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Helicobacter pylori Modulation of Gastric Acid

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Helicobacter pylori *plays major causative roles in peptic ulcer disease and gastric cancer. Elevated acid secretion in patients with duodenal ulcers (DUs) contributes to duodenal injury, and diminished acid secretion in patients with gastric cancer allows carcinogen-producing bacteria to colonize the stomach. Eradication of* H. pylori *normalizes acid secretion both in hyper-secreting DU patients and hypo-secreting relatives of gastric cancer patients. Therefore, we and others have asked how* H. pylori *causes these disparate changes in acid secretion.*

H. pylori *gastritis more or less restricted to the gastric antrum in DU patients is associated with increased acid secretion. This is probably because gastritis increases release of the antral acid-stimulating hormone gastrin and diminished mucosal expression of the inhibitory peptide somatostatin. Bacterial products and inflammatory cytokines including TNFα may cause these changes in endocrine function.*

Gastritis involving the gastric corpus tends to diminish acid secretion, probably because bacterial products and cytokines including IL-1 inhibit parietal cells. Pharmacological inhibition of acid secretion increases corpus gastritis in H. pylori*-infected subjects, so it is envisaged that gastric hypo-secretion of any cause might become self-perpetuating.* H. pylori*-associated mucosal atrophy will also contribute to acid hypo-secretion and is more likely in when the diet is high in salt or lacking in antioxidant vitamins.*

Data on gastric acid secretion in patients with esophagitis are limited but suggest that acid secretion is normal or slightly diminished. Nevertheless, H. pylori *infection may be relevant to the management of esophagitis because: (i)* H. pylori *infection increases the pH-elevating effect of acid inhibiting drugs; (ii) proton pump inhibitors may increase the tendency of* H. pylori *to cause atrophic gastritis; and (iii) successful eradication of* H. pylori *is reported to increase the likelihood of esophagitis developing in patients who had DU disease. Points (ii) and (iii) remain controversial and more work is clearly required to elucidate the relationship between* H. pylori*, acid secretion, gastric mucosa atrophy and esophagitis.*

INTRODUCTION

Gastric acid secretion plays an important role in gastro-esophageal reflux disease (GERD)[b]. It recently became clear that *Helicobacter pylori* is an important etiological factor in other upper gastrointestinal diseases including gastric and duodenal ulcers and gastric cancer, and there is evidence that changes in gastric acid secretion caused by the bacterium contribute to the pathogenesis of these diseases. This article will examine the

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[b]Abbreviations: GERD, gastro-esophageal reflux disease; DU, duodenal ulcer; ECL, enterochromaffin like; TNFα, tumor necrosis factor alpha; GRP, gastrin releasing peptide; MAO, maximal acid output.

evidence, and whether effects of *H. pylori* on gastric physiology are relevant to GERD. First I will consider the effect of *H. pylori* on the endocrine and exocrine cells of the stomach, then consider how and why how *H. pylori* affects acid secretion in differently in different disease groups. Finally I will ask whether *H. pylori*'s effects on acid secretion are relevant to the pathogenesis and treatment of GERD.

EFFECTS OF *H. PYLORI* ON GASTRIC CELLS (SEE FIGURE 1)

G-cells

Gastrins are realized from G-cells in the gastric antrum and proximal duodenum. They act via the circulation to stimulate acid secretion, both by stimulating parietal cells directly and by releasing histamine from nearby enterochromaffin-like (ECL)-cells. *H. pylori* infection elevates plasma gastrin concentrations under all conditions studied so far [1].

Products of *H. pylori* itself, or inflammatory factors from the host might be responsible. *H. pylori's* enzyme urease produces copious ammonia, and diets supplemented with ammonium acetate elevated circulating gastrin in rats. However, the salt also causes gastritis, which might have contributed. However, a urease inhibitor failed to decrease plasma gastrin levels, so other *H. pylori* products might be responsible. The bacterium is reported to produce N-α-methylhistamine which we find to release gastrin from G-cells via histamine H2 receptors [1,2].

H. pylori infection elevates mucosal expression of cytokines including interleukins (IL) 1β, 6 and 8, tumor necrosis factor-α (TNFα), interferon-γ (INFγ) and platelet activating factor. TNFα releases gastrin from a variety of preparations, even in the presence of somatostatin immuno-blockade. INFγ, IL-1β and IL-8 also release gastrin [1, 3, 4]. Interestingly the effect of IL-8 was greatly increased by the presence of sonicates of *H. pylori*,

