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Ileal Release of Glucagon-Like Peptide-1 (GLP-1)

Association with Inhibition of Gastric Acid Secretion in Humans

PETER LAYER, MD, JENS JUUL HOLST, DANIEL GRANDT, and HARALD GOEBELL

There is evidence that the distal intestine participates in the regulation of gastric motor and secretory function. It was the aim of this study to examine in greater detail the effects of ileal nutrient exposure on human gastric acid secretion and to investigate potential intermediary mechanisms. Twelve normal subjects were intubated with an oroileal multilumen tube assembly for gastric, duodenal, and ileal perfusion of marker and test solutions, aspiration, and intestinal manometry. We studied ileal effects on gastric acid output in the unstimulated, interdigestive state (during early phase II, $N = 6$), and during endogenous stimulation by intraduodenal essential amino acid perfusion, $N = 6$) and on release of candidate humoral mediators, peptide YY (PYY) and glucagonlike peptide-1 (GLP-1), both known inhibitors of human gastric acid secretion. Compared with ileal saline perfusion, ileal carbohydrate (total caloric load: 60 kcal) decreased interdigestive gastric acid output by 64% ($P < 0.01$), and endogenously stimulated output by 68%, respectively ($P < 0.005$). Under all experimental conditions, ileal carbohydrate increased plasma GLP-1 by 80–100% (all $P < 0.005$). Ileal lipid perfusion had similar inhibitory effects on gastric acid output and stimulatory effects on GLP-1 release as had ileal carbohydrate. By contrast, ileal perfusion with peptone had no or only weak effects on either acid output or plasma GLP-1. Plasma PYY concentrations and suppression of gastric secretion in response to ileal perfusions were not correlated. In humans, both interdigestive and endogenously stimulated gastric acid output are inhibited in response to intraileal carbohydrate or lipids, but not protein, Decreased acid output is associated with release of GLP-1, but not PYY. These findings support the hypothesis that the distal small intestine may participate in the late postprandial inhibitory regulation of gastric secretory function in humans and that GLP-1 may be an intermediary factor.

KEY WORDS: carbohydrate; lipid; glucagon-like peptide-1; human; interdigestive; peptide YY; protein; postprandial; gastric acid secretion.

Presence of nutrients within the human distal ileal or proximal colonic lumen alters several gastrointestinal secretory and motor functions. Gastric emptying and small intestinal transit are slowed (ileal brake), and intestinal motility is reduced (1–6). In addition, pancreatic and biliary secretions are inhibited (7, 8). There is evidence that gastric secretory function is also regulated by the distal intestine: in humans, diversion of luminal contents at the level of the jejunum causes an increase in gastric outputs of volume and acid, which is reversed when the removed chyme is reinfused into the jejunum (9). Colonic perfusion experiments in dogs and humans demonstrated that lipids or protein within the proximal colon decrease

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From the Division of Gastroenterology, Department of Medicine, University of Essen, Germany; and Department of Medical Physiology, University of Copenhagen, Denmark.

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Address for reprint requests: Dr. Peter Layer, Gastroenterology, Department of Medicine, University of Essen, Hufelandstr. 55, D-45122 Essen, Germany.

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exogenously stimulated gastric acid output (10–12). The regulatory role of carbohydrates within the ileal lumen has not been investigated but is of interest because a considerable proportion of starch remains unabsorbed after carbohydrate meals and reaches the ileum in the late postprandial or early part of the subsequent interdisgestive period (physiologic malabsorption) (13–15).

How the ileum regulates proximal gastrointestinal function is unknown. Important candidate humoral mediators are peptide YY (PYY), a regulatory peptide secreted by the distal intestine that has been demonstrated to inhibit human gastric acid secretion (16), and glucagon-like peptide-1 (GLP-1), a proglucagon-derived enteric peptide that is produced by the ileal mucosa (17, 18), may play a role as an incretin in carbohydrate metabolism (17, 19), and inhibits gastric acid output in humans when infused intravenously (18, 20).

It was the aim of the present study to investigate gastric secretory responses to ileal nutrient challenges and potential intermediary mechanisms in healthy human subjects. Specifically, we determined ileal effects on interdigestive and endogenously stimulated gastric acid output, and on release of PYY and GLP-1.

