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Putative effect of *Helicobacter pylori* and gastritis on gastric acid secretion in cat

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Sobhani, Iradj, Sergio Canedo, Beatriz Alchepo, Christiane Vissuzainé, Catherine Chevalier, Marion Buyse, Laurent Moizo, J. Pierre Laigneau, Michel Mignon, J. Miguel Lewin, and André Bado. Putative effect of *Helicobacter pylori* and gastritis on gastric acid secretion in cat. *Am J Physiol Gastrointest Liver Physiol* 282: G727–G734, 2002. First published November 28, 2001; 10.1152/ajpgi.00282.2001.—*Helicobacter pylori* may increase or inhibit gastric acid. We studied acid variations and plasma gastrin in cats harboring *Helicobacter felis*, harboring *H. pylori*, or free of gastric pathogens with reference to thioperamide (H₃ receptor antagonist) and SR-27417A (PAF receptor antagonist). In cats harboring *H. felis*, gastric mucosa were histologically normal. After *H. felis* eradication, pentagastrin-stimulated acid secretion was increased (40%) compared with the situation before eradication. Thioperamide abolished this inhibitory effect of *H. felis*, whereas SR-27417A did not. Basal and meal-stimulated plasma gastrin levels were not affected by eradication therapy. Acid secretion was inhibited (–80%) in week 3, increased from weeks 5 to 9, and remained constant for up to 42 weeks after *H. pylori* infection. SR-27417A had no effect on acid secretion before week 8 but inhibited it thereafter, and thioperamide increased it (20%) only before week 7 in those cats. *Helicobacter* inhibits gastric acid via an H₃ receptor pathway. Inflammatory mediators are thus involved in adaptation to the inhibitory effects of *H. pylori* on acid secretion.

histamine; gastrin; PAF receptor; H₃ receptor

ACID OVERPRODUCTION HAS LONG been believed to cause ulcers in the gastroduodenal mucosa, i.e., in Zollinger-Ellison syndrome. Antacid secretion drugs heal gastric and duodenal ulcers, and achlorhydria is never associated with peptic ulcers.

Helicobacter pylori induces gastritis and is thought to exert deleterious effects on the mucosa by producing cytokines in humans and animals (12, 13, 20, 31, 34, 38, 40, 46, 47). Proinflammatory mediators are known to modify gastric functions, particularly the secretion of gastrin, somatostatin, and acid. Tumor necrosis factor- α stimulates antral G cells (6, 51) in vitro, and platelet-activating factor (PAF), a proinflammatory

agent, stimulates parietal cells (48–50), whereas interleukin (IL)-1 inhibits acid secretion in vitro (6, 51).

Previous studies have provided conflicting results concerning the effect of *H. pylori* on gastric acid secretion in vivo (9, 29). Gastric acid secretion has been reported to increase 4–8 wk after eradication therapy in humans (28, 52), suggesting that *H. pylori* inhibits acid secretion. In contrast, acid secretion in basal conditions and after stimulation with a meal or gastrin-releasing peptide (6, 9, 47, 51) seemed to decrease after eradication therapy in other studies, suggesting that the bacterium has a stimulatory effect. These authors have also reported acid output to be higher in some *H. pylori*-positive patients and significantly lower in others compared with *H. pylori*-negative individuals (15–18). In both groups, acid abnormalities resolved after eradication therapy. Although decreases in gastric acid levels in prolonged chronic gastritis are due to fundic atrophy with parietal cell rarefaction, it is unclear whether *H. pylori* increases gastric acid secretion during the acute phase before fundic atrophy. Some experimental data suggest that the bacterium may itself directly inhibit gastric acid secretion in vitro. Not only does *H. pylori* have urease activity, enabling it to neutralize acid by an ammonia buffer system, it also produces an inhibitory toxin that binds H⁺-K⁺-ATPase (15). In addition, it produces N α -methylhistamine (N α -MH), a potent H₃ receptor agonist (1, 3, 5, 11). Indeed, H₃ receptor agonists may inhibit gastric secretion by exerting an inhibitory effect on enterochromaffin-like (ECL) cells (41). Thus the putative effects of inflammation and bacteria on gastric acid secretion must be distinguished. The aim of this study was to analyze the effect of the bacterium on gastric acid secretion with respect to gastritis and inflammatory mediators (i.e., histamine and PAF).

