Effect of proximal gastric vagotomy on calculated gastric HCO3- and nonparietal volume secretion in man. Studies during basal conditions and gastrin-17 infusion.

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Research Article

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Effect of Proximal Gastric Vagotomy on Calculated Gastric HCO_3^- and Nonparietal Volume Secretion in Man

Studies during Basal Conditions and Gastrin-17 Infusion

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Abstract

We calculated gastric HCO_3^- and H^+ secretion, as well as nonparietal and parietal volume secretion, in 15 duodenal ulcer patients who had previously undergone successful proximal gastric vagotomy, 15 unoperated duodenal ulcer patients, and 15 normal control subjects. Basal HCO_3^- secretion was not significantly altered after vagotomy, while basal H^+ secretion, parietal volume and nonparietal volume secretion were reduced significantly. Intravenous gastrin-17 infusion increased H^+, parietal volume and nonparietal volume secretion significantly in all three groups. In contrast, gastrin-17 infusion reduced gastric HCO_3^- secretion by ~ 50% in both unoperated ulcer patients and normal subjects ($P < 0.05$). Gastrin-17 infusion did not inhibit gastric HCO_3^- secretion after vagotomy. In fact, mean gastric HCO_3^- secretion increased to a nearly significant extent in response to gastrin ($P = 0.06$). These findings indicate that gastrin inhibits gastric HCO_3^- secretion in humans and that the gastrin-induced reduction in gastric HCO_3^- secretion is dependent upon intact vagal innervation to the oxyntic mucosa.

Introduction

Although the inhibitory effect of vagotomy on gastric acid-pepsin secretion is well documented (1–3), little is known about the effect of vagotomy on alkaline, nonparietal secretion by the stomach. Gastric HCO_3^- secretion is thought to protect the surface epithelium from damage by luminal acid-pepsin (4). Because vagal stimulation increases gastric HCO_3^- and nonparietal volume secretion via a cholinergic mechanism (5, 6), vagotomy might have an opposite effect and reduce gastric HCO_3^- and nonparietal volume secretion. Therefore, the purpose of the present study was to calculate gastric HCO_3^- and nonparietal volume secretion after proximal gastric vagotomy (PGV)[1] in man, using a recently validated method derived from a two-component model of gastric secretion (7). Duodenal ulcer (DU) patients who had undergone PGV, unoperated DU patients, and normal subjects were studied both under basal conditions and after intravenous infusion of increasing doses of gastrin heptadecapeptide (G-17).

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1. *Abbreviations used in this paper:* DU, duodenal ulcer; NL, normal; PGV, proximal gastric vagotomy.

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Methods

Studies were approved by a Human Studies Subcommittee and informed written consent was obtained in each case.

Patients and subjects. Patients who had previously had PGV for DU were identified on a computerized printout. 30 patients agreed to undergo a sham feeding test and, in 15, completeness of PGV was documented using previously described criteria (3). Ages of these 15 patients (12 of whom were male) averaged 54±3 yr and weights averaged 72.3±3.0 kg. 15 unoperated DU patients (12 male) who were attending an outpatient gastroenterology clinic volunteered to serve as controls in these studies, as did 15 healthy volunteers (12 male) who were primarily students and hospital employees. Ages of DU patients and healthy controls averaged 49±3 and 31±2 yr, respectively, and their weights averaged 75.7±3.6 and 71.5±3.5 kg, respectively. Antisecretory medications were discontinued by patients receiving them at least 48 h before experiments.

Intubation and study protocol. After an overnight fast, a nasogastric tube (AN 10, Andersen Products Inc., Oyster Bay, NY) was positioned in the dependent portion of the stomach under fluoroscopic control. Residual gastric secretions were manually evacuated and then secretions were collected by aspiration in 15-min aliquots using a Stedman pump (American Cystoscope Makers, Inc., Stamford, CT). After a 30-min basal period during which 0.15 M NaCl was infused intravenously through an indwelling venous catheter, a solution of G-17 dissolved in 0.15 M NaCl and containing 1% human albumin was infused intravenously in doses of 7, 22.1, 70, 221, and 700 pmol/kg·h (IMED infusion pump 922, IMED Corp., San Diego, CA). Each G-17 dose was infused over a 45-min period in a stepwise fashion as described previously (3). At the end of the 700 pmol/kg·h G-17 infusion, the infusion was stopped and gastric secretion was measured for an additional 30 min.

