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Review

Helicobacter pylori and gut hormones

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Helicobacter pylori infection has been found to decrease the expression of antral somatostatin and to increase the release of the acid-stimulating hormone gastrin. The reversal of these changes in gut hormones by the eradication of *H. pylori*, and in-vivo and in-vitro studies in animals either infected with *H. pylori* or exposed to *H. pylori*-related materials may support the somatostatin-gastrin link theory in the pathophysiology of *H. pylori* infection. The following mechanisms have been proposed to explain the *H. pylori* infection-associated changes in gut hormones; (1) ammonia produced by *H. pylori* and monochloramine, (2) effect on somatostatin receptor subtype-2, (3) action of lipopolysaccharide from *H. pylori* on somatostatin receptor, (4) inflammatory cells and mediators, and (5) bacterial strain diversity. *H. pylori* infection can alter gastric acid secretion in both directions. The elevated acid secretion in patients with duodenal ulcer is decreased by *H. pylori* eradication, and is accompanied by the normalization of gut hormones in patients whose *H. pylori*-induced gastritis is limited to the antrum with hyperacidity. Corpus gastritis and the subsequent development of mucosal atrophy induced by *H. pylori* result in decreased acid secretion, although the mechanism underlying *H. pylori*-induced atrophy in some subjects remains unclear. Hypoacidity enhances corpus atrophy and increases gastrin secretion, mediated via a physiological suppression of somatostatin release, features that are also observed in *H. pylori* infection. Therefore, the capacity of acid secretion and distribution of gastritis or atrophy should be taken into consideration when we discuss the affect of *H. pylori* on gut hormones.

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Introduction

Helicobacter pylori is now known to be the major etiologic agent of chronic active gastritis, and it also plays a crucial role in gastric and duodenal ulcer (DU) disease, as well as in gastric carcinoma.[1,2] *H. pylori* infection can alter acid secretion in both directions. Corpus gastritis and the subsequent development of mucosal atrophy induced by *H. pylori* infection result in a decrease of acid secretion. In contrast, DU patients have approximately twice the normal parietal mass, which increases their maximal acid secretory capacity. Several investigators have demonstrated that the elevated acid secretion in DU patients decreases after *H. pylori* eradication.[3] The distribution of gastritis and gastric acid secretory capacity seem to be crucial in determining the clinical outcome of *H. pylori* infection. For instance, it has been proposed that high acid secretion leads to DUs, while low acid secretion is found in patients with gastric ulcers and gastric cancer.[4]

Gastric acid secretion is regulated by many factors involving the autonomic nervous system and gut hormones. Among several hormones affecting gastric acid secretion directly or indirectly, the most important regulatory peptides in the gastric mucosa include gastrin and somatostatin (SST). In order to understand the relationship between hormonal peptides and gastric acid secretion in *H. pylori* infection, it seems important to distinguish DU in which gastritis is limited to the antrum, with high acid secretion, from gastric ulcer and pangastritis, in which corpus gastritis and atrophy are present, accompanied by low acid output.

In this review, the SST and gastrin link in *H. pylori* infection is summarized, and discussed with specific at-

tention being paid to gastric acid secretion, as well as gastritis distribution. The mechanisms speculated to underlie *H. pylori*-induced gastric peptide regulation are also reviewed.

Somatostatin (SST)

SST is a tetradecapeptide, originally discovered in sheep hypothalamus, which showed an inhibitory effect on growth hormone release. In 1971, the presence of SST-containing D cells (see below for definition) in the canine antral mucosa was suggested by Fujita and Kobayashi,[5] who demonstrated the degranulation of secretory vesicles from certain endocrine cells of the antral mucosa in response to luminal acidification.

Studies of SST have revealed the existence of a whole family of SST-related peptides, which includes the tetradecapeptide (SST-14), an amino-terminal-extended SST (SST-28), and larger preprohormone forms. SST-14 and SST-28 are the two biologically active forms of SST.