MATERIALS AND METHODS

Human Subjects. The protocol was approved by the Institutional Ethical Committee. After giving informed written consent, 12 healthy volunteers (eight males, four females, age range 22–40 years) participated in this study.

Intubation. Subjects were fasted overnight and then intubated at 6:00 AM with two polyvinyl multilumen tubes: First, an 11-lumen oroileal tube (largest outer diameter, 7.2 mm) was positioned with its tip in the distal ileum (240 cm from the mouth). Ports (inner diameter, 1.0 mm) for perfusion of polyethylene glycol (PEG, 45 mg/min) and amino acid solutions were at the papilla of Vater, and for test solutions in the ileum (130 cm from the pylorus), respectively. Aspiration sites (inner diameter, 2.0 mm) were located in the distal duodenum and distal ileum (150 cm from the pylorus). Integrated pressure recording ports (inner diameter, 0.9 mm) were located in the proximal, mid- and distal small intestine and perfused with deionized water; they served to monitor specific fasting motility patterns, which were used for the interdigestive part of the study. Next, a six-lumen gastric tube (outer diameter, 4.7 mm) was placed in the antrum; it had a distal aspiration port at its tip, a port for perfusion of phenolsulfonphthalein (250 μg/ml, 1 ml/min; 20 cm proximal to the tip) used as gastric recovery marker, and three antral pressure recording ports perfused with water. The positions of the gastric and intestinal tubes were verified by fluoroscopy before the start and after the end of each study day.

Experimental Protocol. After correct positioning of the intubation assembly was obtained (usually within 4 hr, range: 2–7 hr), continuous recording of intestinal motility and perfusion of gastric and duodenal marker solutions were begun; the first ileal perfusion was started after 1 hr of marker equilibration. Throughout the study, 15-min gastric, duodenal, and ileal samples were collected by continuous aspiration into vials immersed in ice. Sampling periods were divided into 15-min intervals. Peripheral venous blood samples were taken at intervals by means of a cannula placed into the antecubital vein and collected in tubes containing EDTA and aprotinin (1000 KIU).

The first study day was concluded between 7:30 and 9:00 PM (depending on intubation time and protocol) when subjects ate a standard meal (580 kcal) containing 28 g of protein, 68 g of carbohydrate, and 22 g of fat, followed by an overnight fast. On the second day at 6:00 AM, correct tube location was verified and studies resumed after 1 hr of marker equilibration.

Two sets of studies were performed:

1. Interdigestive Acid Secretion. In six subjects, ileal perfusions were administered in coordination with the interdigestive gastrointestinal motility cycle: perfusions were always started 10 min after the end of a duodenal motility phase III, i.e., during the early part (phase I or initial phase II) of the interdigestive cycle. To prevent carry-over among test solutions, ileal perfusions were separated by two interdigestive cycles.

2. Endogenous Stimulation of Acid Secretion. Six subjects received continuous intraduodenal perfusion (3 ml/min) with a mixture of essential amino acids (450 μmol/min) to induce moderate endogenous stimulation of gastric acid secretion. The concentration (millimoles per liter) of the individual amino acids within the perfusate was: Ile 18.9, Leu 28.7, Lys 21.7, Met 14.6, Phe 15.5, Thr 18.8, Trp 4.8, and Val 26.9. The first ileal test perfusion was administered 1 hr after the start of duodenal amino acid perfusion; the subsequent ileal perfusions were separated by 3 hr in order to avoid carry over effects between solutions.

In all subjects the following isotonic solutions were randomized for intraileal perfusion (15 min): soluble starch and maltose (total carbohydrate concentration: 167 mg/ml); emulsion of triolein and 10 mM sodium oleate (total lipid concentration: 75 mg/ml); peptone (160 mg/ml); NaCl (154 mmol/liter) as volume control (90 ml). Ileal nutrient loads were chosen to be approximately isocaloric with the cumulative amount of physiologically unabsorbed nutrient after a meal (about 60 kcal). These loads inhibit exocrine pancreatic secretion and intestinal motility in humans (7, 14, 15).

