Effect of gastrin on antroduodenal motility: role of intraluminal acidity

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Verkijk, M., H. A. J. Gielkens, C. B. H. W. Lamers, and A. A. M. Masclee. Effect of gastrin on antroduodenal motility: role of intraluminal acidity. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G1209–G1216, 1998.—The effect of gastrin on the migrating motility complex (MMC) was studied in seven healthy subjects. It was hypothesized that a potential effect of gastrin on the MMC may result from intraluminal acidification through increased gastric acid secretion. Therefore, antroduodenal manometry and intraluminal acidity were recorded simultaneously. The effect of gastrin on the migrating motility complex (MMC) was studied in seven healthy subjects. It was hypothesized that a potential effect of gastrin on the MMC may result from intraluminal acidification through increased gastric acid secretion. Therefore, antroduodenal manometry and intraluminal acidity were recorded simultaneously. The effect of gastrin on the MMC was subsequently assessed postprandially using a combination of manometry and pH monitoring. The MMC was induced by the ingestion of a meal, and the effect of gastrin on the MMC was assessed using a combination of manometry and pH monitoring. The effect of gastrin on the MMC was assessed using a combination of manometry and pH monitoring. The MMC was induced by the ingestion of a meal, and the effect of gastrin on the MMC was subsequently assessed postprandially. The effect of gastrin on the MMC was subsequently assessed postprandially. The effect of gastrin on the MMC was subsequently assessed postprandially.

Fasting gastrointestinal motility in humans and several other mammalian species is characterized by a recurrent pattern of cyclic occurring motor activity referred to as the migrating motility complex (MMC) (42). The MMC can be divided into at least three distinct phases. Phase I is characterized by motor quiescence; phase II consists of spontaneous irregular motor activity that is followed by phase III, a short burst of rhythmic contractions. Phase III originates either in the stomach or the small intestine and migrates distally. Feeding interrupts the MMC cycle, i.e., phase III motor activity, at all gastrointestinal sites. The subsequent postprandial or “fed” motor pattern is characterized by persistent, irregular contractile activity resembling in appearance fasting phase II (24, 26). During the postprandial state, small intestinal motor activity is suggested to promote efficient digestion, absorption and propulsion of ingested material (34).

The mechanisms responsible for the postprandial interruption of the MMC are not fully understood. Sham feeding delays the reappearance of phase III motor activity, suggesting that the postprandial disruption of MMC cycling may occur by cephalic neural stimulation (22). After the ingestion of a meal, several gut hormones are released into the circulation, of which cholecystokinin (CCK) is known to suppress the MMC (25, 31). However, the lack of loxiglumide, a specific CCK-receptor antagonist, to prevent disruption of the MMC after ingestion of a meal (31) indicates that additional factors apart from the endogenous release of CCK are involved in the conversion of the fasted into the fed motor pattern.

Some studies indicate that gastrin may be involved in the postprandial interruption of the MMC (15, 28, 41), but other studies argue against this suggestion (13, 14, 43). The aim of the present study was to investigate the effect of gastrin infused to postprandial plasma levels on interdigestive antroduodenal motility. Gastrin is a potent stimulus for gastric acid secretion (18). A potential effect of gastrin on gastrointestinal motility may be dependent on, or regulated through, intraluminal acidification by increased gastric acid secretion. Therefore, intraluminal acidity was recorded simultaneously. In addition, the effect of gastrin infusion combined with gastric acid inhibition and of gastric acid inhibition alone on antroduodenal motility and intraluminal acidity was evaluated.

MATERIALS AND METHODS

Subjects. Seven healthy volunteers (2 men, 5 women; mean age 26 yr, range 18–54 yr) participated in the study. None of the subjects reported a history of gastrointestinal symptoms or surgery or was taking any medication. All were screened for Helicobacter pylori and had a negative serological status for IgG antibodies against H. pylori. (ELISA) (38). Informed consent was obtained from each individual, and the study protocol had been approved by the local ethical committee.

