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ERADICATION OF *HELICOBACTER PYLORI* AND GASTRIN-SOMATOSTATIN LINK IN DUODENAL ULCER PATIENTS

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Helicobacter pylori (Hp) infection may be associated with duodenal ulcer (DU) and accompanied by increased release of gastrin and deficiency of somatostatin (S-S) but the mechanisms of these changes in DU patients after eradication of Hp have been little studied. Cholecystokinin (CCK) has been implicated in the feedback control of gastric acid secretion in healthy subjects but its contribution to secretory disorders in DU patients has been little examined. This study, therefore, investigated whether CCK participates in the impairment of postprandial gastrin release and gastric acid secretion in active DU patients. Tests were undertaken in 10 DU patients without or with elimination of the action of endogenous CCK using loxiglumide (LOX), a selective CCK-A receptor antagonist, before and 4 wk. after eradication of Hp with triple therapy (omeprazole, amoxycillin and bismuth). In Hp positive DU patients, the postprandial acid secretion (measured by continuous intragastric pH monitoring) was accompanied by a pronounced increment in plasma gastrin with negligible increase of intraluminal release of S-S. The administration of LOX in these patients did not affect significantly the postprandial pH profile and the rise in plasma gastrin. After eradication of Hp the median postprandial intragastric pH increased to about 4.3 (compared to 3.5 before the Hp eradication); the postprandial gastrin concentration was reduced by about 40%, while luminal release of S-S was increased 2 folds. The administration of LOX resulted in significantly greater decrease in median pH (3.1) and higher rise in postprandial plasma gastrin in these patients. Also the postprandial plasma S-S showed a small, but significant decline (by about 25%) as compared to that in placebo treated patients. This study provides evidence that: (1) Hp infection in DU patients is accompanied by enhanced gastrin release and the reduction in luminal release of S-S; (2) The failure of LOX to affect gastric secretion and plasma gastrin DU Hp infected patients could be attributed, at least in part, to the failure of endogenous CCK to control gastric acid secretion *via* release of S-S; (3) Hp infected patients appear to exhibit a deficiency of S-S release that can be reversed by the eradication of Hp indicating that both peptides may contribute to the acceleration of the ulcer healing following Hp eradication in DU patients; (4) The test with LOX and gastric luminal S-S assay may be useful in identification of Hp positive DU patients with CCK-mediated impaired feedback control of gastric secretion and deficiency of S-S caused by Hp infection.

Key words: *Helicobacter pylori, gastrin, gastric acid, CCK, CCK-A-receptors, somatostatin*

INTRODUCTION

As previously shown, duodenal ulcer (DU) patients, as a group, tend to secrete more acid than normal subjects both at rest and in response to secretory stimulation (1). After ingestion of meal the major stimulant of gastric acid secretion is an increased plasma gastrin (2—4), and the DU patients have been reported to have higher plasma gastrin response to a meal and to exhibit an impaired inhibition of gastrin release at lower intragastric pH (5). Other studies showed that endogenous cholecystokinin (CCK) may be implicated in the feedback control of gastrin release and gastric acid secretion (6, 7) because the administration of loxiglumide greatly enhanced the plasma gastrin and gastric acid secretion in response to ordinary feeding, protein meal or gastrin releasing peptide (GRP). Moreover, DU patients were found to exhibit a defect in the inhibitory action of endogenous CCK (9—12) on gastrin release and gastric acid secretion suggesting an important role of CCK in the feedback control of gastric secretory functions.

The role of CCK as "enterogastrone" in the control of gastric secretion by duodenal acid or fat has also been tested in dogs using highly selective CCK-receptor antagonist such as L-364.718 (13, 14). These studies confirmed that CCK released by peptone meal, especially when combined with fat (13) or acid (14), exerts a potent inhibitory influence on gastric acid secretion and gastrin release mainly through enhancing the release of endogenous somatostatin. Also in DU patients the defect in the inhibitory action of CCK on gastric secretion (10—12) has been suggested to result from the failure of CCK to activate (through the CCK-A receptors) the D-cells to release somatostatin because in these patients loxiglumide did not affect significantly the plasma somatostatin level (10).