Analyses. Acid concentration in gastric samples was determined by titration with 0.1 M NaOH to end point pH 7.0. In ileal samples, carbohydrate and lipid concentrations were measured by enzymatic or titrimetric routine methods as previously described (3, 7). Concentrations of phenolsulfonphthalein and polyethylene glycol were measured in gastric and duodenal samples, and the ratios of marker concentrations in perfusates and aspirates were used to calculate intraluminal volume flow rates per minute, gastroduodenal transit, and duodenogastric reflux as described earlier (3, 21–24). Briefly, the ratio of phenolsulfonphthalein concentration perfused intragastrically to the concentration recovered in gastric samples represents the dilution factor of this marker by gastric contents; it is multiplied by

the gastric perfusion rate (1 ml/min) to compute intragastric volume flow rate, corrected for duodenogastric reflux by analyzing the duodenal perfusion marker (PEG) in gastric samples, and for gastroduodenal emptying by using phenolsulfonphthalein concentrations in duodenal samples, respectively. Gastric acids output was computed as the produce of intragastric volume flow rate and acid concentration. Duodenal interdigestive phase III motility was defined as uninterrupted periods (of >2 min) of regular phasic contractions (10–12/min) and used to time the beginning of ileal perfusions in interdigestive studies.

Radioimmunoassay of PYY in plasma was performed using antiserum code no. 8412-211 (a gift from R. Ekman, Department of Neurochemistry, University of Lund, Sweden) raised in rabbits against synthetic porcine PYY 1-36 (Peninsula Europe, Merseyside, UK) as previously described (25) but without conjugation to carrier protein (26). Preliminary characterization of the antiserum indicates that the antibodies are directed against the N-terminus of PYY. The antiserum cross-reacts 100% with human PYY. Synthetic human PYY (Peninsula) was used for standards and for preparation of [^{125}I]PYY, which was labeled according to the stoichiometric chloramine T method and purified using high-pressure liquid chromatography as described (25). Assay buffer was 0.05 mol/liter sodium phosphate, pH 7.5, containing in addition 0.1% human serum albumin (Behringwerke, Marburg, Germany), 0.1 mol/liter sodium chloride, 10 mmol/liter EDTA, 0.6 mmol/liter merthiolate. Then 100 μl of unknown samples or standards were preincubated with antiserum, 400 μl, diluted 1:15,000, for 24 hr at 4°C. Tracer (100 μl, 5 fmol, specific activity 70 MBq/nmol) was added and the mixture incubated for 24 hr before bound and free peptide moieties were separated by plasma-coated charcoal (25). Detection limit of the assay was below 1 pmol/liter and 50% inhibition was obtained with 23 pmol/liter PYY. Recovery of PYY added to plasma in concentrations between 5 and 50 pmol/liter deviated less than 15% from expected values. Intraassay coefficient of variation was below 5%. The antiserum showed no cross-reaction with human NPY or human PP in concentrations up to 500 pmol/liter.

Glucagon-like peptide-1 (GLP-1) immunoreactivity was measured as described previously (27). Antiserum 390 was raised against a synthetic C-terminal decapeptide of amidated GLP-1 (PG 98-197) amide coupled to bovine serum albumin with carbodiimide (25). The antiserum requires carboxyterminal amidation for binding and cross-reacts fully with PG 78-107 amide, but neither with C-terminally extended or deleted forms of GLP-1; it does not cross-react with any other members of the glucagon/secretin family of peptides. The experimental detection limit in plasma is approximately 1 pmol/liter, and the intraassay coefficient of variation <6%. Before radioimmunoassay plasma samples were extracted with ethanol (70% v/v final concentration). All plasma samples were measured in duplicate. The recovery of GLP-1 added to plasma before extraction was 78 ± 8% (mean ± SD).

For statistical analysis, responses (acid outputs, hormone concentrations) were first integrated over a 60-min postperfusion period, i.e., from 30 to 90 min after the start of each ileal perfusion. This time span was chosen prospectively because it comprises the main period of increased intraileal nutrient exposure as expected from earlier experiments with a similar protocol (7). Next, preileal-perfusion values were subtracted from post-ileal-perfusion values within each subject. The resulting incremental (or decremental) values were evaluated by using analysis of variance for repeated measures to assess overall effects of ileal perfusions (28).