Experimental design. The subjects were studied on four separate occasions with an interval of at least 7 days. All experiments were performed in a randomized, single-blind (subjects), and placebo-controlled fashion. After an overnight fast the subjects were intubated transnasally with a combined manometry-pH assembly and a separate intragastric pH probe as described below. Two intravenous canulae, one for blood sampling and the other for infusion, were inserted into the antecubital veins of each arm. The subjects were studied in a semirecumbent position. Immediately after the cessation of the first spontaneous phase III of the MMC in the proximal duodenum, defined as time 30 min, the following intravenous infusions were started: saline (control, A), gastrin-17 (B), gastrin-17 combined with acute acid inhibition by famotidine (Pepcidine, Merck Sharp & Dohme, Haarlem, The Netherlands) (C), or famotidine alone (D). Infusion of famotidine (20-mg bolus, continuous infusion 3.75 mg/h) was started at time 30 min and continued until time 360 min (16). Gastrin infusion (20 pmol·kg⁻¹·h⁻¹) was always started 30 min later (time 0 min) and continued for 360 min. Saline infusions were used as placebos for the experiments during which infusion of gastrin, famotidine, or both (control) was not applied. Blood samples for measurement of plasma gastrin were obtained at time 30, 15, 0, 30, 60, 90, 120,

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150, 180, 240, 300, and 360 min. Antroduodenal motility and intraluminal pH were continuously monitored for 390 min after the start of intravenous infusion of saline or famotidine, i.e., for 390 min after the cessation of the first registered spontaneous phase III of the MMC in the proximal duodenum. Monitoring of antroduodenal manometry and intraluminal pH. Antroduodenal motility was measured by means of perfusion manometry. Intraluminal pressures were recorded with a multilumen water-perfused polyvinyl catheter (outer diameter 5 mm) that incorporated six side holes located 0, 10, 12.5, 15, 20, and 25 cm from the distal tip. The catheter was positioned under fluoroscopic control so that the most proximal side hole was in the antrum. The side hole 15 cm from the distal tip was always located in the proximal duodenum ~5 cm distal to the pylorus. To monitor intraluminal acidity, a miniature glass pH electrode (model LoF440, InMedical, Mettler-Toledo, Switzerland) was fixed to the manometry catheter with the tip of the pH electrode 180° opposite from the side hole located 15 cm from the distal tip. A second and separate pH probe was positioned in the gastric corpus, 10 cm below the diaphragm. The manometry catheter was perfused continuously with gas-free distilled water by a low-compliance pneumohydraulic capillary infusion system (Arndorf Medical Systems, Greendale, WI) at a rate of 0.6 ml/min. Resistance to infusion within the system was detected by a series of external transducers (Medex, Hilliard, OH). Pressure and pH profiles were recorded with a polygraph recorder (PC Polygraph VIII, Synectics Medical, Stockholm, Sweden), displayed on a monitor, and stored on a personal computer for later analysis. Intraluminal pH was sampled and stored at a rate of one reading per second. The pH electrodes were calibrated in buffers of pH 1.4, 3.0, 4.0, and 7.0 before and after each experiment. The electrode drift at the end of each experiment the correct positions of the manometry-pH assembly and intragastric pH probe were verified by fluoroscopy. Analysis of manometry data. Antroduodenal motility recordings were analyzed both visually and automatically. The individual tracings were processed by specialized software (Polygram, Synectics Medical) for adjusting baselines and extracting respiratory artifacts. However, the computer program does not recognize simultaneous pressure events as artifacts. Therefore, remaining artifacts obviously caused by increases in intra-abdominal pressure were identified visually and excluded from analysis. Antral motor characteristics were analyzed using the pressure tracings recorded from the side hole located in the distal antrum. Duodenal motor characteristics were analyzed using the pressure tracings recorded from the side hole in the proximal duodenum, 12.5 cm from the distal tip of the manometry catheter and 2.5 cm distal to the pH electrode, and from the most distal side hole (0 cm). Antral phase III activity was defined as regular rhythmic contractile activity at maximum frequency (2–3 contractions/min) lasting at least 2 min in temporal relationship with duodenal phase III activity (24) and was identified visually. Duodenal phases of the MMC were characterized visually according to the following definitions: phase I, motor quiescence; phase II, irregular contractile activity at a rate of >2 contractions/10 min; phase III: regular rhythmic contractile activity at a frequency of 10–12 contractions/min lasting for at least 2 min. Phase III had to be propagated over at least two recording sites. MMC cycle length was defined as the time between the end of a phase III in the duodenum and the end of the next phase III. Phase III reoccurrence time was defined as the time interval between the start of intravenous infusion of famotidine or saline (time – 30 min) and the reoccurrence of a phase III. When no reoccurrence of phase III activity was observed during the total recording period of 390 min, phase III reoccurrence time was arbitrarily set at 390 min. The following duodenal phase III characteristics were determined visually: origin (antrum or duodenum), duration (in s), and propagation velocity (in cm/min). Phase III propagation velocity was defined as the distance occupied by the front of a duodenal phase III to propagate over 12.5 cm to the most distal recording site in the duodenum. The frequency and amplitude of individual contractions were measured for both phase II and phase III using the computer program. Only pressure waves with amplitude ≥10 mmHg and duration ≥1.5 s were considered true contractions. Additionally, motility indexes of the antrum and the proximal duodenum were calculated for the last 30 min of phase II preceding duodenal phase III. Motility indexes were calculated as the area under the contraction curves, i.e., the sum of the area (mmHg·s) under all individual contractions over a period of 30 min. Analysis of intraluminal acidity. Intragastric pH readings, from a total recording period of 390 min, were divided into 10-min intervals. For each 10-min period, the log mean H+ concentration was computed. The log mean H+ concentration was defined as the arithmetic mean of the antilog of the pH data converted back into pH units by taking the log of the mean value (35). Intraluminal pH readings were analyzed for the 360-min recording period during infusion of saline (control) or gastrin. The log mean H+ concentration was computed for 3-min intervals from 15 min before to 15 min after the onset of each phase III in the proximal duodenum. Additionally, the pH frequency distribution over 360 min was plotted. Assay of gastrin. Blood samples were collected in EDTA-containing ice-chilled tubes. The samples were centrifuged at 3,000 rpm for 10 min at 4°C. All samples were assayed in the same run. Plasma gastrin concentrations were measured by a sensitive and specific radioimmunoassay using a rabbit antisera with equal binding to sulfated and unsulfated forms of gastrin, as described previously (20). Statistical analysis. Results are expressed as means ± SE. Data on late phase II and phase III characteristics were not available for three subjects during gastrin infusion because of complete interruption of the MMC. Therefore, these data were pooled per treatment arm and were analyzed for statistical significance by unpaired ANOVA. When ANOVA indicated a probability of <0.05 for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which
values differed significantly (P < 0.05). Differences in onset of phase III (antrum or duodenum) were analyzed by $\chi^2$-square analysis of contingency tables with Bonferroni’s correction for multiple comparisons. The remaining data concerning antroduodenal motility, intraluminal acidity, and plasma gastrin, over time or between treatment arms, were analyzed for statistical significance by multiple analysis of variance (MANOVA). When MANOVA indicated a probability of <0.05 for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which values differed significantly (P < 0.05).