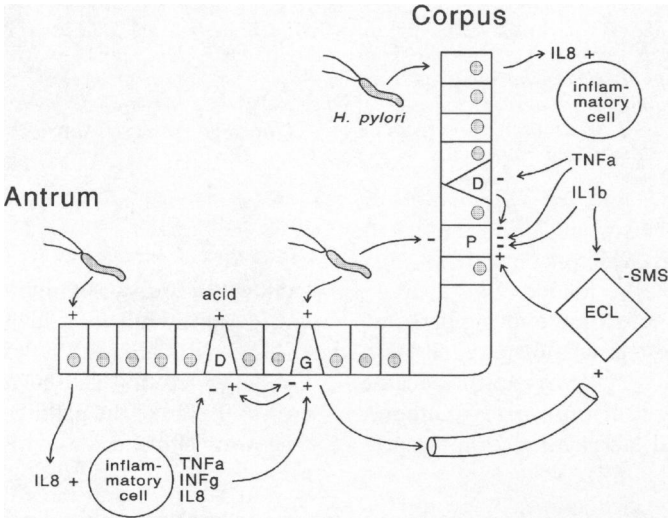

Figure 1. Effects of *H. pylori* on the cells of the gastric corpus and antrum. Gastrin from G-cells (G) stimulates parietal cells (P) to secrete acid by releasing histamine from enterchromaffin-like cells (ECL). All of these cells are normally restrained by release of somatostatin (SMS) from D-cells (D). Bacterial products stimulate G-cells but inhibit parietal cells. Inflammatory cytokines including tumor necrosis factor (TNFα), interferon (INFγ), and interleukins 1 (IL1β) and 8 (IL8) influence the various cells as indicated, resulting in changes in acid secretion which depend on the distribution of gastritis

suggesting synergism between bacterial and inflammatory products.

D-cells

Somatostatin peptides are released from D-cells in the antrum and corpus and mediate the major reflexes that inhibit gastrin release and acid secretion. D-cells are stimulated by luminal acid, fasting, gastrin-releasing peptide and by small intestinal peptides such as cholecystokinin. Patients infected with *H. pylori* have less somatostatin peptide, less somatostatin mRNA and fewer immunoreactive D-cells in their gastric mucosa [1]. This lack of somatostatin may explain increases in gastrin release and acid secretion in infected subjects.

It is difficult to measure responses of gastric D-cells *in vivo,* but we found that a three- hour infusion of gastrin-releasing peptide significantly elevates the somatostatin content of antral biopsies, showing that the cells are capable of responding, but the amount remained well below that present in uninfected persons [5]. The mechanism responsible for diminished somatostatin remains unclear but we found that incubation of D-cells with TNFα for 24 hours diminished somatostatin release [6].

ECL-cells

Histamine is released by ECL-cells in the gastric mucosa and stimulates acid secretion via H_2 receptors on parietal cells. It is produced from histidine by histidine decarboxylase. Mucosal concentrations of histamine have generally been found to be diminished in *H. pylori* gastritis. This probably reflects diminished synthesis because mucosal levels of histidine decarboxylase are also low.

It is not known how *H. pylori* diminishes mucosal synthesis of histamine, but some possibilities have been identified:

1. Prinz et al. found that IL-1β greatly inhibits histamine release from ECL-cells [7].

2. Stimulation of histamine H3 receptors on ECL-cell inhibits histamine release [8]. Therefore N-α-methyl histamine produced by *H. pylori* [1] might be responsible.

Parietal cells

Effects of G-, D-, and ECL-cells on acid secretion depend greatly on the number and responsiveness of parietal cells. This varies from time to time and from patient to patient (see below) and seems to predict disease outcomes. Factors that affect parietal cell function are:

1. Physiological regulators: More gastrin and less somatostatin will tend to increase acid secretion, but suppression of ECL-cells will tend to diminish acid secretion.

2. *H. pylori* products: Cave's group have identified two *H. pylori* products that inhibit parietal cells. One resembles nigericin. The other is a dimer of 46 kDa subunits whose gene has been cloned. *H. pylori* also produces unusual fatty acids that can inhibit parietal cells. However *H. pylori* is also reported to produce N-α-methyl histamine, which is an agnoist of histamine H_2 (as well as H_1 and H_3) receptors, and we found that instillation of N-α-methyl histamine into the gastric lumen of uninfected volunteers increased their acid output [9].

3. Inhibitory cytokines: TNFα and IL-1β, which are upregulated in *H. pylori* gastritis, also inhibit parietal cells [1].

4. Gastric atrophy: It is now recognized that *H. pylori* is a major cause

of gastric atrophy [10], which is a loss of specialized cells including parietal cells from the gastric mucosa and, thus, diminishes acid secretion.

Overall clinical studies suggest that the net effect of corpus gastritis is to decrease acid secretion.

EFFECTS OF *H. PYLORI* ON ACID SECRETION IN PATIENTS

Work in this area shows that *H. pylori* impairs inhibitory control of acid secretion, consistent with depletion of somatostatin, but that the overall effect on acid secretion varies widely between patient groups.