More recently it was found that chronic infection of *Helicobacter pylori* (Hp) can be encountered in up to 95% of DU patients and is usually accompanied by nonspecific antral gastritis (15—17). It has been suggested that chronic Hp infection may lead to DU disease due to an inappropriately high gastrin release and subsequent enhancement of gastric acid secretion. In other reports reduction in postprandial gastrin responses after eradication of Hp in DU patients have been shown (18, 19). Furthermore, studies on asymptomatic (without DU) individuals infected with Hp revealed that these subjects have significantly higher peptone meal-induced plasma gastrin levels and significantly attenuated inhibition of plasma gastrin at low intragastric pH as compared to noninfected asymptomatic subjects (20). Other reports have shown an increase of the G-cells/D-cells ratio in gastric mucosa and decreased release of gastric somatostatin during Hp infection probably due to the decrease of D-cells density (26). Based on currently available data it was proposed that the impaired inhibition of gastrin release and gastric acid

secretion observed previously in DU patients (5) may be related to the infection of Hp in these patients.

This study was designed to assess the possible role of endogenous CCK and somatostatin in the impaired control of gastrin release in DU patients before and after eradication of *Helicobacter pylori.*

MATERIAL AND METHODS

Subjects

Studies were approved by Institutional Research Review Committees at the University of Münster and the Jagiellonian University of Cracow and written informed consent was obtained from each subject. Studies included 13 male patients, their ages ranged from 22 to 28 years (mean age 24 years). All of them had active DU diagnosed by clinical history and actual gastroduodenal endoscopy. All of them have had two or more episodes of symptomatic relapse within 1 year. None had symptoms of ulcer disease at the time of study. The patients had been treated with sucralfate which was withdrawn at least 3 days before the examination.

Study protocol

Subjects were studied on three separate days before and after eradication of Hp. On one day, the subject's Hp status was tested using two endoscopic biopsy specimens obtained from lesser curvature of the middle antrum. One specimen was assessed histologically and one by rapid urease test for evidence of Hp infection. In histologic assessment, the specimen was fixed in 10% buffer formalin, embedded in paraffin and sectioned. Sections were stained with hematoxilin-eosin and with Giemsa for detection of Hp. The second specimen was used for rapid urease CLO test (Delta West Pty Ltd., Bentley, Australia). Additionally each patient underwent the ^{13}C-urea breath test. Only Hp positive subjects were included in further studies.

Gastric secretory studies with intragastric pH monitoring

On a second day, gastric acid secretion was studied for one hour under basal conditions and then for three hours after standard liquid 500 kcal meal (500 ml Fresubin, Fresenius, Bad Homburg, Germany). This meal consisted of protein (3.8%), amino acids (0.6%), carbohydrates (14%), fat (3.8%), minerals, vitamins and water with osmolarity of about 300 mOsm/l and pH of about 6.0.

Throughout the examination period, the intragastric pH was monitored by means of intraluminal system including the pH antimony electrode (Monocrystal, model 9-0215, Synectics, Stockholm, Sweden) connected to a portable apparatus which permitted the pH recording to be sampled every four seconds (Digitrapper MKII, Synectics, Stockholm, Sweden). The antimony electrodes used an external reference fixed on the thorax. At the beginning and at the end of each examination, the pH electrode was calibrated at 21°C with pH 7.01 and pH 1.07 using standard buffers (Synectics, Stockholm, Sweden) and a temperature correction for intragastric reading (37°C) was performed as described before (21, 22). The pH electrode was passed through an anesthetized nostril and positioned in the distal portion of the stomach (antrum) under fluoroscopic control

approximately 15 cm below the lower esophageal sphincter. The pH recordings started at about 8.00 and lasted for 4 hours and this included 60 minutes of basal period and 180 minutes after ingestion of liquid meal.

Data from intragastric pH monitoring were transferred to an IBM compatible computer (80386-IBM) programmed with Gastrogram version 5.50 serial N°E1024 (Gastrosoft, Irvine, USA) for calculation of mean and median pH values for each 3 h postprandial period. Data from all six subjects treated with placebo and loxiglumide were analysed using the program STATpHAC II/PHARM, version 216 D3 (Gastrosoft, Irvine, USA). Gastric acidity was assessed as pH and data from each subject were transferred into 10 min. median values. The median and mean 3 h intragastric pHs were pre-defined for comparison between study days using Wilcoxon's signed rank test. Box and whisker plots of mean and median intragastric pH in six patients were calculated for the 3 h period after standard meal. Statistics of pH profiles were calculated and compared in medians and means with significance level of less than 0.05.

On separate occasions, gastric secretory rate and intragastric, luminal release of somatostatin was determined after stimulation with i.v. pentagastrin infused at 2 μg/kg-h. Gastric content was collected using double lumen naso-gastric tube in 15 min aliquotes during 1 hour basal period and 1 hour after pentagastrin stimulation. Released HCl was determined using back-titration to pH 7 as described previously (7). Samples of gastric content, adjusted immediately to pH 7 after being collected, were stored at −70°C for further determination of somatostatin by specific RIA as described previously (8).