In mammals, the gastrointestinal tract and pancreas contain the largest amounts of SST. Chromatographic studies have shown the predominant form of SST in the human stomach to be the tetradecapeptide, whereas there is a relative increase in the proportion of SST-28 further down the gastrointestinal tract.[6,7]

Most of the gastrointestinal SST immunoreactivity is confined to the mucosal layer,[6] where it is localized in epithelial endocrine cells, called D cells. In the antrum, the D cells have apical membranes that are exposed to the lumen ("open cells"). In the corpus, the D cells are of the "closed" type; they are not exposed to the luminal surface of the mucosa.[8]

By inhibiting gastrin release, SST plays an important role in the regulation of gastric acid secretion. In the antral mucosa, the open D cell releases SST in response to increased acidity in the gastric lumen. Because the apical surface of D cells opens onto the gastric lumen, changes in pH may be sensed directly through chemoreceptors on the apical membranes. Other studies suggest that gastric acid stimulates mucosal nerve endings, releasing calcitonin gene-related peptide (CGRP), which stimulates the release of SST. CGRP released from the primary afferent terminals of splanchnic nerves stimulates the release of SST from D cells. Vasoactive intestinal peptide released from the mucosal nerves stimulates SST release in the stomach. Adrenergic agonists stimulate SST secretion in the stomach, but cholinergic stimuli inhibit SST secretion (Fig. 1).[8,9]

Gastrin and *H. pylori* infection

Gastrin peptides are released into the circulation from G cells in the gastric antrum and duodenum after stimulation by food intake, and strongly stimulate the parietal cells in the corpus to secrete acid (Fig. 1). The two main forms of gastrin in plasma are gastrin-17 and gastrin-34. These are equipotent on a molar basis, but gastrin-34 has a longer plasma half-life. About 95% of antral