RESULTS

Plasma gastrin levels. Basal plasma gastrin levels were not significantly different between the four experiments: 18 ± 3, 21 ± 3, 21 ± 3, and 20 ± 4 ng/l for experiments A–D, respectively. No significant alterations in plasma gastrin levels were observed during control (experiment A). Continuous infusion of gastrin (experiment B) resulted in significant (P < 0.05) increases in plasma gastrin levels (Fig. 1). During infusion of gastrin, plasma gastrin levels at ~140 ng/l were obtained, comparable to peak postprandial levels (32). Concomitant infusion of famotidine together with gastrin (experiment C) resulted in significantly (P < 0.05) higher levels of plasma gastrin. Infusion of famotidine alone (experiment D) induced a significant (P < 0.05) rise in plasma gastrin levels over control, starting from time 90 min.

Intragastric and intraduodenal acidity. Basal intragastric acidity was not significantly different between the four experiments: pH 1.7 ± 0.1, 1.4 ± 0.1, 1.6 ± 0.1, and 1.6 ± 0.1 for experiments A–D, respectively. No significant alterations in intragastric acidity were observed during control. Infusion of gastrin significantly (P < 0.05) increased intragastric acidity within 90 min compared with control (Fig. 2). Famotidine, either with or without gastrin infusion, significantly (P < 0.05) reduced intragastric acidity within 30 min compared with control, and pH > 4 was reached within 50 min after the onset of famotidine infusion.