In addition, to compare the effects of each test (carbohydrate, lipids, protein) perfusion with the saline control more specifically for paired data, these delta values were compared by using paired t tests (28) and applying the Bonferroni correction for multiple comparisons. Significant differences were thus assumed at $P < 0.016$. Generally the level of type-1 error of significance was defined at 0.05; empirically found P values are presented descriptively. Data are expressed as mean values ± standard errors (SE), unless indicated otherwise.

RESULTS

Interdigestive State. Gastric acid outputs during the beginning of the interdigestive cycle were at the expected low level and similar prior to each ileal perfusion. In control studies with ileal saline perfusion, gastric acid outputs increased slightly in association with phase II motility of the interdigestive cycle, compared with preperfusion values. Ileal perfusion with carbohydrate was followed by a decrease in basal acid output ($P = 0.006$ vs NaCl) that persisted for a median of 45 min. Ileal lipid perfusion caused a similar decrease in acid output ($P = 0.007$ vs NaCl). Interdigestive acid output was not affected by ileal perfusion with protein, compared with ileal saline (Figure 1).

Compared to preperfusion values, plasma concentrations of PYY were not altered following ileal perfusion with saline (13.4 ± 1.9 vs 11.9 ± 1.7 pmol/liter), carbohydrate (13.3 ± 2.3 vs 13.6 ± 2.2 pmol/liter, or protein (10.2 ± 1.1 vs 12.0 ± 0.7 pmol/liter), respectively. In response to ileal lipids, there was a slight, consistent increase in plasma PYY concentration from 13.5 ± 2.0 to 16.8 ± 2.3 pmol/liter ($P = 0.08$).

Plasma concentrations of GLP-1 were not changed by ileal saline, but increased markedly in response to ileal carbohydrate (P 0.004) and lipid ($P = 0.008$) perfusion; by contrast, ileal protein had no significant effect on GLP-1 (Figure 1).

Endogenous Stimulation. Gastric acid output increased moderately in response to duodenal perfusion with essential amino acids, as expected; there were no differences prior to the different ileal perfusions (Figures 2 and 3). Duodenal recovery of gastric marker and gastric recovery of duodenal marker (duodenogastric reflux) were <5% in all studies. In-

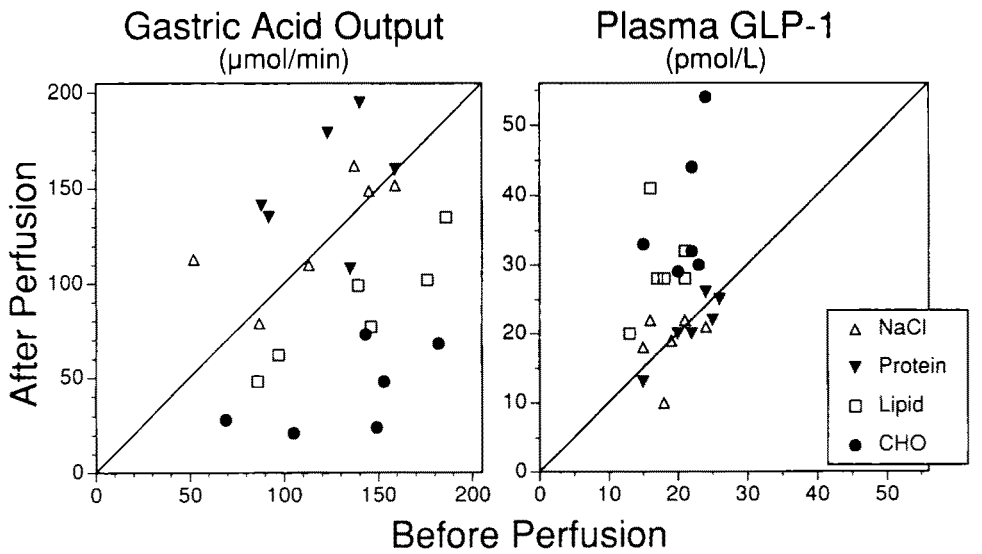

Fig 1. Interdigestive gastric acid output (left panel) and plasma concentration of GLP-1 (right panel) in response to ileal perfusion with normal saline (NaCl; open triangles), protein (solid triangles), lipid (open squares), or carbohydrate (CHO; solid circles). Depicted are integrated mean outputs over 60 min (15–75 min) and GLP-1 concentrations at 60 min following ileal perfusions (y axis) plotted vs mean baseline (preperfusion) values (x axis) for individual subjects. The diagonal line represents equal values before and after perfusion.