The volume of each 15-min sample of gastric juice was measured to the nearest ml and was multiplied by 4 to express results in milliliters per hour. The hydrogen ion concentration of gastric juice and the osmolality of gastric juice and plasma were determined as described previously (7). Plasma osmolality averaged 292±2, 293±1, and 291±2 mosmol/kg in PGV patients, DU patients, and normal subjects, respectively. Gastric HCO_3^- and H^+ secretion rates (in millimoles per hour), as well as nonparietal and parietal volume secretion rates (in milliliters per hour), were then calculated from gastric juice volume, hydrogen ion concentration, osmolality, and plasma osmolality as described previously (7). Saliva was aspirated using a dental suction catheter throughout these experiments.

Statistics. Results are expressed as mean±1 SEM. Differences in mean values among groups were analyzed by two-tailed group t tests. Changes from basal secretion rates during G-17 infusion within groups were tested by analysis of variance. P values < 0.05 were considered significant. Effective doses of G-17 necessary to produce 50% of peak acid output (ED_{50}) were calculated as described previously (8).

Results

Measured gastric volume, acidity, and osmolality. The time course of the experiments and mean results for gastric juice volume in milliliters per hour, acidity in millimoles per liter, and osmolality in milliosmoles per kilogram for each 15-min period

are shown in Fig. 1. Mean gastric juice volume output basally and during intravenous G-17 infusion was lowest in PGV patients, intermediate in normal subjects, and highest in DU patients (Fig. 1, *top*). As indicated in Table I, mean volume output in PGV patients was significantly lower than in DU patients and in normal subjects, whereas volume output in DU patients was significantly higher than in normal subjects. As shown in Fig. 1 *B* and Table I, mean gastric acidity was significantly lower in PGV patients than in unoperated controls and normal subjects; results in DU patients and normal subjects were comparable, although DU patients had a slightly lower mean gastric acidity than normal controls at higher doses of G-17. Gastric juice osmolality was significantly lower in PGV patients than in DU patients and normal subjects (Fig. 1 *C*, and Table I), while osmolality was not significantly different in DU patients and normal subjects. As shown in Fig. 1, when G-17 infusion was discontinued mean gastric juice volume, acidity, and osmolality decreased.

Calculated HCO_3^- secretion. As shown in Fig. 2, in both normal subjects and unoperated DU patients, there was a significant dose-related decrease in gastric HCO_3^- secretion during intravenous G-17 infusion, with maximal inhibition of ~ 50% occurring with G-17 doses of 70 pmol/kg · h and higher. After cessation of 700 pmol/kg · h G-17 infusion, HCO_3^- secretion rates over the ensuing 30 min returned toward basal rates (data not shown). In contrast to results in unoperated DU patients and normal controls, G-17 infusion did not inhibit gastric HCO_3^- secretion in PGV patients (Fig. 2). In fact, mean HCO_3^- secretion during G-17 infusion was higher than basal and this increase approached significance ($P = 0.06$). Mean (±SE) HCO_3^- secretion during G-17 infusion in PGV patients was significantly higher than in normal subjects at G-17 doses of 22.1 to 700 pmol/kg · h and in DU patients at doses of 221 and 700 pmol/kg · h (Fig. 2).

Calculated H^+ secretion. As indicated in Fig. 3, mean basal H^+ secretion of 3.3±0.7 mmol/h in PGV patients was lower