MATERIALS AND METHODS

Animals and Surgery

Nine adult cats (Iffa Credo, St. Albresles, France), each weighing 3–4.5 kg and equipped with a gastric fistula in the

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main stomach (MS), and four of which had a denervated Heidenhain fundic pouch (HFP), were used. The surgical procedure was conducted under pentobarbital sodium anesthesia, as previously described (19). Briefly, the abdomen was opened through a midline incision, and gastric fistula and HFP were constructed. Samples of gastric mucosa were tested for *H. pylori*, using the campylobacter-like organism test, histological examination, PCR, and culture. A specially designed plastic cannula was inserted through the stomach and pulled out through the left side of the abdominal wall. Animals were allowed water and milk the day after surgery, and solid food was gradually introduced 3–4 days later. The experiments were performed 3 mo after surgery. At this time, the MS carried *H. felis* and the HFP was bacterium free. The present model has been validated for functional gastric studies as previously described (4, 5, 19). Briefly, to verify the vagotomized status of the HFP, cats fasted for 18 h were injected with 2-deoxy-D-glucose (100 mg/kg iv) with the fistula of the MS closed. This procedure is used to inhibit vagally induced gastrin release by antral acidification. Gastric juice was collected every 15 min in the HFP. Under these conditions, no effect on basal gastric acid output was observed in the HFP, indicating that the HFP is indeed vagotomized. This experiment was performed before the first and after the last experiment in each cat. The animals were treated in accordance with European Community standards concerning the care and use of laboratory animals (INSERM and Ministère de l'Agriculture et de la Forêt, France, authorization no. 02249).

Experimental Schedule

Gastric biopsy samples were taken through the gastric fistula by using an endoscopic forceps. For each compartment, one biopsy was used for the rapid urease test and two for histology (body and antrum in the MS). Two additional biopsy samples were immediately used for culture. Biopsies were performed before, and at least 1 mo after, eradication therapy.

Eradication therapy involved the addition of 5 mg·kg⁻¹·day⁻¹ omeprazole and two antibiotics, clarithromycin (30 mg·kg⁻¹·day⁻¹) and amoxicillin (20 mg·kg⁻¹·day⁻¹), to the diet for 15 days. Experiments were performed again under similar conditions 5 wk after the end of eradication therapy.

H. Pylori Infection

A well-characterized strain of *H. pylori*, Vac-positive and Cag-positive, (40) was kindly donated by B. J. Marshall. It was maintained in culture throughout the experimental period. In five of the nine cats, 2–5 ml of a suspension of SS1 *H. pylori* [10⁶ colony-forming units/ml] was administered in the MS twice per week for 2 wk, through the fistula. Biopsy samples were taken once per week from gastric mucosa for histology and culture. Gastric secretory tests were performed during week 3 and then repeated in weeks 5, 7, 9, 12, 24, and 42. Pentagastrin-induced gastric acid secretion was determined in weeks 12 and 42.

Gastric Secretory Studies

Gastric acid secretion was studied before and after eradication therapy in cats deprived of food for 18 h. Experiments were carried out no more than twice per week on conscious animals resting in sling frames. After cats were fasted overnight, the gastric cannula was opened, a catheter was inserted into the saphenous vein, and 0.9% NaCl was infused at a flow rate of 15 ml/h. Gastric acid secretion was stimu-

lated by intravenous continuous perfusion or increasing doses of pentagastrin (1–16 µg·kg⁻¹·h⁻¹) or histamine (100–1,600 nmol·kg⁻¹·h⁻¹) for 180 min. We then investigated the effects of the PAF receptor antagonist SR-27417A (1 mg/kg) and of the H₃ receptor antagonist thioperamide (0.3 mg/kg or 10 nmol/kg) on stimulated gastric acid output. These drugs have been shown to modify gastric acid secretion at dosages indicated here (4, 5, 48). They were injected as an intravenous bolus just before a continuous intravenous infusion of pentagastrin (16 µg·kg⁻¹·h⁻¹) or histamine (100 µg·kg⁻¹·h⁻¹) started. Gastric juice was collected over periods of 15 min for 180 min.

In another set of experiments, gastric acid secretion was stimulated by a solid beef meal. Briefly, before each test meal, the stomach was rinsed with water through the gastric fistula. Fifty grams of a solid meal was given to the cats over 60 s, and the gastric cannula was kept closed. Gastric secretion was collected from HFP over periods of 15 min for 120 min.

The volume of gastric juice was measured, and the acid concentration of each sample was determined by titration with 0.01 M NaOH to pH 7. Acid output was subsequently calculated. To exclude effects of the ammonia buffer system on acid titration, samples of gastric juices obtained from *Helicobacter*-infected cats were then analyzed at pH 9.

Histological Examination of Gastric Mucosa

Samples from fundic and antral mucosa were fixed in 10% formol-buffered saline and embedded in paraffin wax, and 4-µm sections were cut and stained with hematoxylin and eosin for histological examination and May-Grunwald Giemsa stain for the assessment of *H. pylori* colonization (32). We screened in particular for polymorphonuclear leukocytes and atrophy, assessed by the loss of parietal cells, using a semiquantitative light microscopy procedure. *H. felis* and *H. pylori* were recognized on the basis of morphology (see below).