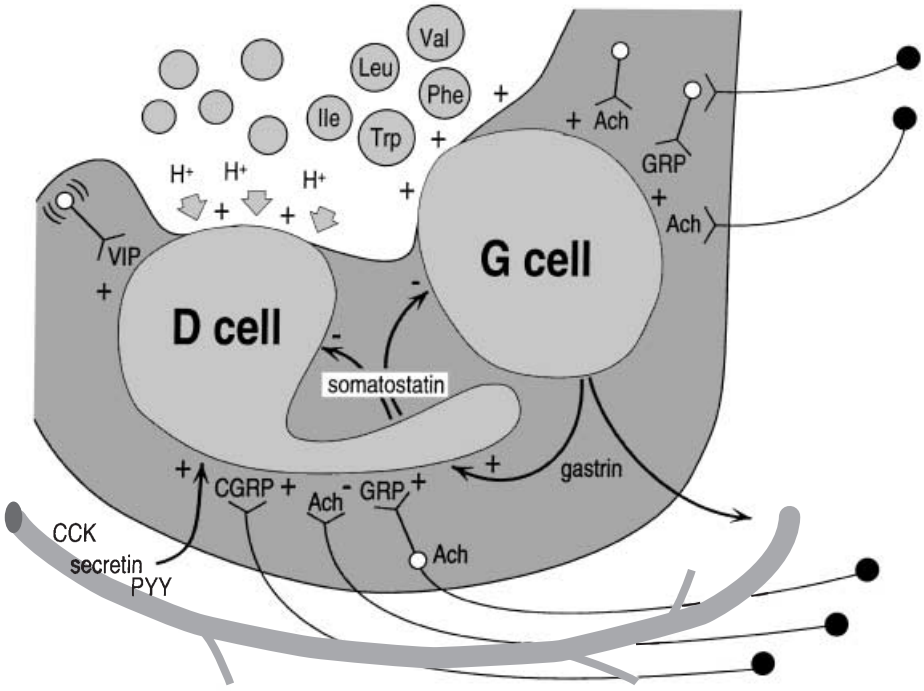

Fig. 1. Gastrin release is stimulated by extramural cholinergic and intramural cholinergic and non-cholinergic factors, and inhibited by somatostatin. Somatostatin release is stimulated by luminal (acid), paracrine, and hormonal factors (gastrin), and by intramural noncholinergic factors, and is inhibited by extramural cholinergic factors. *CCK*, Cholecystokinin; *PYY*, peptide YY; *CGRP*, calcitonin gene-related peptide; *VIP*, vasoactive intestinal peptide; *GRP*, gastrin-releasing peptide; *Ach*, acethylcholine. Adapted from reference 9, with permission

gastrin is gastrin-17, while about 60% of duodenal gastrin is gastrin-34.[9]

Before the discovery of *H. pylori*, numerous abnormalities of gastric physiology were found in DU diseases. An increased number of parietal cells and a general failure of inhibitory reflexes (duodenal break) could explain hyperacidity, which is a typical characteristic of DUs. DU patients have been estimated to have an average of two billion parietal cells, compared with one billion in controls.[10] Maximal acid output (MAO), which reflects the parietal cell number, is higher in patients with DUs than in controls. Acid secretion is normally inhibited by a low intragastric pH, but acid inhibition induced by peptones, intraduodenal fat, or gastric distension is attenuated in DU patients.[11–13] Meal-stimulated gastrin release is considerably greater in DU patients than in controls.

The first report on the relationship between *H. pylori* infection and plasma gastrin concentrations was released by Levi et al. in 1989.[14] They reported that both basal and stimulated acid secretion and basal and meal-stimulated plasma gastrin levels were significantly higher in *H. pylori*-positive DU patients ($n = 25$) compared with *H. pylori*-negative DU patients ($n = 6$) and they named this phenomenon 'the gastrin link'. Their data clearly demonstrated that *H. pylori* infection induced hypergastrinemia that was followed by an increase in acid secretion in DU patients. Others have also made substantial contributions to this area. *H. pylori* infection has been shown to increase plasma gastrin concentrations during fasting, after meals, and after the infusion of bombesin or its mammalian equivalent, gastrin-releasing peptide (GRP).[14–17] In *H. pylori*-infected subjects, gastrin-17 is the predominant form released by a meal or following GRP infusion.[18] Eradication of *H. pylori* reduced the output of gastrin-17 with no effect on gastrin-34.[18,19]

In terms of acid secretion in *H. pylori*-positive DU patients, several investigators have demonstrated that elevated acid secretion decreases after *H. pylori* eradication, with simultaneous reduction of serum gastrin.[20,21] Recently, Iijima et al.[22] reported that peak acid secretion, which was evaluated by endoscopic gastric juice sampling following gastrin stimulation, decreased after *H. pylori* eradication, in agreement with the previous studies. However, in countries such as Japan, where corpus gastritis and mucosal atrophy are even common among *H. pylori*-infected DU patients, the situation is not as simple. Chiba et al.[23] reported very recently that serum gastrin levels, but not MAO, decreased in 21 Japanese DU patients 6 months after *H. pylori* eradication, and that no significant correlation was observed between changes in serum gastrin and acid secretion. After stratification of DU subjects according to the change in MAO, they speculated that corpus gastritis with atrophy might explain why acid secretion was not significantly reduced after *H. pylori* eradication in their DU patients. Japanese researchers previously demonstrated a decrease in fasting gastric juice pH after *H. pylori* eradication in DU patients.[24] Taken together, these findings suggest that much attention should be paid to the involvement of corpus gastritis with atrophy when we discuss the acid secretion in DU patients.