traileal concentrations of glucose or triglyceride increased for approximately 90 min following ileal carbohydrate or lipid perfusion, respectively, with maximal values between 45 and 75 min after the start of perfusions (Figure 2).

In control studies, ileal perfusion with saline had no effect on gastric acid output, compared with preperfusion values. Perfusion of carbohydrate into the ileal lumen caused a marked decrease in gastric acid output in all subjects, compared with saline controls (P = 0.002 vs NaCl; Figures 2 and 3). Reduction of acid output persisted for a median of 75 min. Ileal lipids perfusion also decreased acid output (P = 0.004 vs NaCl); degree and duration of inhibition were similar to those following carbohydrate perfusion (Figures 2–4). by contrast, ileal protein perfusion only weakly and inconstantly decreased acid output (NS; Figures 3 and 4).

PYY remained unchanged by ileal perfusion with saline (concentration preperfusion: 12.3 ± 1.3, postperfusion: 12.9 ± 1.4 pmol/liter, carbohydrate (11.2 ± 3.0 vs 14.0 ± 1.4 pmol/liter), or protein (14.3 ± 2.2 vs 13.4 ± 2.0 pmol/liter), respectively. Only in response to ileal lipid perfusion was plasma PYY increased by about 40% from 12.4 ± 2.1 pmol/liter to 17.2 ± 2.4 pmol/liter (P = 0.04), with peak values at 60 min postperfusion.

During duodenal amino acid perfusion, plasma GLP-1 concentrations were slightly higher (29.6 ± 1.9 pmol/liter) compared with interdigestive values (20.3 ± 1.5 pmol/liter) prior to all ileal perfusions (P < 0.05; Figures 1 and 3). Additional ileal saline perfusion had no effect on plasma GLP-1 concentration. By contrast, ileal perfusion with carbohydrate (P = 0.002) or lipid (P = 0.001) doubled plasma GLP-1, compared with preperfusion values, whereas ileal protein had only weak and inconsistent effects (Figures 2–4). Thus, inhibition of gastric acid secretion and GLP-1 release in response to various ileal challenges were associated (Figure 4).

DISCUSSION

These findings demonstrate that in healthy humans, both unstimulated and endogenously stimulated gastric acid output may be modulated by exposure of the distal ileum to quantities of carbohydrate or lipid as they may be delivered in the course of mild malabsorption. These effects are associated with, and may be partly mediated by, release of GLP-1.

It is assumed that the presence of postprandial nutrient loads within the mid and distal small intestinal lumen exerts an inhibitory influence on human acid secretion because diversion of postprandial chyme at the level of the proximal jejunum increased gastric volume and acid outputs, which is reversed when the removed chyme is reinfused (9). The inhibitory influence of unabsorbed nutrients within the