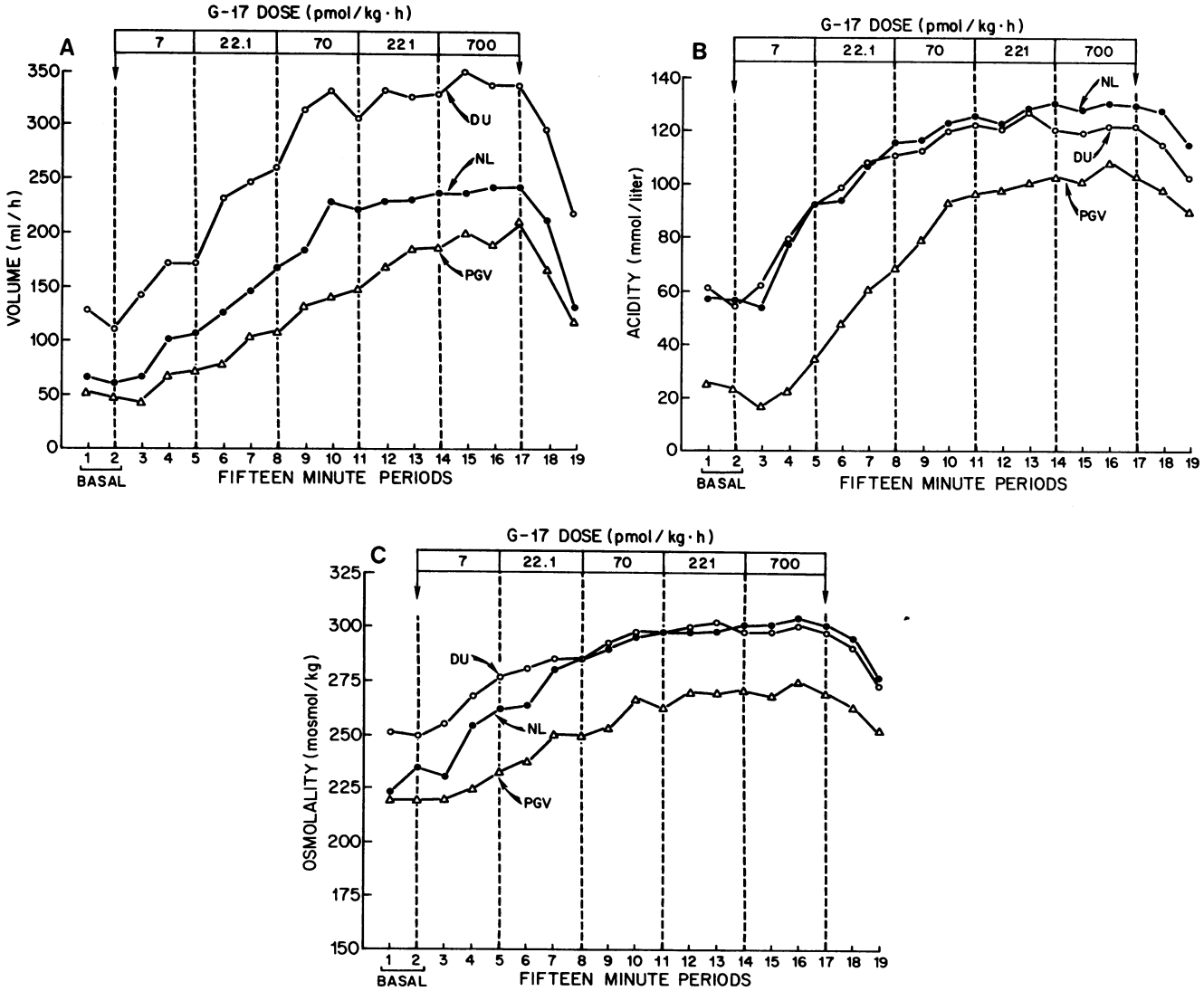

Figure 1. Mean gastric juice volume (*A*), gastric juice acidity ($[H^+]$; *B*), and gastric juice osmolality (*C*) in 15 normal subjects (NL), 15 patients with duodenal ulcer (DU), and 15 DU patients who had been treated by (PGV). Basal secretion was measured for two 15-min periods and then G-17 was infused for the next fifteen, 15-min periods (periods 3–17) (*arrows*), after which G-17 infusion was stopped and secretion measured for two final 15-min periods (periods 18 and 19). Statistical comparisons among groups are made in Table I.

Table I. Comparison of Mean±SE Gastric Juice Volume, Acidity, and Osmolality in 15 Patients after PGV, 15 Unoperated DU Patients and 15 NL Subjects

	G-17 Dose (pmol/kg·h)					
	0 (Basal)	7	22.1	70	221	700
Volume (*ml/h*)						
PGV	50±8*	70±6*‡	106±10*‡	144±16*‡	184±12*‡	198±16*
DU	120±22§	172±18§	254±22§	316±26§	326±28§	336±30§
NL	64±10	104±10	156±14	224±22	234±12	240±20
Acidity (*mmol/liter*)						
PGV	24.6±4.8*‡	35.0±6.5*‡	69.3±8.5*‡	96.6±7.4*‡	102.6±5.0*‡	103.8±4.5*‡
DU	57.4±8.1	92.1±5.9	111.0±4.7	122.2±3.5	120.1±3.1§	120.7±3.5
NL	56.5±8.1	92.3±7.8	114.9±5.9	124.9±3.0	130.1±3.3	128.9±3.0
Osmolality (*mosmol/kg*)						
PGV	220±6*	233±7*‡	251±5*‡	263±8*‡	271±7*‡	269±5*‡
DU	250±7	277±5	286±6	297±5	298±5	298±6
NL	229±10	267±8	286±7	298±4	301±5	301±5