Somatostatin and *H. pylori* infection

Somatostatin in duodenal ulcer

SST deficiency had been proposed in DU patients before the discovery of *H. pylori*.[25] The intravenous infusion of GRP or bombesin leads to a generalized release of both gastrin and SST. Bombesin-stimulated gastrin release is considerably greater in DU patients than in controls.[26] DU patients, also showed a different pattern of acid secretion in response to bombesin. Low doses produced similar acid secretion in DUs and controls. However, in DU patients, acid secretion rose further as the dose of bombesin was increased, whereas in controls the higher doses caused inhibition of acid secretion.[26] This difference may be explained by a lack of bombesin-stimulated SST release in the DU group.[27]

Conventional human study of somatostatin in H. pylori *infection*

In view of the above reports, we asked whether *H. pylori* infection decreases SST in the gastric mucosa. SST release cannot be assessed by measuring plasma levels,[28] because SST is released in many organs and destroyed locally,[8] but SST levels in both gastric mucosa and juice reflect the local SST regulation.[29] In 1992, we reported, for the first time, that antral SST concentrations were decreased in *H. pylori*-infected patients.[30] We also demonstrated that gastric juice SST levels tended to decrease in *H. pylori*-positive subjects. In our study, we used an SST antibody specific against SST-14, with only 0.4% cross-reactivity against SST-28. From the evidence that SST in the gastric juice mainly consists of SST-14, our data strongly suggested that antral SST-14 is depleted in *H. pylori*-infected subjects. Recent studies have clearly demonstrated that antral, but not corpus, SST levels were decreased in *H. pylori* infection, by measuring the SST concentration in specimens biopsied from both sites.[31,32] In the same year, 1992, as our study above,[30] Moss et al.[33] demonstrated that eradication of *H. pylori* from 10 DU patients caused approximately twofold increases in SST messenger RNA (mRNA) in antral, but not in corpus biopsies. They also showed an increase in D cell numbers after *H. pylori*

eradication in 18 subjects with active DU. Their study was introduced as the 'somatostatin-link theory' in selected summaries in the journal *Gastroenterology* in 1993.

The SST-link theory has been supported by substantial reports, with one exception,[34] which demonstrated that *H. pylori* infection decreased mucosal SST content, D cell numbers, and SST mRNA expression in various gastroduodenal diseases in adults and in children.[35–37] Recently, a light and electron microscopic immunohistochemical investigation clearly demonstrated that the D cell granule index, determined by electron microscopy, was similar in patients with *H. pylori*-associated chronic gastritis and controls, and that D cell depletion was typical in *H. pylori* infection.[38]

Interventional human study of somatostatin in H. pylori *infection*

No infection experiment on the effects of *H. pylori* on gut regulatory peptides in humans has been reported. The impact of eradication of *H. pylori* on peptides has demonstrated the close relationship between infection and SST regulation. Several studies have shown the reversal of somatostatin-related parameters by the eradication of *H. pylori* infection.[21,37,39] Because many different kinds of drugs have been used to eradicate *H. pylori* in various studies, one cannot rule out the effect of drugs on SST levels. Tham et al.[40] reported that an increase in D cell density accompanied by *H. pylori* eradication was unlikely to be a nonspecific effect of the eradication therapy itself. They based this idea on the finding that D cell density increased after eradication, but was unchanged under conditions of persistent infection after three different treatment regimens.[40] Our better controlled study, by comparing the changes in antral and gastric juice SST concentrations between success and failure in eradication with dual therapy in peptic ulcer patients, further confirmed that *H. pylori* status, but not drugs, affected gastric SST.[41]

Animal studies of the effect of *H. pylori* infection on peptides

In conventional BALB/c mice, Konturek et al.[42] reported that gastric acid was reduced by over 50% immediately after *H. pylori* inoculation that was accompanied by a significant increase in plasma gastrin and fall in gastric luminal SST content during 28 test days, particularly in animals infected with type I (Cag A- and Vac A-positive) *H. pylori*. They also showed that toxigenic *H. pylori* strain infection markedly delayed the healing of acetic acid-induced gastric ulcers due to a fall in mucosal microcirculation in the ulcer site and the impairment of SST release. A similar depletion of luminal SST release has been demonstrated in male Wistar rats treated with water extract obtained from type I *H. pylori*.[43]

Cats with acquired natural *H. pylori* infection (*cag* A^-, *pic* B^-) demonstrated fasting plasma gastrin concentrations and pentagastrin-simulated acid secretion levels that were similar to those in uninfected cats. The amount of SST and the number of immunoreactive SST cells in antral tissue were lower in uninfected than in *H. pylori*-infected cats,[44] in contrast to other reports.