Bacteria

Morphology was the common criterion that we used on histology and when we worked with pure cultures as described by several authors (23, 32). The best and quickest way to recognize the characteristic morphology of *H. felis* and *H. pylori* was by phase contrast microscopy (using ×1,000 magnification). The morphology of *H. felis*, being a helical bacterium of 5–7 µm, is very distinctive from *H. pylori*, which is a curved bacilli with characteristic S- and U-shaped spiral or short rods (Fig. 1). When morphology was not easily distinguishable, PCR was used.

Culture. Gastric biopsy samples were gently ground and cultured on *Campylobacter*-selective agar medium containing sterile horse blood (5% vol/vol), vancomycin (10 mg/l), Trimetoprim (5 mg/l), polymyxin (2,500 IU/l), and amphotericin B (5 mg/l), as previously described (21, 22, 32). The plates were incubated in an anaerobic jar with a microaerophilic gas-generating kit for 2 days at 37°C. Bacteria that tested positive for urease and oxidase were identified on the basis of PCR analysis, which showed 16S ribosomal DNA sequences to be >98% identical to those of *H. felis* or *H. heilmannii* (22–24). In most cases, *Helicobacter*-like organisms were identified to be *H. felis*, and *H. pylori* was not detected in any of these animals before experimental infection. After *H. pylori* infection, rapid urease test, PCR, and culture were used to check gastric infestation according to procedures described elsewhere by ourselves and others (21, 23, 30). Distinction between *H. felis* and *H. pylori* was based, if necessary, on two

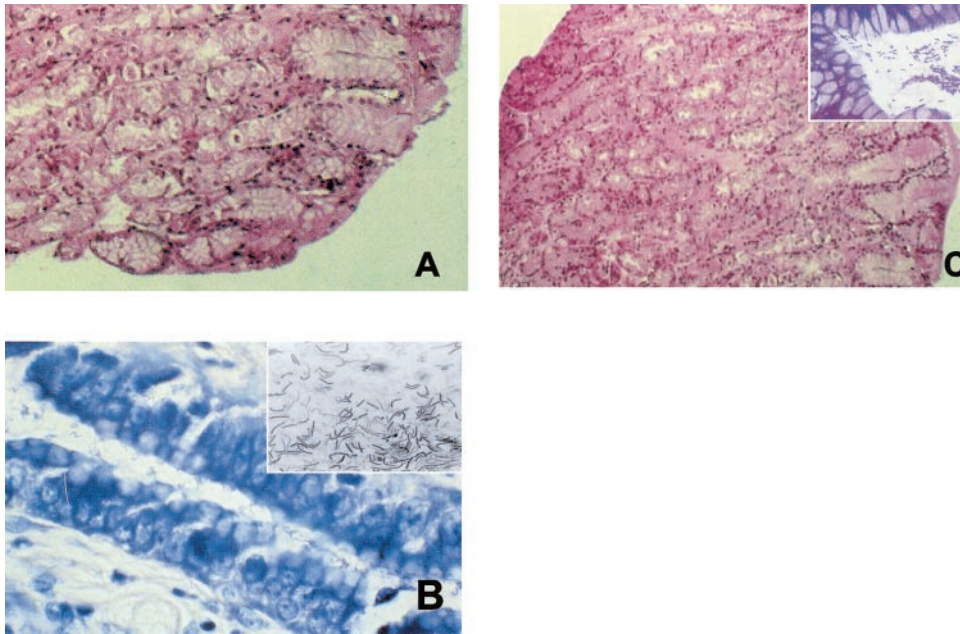


Fig. 1. Cats were equipped with a gastric fistula in the main stomach (MS). Gastric biopsy specimens were collected through the fistula. The MS carried *Helicobacter felis* (A and B) or *Helicobacter pylori* (C). Gastric mucosa harboring *H. felis* was normal (A; no gastritis, no atrophy) (hematoxylin and eosin staining; magnification, $\times 250$); C: gastric mucosa infected by *SSI Vac*-positive and *Cag*-positive *H. pylori* observed at week 5 (gastritis, no atrophy; hematoxylin and eosin staining; magnification, $\times 250$). Morphological characteristics of *H. felis* on histology (B) or culture (B, inset) were clearly different from those of *H. pylori* (C, inset) on histology.

PCR tests, with primer sequences chosen for amplification on 16S RNA and U3 urease genes as previously described (22, 30, 45). Briefly, culture and PCR were used as references to distinguish *H. pylori* from *H. felis*. All of these tests were validated in animals and in humans (21, 24).

