Helicobacter pylori and gastric acid: an intimate and reciprocal relationship

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***Abstract*:** *Helicobacter pylori* (Hp) is the main cause of gastritis, peptic ulcer disease and gastric cancer. There are still unanswered questions related to the interaction between Hp and man, like what determines the susceptibility for the initial infection and the mechanisms for the carcinogenic effect. The initial infection seems to require a temporal gastric hypoacidity. For Hp to survive in the gastric mucous layer, some acidity is necessary. Hp itself is probably not directly carcinogenic. Only when inducing oxyntic mucosal inflammation and atrophy with hypoacidity, Hp predisposes for gastric cancer. Gastrin most likely plays a central role in the Hp pathogenesis of duodenal ulcer and gastric cancer.

Keywords: gastric acid, gastric cancer, gastrin, gastritis, *Helicobacter pylori*, peptic ulcer

Production of acid in the upper gastrointestinal tract has been preserved during phylogenesis [Johnsen, 1998], reflecting the importance of the main function of gastric juice; that is killing of swallowed microorganisms [Wilder-Smith *et al.* 1992]. The normal gastric juice creates a hostile milieu for microorganisms, making the luminal content of the stomach as well as the small intestine relatively sterile. Inflammation of the gastric mucosa was some decades ago so prevalent [Siurala *et al.* 1968] that gastritis even was considered a natural consequence of aging. However, it was rather early recognized that gastritis was related to gastric cancer since gastric cancer only developed in stomachs with gastritis [Morson, 1955]. It was, therefore, a great breakthrough when it was shown that *Helicobacter pylori* (Hp) infection was the major cause of gastritis [Marshall and Warren, 1984]. Although it is more than 25 years since the central role of Hp in the pathogenesis of upper gastrointestinal disease was realized, there are still unresolved questions related to the interaction between Hp and the host, like the mechanism for the carcinogenic effect and the susceptibility for Hp infection. This paper aims to make a concise review of the interactions between Hp and humans.

Acute infection by *Helicobacter pylori*

Whereas it is well known how *Helicobacter pylori* (Hp) can survive in the superficial mucous layer by its urease activity causing a livable pH in its vicinity, the mechanisms by which Hp can survive and proliferate when infecting a normal stomach are not so well understood. Nevertheless, the two known voluntary infections were successful only after inhibition of gastric acidity [Marshall *et al.* 1985; Morris and Nicholson, 1987], suggesting the role of gastric juice in the defense against the initial infection. Both these subjects developed self-limited symptoms from the epigastric area with fullness, nausea and vomiting some days after the infection and lasting for about a week. Similarly, in an outbreak of gastritis due to contamination of equipment used in a study where gastric acid secretion was determined multiple times in healthy subjects, the participants developed hypoacidity, gastritis and similar symptoms [Ramsey *et al.* 1979] as those voluntarily infected with Hp. Hp has retrospectively been presumed to be the causative agent. Also in these subjects, Hp may have been introduced to the stomach without gastric juice, which was continuously aspirated or as part of studying meal-stimulated acid secretion where the luminal content *in vivo* was titrated to pH 5.0. Thus, during the two voluntary infections [Marshall *et al.* 1985; Morris and Nicholson, 1987], as well as the transmission by the nasogastric tube [Ramsey *et al.* 1979], Hp entered a stomach without acid [Figure 1(a)], allowing the bacterium to bury into the mucous layer before normal gastric acidity was reestablished. In most cases of chronic Hp gastritis, there is no

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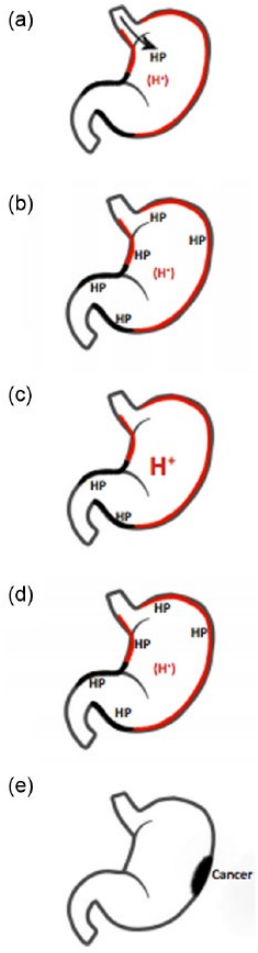