Gastric volume during G-17 infusion was expressed as the last 30 min of each G-17 dose, multiplied by 2. Acidity and osmolality for 30 min basal period (0 dose) represent average values; during G-17 infusion the last 15-min period of each G-17 dose was used. * $P < 0.05$, PGV vs. DU by two-tailed group t test. ‡ $P < 0.05$, PGV vs. NL by two-tailed group t test. § $P < 0.05$, DU vs. NL by two-tailed group t test.

than in normal control individuals (6.1±1.2 mmol/h; $P = 0.06$) and DU patients (11.1±2.6 mmol/h, $P < 0.001$). As anticipated, H^+ secretion increased significantly and in a dose-related fashion during G-17 infusion in all three groups. For each G-17 dose, H^+ secretion was significantly lower in PGV patients than in normal subjects ($P < 0.05$) or DU patients ($P < 0.001$). The calculated ED_{50} to G-17 was significantly higher in PGV patients than in unoperated DU patients and normal controls (Table II). Thus, the rightward shift in the G-17 dose-response curve for H^+ secretion in PGV patients was statistically significant. H^+ secretion was significantly higher in DU patients than in normal controls for each dose of G-17.

Calculated nonparietal and parietal volume secretion. As shown in Fig. 4, basal nonparietal volume secretion in PGV patients and normal controls was similar and significantly lower than in DU patients (29.1±4.1 and 24.8±3.2 ml/h vs. 50.1±6.6 ml/h, $P < 0.02$). In all three groups, nonparietal volume secretion increased significantly above basal rates during G-17 infusion. Throughout G-17 infusion, nonparietal volume secretion in PGV patients was comparable to that of normal subjects and 20–30 ml/h below nonparietal secretory rates of DU patients ($P < 0.02$ for each G-17 dose, PGV patients or normal subjects versus DU patients). Curves for parietal volume secretion (not shown) were similar to H^+ secretion curves previously shown in Fig. 3.

Ratios of HCO_3^- to H^+ secretion and nonparietal to parietal secretion. In Fig. 5 *A*, mean (±SE) ratios of HCO_3^- secretion to H^+ secretion basally and with each dose of G-17 are shown for each group of 15 subjects. In both normal subjects and DU patients, basal HCO_3^- secretion averaged ~ 35–40% of basal H^+ secretion. On the other hand, the ratio of basal HCO_3^-/H^+ secretion after PGV was 66±5% ($P < 0.005$ versus normal subjects or DU patients). In response to G-17 infusion in normal controls and DU patients there was a significant dose-related decrease in the HCO_3^-/H^+ secretory ratio to a steady value of around 3% at G-17 doses of 70 pmol/kg·h and above. The HCO_3^-/H^+ ratio also fell significantly during G-17 infusion in PGV patients, but the decrement was less pronounced than in controls; with maximal stimulation of H^+ secretion by gastrin-17, the HCO_3^-/H^+ secretory ratio reached a steady value of ~ 15% ($P < 0.05$, PGV versus DU patients or normal subjects with each G-17 dose).

Mean (±SE) ratios of nonparietal to parietal volume secretion are shown in Fig. 5 *B*. In each group this ratio decreased significantly during G-17 infusion. In PGV patients, the ratio of nonparietal to parietal volume secretion basally and during G-17

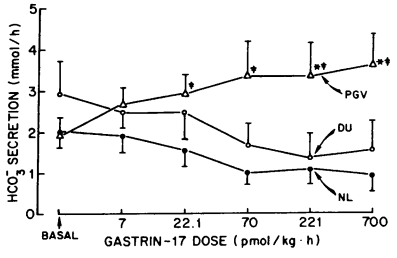

Figure 2. Mean (±SE) HCO_3^- secretion basally and during the last two 15-min periods of each G-17 dose in 15 NL subjects, 15 DU patients, and 15 DU patients after PGV. *Significant ($P < 0.05$) differences between PGV patients and DU patients; ‡significant differences between PGV patients and normal subjects. None of the differences between DU patients and NL subjects was significant.