Radioimmunoassay of Gastrin and Somatostatin

Blood samples were collected under basal and meal-stimulated conditions. Gastric juices were collected under basal conditions and under pentagastrin infusion. Blood and luminal juices were centrifuged at 10,000 *g* for 3 min, and plasma was collected and stored at -20°C until gastrin assay. Gastrin was determined by radioimmunoassay (RIA), using antibodies directed against G5-CT, G17-CT, and G34-CT (Amersham, Les Ulis, France). Luminal somatostatin was measured (RIA) using a specific rabbit polyclonal somatostatin-14 antibody (Amersham). The method has been previously validated in cat for gastrin and somatostatin with IC_{50} of 18 pg/ml and 16 pg/ml, respectively (2, 4). Serial dilution curves of feline plasma and gastric juice were performed, and the curves were similar to those produced by the standard hormones used in the RIAs.

Statistical Analysis

At least three experiments were performed in each cat. A mean value per cat has been established, and values indicated (expressed as gastric acid output in microequivalents per 15 min or peptide concentration in the serum) are the means \pm SE of mean individual values. Similarly, mean individual values per cat were used for statistical analysis. ANOVA and Student's paired *t*-test were used as appropriate to compare means, and the significance threshold was set at $P < 0.05$.

RESULTS

Before and After Eradication of *Helicobacter Felis*

The urease CLO test was positive for the MS mucosa, and histological examination showed microorganisms resembling *Helicobacter*. In contrast, in the iso-

lated fundic pouch, the CLO test and PCR were negative and histological examination showed no microorganisms. There was no evidence of inflammatory cell infiltration or gastric atrophy in the mucosa in the MS (Fig. 1A) and in the HFP.

Five weeks after eradication therapy, and at the end of each experiment, biopsy samples from the MS and HFP were analyzed and showed no stigmata of inflammation or bacterium, as assessed by histology, urease CLO test, and PCR. Somatostatin-like immunoreactivity in the gastric juice under basal conditions before (3 ± 1.5 ng/ml) was not significantly higher than that after eradication therapy (3.2 ± 2.3 ng/ml). The time course of luminal somatostatin outputs in response to pentagastrin remained unchanged by eradication therapy (Table 1).

Gastric acid output from the MS. Intravenous pentagastrin and histamine infusions stimulated gastric acid output in a dose-dependent manner both before and after eradication therapy. As shown in Fig. 2A, eradication of *H. felis* induced a shift to the right of the dose-response curve for pentagastrin stimulation of gastric acid output from the MS, with acid output being significantly increased by $\sim 40\%$ ($P < 0.01$) at each dose of pentagastrin. A similar dose-response curve was obtained with histamine (data not shown).

Table 1. Basal and pentagastrin-induced luminal somatostatin in *Helicobacter felis*-positive, germ-free, and *H. pylori*-positive cats

Cats	n	0	15 min	30 min	60 min
<i>H. felis</i> +	9	3.5 ± 1.5	6 ± 2.8	9.6 ± 2.7	14.2 ± 2.8
<i>H. felis</i> -, <i>H. pylori</i> -	9	3.2 ± 2.3	5.7 ± 1.9	8.9 ± 1.5	15.6 ± 3.5
<i>H. pylori</i> + 6-8 wk after infection	5	3.9 ± 2.5	6.1 ± 2.2	9.1 ± 2.6	16.2 ± 2.7

Values are means \pm SE (ng/ml). Differences are not statistically significant between three groups.