Each subject was tested four times before, twice during and again four times after eradication of Hp using 1. standard liquid meal with p.o. administration of placebo tablet 30 min. before meal, 2. standard meal and p.o. loxiglumide tablet (1200 mg) given also 30 min. before meal, 3. 0.9% NaCl i.v. given for the period of 1 hour during collection of gastric content for basal and stimulated gastric secretion and 4. pentagastrin (2 μg/kg-h) i.v. given for 1 hour after gastric content was collected for determination of basal seretory rate. Gastric acid secretion has been studied three times namely before, after termination of the antimicrobial therapy (third week during eradication therapy) and five weeks after the entire eradication therapy was successfully completed.

Eradication of Hp was achieved with triple therapy including amoxycillin, 500 mg three times daily for two weeks, omeprazole (20 mg) twice daily for 4 weeks and colloidal bismuth subcitrate (CBS, 120 mg) four times daily for 4 weeks. Endoscopy performed 4 weeks after ending of treatment showed complete ulcer healing in all examined patients but the second series of tests for eradication of Hp including ^{13}C-urea breath test revealed Hp eradication only in ten out of thirteen treated patients. Final gastric secretory examinations were performed five weeks after ending the therapy and carried out only in Hp negative patients.

Radioimmunoassays

Venous blood samples were obtained from a peripheral vein under basal conditions (twice) at 30 min. intervals before and after standard meal (6 times) before and after eradication of Hp in subjects receiving placebo or loxiglumide tablets. Plasma gastrin was determined using gastrin antiserum 4562 (kindly donated by Professor J.E.Rehfeld of Copenhagen, Denmark) in a final dilution of 1:140000. The antibody used recognizes G17 and G34 equally. The sensitivity of the gastrin measurement in the present assay was 2.5 pmol/ml serum equivalent to human G17 as described previously (22).

Plasma CCK concentrations were determined by radioimmunoassay using antiserum NY 112 (kindly provided by Professor N. Yanaihara, Shizuoka, Japan) which recognizes equally the sulfated residue of CCK-8 and CCK-39but has only negligible cross-reactivity with sulfated G17 (<5%) and does not cross react with unrelated gastrointestinal peptides. Plasma samples were extracted with ethanol/acetic acid mixture, dried in vacuum and restituted with assay diluent just

before the assay. Synthetic sulfated human CCK-8 (gift of Professor N. Yanaihara) was used as a standard and ^{125}I-labeled with Bolton and Hunter reagent (Amersham, UK) as a tracer (11). The detection limit of the assay was 0.5 pmol/ml plasma CCK-8 standard. Intraassay and interassay coefficients of variation were 8% and 12%, respectively.

Plasma and intragastric, luminal somatostatin was measured using a commercially available radioimmunoassay kit purchased from Milab, Malmö Immun-Labs Ab, Malmö, Sweden as described previously (11). The antiserum used recognizes only cyclic forms of somatostatin-14 and somatostatin-28 equally and does not cross react with any known gastrointestinal peptide. Plasma gastric juice somatostatin was extracted with ethanol/acetic acid mixture, dried in vacuum and restituted as in case of CCK. The detection limit was 0.5 pmol/ml. Intraassay and interassay variations were 8% and 12%, respectively.

Results of plasma hormones are expressed as means $\pm$ SEM. Statistical significance was determined by both the Wilcoxon signed rank test and the pairedt-test. Significance was accepted with p values of less than 0.05.

RESULTS

Out of thirteen Hp positive patients initially included into the study, only ten had negative histological, rapid urease (CLO test) and ^{13}C-urea breath tests four weeks after the end of triple therapy. The results presented in this report concern only the ten subjects who showed negative Hp status and who completed the intragastric pH monitoring tests with placebo and loxiglumide and gastric secretory tests after pentagastrin stimulation before and after eradication of Hp.

Table 1. Median postprandial, intragastric pH in DU patients before and following Hp eradication after standard meal with and without pretreatment with loxiglumide. Median of 6 tests on ten patients. Asterisk indicates significant change as compared to the values obtained with placebo.