Figure 1. The different phases of the relationship between *Helicobacter* and gastric acid.
(a) The initial infection is facilitated by reduced gastric acidity. (b) The initial infection causes reduction in gastric acidity. (c) Although the infection persists, gastric acidity is by some reason or the other restored. (d) When the Hp infection causes atrophy of the oxyntic glands, gastric acid secretion declines. (e) When the oxyntic atrophy is so pronounced that sufficient gastric acidity is not reached, hypergastrinemia develops and the patient is concomitantly predisposed for gastric cancer.

information of any symptomatic episode. This may indicate that most of the acute infections are asymptomatic, or alternatively, a gastroenteritis due to Hp infection has been misdiagnosed as viral. Moreover, childhood Hp infection seems to be prevalent [Thomas *et al.* 1999], which may be explained by reduced gastric acidity during early life [Agunod *et al.* 1969; Rodbro *et al.* 1967]. Alternatively, gastroenteritis by other causes may make the gastric content hypoacidic and thus give time and possibility for Hp to proliferate and infect the stomach. The higher frequency of Hp infection in underdeveloped countries [Weaver, 1995] may perhaps be explained by a higher frequency of gastroenteritis in these countries. The initial infection affects both oxyntic and antral mucosa [Ramsey *et al.* 1979; Morris and Nicholson, 1987]. We do not know the mechanisms behind the resolution of the initial infection resulting in loss of symptoms and restoration of acid secretion [Morris and Nicholson, 1987; Ramsey *et al.* 1979]. Nevertheless, it seems that the infection persists in all infected subjects, with some having the ability to limit the infection to the antral mucosa whereas others develop a chronic pan-gastric infection at an early stage.

Thus, gastric acidity probably has a protective role in the defense against the initial Hp infection. The use of inhibitors of gastric acid secretion in small children, which recently has been reported to predispose for *Clostridium* infection [Nylund *et al.* 2014], may also make these children more susceptible to Hp infection.

Mechanisms of hypoacidity during the initial infection

The course of acute Hp gastritis or epidemic hypochlorhydria, which has been used synonymously, may last for weeks or months [Marshall *et al.* 1985; Morris and Nicholson, 1987; Ramsey *et al.* 1979]. The mechanism behind the reduced gastric acidity in the acute phase of Hp infection is not known, but properties both by Hp itself and the inflammation this infection provokes have been implicated [Calam, 1995] [Figure 1(b)]. Thus, Hp infection may induce the production of cytokines like interleukin (IL)-1β [Noach *et al.* 1994] having an inhibitory effect on gastric acid secretion [Wallace *et al.* 1991]. A direct effect on acid secretion by Hp itself is supported by studies in isolated parietal cells [Cave and Vargas, 1989]. Among the Hp-derived factors involved in the reduction of gastric acidity during acute infection are NH_3, fatty acids or a substance having inhibitory effects on the H^+/K^+-ATP-ase [Calam, 1995]. For more than 20 years it has been shown that Hp and fatty acids produced by Hp block H^+/K^+-ATP-ase [Beil *et al.* 1994] and more recently that Hp represses proton-pump expression as well [Saha *et al.* 2010]. Some cytokines liberated by the inflammation may also have a profound effect on acid secretion [Saperas *et al.* 1990].

Transition to chronic infection

We do not know for sure, but the prevailing hypothesis is that, once infected, Hp gastritis becomes chronic; if not, Hp is eradicated by

treatment. The transition from acute to chronic gastritis is accompanied by restoration of gastric acid secretion [Ramsey *et al.* 1979; Morris and Nicholson, 1987]. However, what happens in the stomach in this phase is not known. Moreover, why the infection is confined to the antral mucosa in some patients whereas pan-gastritis occurs in others is unknown, although differences in mucosal acidity may play a role. The oral spread of infection caused by inhibition of gastric acid secretion [Logan *et al.* 1995] also suggests that local acidity plays a role in the distribution of Hp infection.

The spiral shape and flagella help Hp to bore into the mucous layer [Calam, 1995] where there is a pH gradient due to H^+ diffusing from the luminal side and HCO_3^- from the epithelial cells. Hp is dependent on a near neutral pH to thrive; the urease activity of Hp [Marshall *et al.* 1990] increases pH in the vicinity, thus making it possible for Hp to survive at a more acidic place. In many ways, a slightly acidic milieu is ideal for Hp growth since its NH_3 production otherwise could induce too alkaline milieu for the bacterium [Scott *et al.* 1998].