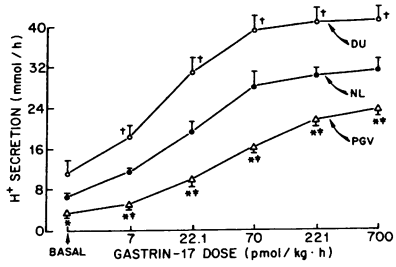

Figure 3. Mean (±SE) H^+ secretion basally and during the last two 15-min periods of each G-17 dose in 15 NL subjects, 15 DU patients, and 15 DU patients after PGV. *Significant ($P < 0.05$) differences between PGV and DU patients, ‡between PGV patients and NL subjects; and +between DU patients and NL subjects.

Table II. Comparison of Mean±SE Effective Dose of Gastrin-17 Necessary to Produce 50% of Peak Acid Output (ED_{50}) in 15 Patients after PGV, 15 Unoperated DU Patients, and 15 NL Subjects

	ED_{50}
	pmol/kg·h
PGV	61.3±31.3*
DU	11.0±2.2
NL	24.0±8.1

* $P < 0.001$ vs. DU and < 0.05 vs. normal by group t test. Because of the large intersubject variation in calculated ED_{50}, especially in the PGV group, data were normalized by using log ED_{50} before performing t tests.

infusion was significantly greater than in both nonvagotomized control groups. Ratios were not significantly different in DU patients and normal subjects, except that DU patients reached a steady ratio of ~ 28% with the two highest G-17 doses, while normal subjects achieved a ratio of ~ 22% ($P < 0.05$).

Discussion

We previously reported in normal subjects and DU patients that mean steady state gastric HCO_3^- secretion during a 2- or 3-h intravenous infusion of a single, submaximal dose of pentagastrin was lower than basal HCO_3^- secretion; however, the reduction in gastric HCO_3^- secretion during pentagastrin infusion did not reach statistical significance (7, 9). The present study examined the effect of gastrin on gastric HCO_3^- secretion in considerably more detail, using a wide range of doses of synthetic human gastrin heptadecapeptide I (G-17). In both normal subjects and DU patients, G-17 inhibited gastric HCO_3^- secretion significantly, and in a dose-related fashion, with a maximal inhibition of HCO_3^- secretion of ~ 50% of basal HCO_3^- secretion. In both groups there was a prompt increase in HCO_3^- secretion after cessation of G-17 infusion as serum gastrin concentrations fell toward basal levels (3, 10). We have recently shown in these same 15 normal subjects and 15 DU patients that steady state serum gastrin concentrations during infusion of 7, 22.1, and 70 pmol/kg·h G-17 are within the physiologic range (10). Thus, when gastric H^+ secretion is stimulated by physiologic or supraphysiologic amounts of gastrin, gastric HCO_3^- secretion is inhibited in parallel. Because gastric HCO_3^- neutralizes acid under normal conditions, inhibition of gastric HCO_3^- secretion probably contributes to the large increase in gastric acidity that occurs during G-17 infusion in normal subjects and nonvagotomized DU patients (Fig. 1 *B*). That gastric HCO_3^- secretion was significantly reduced by G-17 is even more interesting since G-17 also increased H^+ secretion in our studies and since H^+ within the gastric lumen is known to augment, rather than reduce, gastric HCO_3^- secretion (11–13).

An unexpected finding in this study was that G-17 infusion did not inhibit gastric HCO_3^- secretion after PGV. In fact, mean gastric HCO_3^- secretion increased during G-17 infusion in patients with PGV and this increase was very nearly statistically significant ($P = 0.06$). Normal or even enhanced gastric HCO_3^- secretion coupled with reduced H^+ secretion led to reduced gastric luminal acidity and osmolality after PGV (Fig. 1 *B* and *C*). We can only speculate why G-17 did not reduce gastric HCO_3^- secretion after PGV. It is possible that the amount of HCO_3^- that refluxed into the stomach from the duodenum increased after PGV, but this seems unlikely since the pylorus remained intact after this operation and bile staining of gastric samples did not occur with increased frequency in PGV patients compared with DU patients or normal controls. Gastric HCO_3^- secretion arises from both the fundus and antrum of the stomach (14). Thus, it is possible that gastrin may effect gastric HCO_3^- secretion differently in these two regions. For example, gastrin may inhibit the output from fundic HCO_3^--secreting surface cells to maximize H^+ secretion into the lumen. If a substantial portion of gastric HCO_3^- secretion originates from the fundus rather than the antrum (14), total gastric HCO_3^- secretion