	INTRAGASTRIC pH							
	−30 min	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Placebo, before eradication	1.2±0.1	1.2±0.1	6.1±0.5	4.2±0.4	1.4±0.2	1.2±0.1	1.2±0.15	1.1±0.05
Lox, before eradication	1.15±0.1	1.2±0.1	6.3±0.8	5.1±0.4	3.9±0.3	2.1±0.3	1.3±0.2	1.1±0.05
Lox, after HP-eradic.	1.1±0.05	1.2±0.1	5.9±0.6	3.2±0.4*	1.2±0.1*	1.1±0.05*	1.2±0.15	1.1±0.05

Tab. 1 demonstrates the median values of intragastric pH recorded during 30 min of basal state and during 3 h after ingestion of standard liquid meal. The median pH value in Hp positive patients during the basal period was about 1.2 and was not significantly different between placebo and loxiglumide treated subjects. With the ingestion of meal, the median pH immediately rose

to about 6 and then slowly declined within about 90 min. to the pre-meal value, the median pH for 3 h of postprandial period being about 3.5. In subjects treated with loxiglumide, the median pH also rose to pH 6.0 and then declined to pre-meal value within about 60 min., the median pH for the examined period (3 h) being about 3.1. The difference in the median postprandial pH between placebo and loxiglumide treated Hp positive DU patients was not statistically significant.

The pH profile in DU patients with negative Hp status, showed similar basal pH value (pH 1.3) and similar pH peak (about pH 6) after ingestion of standard meal. The return of intragastric pH after meal to the pre-meal value occurred after about 120 min. in placebo treated subjects and after about 60 min. in loxiglumide treated subjects. The median pH for the examined period (3 h) was significantly lower in tests with loxiglumide (pH 3.1) than in tests with placebo (pH 4.2).

Basal plasma gastrin, CCK and somatostatin in placebo-treated Hp positive DU patients averaged 27 ± 3, 0.8 ± 0.2 and 3.8 ± 0.3 pmol/l. Ingestion of standard liquid meal by these patients treated with placebo resulted in significant increments (above basal) of plasma levels of gastrin (*Fig. 1*), plasma CCK (*Fig. 2*) and somatostatin (*Fig. 3*) by about 88%, 50% and 68%,

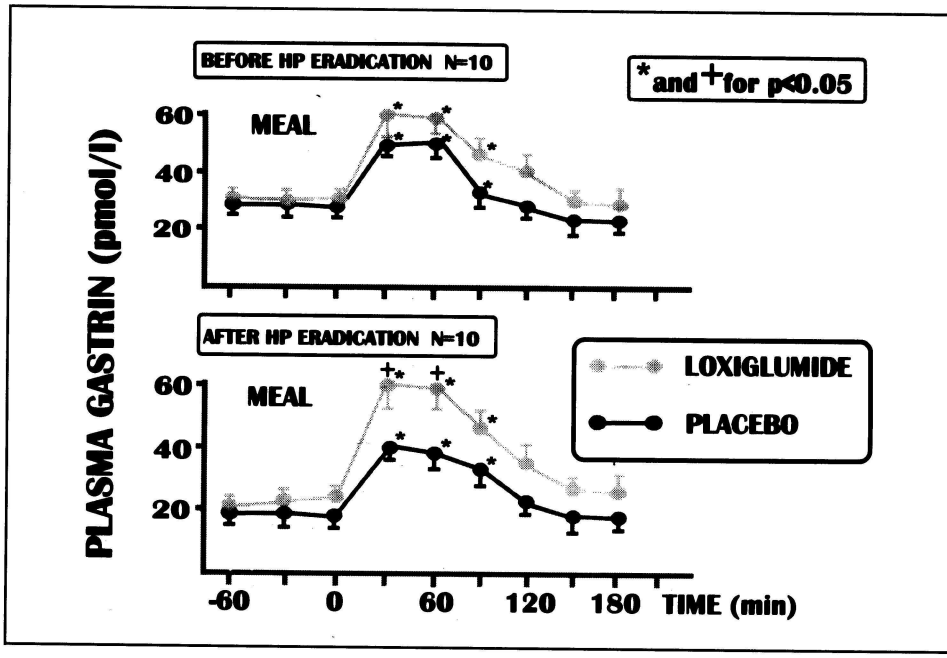

Fig. 1. Plasma gastrin under basal conditions and following standard meal in DU patients before and after eradication of Hp in tests with placebo or loxiglumide. Mean of 6 tests on six patients. Asterisk indicates significant increase above the basal value. Cross indicates significant change as compared to the value obtained with placebo. $P < 0.05$.