When Hp infection is mainly confined to the antral mucosa, there may be increased gastrin release leading to augmented gastric acid secretion predisposing to duodenal ulcer [Levi *et al.* 1989]. The mechanism for the increased gastrin release is possibly local alkalization by NH_3 produced by Hp urease. The urease theory for the stimulation of gastrin release is attractive, but is admittedly not well supported experimentally. Thus an infusion of urea into the stomach of seven patients with duodenal ulcer infected with Hp increased intragastric ammonium concentration threefold, but did not affect plasma gastrin [Chittajallu *et al.* 1991]. However, it is not clear whether ammonium produced intragastrically will reach and affect the function of the G cell directly or the somatostatin D cell, both being localized deep in the glands. Interestingly, when Chittajallu and colleagues determined the ammonium concentration 1 month after Hp eradication, it was significantly reduced compared with the baseline value before eradication [Chittajallu *et al.* 1991]. Thus, it may be that the ammonium concentration before starting the urea infusion had maximal effect? More problematic for the urease theory with respect to stimulation of gastrin release by Hp is the lack of a reduction in gastrin in six patients with Hp-positive duodenal ulcer dosed with the urease inhibitor acetohydroxamic acid [El Nujumi *et al.* 1991]. The efficacy of the urease inhibitor was controlled by the urease breath test [El Nujumi *et al.* 1991]. However, since the degree of hypergastrinemia in patients with duodenal ulcer secondary to Hp is very small [Lanzon-Miller *et al.* 1987] and well within the normal range, gastrin has to be determined with a sensitive and accurate method to detect any difference, and only six subjects may be too few to detect a significant change [El Nujumi *et al.* 1991]. Moreover, the ammonium concentration after acetohydroxamic acid intake was about half of that measured the placebo day. Since we do not know the concentration relationship between intragastric ammonium and gastrin release, this single point study does not exclude that the urease activity of Hp is responsible for the hypergastrinemic effect. In another study from the same group [El-Omar *et al.* 1993] gastrin and acid secretion in Hp-positive patients with duodenal ulcer, Hp-positive healthy individuals and Hp-negative healthy individuals were determined at the basal state and during stimulation with gastrin-releasing peptide (GRP). They found that basal and GRP induced gastrin release as well as acid secretion were highest in patients with duodenal ulcer and Hp, but also augmented compared with Hp-positive healthy controls. At reexamination 1 month after Hp eradication, gastrin was at the level of healthy Hp negative controls whereas gastric acid secretion, although markedly reduced, apparently still was higher than in controls [El-Omar *et al.* 1993]. From these results it may be interpreted that Hp is responsible for inappropriate gastrin release, whereas trophic effects by this slight hypergastrinemia, particularly on the enterochrommafine like (ECL) cell [Brenna and Waldum, 1992], still results in elevated gastric acid secretion. It is also tempting to suggest that the difference in gastric acid secretion between Hp-positive persons with or without duodenal ulcer [El-Omar *et al.* 1993] may reflect different degrees of trophic effect on the cells regulating acid secretion.

There have been reports indicating that antral Hp infection could have trophic (positive or negative) effects on G and especially D cells [Moss *et al.* 1992], which would be expected to influence gastrin release even at neutral pH. In this context it should be recalled that neuroendocrine (NE) cells have a long lifespan [Fossmark *et al.* 2005], and thus any effect could persist for a long time after Hp eradication. The trophic effects could be

caused by chronic effects of alkalization by ammonium. Therefore, it is difficult to exclude from the present literature that the effect of Hp on gastrin release is not caused by urease activity. Whether H^+ directly affects the G cell or the antral D cell is not settled, but is not important from a functional point of view. Both the G cell and the antral D cell are of the open type and thus influenced by the gastric content. From this it is probable the gastrin release from the G cell is affected both directly from the gastric content and indirectly *via* somatostatin from D cells. However, there is an indication for an increase in antral gastrin and a fall in antral somatostatin in patients infected with Hp [Odum *et al.* 1994]