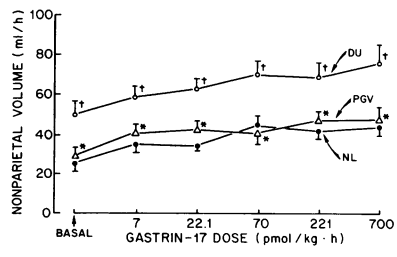

Figure 4. Mean (±SE) nonparietal volume output basally and during the last two 15-min periods of each G-17 dose in 15 NL subjects, 15 DU patients, and 15 DU patients after PGV. *Significant differences ($P < 0.05$) between PGV and DU patients; and +between DU patients and NL subjects. When secretion rates with G-17 were compared with basal rates in each group, nonparietal volume secretion was significantly greater than basal in NL subjects (all G-17 doses), DU patients (G-17 doses of 70 pmol/kg·h and above), and PGV patients (G-17 doses of 221 pmol/kg·h and above).

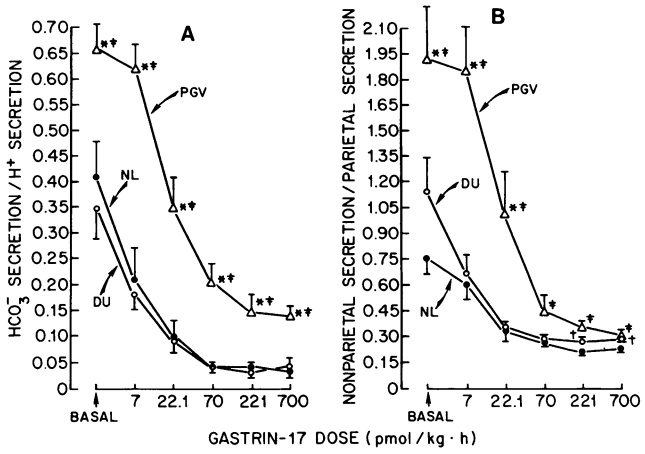

Figure 5. Mean (±SE) ratio of HCO_3^- secretion to H^+ secretion (*A*) and ratio of nonparietal volume secretion to parietal volume secretion (*B*) in 15 NL subjects, 15 DU patients, and 15 DU patients with PGV. Results are shown basally and during the last two 15-min periods of each G-17 dose. *Significant ($P < 0.05$) differences between PGV and DU patients; ‡significant differences between PGV patients and NL subjects. None of the differences between DU patients and NL subjects was significant, except for the ratio of nonparietal to parietal volume secretion with G-17 doses of 221 and 700 pmol/kg·h, in which DU patients had a significantly higher ratio (+). When ratios during G-17 infusion were compared with basal ratios in each group, HCO_3^-/H^+ secretion decreased significantly in all three groups, as did nonparietal/parietal volume secretion. This was true for each G-17 dose in each group except the 7-pmol/kg·h dose in PGV patients.

would be inhibited in normal humans or DU patients by G-17 as H^+ is stimulated. After PGV, however, gastrin-induced inhibition of fundic HCO_3^- secretion may be absent due to denervation of the fundus by PGV. Since the antrum is not denervated after PGV and continues to secrete HCO_3^-, the net result would be no inhibition of total gastric HCO_3^- secretion during G-17 infusion after PGV.

If the above hypotheses regarding regional differences in HCO_3^- secretory responses to G-17 are correct, it would suggest that gastrin's inhibitory effect on gastric HCO_3^- secretion may be indirect and dependent upon intact vagal innervation to the proximal stomach. Of interest, in vitro studies in amphibians, using chambered preparations of stomach stripped of muscle layers and submucosal tissue, have found no direct inhibitory effect of either 10^{-6} M pentagastrin or 10^{-8} M G-17 on fundic or antral gastric HCO_3^- secretion, respectively (15, 16). Assuming that inter-species differences are not the explanation for differing effects of gastrin on gastric HCO_3^- secretion in these in vitro studies and our present study, the findings taken together suggest that the inhibitory effect of gastrin on gastric HCO_3^- secretion in vivo is an indirect one, perhaps mediated via the vagus nerves. It would be of interest to compare in vivo effects of gastrin on gastric HCO_3^- secretion in the fundus and antrum separately, for example in animals with vagally innervated fundic and antral pouches. Moreover, by also studying animals with vagally denervated fundic pouches, it may be possible to confirm the importance of vagus nerves in mediating fundic inhibition of gastric HCO_3^- secretion. Konturek et al. recently reported that a large dose of G-17 (500 pmol/kg·h i.v.) did not inhibit gastric HCO_3^- secretion in vivo in ranitidine-treated dogs with vagally denervated fundic pouches or in dogs with vagally denervated antral pouches (17), agreeing with our present findings in humans after PGV.