Fluctuations in intraduodenal pH mainly occurred during phase II of the MMC (Fig. 3). Infusion of gastrin significantly (P < 0.05) increased intraduodenal acidity for phase II compared with control (Fig. 4). The onset of phase III motor activity in the proximal duodenum was always associated with a significant (P < 0.05) decline in intraduodenal acidity to pH > 7, even during gastrin infusion (Fig. 5). Intraduodenal pH remained >6 during the subsequent phase of motor quiescence (phase I), and fluctuations did not occur until phase II motor activity had again returned in the proximal duodenum. During concomitant infusion of famotidine together with gastrin and during infusion of famotidine alone, intraduodenal pH was >6 for 96 ± 3 and 98 ± 1%,
respectively, of the total recording time of 360 min (data not shown).

Antroduodenal motility. The time interval between the start of the manometry recording and the onset of the first spontaneous phase III in the proximal duodenum did not significantly differ among the four experiments: 117 ± 38, 88 ± 22, 91 ± 25, and 104 ± 26 min for experiments A–D, respectively. Individual manometry tracings are shown in Fig. 6. During the control experiment, the cycling frequency of the MMC, over a total recording period of 390 min, was 0.4 ± 0.1 h⁻¹ with a phase III reoccurrence time of 136 ± 18 min (Table 1).

Infusion of gastrin completely interrupted the cycling pattern of the MMC in three of the seven subjects and prolonged phase III reoccurrence time over control in three other subjects. In one subject, phase III reoccurrence time was shorter during infusion of gastrin (97 min) compared with control (203 min). Overall, phase III reoccurrence time (7 subjects) was significantly (P < 0.05) prolonged during gastrin infusion (271 ± 45 min) compared with control (136 ± 18 min). The number of occurrences of phase III recorded for each subject, over a total recording period of 390 min, was reduced during infusion of gastrin (1.7 ± 0.7), although not significantly, compared with control (2.3 ± 0.4) (Table 1). Because infusion of gastrin disrupted the cycling pattern of the MMC, either by prolonging phase III reoccurrence time or by completely suppressing phase III motor activity, complete MMC cycle length for this experiment could not be determined. With regard to the different phases of the MMC, relatively, although not significantly, less time of the 360-min manometry recording period was occupied by phase I and phase III motor activity compared with control (Table 2). Occurrences of phase III during infusion of gastrin were all of duodenal origin (Table 3). The other phase III characteristics were not significantly different from control. The suppression of antral motor activity during gastrin infusion was further reflected by a significantly (P < 0.05) reduced motility index for the antrum compared with control (Table 4). Similarly, the motility index for the proximal duodenum was significantly (P < 0.05) reduced during gastrin infusion. Reduction of antral and duodenal motility indexes during gastrin infusion resulted mainly from a significant (P < 0.05) decline in contraction frequency compared with control (Table 4).

Concomitant infusion of famotidine completely antagonized the effect of gastrin on the MMC (Tables 1–4). In fact, phase III reoccurrence time tended to be shorter compared with control. The latter was reflected by a significantly (P < 0.05) reduced individual mean MMC cycle length compared with control (Table 1). This shorter duration of the MMC cycle resulted from a significant (P < 0.05) reduction in phase II duration compared with control. Furthermore, the relative contribution of phase I (P = 0.14) and phase III (P < 0.05) motor activity to the 360-min manometry recording period was increased over control during concomitant infusion of famotidine together with gastrin. The latter was further reflected by a significant (P < 0.05) reduction in the contribution of phase II motor activity (Table 2). Phase III characteristics did not significantly
differ from control (Table 3). Likewise, antral and duodenal motility indexes for phase II were not significantly different from control (Table 4). The effect of concomitant infusion of famotidine together with gastrin on the MMC was similar to that of infusion of famotidine alone (Tables 1–4).