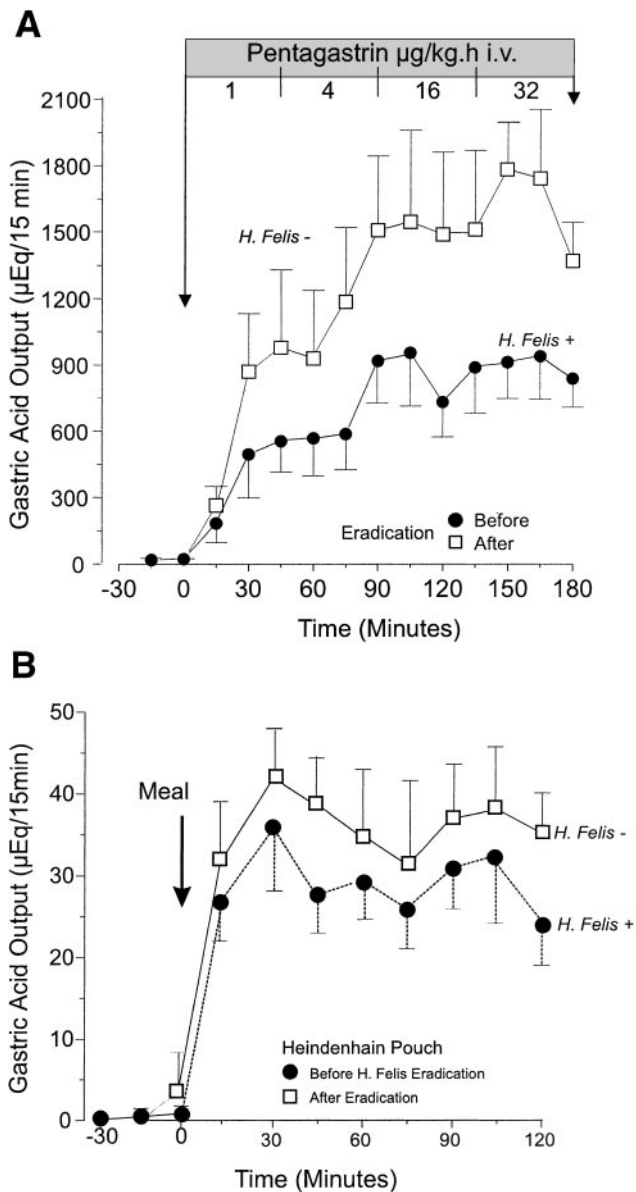


Fig. 2. A: cumulative dose-response curves for pentagastrin stimulation of gastric acid output before and after eradication of *H. felis* from the MS. Each dose was intravenously infused for 45 min, then increased. Data are expressed in $\mu\text{eq}/15\text{ min}$ and are means \pm SE from 9 cats tested at least 3 times. B: meal stimulated gastric acid output from the denervated Heidenhain fundic pouch in 4 cats before and after eradication therapy. Data are expressed in $\mu\text{eq}/15\text{ min}$ and are means \pm SE from 4 cats tested at least 3 times.

Gastric acid output from the HFP. In the HFP that is free of germs, gastric acid outputs induced by pentagastrin, histamine, and meal were not affected by eradication therapy. As shown in Fig. 2B, ingestion of a solid meal stimulated gastric acid output from the HFP: it peaked at 30 min, reaching $43 \pm 6\ \mu\text{eq}/15\text{ min}$ and then leveling off by 120 min. Similarly, meal induced a twofold plasma gastrin level elevation that was unaffected by eradication therapy (Fig. 2 and Table 2).

Effect of thioperamide, an H_3 receptor antagonist. Before eradication therapy, the thioperamide ($10\ \text{nmol}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) significantly increased pentagastrin-

stimulated gastric acid output in the MS (Fig. 3A) but not in the HFP. Similar results were obtained with histamine both from the MS and the HFP (Fig. 3B).

Effect of SR-27417A, a PAF receptor antagonist. Before and after eradication therapy, SR-27417A did not affect either basal acid output or pentagastrin- and histamine-induced acid outputs from the MS and the HFP (data not shown).

After *H. Pylori* Infection

The urease CLO test was positive, and culture showed *H. pylori* from week 3 to 42 (Fig. 1). Histological examination showed microorganisms resembling *H. pylori* during week 3, with no inflammatory cells in the mucosa. The severity of gastritis increased with time from week 3 to 9 and did not change thereafter (Table 3). No gastric atrophy was observed at any time. Plasma gastrin levels under basal conditions and in response to meal did not differ significantly ($P = 0.15$) before and after *H. pylori* infection (Table 2). Somatostatin-like immunoreactivity in the gastric juice under basal conditions before ($3.2 \pm 2.3\ \text{ng/ml}$) was not significantly ($P = 0.10$) lower than that 8 wk after *H. pylori* infection ($3.9 \pm 2.5\ \text{ng/ml}$). The time course of luminal somatostatin outputs in response to gastrin remained unchanged 5 wk after *H. pylori* infection compared with baseline (Table 1).

Infection by *H. pylori* resulted in an 80% ($P < 0.01$) inhibition of pentagastrin-stimulated gastric acid output at week 3 after infection (maximal output, $620 \pm 30\ \mu\text{eq}/15\text{ min}$; Fig. 4A). This inhibition progressively disappeared between weeks 5 and 9: it increased significantly from week 5 ($P < 0.05$) to week 7 ($1,250 \pm 280\ \mu\text{eq}/15\text{ min}$; $P < 0.01$), reaching the level in uninfected animals by week 9 and remaining constant for up to 42 wk after *H. pylori* infection (Fig. 4B). Gastric acid secretion remained constant after week 9, at a slightly (5–10%) higher level than that in uninfected animals.

Effect of thioperamide, an H_3 receptor antagonist. Between weeks 5 and 9, when gastric secretion was low, thioperamide significantly ($P < 0.05$) increased pentagastrin-stimulated acid output by 18–25% (mean 20%), but the level of acid output remained below normal. However, from weeks 9 to 42 after infection, thioperamide had no effect on acid secretion induced by all the secretagogues.

Effect of SR-27417A, a PAF receptor antagonist. Between weeks 5 and 9, when gastric secretion was low,

Table 2. Plasma gastrin levels in response to ingestion of a solid meal in *H. felis*-positive, germ-free, and *H. pylori*-positive cats

Cats	n	0	30 min	60 min	90 min
<i>H. felis</i> +	9	25 ± 4	62 ± 18	66 ± 17	61 ± 18
<i>H. felis</i> -, <i>H. pylori</i> -	9	26 ± 5	52 ± 16	60 ± 15	66 ± 15
<i>H. pylori</i> + 6–8 wk after infection	5	29 ± 4	63 ± 12	69 ± 15	69 ± 17

Values are means \pm SE (pg/ml). Differences are not statistically significant between three groups.