Previously it was hypothesized that duodenal ulcers developed at spots of gastric metaplasia [Carrick *et al.* 1989]. However, patients with gastrinoma develop ulcers without Hp infection [Weber *et al.* 1997], showing that increased acid secretion is sufficient to induce peptic ulcers. It should be added that the degree of gastrin increase in blood in patients with duodenal ulcer is small [Lanzon-Miller *et al.* 1987] due to the restraint on gastrin release by the increase in gastric acidity [Walsh *et al.* 1975] provoked by the small gastrin elevation. The sensitivity for gastrin with respect to its main physiological action, that is stimulation of histamine release from the ECL cell, is very high [Sandvik and Waldum, 1990]. Therefore, in most patients with duodenal ulcer there is no hypergastrinemia, but nevertheless a certain inappropriate hypergastrinemia in relation to gastric acidity [Smith *et al.* 1990]. There is a case report describing increased gastric acid secretion and a moderate hypergastrinemia in two patients with peptic ulcer where both gastrin and gastric acid secretion fell to normal levels after eradication of Hp [Metz *et al.* 1995]. The mechanism for the higher gastrin values than expected from gastric acidity in these two patients was not explained.

Mechanism for the hypersecretion of acid in patients with Hp-related duodenal ulcer

Patients with duodenal ulcer have for a long time been known to have increased gastric acid secretion [Wormsley and Grossman, 1965] and inappropriate gastrin release induced by antral Hp infection is now the accepted cause since gastrin as well as acid secretion (both basal and stimulated GRP and pentagastrin) are reduced 6 months after eradication of Hp [Harris *et al.* 1996] [Figure 1(c)]. The reduction in pentagastrin-stimulated acid secretion after Hp eradication probably reflects a reduction in the trophic effect on the ECL cell by gastrin, which is evident even at rather low gastrin concentrations which affect ECL cell proliferation [Brenna and Waldum, 1992]. At the time when many of the studies on the role and mechanism for Hp-induced gastric acid hypersecretion were done, many of the researchers apparently did not accept the central role of the ECL cell in the regulation of gastric acid secretion [Waldum *et al.* 1991]. Meals and GRP would by an increase in gastrin release be expected to augment their maximal acid secretion in people infected with Hp. In common with pentagastrin stimulation, meal and GRP will also increase acid secretion due to the trophic effects of gastrin on the ECL cell mass. Histamine release is the restrictive factor in maximal gastrin-stimulated acid secretion [Kleveland *et al.* 1987]. The fall in pentagastrin-stimulated acid secretion after Hp eradication seen in patients with duodenal ulcer [El-Omar *et al.* 1993] most probably reflects a reduction in ECL cells secondary to a reduction in gastrin.

With time, Hp-induced inflammation spreads to the oxyntic mucosa. What makes the oxyntic mucosa more resistant to Hp infection compared with the antral mucosa is not known, although acidity has been proposed to play a role. Naturally, the acid-producing oxyntic glands are located in the oral part of the stomach where they empty their content to the lumen. It is, however, hard to imagine how this should affect the acidity in the mucous layer. However, the local luminal acidity is higher in the oxyntic area, and this could be of importance in the defense against Hp infection and also explain the oral spread of the infection from the antral mucosa. In any way, also the oxyntic mucosa is infected, starting as a superficial gastritis to begin with and developing into a gastritis affecting the deeper layer of the mucosa leading to hypoacidity and marked atrophy of most elements but not the target cell of gastrin, the ECL cell. At the early phases of oxyntic gastritis, gastric acidity is only slightly reduced and may be restored by Hp eradication [Tari *et al.* 2007]. As the oxyntic glands are destroyed, the capacity to produce acid is reduced, leading to hypoacidity and marked secondary hypergastrinemia. At this stage the capacity to restore normal acid secretion is limited [Iijima *et al.* 2004]. In this context we will also mention our previous study on Mongolian gerbils where we showed that the gastrin antagonist netazepide prevented the oxyntic inflammation provoked by Hp infection [Sordal *et al.* 2013]. The functions of the

superficial cells (production of HCO_3^- and mucous) are also reduced by the gastritis and thus predisposing for gastric peptic ulcer [Byrd *et al.* 2000] [Figure 1(d)].

It may be concluded that the confusion related to the mechanisms for Hp-induced inappropriate hypergastrinemia and acid hypersecretion are mainly due to the trophic changes induced on long-living NE cells. Furthermore, an incorrect view on the regulation of gastric acid secretion at the time of most of these studies has also contributed to misunderstandings.