**DISCUSSION**

The present study shows that exogenous gastrin infused to postprandial plasma levels interrupts the cycling pattern of the MMC by suppressing gastric onset of phase III motor activity and prolonging the reoccurrence of phase III motor activity in the duodenum. Infusion of gastrin reduced phase II motor activity in both the antrum and the duodenum. Our findings indicate that the effect of gastrin on gastrointestinal motility results from increased intraluminal acidity, because it is no longer observed during gastrin infusion and concomitant gastric acid inhibition with famotidine. Finally, we have shown that inhibition of gastric acid secretion with famotidine has a promoting effect on the occurrence of the MMC by shortening its cycle length.

Our results are in agreement with those of Erckenbrecht et al. (15), showing that infusion of pentagastrin without gastric acid inhibition interrupts the interdigestive motor pattern. These authors concluded that gastrin is a likely candidate for the postprandial interruption of the MMC. Our results suggest that gastrin itself is probably not involved in the postprandial interruption of the MMC, because gastric acid inhibition with famotidine completely antagonized the effect of gastrin on antroduodenal motility. Similarly, Dooley et al. (13) have shown that gastrin-17 infused to postprandial plasma levels combined with continuous gastric aspiration does not affect interdigestive intestinal motility. In contrast to our study, however, the interventions in the latter study were not timed with respect to the different phases of the MMC cycle. Furthermore, only the number of occurrences of intestinal phase III were included in their analysis on MMC cycling, which therefore neglected the temporal organization of the MMC. In the

**Table 1. MMC cycle characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Gastrin</th>
<th>Gas + Fam</th>
<th>Fam</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of phase III/390 min</td>
<td>2.3 ± 0.4</td>
<td>1.7 ± 0.7</td>
<td>3.4 ± 0.4</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>Phase III recurrence, min</td>
<td>136 ± 18</td>
<td>271 ± 45*</td>
<td>78 ± 13</td>
<td>87 ± 23</td>
</tr>
<tr>
<td>MMC cycle length, min</td>
<td>149 ± 16</td>
<td>106 ± 12*</td>
<td>107 ± 12*</td>
<td></td>
</tr>
<tr>
<td>Phase I length, min</td>
<td>13 ± 3</td>
<td>13 ± 2</td>
<td>12 ± 2</td>
<td></td>
</tr>
<tr>
<td>Phase II length, min</td>
<td>131 ± 16</td>
<td>88 ± 11*</td>
<td>90 ± 11*</td>
<td></td>
</tr>
<tr>
<td>Phase III length, min</td>
<td>3.8 ± 0.6</td>
<td>5.0 ± 0.7</td>
<td>4.5 ± 0.6</td>
<td></td>
</tr>
</tbody>
</table>

Data (means ± SE) relate to 7 healthy subjects during intravenous infusion of saline (control), gastrin-17, gastrin-17 combined with acute acid inhibition by famotidine (Gas + Fam), and famotidine alone (Fam) for 390 min. MMC, migrating motility complex. *P < 0.05 compared with control.

**Table 2. Relative contribution of phases of MMC to 360 min of manometry recording**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Gastrin</th>
<th>Gas + Fam</th>
<th>Fam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>8 ± 2</td>
<td>4 ± 2</td>
<td>11 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Phase II</td>
<td>90 ± 2</td>
<td>94 ± 3</td>
<td>84 ± 2*</td>
<td>82 ± 2*</td>
</tr>
<tr>
<td>Phase III</td>
<td>3 ± 1</td>
<td>1 ± 1</td>
<td>5 ± 1*</td>
<td>5 ± 1*</td>
</tr>
</tbody>
</table>

Data (% time; means ± SE) relate to 7 healthy subjects during intravenous infusion. *P < 0.05 compared with control.
Table 3. Phase III characteristics of proximal duodenum

