Inflammation, Acid and Ulcers

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Chronic active type B gastritis is invariably the result of Helicobacter pylori infection and is an important factor in duodenal ulcer disease. The actions of mediators produced (a protein factor, a lipid soluble “pore-forming factor” and urease) or induced (immune/inflammatory cell mediators) by this bacterium on the control of gastric acid secretion are currently being investigated. These studies are reviewed in light of our current knowledge of the physiological control of gastric acid secretion.

INTRODUCTION

It is now generally accepted that human infection of the gastric antrum with Helicobacter pylori is the most important cause of histological type B chronic active antral gastritis, with almost a 100 percent association between H. pylori infection and antral gastritis [1, 2]. H. pylori is a curved, S-shaped, motile, microaerophilic, Gram-negative rod, which is 2.5 μm long and 0.5 μm in diameter and has four to six unipolar sheathed flagella [3]. It lives adjacent to the gastric epithelium underlying the mucus bicarbonate layer in the human stomach, adherent to the gastric epithelial cell and within areas of gastric metaplasia [4-6].

A number of studies provide strong evidence to support the hypothesis that H. pylori plays an important etiological role in duodenal ulcer disease. Thus, H. pylori is found in 95 to 100 percent of duodenal ulcer patients [7-9]. Furthermore, the relative risk of a number of factors in duodenal ulcer disease have been quantified: duodenal gastric metaplasia, antral H. pylori and duodenal H. pylori yielded relative risk values of 6.22, 7.67 and 51.0, respectively [10]. Finally, eradication of H. pylori reverses chronic active gastritis and reduces the one-year duodenal ulcer relapse rate to virtually zero [11]. It should be noted, however, that only a minority of H. pylori-infected individuals develop duodenal ulcers [12]; therefore, this bacterium is probably not solely responsible for duodenal ulcer formation. Rather, H. pylori infection should be viewed as an important contributing factor to the pathophysiology of duodenal ulcer disease.

It is generally accepted that duodenal ulcer patients secrete more gastric acid than normal individuals [13]. Recent studies have examined the effects of H. pylori and H. pylori-induced inflammation on gastric acid secretion. These recent studies are reviewed in light of our current understanding of the physiological mechanisms that are involved in the control of gastric acid secretion.

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Abbreviations used: EGF, epidermal growth factor; IL, interleukin; TNF, tumor necrosis factor; NSAID, non-steroidal anti-inflammatory drug; IFN, interferon; ECL, entero-chromaffin like (cell).
H. PYLORI AND GASTRIC ACID SECRETION

The effect of *H. pylori* infection on gastric acid secretion appears to be complex and probably depends on the stage of infection. Hypochlorhydria may occur in the early stages of infection with this bacterium (for review see Ref. 14). Later in *H. pylori* infection, hypersecretion of gastric acid probably occurs, at least in individuals who have developed duodenal ulcers. This is supported by recent studies in which well-defined populations of *H. pylori*-negative, normal volunteers and *H. pylori*-positive, duodenal ulcer patients were used to study acid secretion. These studies demonstrated significantly greater basal and maximum pentagastrin- and gastrin-releasing, peptide-stimulated acid output in the duodenal ulcer group than in the control group [15, 16]. Furthermore, eradication of *H. pylori* in duodenal ulcer patients resulted in decreased acid secretion [15-17].

*H. pylori* and hyposecretion of gastric acid

*H. pylori* produces a number of compounds that directly inhibit acid secretion. This was first suggested in studies in which application of *H. pylori* to isolated guinea pig parietal cell or isolated rabbit gastric gland preparations resulted in an inhibition of acid secretion as measured indirectly by the accumulation of the weak base 14C-aminopyrine [18, 19]. The inhibition of acid secretion apparently occurs via two factors produced by *H. pylori*: a protein factor [19] and a lipid soluble "pore-forming factor" [20], possibly tetradecanoic acid, which is found in large amounts in *H. pylori* [21]. Whether these compounds alter acid secretion in vivo has been questioned by Danon et al. [22] who found that large numbers of *H. pylori* are needed to inhibit acid secretion in the isolated rabbit parietal cell preparation and that the effect can be mimicked by sonicates from a number of other bacteria. Interestingly, Jablonowski et al. [23] have recently reported that *H. pylori* sonicates from gastritis patients inhibited acid secretion in isolated human gastric glands more effectively than those from duodenal ulcer patients. Whether these *H. pylori*-factors act only on the parietal cell or whether they also act on other cell types involved in the control of acid secretion (nerves, mast cells, ECLb cells, D cells, G cells, etc.) is not known.