Effects of H. pylori on inhibitory control of acid secretion

H. pylori infection causes defects in the reflex inhibition of acid secretion that were previously observed in patients with duodenal ulcer (DU) disease and are attributable to the paucity of mucosal somatostatin.

Basal acid secretion. Eradication of *H. pylori* produces a significant fall in basal acid secretion in DU patients [11, 12], but this has not generally been found in non-ulcer patients. Perhaps acid secretion in DU patients, who have less corpus gastritis, reflects changes in hormonal influences, while in non-ulcer patients an improvement in corpus gastritis after eradication causes a confounding increase in acid.

Meal-stimulated acid secretion at a low intragastric pH. H. pylori impairs inhibition of peptone-stimulated acid secretion by a low intragastric pH. The low pH suppressed acid secretion by greater than 80 percent in uninfected persons but by less than 50 percent in infected volunteers [13]. Acid secretion stimulated by neutral peptone was similar in both groups, indicating that the abnormality lies in the inhibitory pathway.

The inhibitory effect of antral distension. Antral distension normally inhibits pentagastrin-stimulated acid secretion, but this reflex is also attenuated by *H. pylori* infection [1].

The inhibitory effect of cholecystokinin infusion. It was recently found that CCK infusions inhibit GRP-stimulated acid secretion less in *H. pylori* infected persons [1]. This is consistent with a lack of cholecystokinin-stimulated somatostatin release.

Gastrin-releasing peptide-stimulated acid secretion. Infusions of GRP test inhibit responses because this peptide stimulates D-cells as well as G-cells. GRP stimulates D-cells in the antrum via gastrin and in the corpus through neural reflexes. D-cells may also be stimulated by small intestinal hormones such as CCK which GRP also releases. Acid secretion stimulated by GRP is elevated about three times in *H. pylori* infection, and about six times in DU persons when compared with uninfected controls [12]. *H. pylori*-related elevations of GRP-stimulated acid secretion disappears slowly during the first year after successful eradication.

Effects on acid secretion in different patient groups

Defective inhibitory control increases acid secretion under specific circumstances, but different patient groups also show global differences in acid secretion. These are seen during infusions of GRP, but are classically measured during infusions of gastrin, pentagastrin or histamine which stimulate maximal acid output (MAO).

High acid secretion in patients with duodenal ulcers. The mean MAO in *H. pylori*-infected DU patients is about twice normal. This abnormality was regarded as being more or less fixed because MAO was unchanged one month after eradiation. However, recent studies have shown that MAO does eventually fall when *H. pylori* is eradicated from DU patients [14]. Therefore, the raised MAO in DU patients seems to be a response to *H. pylori* infec-

tion, which might be mediated by the trophic effect of gastrin, or some other growth factor on the corpus mucosa.

Low acid secretion on first infection and in patients with gastric cancer. In contrast, acid secretion more or less disappears for the first few weeks or months of *H. pylori* infection [15], and is markedly diminished in patients who develop gastric cancer [16]. Interestingly about half of the first-degree relatives of patients with gastric cancer have diminished acid secretion, which rises when the infection is eradicated [17] indicating that low acid secretion can also be a response to the infection. Infected patients with low acid secretion tend to have corpus gastritis, which is probably responsible.

Intermediate rates of acid secretion in other patient groups, including patients with esophagitis. Maximal acid output in infected person without ulcers tends to be normal or slightly diminished. Few have measured acid in patients with esophagitis. A study before *H. pylori* was discovered showed that 47 Finnish patients with GERD had an MAO similar or slightly below that of Finnish controls. There was no correlation between acid output and symptoms or the duration of reflux [18], so gastro-esophageal reflux disease (GERD) is regarded as a disorder of motility rather than secretion. However, the effect of *H. pylori* infection on responses to proton pump inhibitors [19], which are the main medical treatment for esophagitis, may be clinically important, and provides an important insight into the relationship between the bacterium and altered gastric physiology.

WHY DO DIFFERENT PATIENTS REACT DIFFERENTLY TO THE SAME INFECTION?

An individual's acid response to *H. pylori* seems to predict complications. Moreover, the acid response might cause the outcome; excessive acid ulcerates the duodenum, while diminished acid allows overgrowth of carcinogen-producing bacteria in the stomach lumen. Therefore, what determines the acid response is of interest.