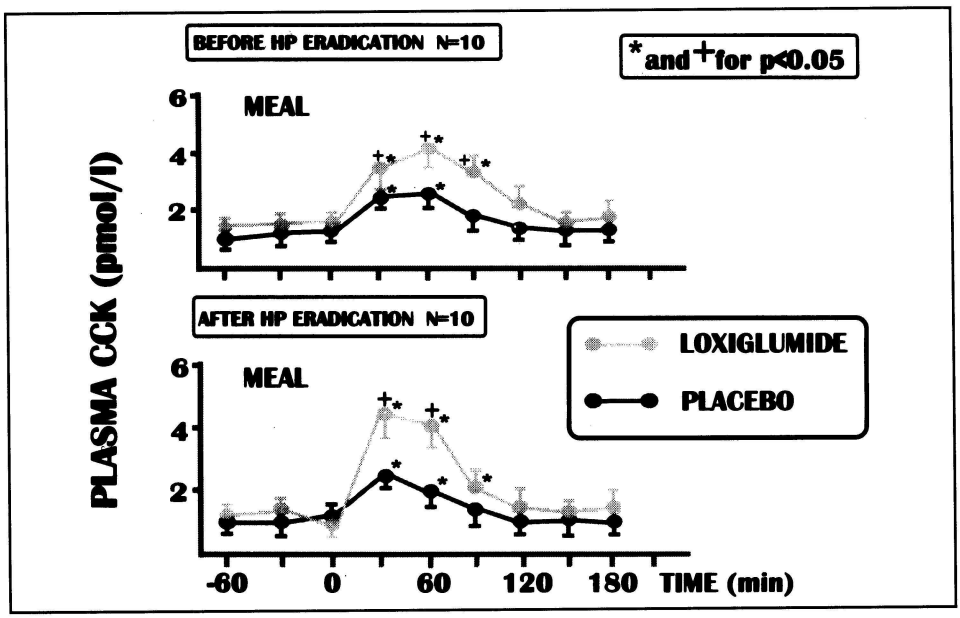

Fig. 2. Plasma CCK levels under basal conditions and following standard meal in DU patients before and after eradication of Hp in tests with placebo or loxiglumide. Mean of 6 tests on six patients. Asterisk indicates significant increase above the basal value. Cross indicates significant change as compared to the value obtained with placebo. $P<0.05$.

respectively. In tests with loxiglumide basal plasma hormones were not significantly affected as compared to placebo but the postprandial increments of plasma gastrin and somatostatin were similar to those observed in these patients after treatment with placebo. The increment of meal-induced plasma CCK was almost twice as high in tests with loxiglumide as with placebo.

Following eradication of Hp in DU patients, the basal levels of gastrin, CCK and somatostatin were similar to those in these patients before the Hp eradication. The postprandial rise in plasma gastrin in placebo-treated patients was significantly smaller than that observed in these subjects before the eradication. In tests with loxiglumide, the increment in the postprandial plasma gastrin was about twice as high as in tests with placebo administration (*Fig. 1*). The postprandial increments in plasma CCK levels in Hp negative DU patients treated with placebo were significantly lower than those in tests with loxiglumide. Thus, the administration of loxiglumide resulted in a significant rise in plasma CCK over that observed in placebo-treated subjects both before and after the eradication of Hp (*Fig. 2*).

Plasma somatostatin levels showed only small increase over basal values when a standard meal was administered in placebo-treated patients both with

Hp positive and Hp negative status. On the other hand, in Hp negative DU patients, the increment in plasma somatostatin in tests with loxiglumide was significantly smaller than that in tests with placebo (*Fig. 3*).