The immune/inflammatory response of the host to *H. pylori* infection may also alter gastric acid secretion (for recent review see Ref. 24). In this regard, *H. pylori* infection results in gastric mucosal infiltration with neutrophils, eosinophils, basophils, macrophages, monocytes, plasma cells and mast cells [12]. Together, these immune/inflammatory cells are known to release a variety of mediators, including immunoglobulins, biogenic amines, purines, eicosanoids, platelet-activating factor, reactive oxygen metabolites and cytokines. The present discussion is restricted to recent studies concerning the effects of cytokines on acid secretion. There are over 30 known cytokines [25], but of these, only a few have been studied with respect to *H. pylori* infection. Thus, the levels of interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-α have been shown to be higher in *H. pylori*-positive than *H. pylori*-negative human antral biopsies [26, 27]. Furthermore, interferon (IFN)-γ production has been shown to be induced by contact of lymphocytes with *H. pylori* in vitro [28].

IL-1 is produced by activated macrophages/monocytes and other cell types and released during immune/inflammatory processes [29-31], *H. pylori*-induced gastritis being no exception [27]. It has many biological actions, which may be involved in acute immune/inflammatory processes (for review see Refs. 29-31). Uehara et al. [32] were the first to show that IL-1, in very low concentrations, causes prolonged inhibition of basal acid secretion in the pylorus-ligated rat preparation. This finding has been confirmed [33-39]. Central administration of IL-1 results in inhibitory effects at 100-1000 times lower concentrations than required for effects by peripheral administration. Centrally, the actions
of IL-1 appear to involve prostaglandins and the vagus nerve, but not the central adrenergic nervous system, corticotropin releasing factor or the adrenal glands [38, 39]. Peripherally, prostaglandins and IL-1 receptors appear to be involved, but not corticotropin releasing factor, somatostatin or capsaicin-sensitive afferent nerves [32-34]. In the pylorus-ligated, urethane-anæsthetized rat preparation, IL-1 selectively inhibits pentagastrin-stimulated histamine release [35]; this effect involves nitric oxide [40]. In the isolated canine gastric parietal cell preparation, IL-1 inhibits histamine- and carbachol-mediated acid secretion by acting directly on the parietal cell [41].

IL-1 has also been studied in a number of rat models of acute gastrointestinal damage. It reduced gastrointestinal damage due to water-immersion restraint stress [36, 37, 42], thyrotropin releasing hormone [43], ethanol [43-45], non-steroidal, anti-inflammatory drugs (NSAID) [44-47] and cysteamine [44]. Central prostaglandins, but not corticotropin releasing factor, appear to be involved in the effects of IL-1 in the water-immersion stress model [36, 37, 42]. Endogenous prostaglandins and inhibition of acid secretion appear to be involved in the ethanol model of gastric damage [44]. Although the later mechanisms may also be involved in the effects of IL-1 on NSAID-induced gastric damage, interactions with endogenous glucocorticoids [46], and inhibition of neutrophil function may also play a role [47].

A number of other cytokines, which are increased by *H. pylori* infection, have also been studied with respect to gastric acid secretion. In this regard, TNF-α does not alter secretagogue-stimulated acid secretion [35] or NSAID-induced gastropathy [47] in the rat, although it shares many other biological actions with IL-1 [30]. On the other hand, acid secretion is inhibited by this cytokine in the isolated canine parietal cell preparation [41] and the isolated murine gastric gland preparation (Muller, Padol and Hunt, unpublished observation). The potent neutrophil chemotactic agent IL-8 [48] also inhibits acid secretion in the isolated murine gastric gland preparation (Muller, Padol, Ernst and Hunt, unpublished observation). It is selectively released from epithelial cells by co-culturing *H. pylori* with the gastric adenocarcinoma cell line KATO III, suggesting that the gastric epithelium may initiate neutrophil recruitment and local inflammation [49]. We have recently shown that IFN-γ inhibits secretagogue-stimulated acid secretion in the isolated murine gastric gland preparation [50]. This effect was concentration-dependent, rapid, non-competitive and selectively blocked by rat anti-mouse IFN-γ antibodies [50]. Taken together, these results, and the above-mentioned demonstration that IFN-γ, TNF-α and IL-8 levels are elevated by *H. pylori*, suggest that these cytokines may be involved in the down-regulation of acid secretion in the early stages of infection by this bacterium. The potential roles of TNF-α, IL-8 and IFN-γ in *H. pylori* infection require further study.