Gastric acid secretion is decreased and serum gastrin levels are increased in Mongolian gerbils infected with type I *H. pylori*.[45] These recent data suggested that a toxigenic strain may be involved in gut peptide regulation that is accompanied by a decrease in gastric acid secretion.

Mechanisms underlying *H. pylori*-induced peptide change

Urease and ammonia

Levi et al.[14] originally proposed that the alkaline condition generated locally by *H. pylori* urease increased gastrin release. Measurements of the pH in the gastric mucus layer have shown that *H. pylori* infection causes a more alkaline milieu, although the difference is only 0.3–0.8 of a pH point.[15] Increasing intragastric urea did not elevate gastrin in infected persons.[16] Inhibition of urease by acetohydroxamic acid or bismuth plus antibiotics did not decrease gastrin release in a short-term experiment.[46] In contrast, long-term exposure of the rat antral mucosa to elevated levels of ammonia in the gastric juice induced G-cell hyperfunction in rats.[47] and monochloramine (NH_2Cl) was shown to be a more potent stimulant of gastrin release and acid secretion than ammonia itself.[48] It is unclear as to how long it takes for endocrine cells to be reversed by alkalization: plasma gastrin levels remained considerably elevated 3 h after the acidification of the stomach in achlorhydric patients.[49]

Convergent evidence indicates ammonia-induced suppression of SST. First, an inverse correlation between gastric juice ammonia levels and antral SST concentrations was observed in humans.[30] Secondly, 4-week-long oral treatment with 0.01% ammonia, which was clinically estimated as the concentration in the gastric juice in patients with *H. pylori* infection, decreased the release of SST and the number of D cells in the rat stomach.[50,51] Thirdly, 20-min-long administration of 0.025% ammonia solution was shown to decrease SST release from the rat gastric mucosa into the culture medium in vitro.[52] Sodium hydroxide, at a similar pH to

ammonia examined in rat experiments had no effect on SST, indicating that certain factors inherent to ammonia, rather than the effect of pH, may modify SST. In contrast, 0.3% ammonia solution, which itself induced gastric mucosal lesions, did not affect rat gastric SST levels,[53] therefore suggesting that narrow ranges of ammonia concentration affect SST.[51]

Somatostatin receptors

SST acts through a family of homologous receptors: they are termed SST receptors (SSTRs) 1–5 according to the chronology of their discovery.[54] Functional, histological and molecular biological studies indicate that several SSTRs exist in the rat stomach at a mRNA level and are involved in gastric function, including acid secretion and motility.[55–61] Of the five SSTRs, SSTR-2 has been most extensively investigated in terms of the gastric secretion of acid, histamine, and gastrin.[55,56,58,59,62] An immunohistochemical study, carried out by a double-staining method, revealed that SSTR-2-positive cells were co-localized in 85% of G cells and one-third of D cells.[51] The percentage of SSTR-2-labeling cells among D cells was significantly increased in rat antrum after 2- to 4-week treatments with 0.01% ammonia solution, but not with NaOH. Ammonia may cause a decrease in the inhibitory potency of SST on G-cell function not only through a decrease in D cell number but also through the additional inhibition of SST release, via an SSTR-2 in the residual D cells, in a paracrine manner, resulting in an increase in serum gastrin levels in rats[51] (Fig. 2). Retallack et al.[63] speculated that a decrease in SSTR-2 mRNA on G cells may be responsible for the *H. pylori* infection-induced increase in gastrin secretion from the G cell rich fraction of human antral cell preparations[64] infected with *H. pylori*.