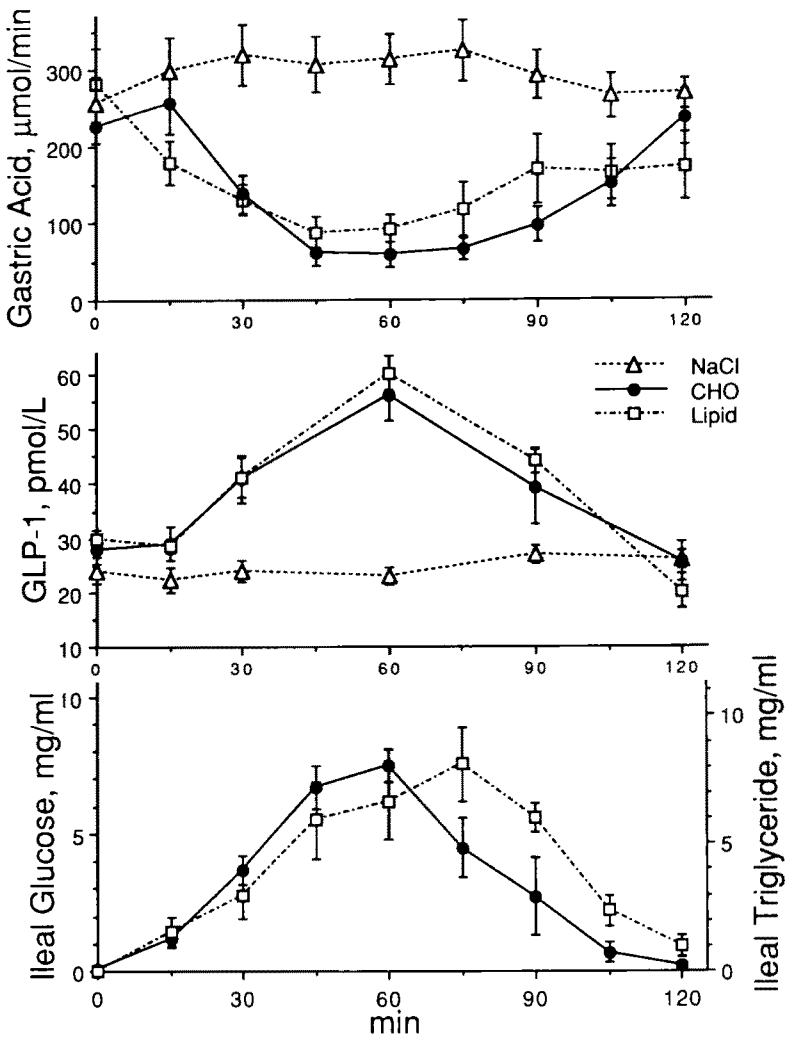

Fig 2. Effects of ileal perfusion (0–15 min) with carbohydrate (solid circles), lipid (open squares), or normal saline (open triangles) on gastric acid output stimulated by continuous duodenal perfusion with essential amino acids (top panel), plasma concentration of GLP-1 (middle panel), and intraileal nutrient concentrations (bottom panel), respectively. Mean values (N = 6) ± SE.

jejunoileum on gastric secretion has been attributed mainly to the fat component, while the protein component exerted lesser effects (29), which suggests that inhibition may not be elicited uniformly by all meal components. Conversely, in patients with jejunoileal bypass operations and increased nutrient loads within the distal small intestine, gastric acid outputs were decreased compared with preoperative values (30). Likely the colon also contributes to these effects, because exogenously stimulated gastric acid secretion was decreased after perfusion of oleate into the proximal colon of dogs (11), and analogous findings were reported in colostomy patients and intubated subjects (10, 12).

Our data now demonstrate that intraileal carbohydrate has similar inhibitory potency compared with isocaloric quantities of ileal fat. Moreover, they show that intraileal carbohydrates and lipids decrease stimulated gastric acid secretion below the basal range and markedly inhibit not only stimulated, but also periodic, interdigestive gastric acid secretion. By contrast, intraileal protein did not affect stimulated or interdigestive acid secretion. Thus, it appears that the protein component of the meal stimulates gastric acid