Some cytokine growth factors also inhibit gastric acid secretion and reduce gastrointestinal damage in rat models. Epidermal growth factor (EGF), originally characterized as urogastrone [51], is a good example [51-57]. A novel EGF-producing cell lineage develops in the setting of chronic ulceration [58, 59]. Active duodenal ulcers have been associated with a decrease in the levels of gastric juice EGF [60]. Transforming growth factor-α, which appears to be normally produced by parietal cells [61, 62], also inhibits gastric acid secretion [63-65], and protects in animal models of gastrointestinal damage [57].

In summary, an early response of the host to infection by *H. pylori* appears to be suppression of gastric acid secretion, which probably aids in bacterial colonization. A number of compounds produced by *H. pylori* (a protein factor, a lipid soluble "pore-forming factor") and by the host (cytokines) in response to bacterial infection have recently been shown to be able to inhibit gastric acid secretion. The control of gastric acid secretion is complex, involving neural (cholinergic nerves), endocrine (gastrin), paracrine (histamine and somatostatin) and autocrine (prostaglandins) influences (for recent reviews see Refs.
66-68); each of these influences, in turn, is controlled by multiple physiologic processes. The parietal cell appears to be the site of action of many of these acid inhibitory compounds, although preliminary studies suggest that other cell types may also be involved, i.e., ECL cells and the central nervous system. No data are available concerning the effects of these acid inhibitory compounds on cholinergic nerves, which are involved in the control of acid secretion. Much remains to be learned about where (which cell types) and how (receptor and post-receptor mechanisms) these compounds inhibit gastric acid secretion.

**H. pylori and hypersecretion of gastric acid**

A number of studies have now shown that *H. pylori*-positive individuals have higher fasting and meal-induced serum gastrin levels than *H. pylori*-negative controls [69-72] and that eradication of *H. pylori* results in the return of gastrin levels to normal [17, 69, 72, 73]. Gastrin is the main stimulus for meal-stimulated acid secretion, and it exerts trophic effects on a number of gastric mucosal cells, including parietal cells, chief and ECL cells.

The first working hypothesis to explain *H. pylori*-induced hypersecretion of gastric acid was the "Gastrin Link" hypothesis [69, 74]. This hypothesis suggested that urease produced by *H. pylori* increases gastrin release by converting urea to ammonia and thus raising the pH in the vicinity of G cells. Recent studies, concerning the effects of antral alkalinization on basal and meal-stimulated gastrin levels in duodenal ulcer patients before and after eradication of *H. pylori*, provide strong evidence that the hypergastrinaemia is not due to elevated antral surface pH [75, 76]. It is not known whether bacterial products, other than urease, are involved in *H. pylori*-associated hypergastrinaemia.

A number of studies suggest that the hypergastrinaemia associated with *H. pylori* infection may be caused by the immune/inflammatory response to the bacterium. Thus, systemically immunized dogs showed a significant increase in gastrin levels with an oral challenge by specific human gamma globulin in comparison to controls [77]. A more recent study showed that mononuclear cells, but not *H. pylori*, release gastrin from cultured G cells via diffusible factors [78]. In vitro studies have shown that IL-1, IL-2 and IFN-γ cause gastrin release [79, 80]. In cultured canine antral G cells, IFN-γ and TNF-α have been shown to release gastrin [81]. TNF-α also released gastrin from human antral biopsies [82].

The physiological control of gastrin secretion in the normal gastric antrum is complex, involving neural (cholinergic, vasoactive intestinal polypeptide and bombesin/gastrin-releasing peptide nerves), paracrine (somatostatin) and luminal factors (small peptides, amino-acid fragments and gastric acidity) as well as gastric motility; several excellent reviews are available [67, 68, 83, 84]. Any one or any combination of these mechanisms could potentially be altered by *H. pylori*-produced and/or *H. pylori*-induced products. Recent studies have focused on somatostatin.