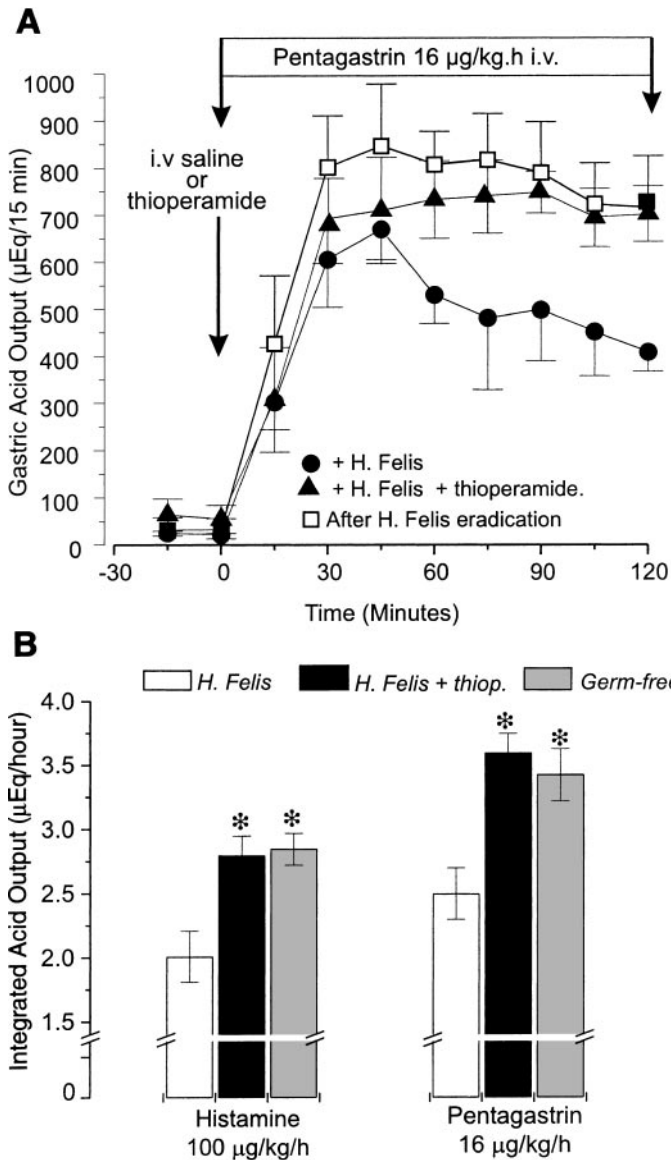


Fig. 3. A: time course of pentagastrin-stimulated gastric acid output with and without thioperamide, an H₃ receptor antagonist, in the MS before and after eradication therapy. Data are expressed in µeq/15 min and are means ± SE from each cat tested at least 3 times (n = 9 before eradication; n = 5 after eradication). B: hourly gastric acid output for histamine and pentagastrin. Effects of *Helicobacter* eradication and thioperamide are indicated. *P < 0.05 vs. reference. Data are expressed in µeq/h and are means ± SE from 9 cats tested at least 3 times.

SR-27417A did not affect pentagastrin-stimulated acid output (Fig. 5). However, from weeks 9 to 42 after infection, it significantly (P < 0.05) inhibited this acid output by 30% (range 27 to 32%).

DISCUSSION

This study shows that *H. felis* and *H. pylori* inhibit gastric acid secretion in cats. This inhibition is probably mediated by the histamine H₃ receptor. We also report changes over time in gastric acid secretion after *H. pylori* infection: an initial inhibitory period corresponding to mild gastritis and a second period with

Table 3. Gastritis in *H. pylori*-infected cats

After <i>H. pylori</i> Infection	Week 3	Week 5	Week 7	Week 9	Week 24
Polymorphonuclear cell infiltration	+/-	+	+	++	++
Lymphocyte cell infiltration	-	+/-	+	+/-	+/+
<i>H. pylori</i>	+	++/++	++/++	++	++

Histological examination of fundic mucosa at various times after *H. pylori* infection in cats are shown. Densities of polymorphonuclear cells, monocytes, and *H. pylori* in gastric mucosa were estimated semiquantitatively as +/- rare; + significant; ++ high. Biopsies were taken using an endoscopic forceps and were fixed in formalin and paraffin embedded and stained using hematoxylin and eosin. Gastritis remained unchanged from weeks 24 to 42.

higher levels of acid secretion corresponding to severe gastritis. This stimulation of acid secretion was blocked by a PAF receptor antagonist, suggesting that inflammatory mediators are involved in adaptation to gastric *H. pylori* infection.