Several peptide hormones including pancreatic glucagon (18), neurotensin (19), and peptide YY (20) have recently been reported to inhibit net gastric acid output only in individuals or animals with intact vagal innervation of the oxyntic mucosa. (Net gastric acid output refers to H^+ secretion minus HCO_3^- secretion. A decrease in net gastric acid output can be due to a decrease in H^+ secretion, an increase in HCO_3^- secretion, or both.) It is possible that some of the reduction in net gastric acid output induced by these peptides is due to a vagally dependent stimulation of gastric HCO_3^- secretion. In support of this hypothesis, both glucagon and neurotensin have been shown to augment gastric HCO_3^- secretion (16, 17). Thus, it is conceivable that some peptide hormones such as glucagon and neurotensin that inhibit H^+ secretion also augment fundic HCO_3^- secretion, while peptide hormones such as gastrin, which stimulate H^+ secretion inhibit fundic HCO_3^- secretion. Furthermore, these hormone-induced reciprocal changes in HCO_3^- secretion (relative to effects of these peptides on H^+ secretion) may be mediated by the vagus nerves.

As anticipated, PGV led to a marked decrease in H^+ (parietal) secretion, both basally and during G-17 infusion, with a significant rightward shift in the G-17 dose response curve. This extends our previous observations in vagotomized patients in which only net gastric acid output was reported (3). Lower net gastric output during G-17 infusion after PGV is thus due to both significantly lower H^+ secretion and significantly higher HCO_3^- secretion. PGV also decreased nonparietal volume secretion significantly, indicating that cells and glands that contribute to nonparietal volume secretion in the proximal stomach are under vagal control. Since atropine also decreases nonparietal volume secretion (5), this fluid may be under vagal-cholinergic regulation. Of interest, nonparietal volume hypersecretion in DU patients was reduced to normal rates after PGV, both basally and during G-17 infusion, whereas parietal volume hypersecretion was reduced to well below normal rates after PGV. This may be because parietal hypersecretion in DU patients arises entirely from the proximal stomach, which is denervated after PGV, whereas nonparietal volume hypersecretion in DU patients may arise from both the proximal stomach and the nondenervated distal stomach. Thus, PGV may have markedly reduced fundic nonparietal volume hypersecretion without altering antral nonparietal volume hypersecretion. The net results of these events in DU patients after PGV would be a decrease in total nonparietal secretion to near normal rates and also an increased ratio of nonparietal to parietal volume secretion basally and during G-17 infusion. Assuming that patients with hypergastrinemia due to gastrinoma (Zollinger-Ellison syndrome) behave like our normal subjects and DU patients during intravenous G-17 infusion, our findings suggest that PGV, an operation that is clinically efficacious in patients with gastrinoma (21), should increase the ratio of nonparietal to parietal volume secretion and also the ratio of HCO_3^- to H^+ secretion at any given, elevated serum gastrin concentration (Fig. 5).

While inhibiting gastric HCO_3^- secretion in normal subjects and DU patients, G-17 caused a dose-related increase in nonparietal volume secretion, agreeing with our earlier study using a single, submaximal dose of pentagastrin (9). Because of the opposite effects of G-17 on gastric nonparietal volume secretion and gastric HCO_3^- secretion in both normal subjects and DU patients (Figs. 2 and 4), it seems likely that conventional two-component models of gastric secretion (22, 23) are overly simplified. Although the acidic component almost certainly derives only from parietal cells, the alkaline, nonparietal component probably arises from several different kinds of cells. Current evidence suggests that surface epithelial cells are most responsible for gastric HCO_3^- secretion, via a volume-independent chloride/bicarbonate exchange mechanism (14), whereas nonparietal volume secretion may arise primarily from other, more deeply positioned cells within gastric glands (e.g., chief cells, mucous neck cells). Thus, G-17 may indirectly inhibit HCO_3^- secretion by surface epithelial cells via a vagal-dependent mechanism and at the same time stimulate fluid secretion from chief cells, mucous neck cells, or some other cells.

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