The possibility has been raised that the D cell, which provides a tonic "brake" on gastrin release, might be involved in *H. pylori*-induced changes in gastrin release. In this regard, although the density of antral G cells is not different in *H. pylori*-infected individuals as compared to *H. pylori*-negative controls [85, 86], the density of antral D cells and the D:G cell ratio is decreased in the experimental group [85, 87]. Also, the concentration of immunoreactive-somatostatin is decreased in the human stomach during *H. pylori* infection [88]. Moreover, eradication of *H. pylori* significantly increases antral D cell density [89, 90]. Together, these studies suggest that a decrease in the "braking" mechanism for gastrin release may be responsible for the increased gastrin release observed in *H. pylori* infection. It should be noted, however, that a decreased density of D cells in
H. pylori-positive patients has not been found by other investigators [91]. Thus, the effect of H. pylori infection on D cell density is controversial, perhaps due to methodological difficulties associated with measuring D cell densities. Interestingly, preliminary reports have suggested that chronic administration of ammonia to rats decreases antral D cell density and somatostatin concentration [92] and that TNF-α inhibits somatostatin secretion in human antral biopsies [82]. Clearly, the role of D cells in H. pylori-associated gastritis and duodenal ulcer disease requires further investigation.

In summary, H. pylori-induced hypergastrinaemia may contribute to gastric acid hypersecretion in duodenal ulcer patients. One hypothesis is that the normal negative-feedback mechanism for gastrin secretion is interrupted by the production of base by H. pylori-derived urease in the vicinity of antral D- and G cells. Another hypothesis is that mediators of the immune/inflammatory response to H. pylori act on the G- and/or D cell to increase gastrin secretion. Yet another hypothesis is that D cell density is decreased in H. pylori infection, resulting in a decrease in the “braking” mechanism for gastrin release. Future studies, aimed at testing these hypotheses, will undoubtedly add tremendously to our understanding of immunophysiological processes in the stomach.

**SIGNIFICANCE AND CONCLUSIONS**

H. pylori-induced changes in gastric acid secretion probably play an important role in the development of duodenal ulcers. In the early stages of H. pylori infection, acid hyposecretion would aid in bacterial colonization of the gastric antrum. H. pylori-induced hypergastrinaemia probably causes acid hypersecretion directly, by stimulating acid secretion at the level of the parietal cell and by releasing histamine from ECL cells and mast cells, and indirectly, by causing hypertrophy of parietal cells and ECL cells. Increased acid secretion would cause gastric metaplasia in the duodenal cap and allow H. pylori to colonize the duodenum, where the bacterially induced inflammation, together with acid, would cause duodenitis. Eventually, a duodenal ulcer could develop as a result of a combination of the following processes: H. pylori-induced decrease in mucosal defense mechanisms (mucus, bicarbonate, prostaglandins and blood flow); H. pylori-induced increase in aggressive factors (acid, as already discussed, and pepsinogens [activated to pepsins] via gastrin-mediated hypertrophy of chief cells and H. pylori-derived lipopolysaccharide); direct damage to the mucosa by urease, cytotoxin and other H. pylori-derived products.

From the above discussion, a number of conclusions can be drawn and questions asked about the effects of H. pylori on gastric acid secretion. H. pylori produces compounds, such as a protein factor and a lipid soluble “pore-forming factor,” which decrease acid secretion, as well as urease, which increases acid secretion. The level of some immune/inflammatory mediators (IL-1, IL-6, IL-8, TNF-α and IFN-γ) are increased by H. pylori; however, most cytokines have not yet been studied in this regard. In the gastric fundus, many of these cytokines appear to decrease acid secretion. In the gastric antrum, at least some of these compounds may increase acid secretion by increasing gastrin secretion and/or by decreasing somatostatin secretion. No cytokines or H. pylori-produced factors have yet been reported to increase acid secretion by acting on parietal cells, ECL cells, mast cells or D cells in the gastric fundus or to decrease acid secretion by acting on G or D cells in the gastric antrum. Whether H. pylori-induced cytokines or H. pylori-produced factors alter acid secretion by altering neurotransmitter release anywhere in the stomach has not yet been investigated.

The realization that H. pylori may play a central role in the regulation of gastric acid secretion and that this contributes to the pathogenesis of duodenal ulcer disease has been the impetus for many recent investigations concerned with the immunophysiology of
gastric secretions. It is apparent that the stomach is similar to the rest of the gastrointestinal tract, since it is in a constant state of inflammation in a large percentage of the population: approximately 50 percent of the population in the industrialized world is infected with *H. pylori* by the age of 60 [93]. We are just beginning to ask important questions (who, what, where, when and why) about the *H. pylori*-mediated control of gastric acid secretion. As a result, our understanding and concepts of the regulation of gastric acid secretion is rapidly changing.

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