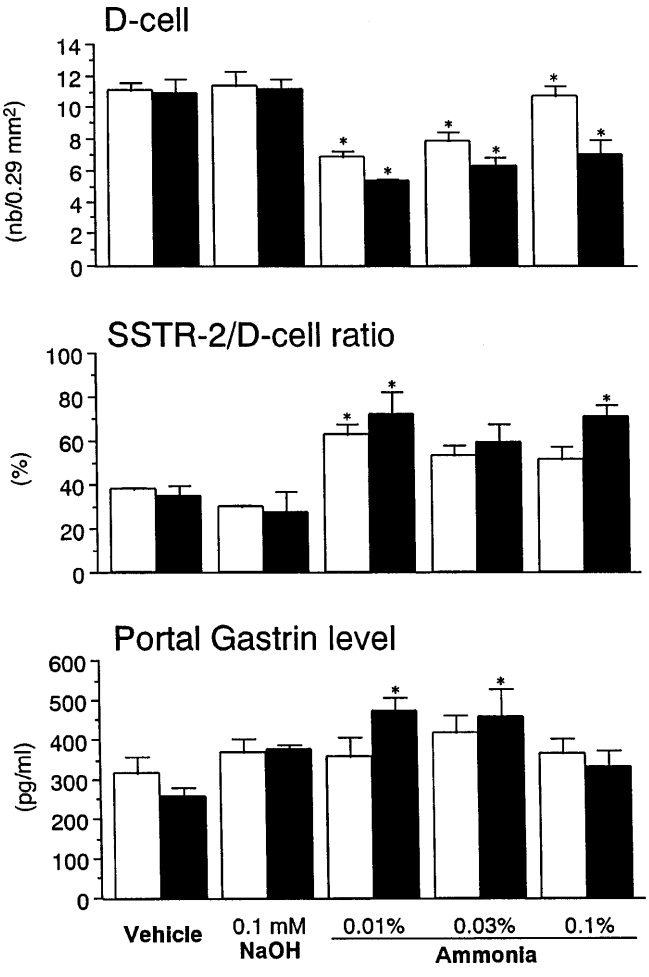

Fig. 2. Effects of ammonia solution, administered orally for 2 weeks (*white bars*) or 4 weeks (*black bars*), on the number (nb) of somatostatin (*D*)-, and somatostatin receptor subtype 2 (*SSTR-2*) peptide [31–41]-labeled cells per unit area (0.29 mm²) in the antral mucosa, and on portal gastrin levels in rats. *Each bar* represents the mean ± SE value of five rats. $^*P < 0.05$ compared with the respective vehicle-treated group. Adapted from reference 51, with permission

Lipopolysaccharide

Effects of lipopolysaccharide (LPS) from *H. pylori* on acid secretion and its effects on the binding capacity of SSTRs are conflicting. *H. pylori* LPS inhibited gastric acid secretion in pylorus-ligated conscious rats.[65] Piotrowski et al.[66] demonstrated that the binding of SST to its receptor on gastric mucosal cell membranes was inhibited by LPS from *H. pylori*, suggesting that *H. pylori*, through its LPS, is capable of interfering with SST regulatory effects on gastric mucosal G-cell function. Recently, *H. pylori* LPS was shown to have neither a direct effect on acid secretion nor any potential interference with SSTRs on parietal cells and the subsequent inhibition of acid secretion in mouse gastric gland in vitro.[67]

Inflammatory mediators

One of the characteristic features of *H. pylori*-induced mucosal damage is an inflammatory response in the host mucosa. All of the cytokines so far examined are increased in *H. pylori* gastritis; interleukin (IL)-1, IL-6, and IL-8; tumor necrosis factor-α (TNF-α); interferon-γ; macrophage inflammatory protein-1α; and platelet-activating factor.[68,69] Cytokines such as IL-2 and IL-8 increase gastrin secretion from isolated canine G cells, which secrete gastrin and interact with D cells.[70,71] TNF-α directly affects G cells in dogs and humans to increase gastric secretion.[72] This cytokine also has the ability to regulate SST secretion in isolated canine fundic D cells.[73]