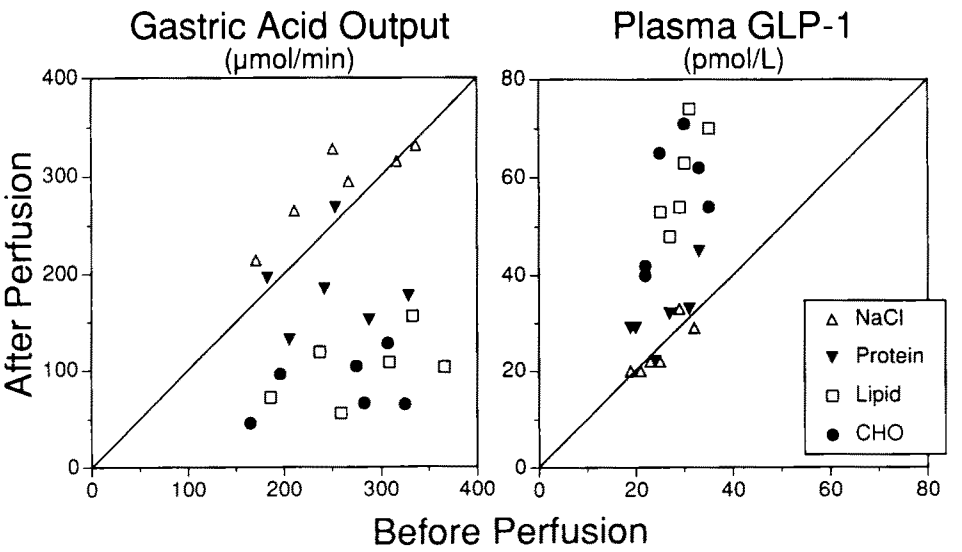

Fig 3. Effect of ileal perfusion with normal saline (NaCl; open triangles), protein (solid triangles), lipids (open squares), or carbohydrate (CHO; solid circles) on gastric acid output stimulated by continuous duodenal perfusion with essential amino acids (left panel) and plasma concentration of GLP-1 (right panel). Depicted are integrated mean outputs over 60 min (15–75 min) and GLP-1 concentrations at 60 min following ileal perfusions (y axis) plotted vs mean baseline (preperfusion) values (x axis) for individual subjects. The diagonal line represents equal values before and after ileal perfusion.

secretion within the duodenum (31), has lesser or no effects in the jejunum (29) and ileum, and is a weak inhibitor in the colon (10–12).

Increased exposure of the ileocolonic region to unabsorbed nutrient occurs in states of small bowel resection or bypass or in malabsorption syndromes. Increased ileal or cecal carbohydrate exposure induced changes not only in gastric acid secretion but also in gastric motor functions (2, 3, 32); in addition, small intestinal motility and pancreatic enzyme secretion may be altered (7, 33). On the other hand, carbohydrate is absorbed incompletely even under physiological conditions, and major quantities of starch may reach the ileum after normal meals ingested by healthy individuals (13–15). Hence, gastric secretory responses to ileal carbohydrate may be of importance not only under pathological conditions but may also contribute to the intestinal phase of the normal gastric secretory response to a meal.

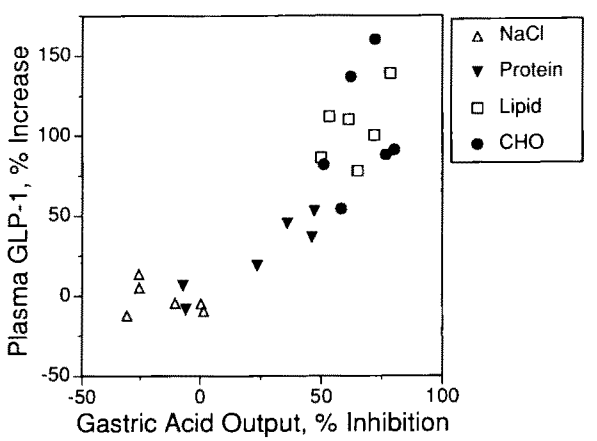

Fig 4. Inhibition of endogenously stimulated acid output (x axis) and stimulation of GLP-1 release (y axis) in response to ileal perfusion with normal saline (NaCl; open triangles), protein (solid triangles), lipids (open squares), or carbohydrate (CHO; solid circles). Depicted are percent changes vs baseline values for individual subjects.

The intermediary mechanism by which the ileum inhibits gastric secretion is uncertain. In contrast to stimulated and interdigestive pancreatic enzyme outputs (7, 34), both stimulated and interdigestive gastric acid outputs were decreased by ileal perfusion of carbohydrate or lipid even below unstimulated values. This suggests that activation of inhibitory pathways rather than reduced stimulation of acid output occurred.