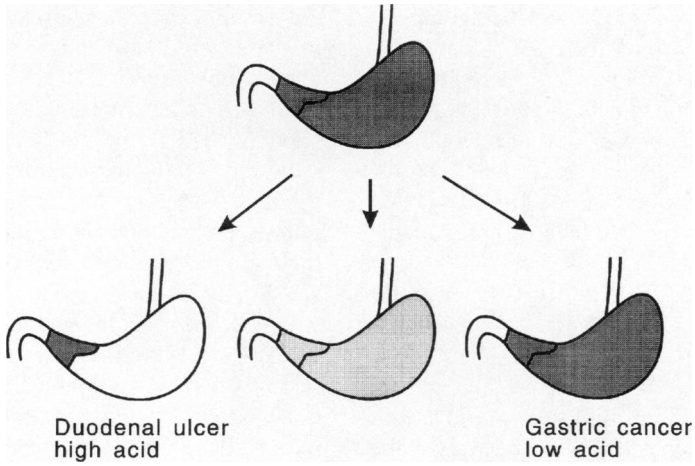

Figure 2. Distribution of gastritis, acid secretion, and disease outcome in *H. pylori* infection. Involvement of the gastric corpus on first infection and in patients with gastric cancer leads to low acid secretion. Antrum-predominant gastritis in patients with duodenal ulcers is associated with acid hypersecretion. Most other infected patients show an intermediate pattern with near-normal or slightly diminished acid secretion

Parietal cell mass. In the past, an individual's parietal cell mass and MAO were regarded as closely related and more-or-less fixed. It was appreciated that gastric atrophy produces a parallel fall in both as parietal cells are lost. However, it is now appreciated that parietal cells remain but fail to secrete acid on first infection [15], and that bacterial products and cytokines decrease the maximal secretory capacity of parietal cells *in vitro* [20].

Distribution of gastritis (Figure 2). There is a two-way relationship between distribution of gastritis and acid output. The antral predominant gastritis found in DU patients is associated with hypersecretion, while the pangastritis is found in patients with gastric cancer who secrete little acid. One direction is that the distribution of gastritis determines acid output, depending on whether corpus mucosa is healthy enough to respond to gastrin. However, the effect of suppressing acid with omeprazole suggests that the reverse also occurs. Omeprazole decreases gastritis and colonization in the antrum while in the corpus, gastritis increases and colonization increases or stays the same [21]. Therefore, it is possible to envisage a vicious circle whereby hyposecretion and corpus gastritis become self-perpetuating.

Gastric atrophy. H. pylori infection promotes the development of atrophy [10], and suppression of acid secretion with proton pump inhibitors may accelerate this process [22], although this remains controversial. Environmental factors associated with atrophy include lack of antioxidants vitamins, and a high salt diet.

ECL-cell density. It was recently reported that DU patients who were all infected with *H. pylori* had about three times as many ECL-cells in their gastric mucosa as either infected non-ulcer, or uninfected controls [23]. This raises the possibility that elevated acid secretion in DU patients might be due to excessive histamine release from ECL cells in their gastric corpus mucosa.

Bacterial strain. There is currently no evidence to link any particular strain of bacteria to high or low acid secretion. The presence of antibodies to cagA protein have been linked with mucosal atrophy and gastric carcinoma both of which are associated with low acid secretion, and with DU disease, which is associated with high acid secretion.

THE RELATIONSHIP BETWEEN *H. PYLORI* INFECTION, ACID AND GERD

At present this relationship is potentially important in three respects: 1) Long term proton pump inhibitor therapy was reported by Kuipers et al. to increase the likelihood of gastric mucosal atrophy developing in patients infected with *H. pylori* [22]. However, the validity of this finding and its clinical relevance remain highly controversial. 2) *H. pylori* infection significantly increases the pH-elevating effect of proton pump inhibitors [19]. This may be due to generation of alkali by the bacterium's urease or an increase in corpus gastritis. We find that both *H. pylori* sonicates and IL-1β add to the antisecretory effect of omeprazole on parietal cells *in vitro* [24]. 3) German studies suggest that eradicating *H. pylori* from DU patients increases the likelihood of GERD subsequently appearing [25]. The initial severity of corpus gastritis predicted the likelihood of GERD, so an elevation of acid secretion following cure might have contributed. However weight gain was also implicated, and it remains unclear whether the main observation is reproducible.

Points 2) and 3) argue against eradicating *H. pylori* from patients with GERD, and clinical studies largely show no improvement in symptoms when this is done. However the possibility, however remote, that proton pump inhibitor therapy exacerbates *H. pylori* gastritis persuades most clinicians to eradicate before long-term therapy.

CONCLUSION

In summary, therefore, there is currently no evidence that *H. pylori*-related changes in acid secretion contribute to the pathogenesis of GERD, although the data on the topic are distinctly scanty. Further research is required to clarify whether *H. pylori* should be eradicated prior to long-term administration of proton pump inhibitors to patients with GERD. This is likely to render therapy less effective, but might protect the stomach from developing atrophy, although this remains highly controversial.

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