We have demonstrated that a decrease in antral SST levels or an increase in antral IL-8 is correlated with inflammatory severity.[30,74] Eradication of *H. pylori* has been reported to induce a decrease in antral IL-8 levels and an improvement in histological inflammatory findings.[41,75–79] In patients with the disappearance of epithelial neutrophils, which is a characteristic pathologic finding of *H. pylori*-induced gastritis,[80] antral SST concentrations were significantly decreased after eradication therapy.[41] A negative correlation has been demonstrated between antral SST concentrations and IL-8 secretion in organ cultures of mucosal biopsies.[74] These findings suggest that certain mutual interactions between IL-8 and SST might be present in *H. pylori* infection in humans. In addition, a close correlation between an increase in gastric SST levels and the normalization of neutrophil infiltration indicated peptide-inflammation interactions in *H. pylori*-induced gastritis.[41]

Bacterial factors

Certain strains are more likely to cause clinical diseases, and these strains may produce greater changes in endocrine function. Among infected patients, those who have antibodies to CagA protein have higher plasma gastrin concentrations than those who do not have these antibodies.[81] Those with the s1/m1 variant of the *vacA* gene, which is more likely to cause ulcers,[82] have less antral SST peptide than those with the less virulent type s2/m2.[83] Kim et al.[84] demonstrated that hypergastrinemia, with a decrease in the number of antral D cells in *H. pylori*-associated gastritis, is relevant to the presence of CagA. These findings seem to support the concept that D cell deficiency may be relevant in toxigenic *H. pylori*-associated chronic active gastritis.[41,44,85,86] In contrast, Konagaya et al.[87] reported that an inhibitory effect of *H. pylori* strains on acid secretion and gastric SST contents in pylorus-ligated conscious rats was, likely, dependent on disease-associated bacterial factors rather than the status of *cag A*.

H. pylori-*related products*

Courillon-Mallet et al.[88] proposed that N^{α}-methyl histamine (NMH; a histamine 3 agonist) produced by *H. pylori* acted against a histamine 3 receptor localized on D cells to lower SST content. However, Beales and Calam[89] reported that NMH directly stimulated acid secretion by parietal cells via a histamine 2 receptor in isolated cultured rabbit parietal cells. They also clearly demonstrated that NMH did not alter SST release from cultured rabbit fundic D cells.[90] In our preliminary in-vitro experiment, an inhibitory effect of *H. pylori* product on SST release from rat mucosa into the medium was blocked by a histamine 3 receptor antagonist, thioperamide.[91] Binding sites of NMH on D cells and the specificity of NMH against a histamine 3 receptor should be further examined.

Secondary endocrine changes to gastric acid?

Another important issue to be solved is why a patient's *H. pylori* gastritis mainly affects the antrum or the corpus of the stomach. Gastritis is typically restricted to the antrum in patients with DUs.[92] However, *H. pylori* also predisposes to gastric ulcers and gastric cancer, which are associated with low acid secretion.[93] Patients with *H. pylori* and acid hyposecretion tend to have corpus gastritis that is believed to be related to diminished acid secretion brought about by a specific *H. pylori* product or by inflammatory cytokines, including IL-1β and TNFα, which inhibit parietal cells[94]. IL-1β also inhibits enterochromaffin-like (ECL) cells, which normally release histamine onto parietal cells.[95] Finally, *H. pylori* infection accelerates the development of corpus atrophy, which further diminishes acid secretion through the loss of parietal cells.[96] A recent study clearly demonstrated that *H. pylori* (*cag A*-positive) infection induced a decrease in acid secretion and an increase in serum gastrin, with these phenomena returning to control levels after treatment with an IL-1 receptor antagonist in Mongolian gerbils.[45] Because gastrin is a physiological stimulant of acid secretion, gastrin release seems to correspond to a decrease in intragastric acidity induced by *H. pylori*-related corpus gastritis with atrophy. However, at least two possibilities should be taken into consideration. First, gastric acid secretion is not suppressed under the expression of mucosal IL-1β in cats.[44] Secondly, the recovery of SST secretion into the gastric lumen seems to precede that of acid secretion by 4–8 weeks after the eradication of *H. pylori* in gastric ulcer patents with corpus gastritis.[97]