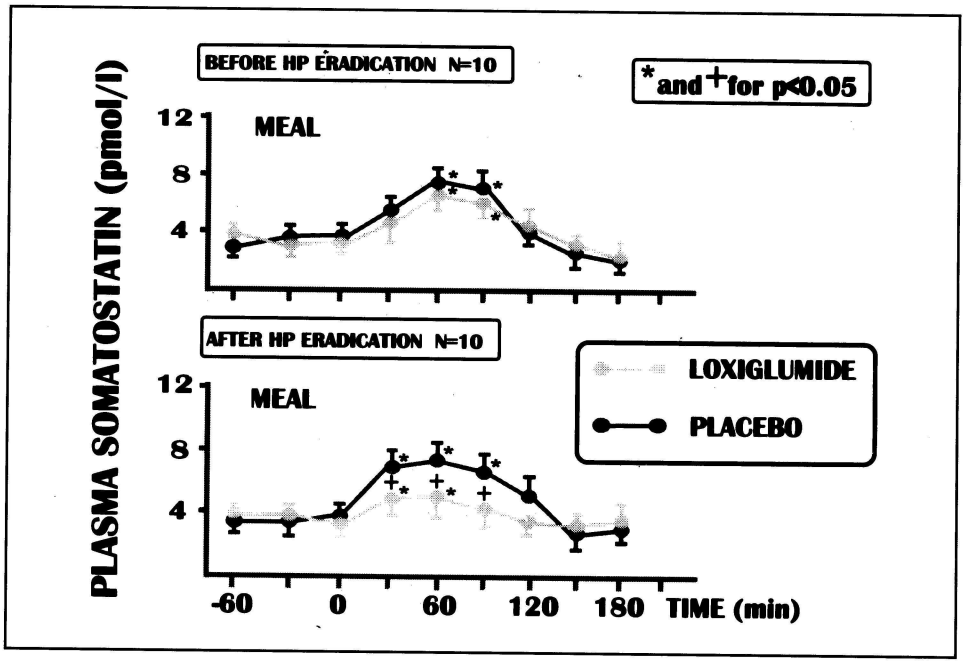

Fig. 3. Plasma somatostatin levels under basal conditions and following standard meal in DU patients before and after eradication of Hp in tests with placebo or loxiglumide. Mean of 6 tests on six patients. Asterisk indicates significant increase above the basal value. Cross indicates significant change as compared to the value obtained with placebo. $P<0.05$.

Before Hp eradication gastric acid secretion under basal conditions was significantly higher in DU patients when compared to healthy volunteers (8.3 ± 0.4 vs 4.8 ± 0.5 mmol/h H^+, respectively) and this secretory rate rose significantly after stimulation with pentagastrin reaching in DU patients 27.7 ± 3.9 mmol/h and in healthy subjects 18.2 ± 2.7 mmol/l (*Fig. 4*). The maximal secretory rate was significantly higher in Hp-positive DU patients than in healthy subjects. After termination of the antimicrobial therapy with amoxycillin the basal acid secretion did not show any significant changes in DU patients and after pentagastrin stimulation only a tendency towards reduction in the maximal secretory response could be observed. Five weeks after successfull eradication therapy, basal acid secretion decreased to the level not significantly different from that observed in healthy controls. Also the maximal secretory response after pentagastrin stimulation did not differ from that observed in healthy subjects (*Fig. 4*).

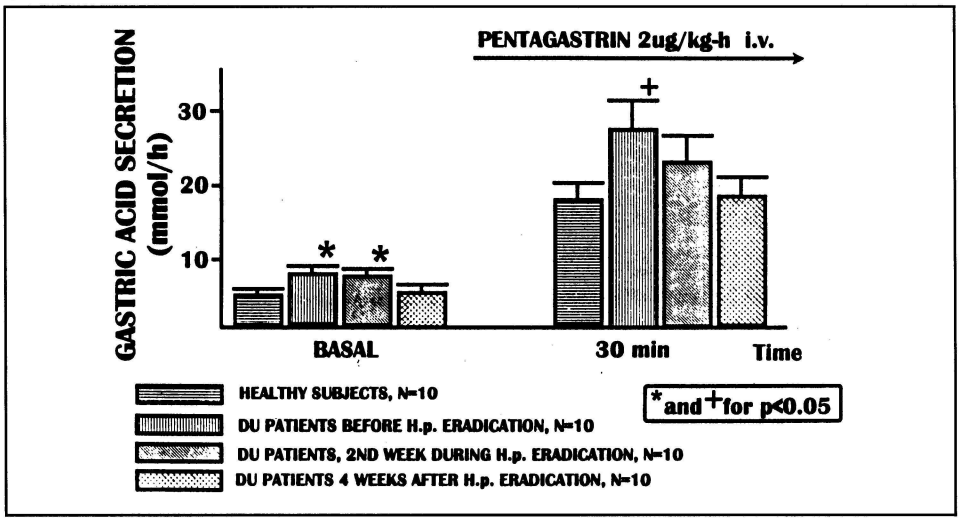

Fig. 4. Gastric acid secretion under basal conditions and after pentagastrin stimulation in healthy subjects and DU patients before, during and five weeks after successfull eradication of Hp. Mean of 6 tests on ten patients and ten healthy, Hp-negative volunteers. Asterisk and cross indicate significant difference as compared to the values obtained in healthy controls. $P < 0.05$.