Passage of pathological amounts of unabsorbed nutrient into the distal gut, as in the short bowel syndrome or in exocrine pancreatic insufficiency, has been shown to be associated with increased release of PYY, an enteric peptide produced by endocrine cells of the distal ileum and colon (35–38). Indeed, direct

perfusion of nutrients into the distal intestinal lumen, particularly at larger loads, has been reported to increase plasma concentrations of PYY in humans or dogs (2, 39). Since PYY is a potent inhibitor of human gastric secretion (16), we hypothesized that PYY release may participate in the mechanism mediating ileum-induced inhibition of acid output. However, with the small intraileal nutrient loads used in the present study, only small increases in plasma PYY concentrations were observed in response to ileal lipids, which probably were too low to affect gastric functions; with ileal carbohydrate, no PYY release occurred at all, although gastric secretory responses were similarly pronounced as those following ileal lipids. In conjunction, these findings suggest that PYY release is not involved in the mediation of effects of ileal perfusion with small nutrient loads on human gastric acid secretion. Moreover, they support the concept that PYY release is controlled mainly by proximal intestinal mechanisms and that direct contact of nutrient with the ileal mucosa may not be required (40).

The remaining endocrine peptides of the ileal mucosa are neurotensin and the enteric proglucagon-derived peptides. Neurotensin is known to inhibit gastric acid secretion but has been shown to be broken down rapidly into inactive fragments, with resulting circulating concentrations of the intact peptide that are far too low to affect human gastric functions under physiological circumstances (41, 42). Moreover, there is no evidence that increased ileal nutrient exposure (by malabsorption or direct intraluminal perfusion) causes release of neurotensin in humans (4, 38).

Among the proglucagon-derived peptides, glicentin (proglucagon 1-69) has been shown to inhibit gastric acid secretion in rats (43), but little is known about its physiological role. In addition, in a previous study, glicentin was not released in response to ileal nutrient perfusion in humans (4). Oxyntomodulin (proglucagon 33-69) inhibits gastric acid secretion in man when infused in amounts that elevate the plasma concentration to 200 pmol/liter (44), but it is doubtful if such concentrations are ever reached under physiological circumstances (27).

Truncated glucagon-like peptide-1 (proglucagon 78-107 amide; GLP-1), a potent insulinotropic hormone (17, 45, 46), is released from the ileum in response to ingestion of standard meals (17, 18) and oral glucose loads (27). Upon intravenous infusion at "physiological" doses, ie, with resulting increases in plasma concentrations by about 20 pmol/liter, which are similar to those elicited by ingestion of a standard meal (17, 18), GLP-1 has been demonstrated to inhibit markedly pentagastrin-stimulated acid secretion in humans (18, 20). Moreover, GLP-1 at such physiological concentrations is a potent inhibitor of postprandial gastric acid output as well as of gastric emptying in normal subjects (47).

The present study is the first to demonstrate release of GLP-1 in response to direct ileal exposure to small quantities of nutrient. Under these experimental conditions, GLP-1 plasma concentrations induced by ileal nutrient perfusion reached or even exceeded those known to cause pronounced inhibition of gastric acid secretion in previous investigations (18, 20, 47). We therefore suggest that GLP-1 may be responsible for at least part of the inhibition noted in response to ileal carbohydrate and lipid perfusion.

Direct evidence of such a regulatory role of GLP-1 could only be obtained by performing studies with a selective GLP-1 receptor antagonist, which to date is not available for use in humans. However, out hypothesis is supported indirectly by the tight quantitative association between GLP-1 levels and secretory inhibitory responses within individual experiments, as well as by the observation that GLP-1 and secretory responses to different perfusates were always correlated (eg, ileal protein challenge had no effect on either GLP-1 release or acid output).

The mechanism by which GLP-1 inhibits human gastric is unknown. In an *in vitro* system of isolated rat parietal cells, GLP-1 stimulated rather than inhibited parietal cell function (48). These observations suggest that GLP-1 exerts its potent inhibitory *in vivo* action on gastric acid output (18, 20, 47) via an indirect mechanism, possibly by a stimulatory effect on somatostatin release (49, 50). Further interactions with other neurohormonal regulatory systems are conceivable in view of the complex effects of GLP-1 on multiple exocrine, endocrine, metabolic, and motor functions.

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