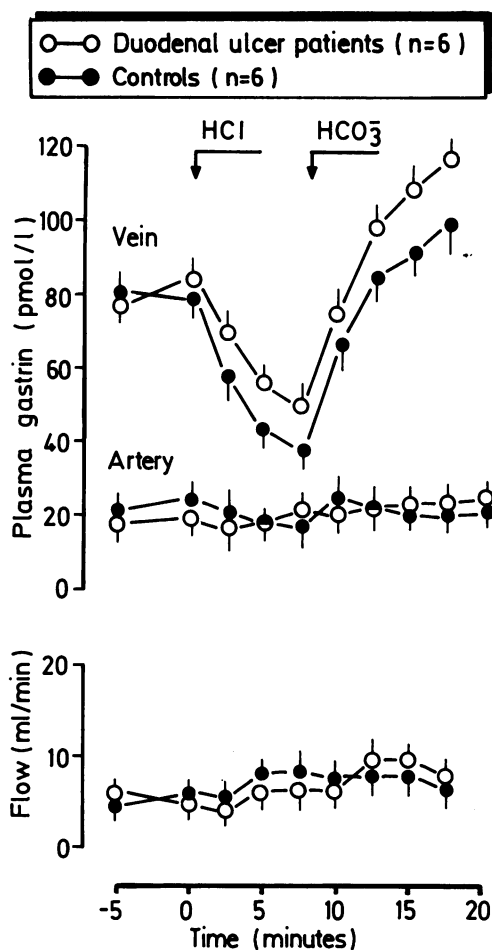


Fig. 1 Effect of acidic and alkaline intragastric pH on antral venous blood flow and the secretion of gastrin into the right gastroepiploic vein and artery of anaesthetised, atropinised duodenal ulcer subjects and controls.

somatostatin in either group of subjects. The arterial somatostatin concentrations did not differ significantly from the venous concentrations.

No subject experienced any unwanted effect.

Discussion

The present study in anaesthetised atropinised duodenal ulcer and control subjects showed that gastrin release into antral venous blood was influenced by intragastric pH. Somatostatin release was not affected. Thus, under these conditions an inverse relation between gastrin and somatostatin release could neither be shown in controls nor in duodenal ulcer subjects. Duodenal ulcer subjects had significantly higher gastrin concentrations during acidic and

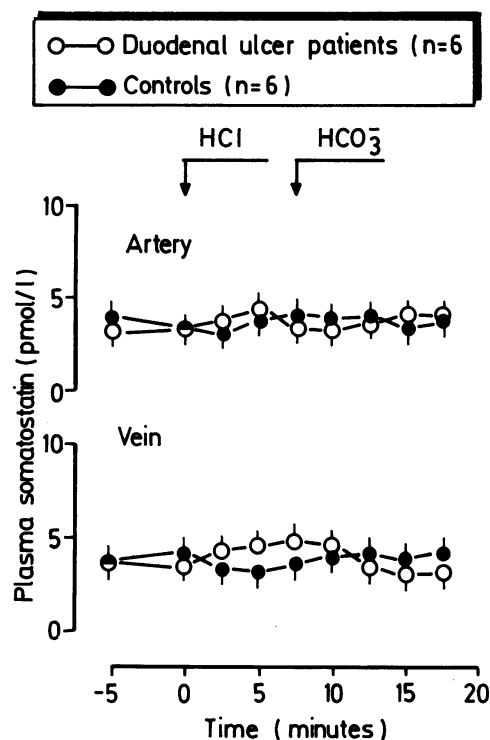


Fig. 2 Effect of acidic and alkaline intragastric pH on the secretion of somatostatin into the right gastroepiploic vein and artery of anaesthetised, atropinised duodenal ulcer subjects and controls.

alkaline intragastric pH in antral venous blood compared with control subjects. No differences in basal gastrin and somatostatin concentrations were observed between the two groups of subjects.

It is difficult to show paracrine interactions between peptides in human subjects by measuring their concentrations in peripheral venous blood.¹⁰ Experiments must be designed in animals,¹¹⁻¹³ which allow sampling of blood directly from the target organs under different conditions of stimulation. In order to study the paracrine relationship between antral somatostatin and gastrin we catheterised the right gastroepiploic vein in human subjects. This vein drains exclusively the antrum.¹³ The study is open to criticism, however, as the investigations were only carried out in atropinised subjects. For ethical reasons the department of anaesthesiology did not approve a protocol without atropine as premedication. Nevertheless, the finding of an uncoupled inverse relationship between gastrin and somatostatin release is in contrast with our previous findings in the isolated perfused porcine antrum.¹¹ In this preparation gastrin and somatostatin release were always inversely affected by the applied stimuli.

Similar findings have been made in other systems,¹⁴⁻¹⁷ but other results point to an independent regulation of gastrin and somatostatin secretion. Thus luminal peptone,¹⁶ nicotine agonists,¹⁷ and the bombesin nonapeptide¹⁸ stimulate both somatostatin and gastrin release in various preparations.

In the present study the reason for an uncoupled inverse gastrin and somatostatin release could be the atropinisation of the subjects. In the isolated perfused porcine antrum we have recently shown that gastrin responses to vagal stimulation were atropine resistant, whereas the vagally induced somatostatin inhibition was abolished.¹³ Therefore in these circumstances other factors than local changes in somatostatin release must be responsible for the changes seen in gastrin release. A possibility could be changes in the release of the newly discovered neuropeptide 'gastrin releasing polypeptide' localised exclusively to nerves in the antrum.^{3,19} Gastrin releasing polypeptide (GRP) is capable of influencing the gastrin release and the GRP responses are atropine resistant.¹³ Like the somatostatin cells, however, gastrin cells are of 'the open type' with microvilli protruding into the glandular lumen. Thus the morphology might support the possibility that the gastrin cells themselves may recognise intragastric pH changes without intervening paracrine somatostatin release.

It is well known from earlier studies that gastrin levels in peripheral venous blood are pH dependent in normal and duodenal ulcer subjects,²⁰ but no evidence of a defective feedback inhibition of gastric acid on gastrin release has been documented in duodenal ulcer patients. In the clinical study reported here, the two groups studied were similar with respect to age and sex distribution; and it is clear that acid inhibition and alkaline stimulation of gastrin release are defective in some way in our duodenal ulcer patients. Inhibited and stimulated gastrin concentrations in antral venous blood were higher in duodenal ulcer subjects than in control subjects. This offers further support for the impression that duodenal ulcer patients have varying degrees of hypergastrinaemia.²¹

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