In regard to DU in which gastritis is strictly limited to the antrum, the *H. pylori*-induced suppression of SST (D cell number) that is accompanied by hypergastrinemia enhances gastric acid secretion.[4,98] The SST-gastrin-acid link theory in DU makes sense in subjects who originally had acid hypersecretion, especially in Japanese patients, as Chiba et al.[23] pointed out recently.

Conclusions

The mechanisms speculated to underlie *H. pylori*-induced gut peptide change are summarized in Fig. 3. Gut hormones such as gastrin and SST are regulated by neuronal, hormonal, and immune systems. A major question in helicobacterology is why the same germ causes different diseases: gastric ulcer, DU, gastric can-

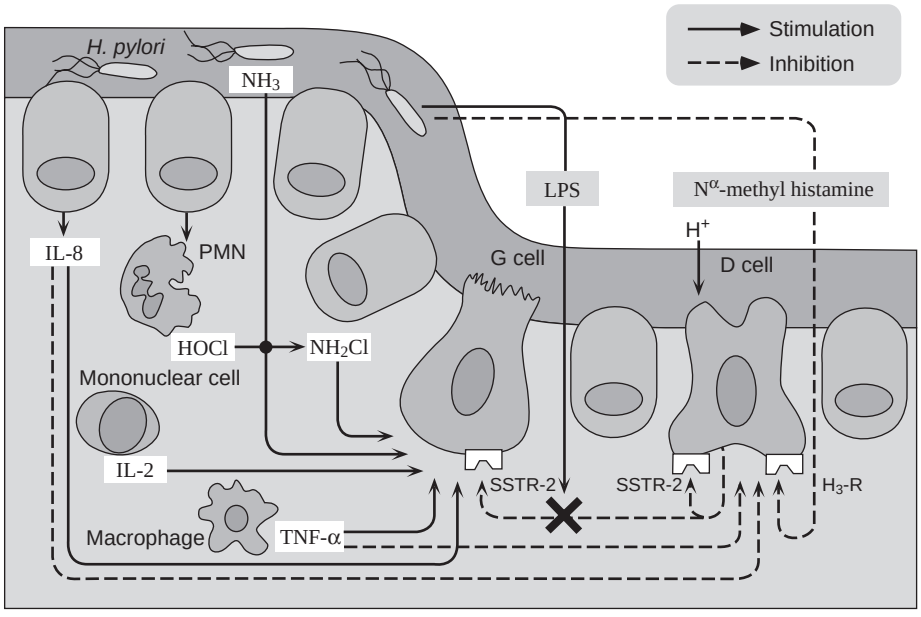

Fig. 3. Mechanisms speculated that are to underlie *Helicobacter pylori*-induced gut peptide change. *PMN*, Polymorphonuclear leukocyte; *IL*, interleukin; *LPS*, lipopolysaccharide; *TNF-α*, tumor necrosis factor-α; *H_3-R*, histamine 3 receptor; *SSTR-2*, somatostatin receptor subtype 2

cer, or asymptomatic histologic gastritis. The bacterial strain, host status, and environmental factors may affect the outcome. Especially, the capacity of acid secretion and the distribution of gastritis or atrophy should be taken into consideration when we discuss the effect of *H. pylori* on gut hormones.

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