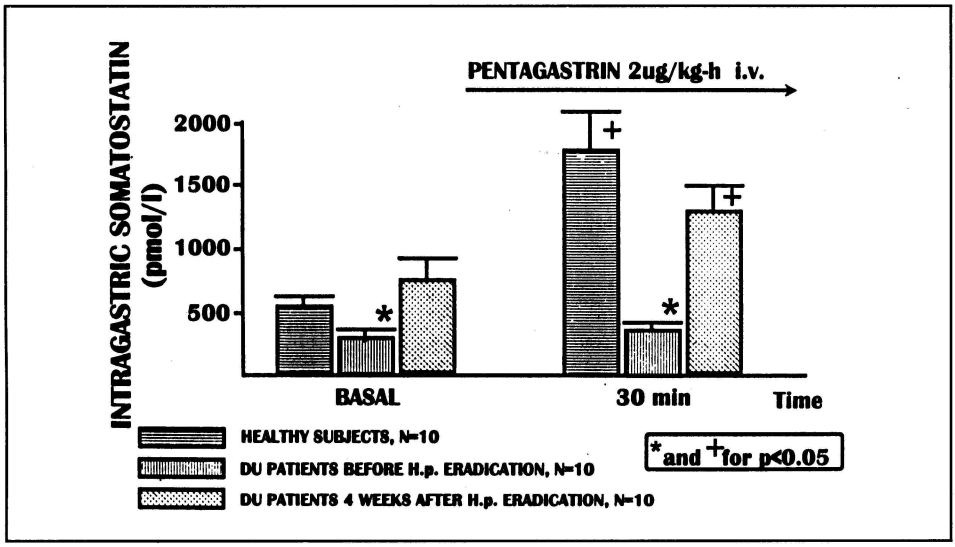

Fig. 5. Luminal release of somatostatin under basal conditions and after pentagastrin stimulation in healthy subjects and DU patients before and five weeks after successfull eradication of Hp. Mean of 6 tests on ten patients and ten healthy, Hp-negative volunteers. Cross indicates significant increase above the basal value. Asterisk indicates significant change as compared to the value obtained in healthy controls. $P < 0.05$.

Before Hp-eradication, intragastric, luminal level of somatostatin was significantly ($p<0.05$) lower in Hp-positive DU patients when compared to healthy, Hp-negative controls (265 ± 42 vs 580 ± 63 pmol/l, respectively). Following pentagastrin stimulation in DU patients the intragastric release of somatostatin showed only tendency to increase but this rise did not reach statistical significance before the eradication of Hp (*Fig. 5*). In healthy subjects, pentagastrin stimulation led to a significant rise of luminal somatostatin reaching values of 1680 ± 195 pmol/l. Following Hp-eradication therapy the pentagastrin-stimulated intragastric somatostatin significantly inreased reaching similar values to those observed in healthy controls (*Fig. 5*).

DISCUSSION

This study confirms that eradication of Hp in DU patients greatly reduces an excessive plasma gastrin response to a meal (29—32) and attenuates the postprandial gastric acid response in these patients (27, 28). A major finding of this study is the observation that the blockade of CCK-A receptors with loxiglumide in DU patients infected with Hp did not influence significantly the postprandial gastrin levels or gastric acid secretion, whereas after eradication of Hp in the same patients, loxiglumide resulted in a marked increment in plasma gastrin levels similar to that observed previously in healthy subjects (6, 7). Moreover, we demonstrated that Hp-positive DU patients show an impaired intragastric release of somatostatin in response to pentagastrin stimulation and that the Hp-eradication leads to an increase of this release to the level similar to that observed in healthy, Hp-negative subjects.

These results might be interpreted as that the Hp infection in DU is responsible for the postprandial hypergastrinemia and increased gastric acid secretion and that these effects of Hp infection could be due, at least in part, to the abolition of the normal gastric inhibitory effects of endogenous CCK on local, paracrine release of somatostatin. Previous studies on healthy subjects revealed that CCK exerts a potent inhibitory influence on gastrin release and gastric acid secretion in response to sham-feeding, ordinary feeding or administration of GRP (6, 7). It has been proposed that CCK is involved in the negative feedback control of gastrin release and gastric secretion. This notion was supported by the finding that the removal of the biological effects (by loxiglumide) of CCK either administered exogenously or released endogenously by peptone meal or infusion of GRP resulted in a marked increase in plasma gastrin and gastric acid secretion (6—8).

Our further studies on DU patients revealed that blockade of CCK-A receptors with loxiglumide failed to influence the enhanced plasma gastrin and gastric acid secretion in these patients suggesting an impaired inhibition of

gastric functions by endogenous CCK possibly due to the failure of this CCK to stimulate somatostatin release from the D-cells (10—12). The implication of somatostatin in the "enterogastrone-like" action of CCK originates from studies on dogs (10, 13) in which addition to a peptone meal of fat or acid (known releasers of CCK) significantly inhibited gastrin release and gastric acid secretion. These inhibitory effects were completely eliminated by the blockade of CCK-A receptors with L-364.718, a specific antagonist of these receptors. Since CCK is known to stimulate the release of somatostatin from isolated canine fundic D-cells *in vitro* (23) and the administration of L-364.718 *in vivo* also reduces the postprandial release of somatostatin (13, 14) it was proposed that the major factor in the mechanism of gastric acid inhibition by CCK in dogs is probably somatostatin acting predominantly *via* paracrine pathways on the G-cells and oxyntic cells.