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Gastrin</th>
<th>Gas + Fam</th>
<th>Fam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral origin, no./</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total no.</td>
<td>8/16 (50%)</td>
<td>0/12 (0%)*</td>
<td>17/24 (71%)</td>
<td>15/24 (63%)</td>
</tr>
<tr>
<td>Duration, s</td>
<td>237 ± 24</td>
<td>176 ± 11</td>
<td>316 ± 30</td>
<td>282 ± 24</td>
</tr>
<tr>
<td>Velocity, cm/min</td>
<td>22.7 ± 4.4</td>
<td>16.7 ± 2.4</td>
<td>17.0 ± 2.7</td>
<td>15.8 ± 2.7</td>
</tr>
<tr>
<td>Frequency, min⁻¹</td>
<td>11.4 ± 0.1</td>
<td>11.6 ± 0.2</td>
<td>11.5 ± 0.1</td>
<td>11.3 ± 0.2</td>
</tr>
<tr>
<td>Mean amplitude, mmHg</td>
<td>31.6 ± 1.5</td>
<td>32.6 ± 1.7</td>
<td>29.6 ± 1.2</td>
<td>28.7 ± 1.3</td>
</tr>
</tbody>
</table>

Data (means ± SE) relate to 7 healthy subjects during intravenous infusion for 360 min. *P < 0.05 compared with control.

Table 4. Motility characteristics of antrum and proximal duodenum for last 30 min of phase III preceding duodenal phase III

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Gastrin</th>
<th>Gas + Fam</th>
<th>Fam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antrum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, min⁻¹</td>
<td>0.40 ± 0.07</td>
<td>0.11 ± 0.05*</td>
<td>0.64 ± 0.07</td>
<td>0.63 ± 0.09</td>
</tr>
<tr>
<td>Mean amplitude, mmHg</td>
<td>67.5 ± 7.7</td>
<td>50.2 ± 9.3</td>
<td>64.9 ± 6.4</td>
<td>49.7 ± 5.3</td>
</tr>
<tr>
<td>Motility index, mmHg·s</td>
<td>2,777 ± 733</td>
<td>448 ± 253*</td>
<td>3,707 ± 629</td>
<td>2,425 ± 377</td>
</tr>
<tr>
<td>Duodenum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, min⁻¹</td>
<td>2.98 ± 0.33</td>
<td>2.17 ± 0.25*</td>
<td>2.82 ± 0.26</td>
<td>3.30 ± 0.28</td>
</tr>
<tr>
<td>Mean amplitude, mmHg</td>
<td>23.1 ± 0.9</td>
<td>20.2 ± 1.1</td>
<td>23.0 ± 0.9</td>
<td>25.6 ± 1.1</td>
</tr>
<tr>
<td>Motility index, mmHg·s</td>
<td>3,771 ± 615</td>
<td>2,100 ± 333*</td>
<td>2,878 ± 304</td>
<td>4,197 ± 332</td>
</tr>
</tbody>
</table>

Data (means ± SE) relate to 7 healthy subjects during intravenous infusion for 360 min. *P < 0.05 compared with control.

In the canine species, both pentagastrin and gastrin-17, with or without continuous gastric aspiration, were reported to interrupt the MMC (28, 41, 43). Despite these observations, the role of gastrin in the postprandial interruption of the MMC has been questioned in this species because 1) certain food substances that interrupt the MMC lack the ability to stimulate endogenous gastrin release (14) and 2) infusion of pentagastrin fails to interrupt the MMC in the distal small intestine (43). Suppression of interdigestive gastrointestinal motility by gastric acid was also demonstrated in patients with gastric acid hypersecretion. In these patients, interdigestive gastrointestinal motility is characterized by a reduced occurrence of both antral and duodenal phase III compared with normosecretory subjects (8, 19). Pharmacological inhibition of gastric acid secretion (6) and intragastric neutralization of pH with sodium bicarbonate (9) restore the interdigestive motor pattern in this group of patients to that seen in healthy subjects. Similarly, stimulation of gastric acid secretion in healthy subjects prolongs the cycling rate of the MMC (6, 8). Although intraluminal acidification appears to be a potent inhibitor of gastrointestinal motility, it might be questioned at this point whether its effect on motility originates in the stomach or the duodenum.

Previous studies in the canine species suggest that the proximal duodenum is a sensitive site for inhibition of gastric emptying through intraluminal acidification (11, 30). In humans, Misiewicz et al. (33) demonstrated that infusion of pentagastrin during continuous aspiration of gastric contents did not inhibit gastric motility until gastric acid was allowed to enter the duodenum. Likewise, Couturier et al. (12) showed that intragastric acid infusion in humans inhibits gastric myoelectrical activity to the same extent as intraduodenal infusion of acid at infusion rates that resembled gastric emptying of the solution studied during intragastric infusion. Therefore, the duodenum should be considered as a potential site through which gastrin exerts its effect on antroduodenal motility by intraluminal acidification as in the present study. Our study design, however, does not allow us to exclude an effect of gastrin on motility resulting from intragastric acidification.