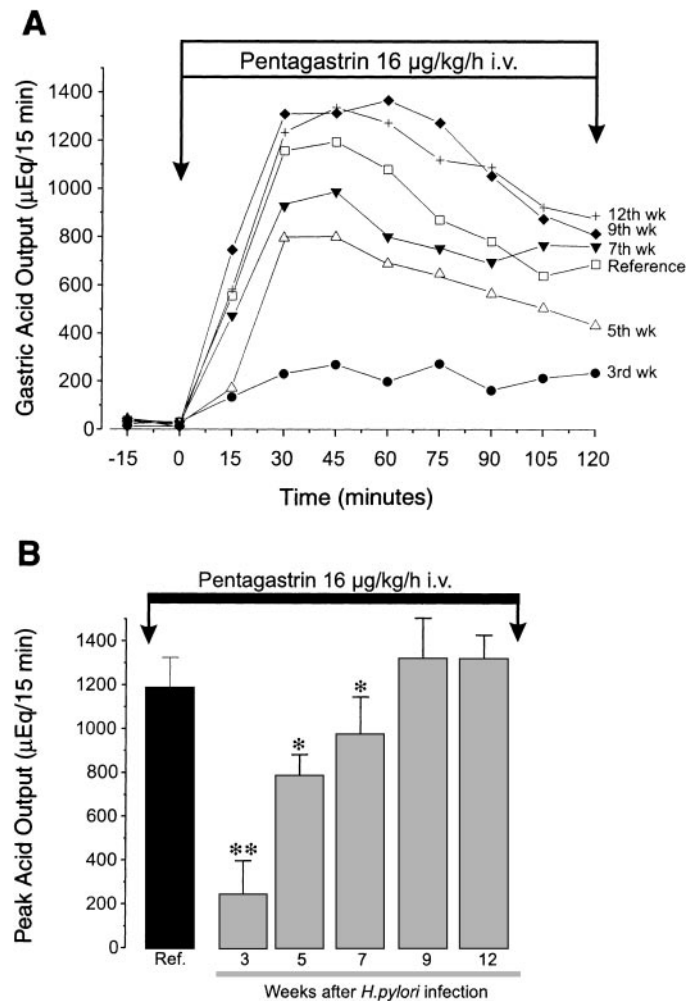


Fig. 4. Evolution of gastric acid output from the MS after *H. pylori* infection. A: at indicated week, gastric acid was stimulated by continuous intravenous infusion of pentagastrin for 120 min. Data are expressed in µeq/15 min and are means ± SE from 5 cats. B: peak acid outputs from the MS after *H. pylori* infection are indicated in response to pentagastrin at weeks 3–12. From week 12 up to 42, the peak acid outputs remained unchanged. *P < 0.05 and **P < 0.01 compared with reference (Ref.).

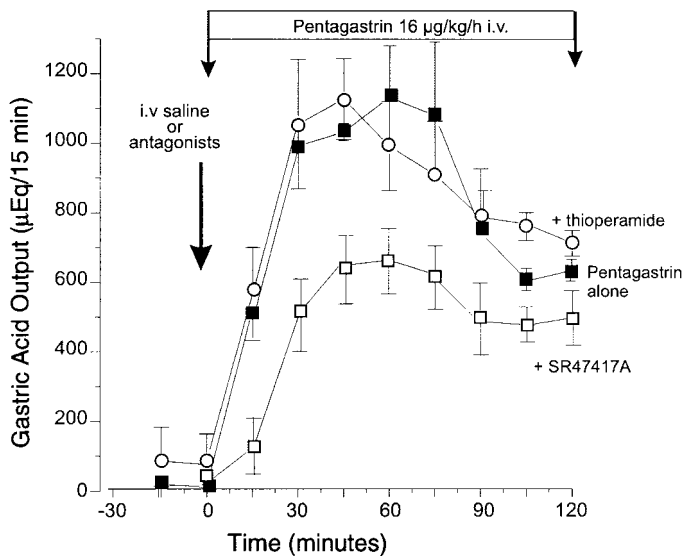


Fig. 5. Time course of pentagastrin-stimulated gastric acid output at week 9 after *H. pylori* infection, without (control) and with thioperamide, an H_3 receptor antagonist, or SR-27417A, a PAF receptor antagonist. Data are expressed in $\mu\text{eq}/15$ min and are means \pm SE from 5 cats.