The somatostatin hypothesis in the control of gastric secretion in humans, particularly in DU patients, is attractive because the deficiency of somatostatin in DU patients was suggested previously (24—26). The reports (27, 28) that gastric D-cells are suppressed in Hp positive duodenal ulcer disease offered an explanation for the deficient inhibitory pathway and support the somatostatin link in this disease. Our present results indicate that following standard meal in DU patients without or with Hp infection, there is a small but significant increment in plasma somatostatin that may not be able by itself to inhibit gastrin release or gastric acid secretion but it may reflect the major changes in paracrine release of somatostatin by CCK just around the G-cells or oxyntic cells. Indeed our present study shows that Hp infection by itself reduces gastric luminal release of somatostatin and this reduction is greatly enhanced following pentagastrin stimulation. At the same time plasma levels of somatostatin were not significantly altered whereas gastric acid secretion both basal and pentagastrin stimulated was significantly increased. This support the concept that locally released somatostatin exerts a potent influence on gastric acid secretion. This local action of somatostatin could explain the discrepancy between the marked increment in the postprandial plasma gastrin following loxiglumide in Hp negative DU patients and relatively small decrease in the levels of circulating plasma somatostatin. DU patients infected with Hp may exhibit the defective inhibitory action of endogenous CCK on paracrine release of somatostatin resulting in greatly augmented plasma gastrin release and gastric acid secretion in response to a meal in these patients. Following eradication of Hp, loxiglumide was capable of suppressing the release of somatostatin from D-cells possibly by antagonizing CCK-A receptors localized on these cells. The antagonism of CCK-A receptors and subsequent fall in somatostatin output removes the G-cells from the tonic paracrine inhibitory influence of somatostatin with subsequent excessive release of gastrin and greatly increased gastric acidity. This is in keeping with our data that following

the eradication of Hp, a marked decrease in plasma gastrin and gastric acid responses to meal were observed while the blockade of CCK-A receptors with loxiglumide resulted in a greatly increased post-meal gastrin release and enhanced gastric acid secretion, similar to those effects observed previously in healthy subjects (6,7).

It is of interest that administration of loxiglumide resulted in an excessive postprandial gastrin release only in Hp negative DU patients but caused a marked elevation in postprandial plasma CCK level both in Hp positive and Hp negative DU patients. This actually confirms previous findings (6) regarding higher postprandial levels of circulating CCK in loxiglumide-treated patients as compared to placebo-treated subjects. Higher plasma CCK levels in tests with loxiglumide were reported previously in healthy subjects (6, 11, 12) and, according to the present study, this holds also true for DU patients after eradication of Hp. As discussed above, the major mechanism underlying this phenomenon is a negative feedback mechanism mediated by CCK.

Our results are in agreement with previous studies showing that the infection with Hp resulted in hypergastrinemia attributable to the impaired feedback inhibition of gastrin release (15—19). Our data indicate that the infection by Hp not only enhances gastrin release but also increases postprandial gastric acid secretion which is in accord with reports from previous investigators (15, 29, 30). However, this point is a controversial issue because other reports showed that Hp infection is accompanied by hypergastrinemia but not by hyperchlorhydria (31—33) or increased integrated 24-hour intragastric acidity (34).

It is of interest that some healthy subjects without DU but infected with Hp also exhibited gastric regulatory defect just like DU patients (5), namely, significantly higher meal-stimulated plasma gastrin levels and impaired low pH-inhibition of gastrin release and gastric acid secretion after peptone meal (20). This study might suggest that Hp infection may result in abnormal gastrin release and enhanced acid secretion as previously described in DU patients (5). This disorder might be unrelated to the pathogenesis of DU disease and may merely reflect infection with Hp and the action of oxygen free radicals (35) and inflammatory cytokines such as tumor necrosis factor-alpha and interferon-gamma inhibiting the D-cells to release somatostatin and the G-cells to release gastrin (38). Further studies are needed to determine whether eradication of Hp in these asymptomatic non-DU subjects restores normal gastrin release and gastric acid secretion in response to a meal. Since the blockade of CCK-A receptors was effective in enhancing plasma gastrin and gastric acid secretion only in healthy young subjects (6, 7) (presumably not infected with Hp), and only in Hp negative DU patients, the test with loxiglumide combined with determination of plasma gastrin and gastric acid response to a meal could serve to identify subjects with normal feedback

control of gastric secretion e.g., following attempts at eradication of Hp. On the other hand, enhancement of plasma gastrin and gastric secretory responses after meals in subjects treated with loxiglumide should indicate normalization of the usual inhibitory action of endogenous CCK on gastric secretory functions.

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