Motilin may play an important role in the initiation of phase III in the stomach. Motilin is released periodically during the interdigestive state, and two- to threefold increments in plasma motilin are related to occurrences of phase III that originate in the stomach (36). Furthermore, infusion of motilin induces premature phase III motor activity in the stomach (21) and anti-motilin serum in the canine species suppresses the occurrence of spontaneous gastric phase III (27). Woodtli and Owyang (44) showed that intraduodenal acid infusion in humans suppresses antral motor activity without affecting the cycling pattern of plasma motilin levels, suggesting that, at least in humans, intraduodenal acidification may reduce the action of motilin on the stomach. The intestinal motor response to intraduodenal acid infusion may include postponement of phase III motor activity but, occasionally, also induction of phase III-like complexes (29, 44). Animal studies suggest the involvement of both vagovagal and intramural neural pathways in the gastrointestinal motor response to intraluminal acidification (1, 17, 45).

Apart from neural pathways mediating the effect of intraluminal acidification on gastrointestinal motility, hormonal mechanisms should not be ruled out. For instance, duodenal acidification is known to release secretin (5) and could thereby influence gastric motility (37). Furthermore, release of CCK (10) and motilin (5) has been reported during intraduodenal acidification of which CCK is known to suppress the MMC (25, 31). The role of motilin is probably limited as discussed above.

The role of gastric acid as a potential modulator of interdigestive gastrointestinal motility is further emphasized by our present data demonstrating that gastric acid inhibition with famotidine significantly shortens MMC cycle length. In vitro studies have shown that histamine H₂-receptor antagonists exhibit cholinergic-like effects (3, 4). In fact, H₂-receptor antagonists dose-dependently inhibit acetylcholinesterase activity (2, 39). It might therefore be questioned whether famotidine exerts its promoting effect on the occurrence
of the MMC through a direct interaction with the cholinergic system rather than through inhibition of gastric acid secretion. Several studies, however, have shown that the cholinergic effect of H₂-receptor antagonists varies widely between different compounds (2, 4), that of famotidine being the weakest (2). Furthermore, no inhibition of acetylcholinesterase activity could be demonstrated in vivo when therapeutic doses of H₂-receptor antagonists were applied (40). Finally, our results are in accordance with those of Bertaccini et al. (7) who used the proton-pump inhibitor omeprazole instead of a H₂-receptor antagonist to inhibit gastric acid secretion.

We have demonstrated, in agreement with previous studies (19, 44), that intraluminal acidity of the proximal duodenum is closely related to the different phases of the MMC. Fluctuations in intraduodenal pH mainly occurred during phase II of the MMC. Onset of phase III motor activity in the duodenum was always characterized by a rapid increase in intraduodenal pH that remained in the normal range during the subsequent phase of motor quiescence. During the interdigestive state, the MMC is accompanied by a true cycling secretory component involving pancreatic, biliary, and gastric secretion (23). It has been suggested by Wooddti and Owyang (44) that the cycling variation of intraduodenal pH most likely results from these secretory processes. We have shown, however, that the onset of duodenal phase III motor activity always preceded the onset of intraduodenal neutralization of pH, even during continuous stimulation of one of these secretory processes, i.e., gastric acid secretion. Although our study does not allow us to exclude an effect resulting from gastrointestinal secretion, the temporal sequence of these events suggests that duodenal phase III motor activity itself may be an important factor contributing to the increase in intraduodenal pH around duodenal phase III.

It is concluded that in humans 1) gastrin infused to postprandial plasma levels increases intraluminal acidity and suppresses interdigestive antroduodenal motility; 2) the effect of gastrin on antroduodenal motility results from increased intraluminal acidity; 3) inhibition of gastric acid secretion significantly shortens MMC cycle length; and 4) gastrin itself seems not to be involved in the postprandial interruption of the MMC.

REFERENCES