Cats are spontaneously infected by *H. felis* and, in some cases, by *H. heilmanii*. This model has been widely studied (12, 13, 20, 31, 38, 40, 46). One study reported gastric lymphoid follicular hyperplasia in response to *H. felis* infection (46), but in the vast majority of studies these bacteria were found not to induce inflammatory cell infiltration in the gastric mucosa. These bacteria are therefore considered to be saprophytes (12, 13, 38). In the present study, the effect of *H. pylori* was analyzed in cats that had gastric *H. felis* infections and in cats free of gastric pathogens. This is the first sequential analysis of gastric changes induced by this type of *Helicobacter*. The model used enabled us to demonstrate that the bacterium itself inhibited acid secretion, because acid secretion increased in the MS after eradication therapy but remained constant in the fundic isolated pouch, which was free of bacteria. This does not seem to be an inhibitory effect induced by urease activity due to the ammonia buffer system because: 1) rapid urease test on mucosa did not change over the 42-wk experimental period, 2) acid secretion increased from weeks 5 to 9, whereas *H. pylori* and high-grade gastritis were detected on gastric biopsies, and 3) acid titration of gastric juices at two different pH values showed no significant difference. Thus this inhibitory effect was probably direct and did not involve hormonal or vascular pathways because 1) plasma gastrin levels in response to meal were not affected by eradication therapy or *H. pylori* infection and 2) somatostatin, which is known to act as a paracrine hormone in the stomach, did not change under these conditions. This was also consistent with the absence of gastritis in *Helicobacter*-free and *H. felis*-infected cats, in which the PAF receptor antagonist, which is known to inhibit the PAF-induced increase in acid secretion in vitro, did not affect acid secretion.

This inhibitory effect of *H. pylori* is not related to fundic atrophy because histological examination showed no significant difference in the fundic mucosa. However, we cannot exclude a direct inhibitory effect on parietal cells. Such an effect has previously been reported in vitro, and two possible mechanisms have been suggested. One of these mechanisms involves a toxic effect because a toxin peptide purified from *H. pylori* has been shown to inhibit the H^+-K^+ -ATPase (8, 25). We cannot exclude the possibility that a similar mechanism operates in the model studied here. Alternatively, the inhibition of gastric acid secretion may be accounted for by changes in histidine decarboxylase (HDC) activity (11, 16, 42, 43). *H. pylori* infection is indeed usually associated with a decrease in the histamine content in the mucosa, probably due to the down-regulation of HDC activity. This may be brought about by the action of $N\alpha$ -MH on H_3 receptors (7, 11). Histamine, released from ECL or mast cells, stimulates acid secretion via H_2 receptors on parietal cells. Because the stimulation of H_3 receptors on ECL inhibits HDC, it has been suggested that *H. pylori* abolishes histamine release by $N\alpha$ -MH production. Further evidence for this is provided by the increase in acid secretion induced by thioperamide before eradication therapy, resulting in levels of acid secretion similar to those recorded after eradication. These findings are consistent with previous data obtained in vitro and in vivo by ourselves (3, 11) and others (7, 16, 42, 43, 52).

H. pylori-induced gastritis in the gastric mucosa, as shown by infiltration of monocytes and polymorphonuclear cells within the mucosa (6, 23, 26, 33, 35, 36, 41) is similar to that observed in humans. The increase in acid secretion reported in individuals infected by *H. pylori* has been attributed to inflammatory phenomena by some authors (18, 36, 37, 47). This view has been strengthened by data showing that cytokines such as IL-6 and tumor necrosis factor stimulate gastric acid secretion by activating antral G cells (6), whereas inflammatory lipid mediators such as PAF also stimulate the parietal cell via a specific receptor (48). After the colonization of gastric mucosa by *H. pylori*, there are two distinct periods, as demonstrated in this study. In the first period, there is no inflammatory cell infiltration into gastric mucosa and acid secretion is reduced (2, 27, 39, 44). This resembles acute infection in humans, which results in hypochlorhydria that may regress, completely in some cases (37, 39). This effect observed in vivo may be due to *H. pylori* itself (27, 25, 44, 52) or to IL-1 β overproduction, which is known to inhibit acid secretion (10, 14). In the second period, 1 mo after *H. pylori* colonization, acid secretion returned to normal, suggesting adaptation involving inflammatory mediators. Several lines of evidence support this hypothesis. First, proinflammatory mediators (e.g., PAF) are overproduced in gastritis (50) and PAF receptor antagonist inhibited acid secretion in this model only in the second period. Second, plasma gastrin levels did not change after *H. felis* eradication. This is consistent with the absence of gastritis. That even after *H. pylori* infection, especially in the second pe-

riod, plasma gastrin levels did not appear to increase would suggest that gastrin increase leads with a period longer than 42 wk in cats. Thus we cannot exclude that, in a period longer than 42 wk, gastrin and luminal somatostatin would not change significantly as reported in other models.

In summary, *H. pylori* may affect acid secretion directly as well as via inflammatory phenomena. This study may account for the differences in results obtained in other studies, with some reporting higher levels of gastric acid secretion and others showing lower levels of acid secretion in *H. pylori*-infected individuals than in individuals not infected with *H. pylori*.

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