Hp and gastric cancer

As previously stated, gastric cancer seldom develops in a stomach without gastritis [Morson, 1955]. Similarly, Hp is an accepted cause of gastric cancer [Parsonnet *et al.* 1991]. It is also well known that Hp gastritis, when affecting the antrum only, predisposes to duodenal ulcer [Levi *et al.* 1989], which rarely occurs together with gastric cancer [Hansson *et al.* 1996]. First when Hp has induced an atrophic gastritis in the oxyntic mucosa, there is an increased risk of gastric cancer [Fossmark *et al.* 2015]. The central role of oxyntic mucosal atrophy in gastric carcinogenesis has previously been shown [Iijima *et al.* 2004]. All together, these facts suggest that the carcinogenic effect of Hp infection is related to the oxyntic atrophy and not directly to the inflammation or the agent itself [Figure 1(e)]. This view is also supported by the long unsuccessful search for a carcinogenic factor in Hp. Hp strains differ in their expression of certain genes; cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA). Particularly, CagA has been implicated in gastric carcinogenesis [Parsonnet *et al.* 1997; Gwack *et al.* 2006; Amieva and Peek, 2016]. However, even the carcinogenic effect of CagA cannot be separated from its effect on inflammation, gastric acidity and gastrin in blood [Konturek *et al.* 2002]. In general, the role of virulence factors associated to Hp were reviewed some years ago [Wen and Moss, 2009]. Oxyntic mucosal atrophy leads to hypoacidity with secondary microbiological intragastric changes. If changes in gastric milieu should be the cause of Hp-induced gastric cancer, it is strange that patients with so-called 'autoimmune' gastritis affecting only the oxyntic mucosa develop cancers in the oxyntic area [Walker *et al.* 1971]. Oxyntic atrophy also leads to hypergastrinemia as a consequence of gastric hypoacidity, and we have previously implicated gastrin in Hp-induced gastric carcinogenesis [Waldum *et al.* 2015]. The target cell of gastrin, the ECL cell, is regulated functionally and trophically by gastrin [Waldum *et al.* 2014a]. The role of the ECL cell in gastric carcinogenesis seems hitherto to have been greatly underestimated [Waldum *et al.* 2014a]. The two types of gastric cancer according to Lauren [Lauren, 1965], the intestinal and diffuse types, seem to represent separate entities since they do not transform into each other. The ECL cell may be the cell of origin for the diffuse carcinomas [Waldum *et al.* 1998]. Lack of E-cadherin is an important factor in the pathogenesis of diffuse gastric carcinomas [Becker *et al.* 1994], and interestingly, we did not find E-cadherin expression even in normal ECL cells [Waldum *et al.* 2014b]. Hp infection plays a central role in the pathogenesis of both types [Parsonnet *et al.* 1997], although metaplasia is mainly associated to the intestinal type [Solcia *et al.* 1996]. In any ways, hypergastrinemia has been shown to be implicated in Hp-associated gastric carcinogenesis [Konturek *et al.* 2002; Sun *et al.* 2014]. A central role of gastrin in Hp-induced gastric carcinogenesis is also supported by animal studies [Sordal *et al.* 2013; Takaishi *et al.* 2009]. Very recently it was reported that Hp could infect deep into the glands and reach the stem cell area [Sigal *et al.* 2015]. Such deep localization of Hp was mainly found in the antral area, whereas the oxyntic area seems to be mostly involved in Hp-induced gastric carcinogenesis [Fossmark *et al.* 2005]. Moreover, in contrast to virus bacteria, it has hitherto not been shown to have a direct carcinogenic effect.

Hp and gastrinoma

Most patients with peptic ulcer due to gastrinoma are not infected with Hp [Weber *et al.* 1997], demonstrating that increased gastric acid secretion alone is sufficient to provoke peptic ulcers. Gastrinomas seldom manifest themselves before adulthood [Soga and Yakuwa, 1998], whereas Hp infection most often occurs during childhood [Thomas *et al.* 1999]. The lower incidence of Hp infections in patients with gastrinoma compared with age-matched controls indicates that increased gastric acidity may eradicate Hp.

Hp and hypoacidity/anacidity

During the early phases of oxyntic gastritis caused by Hp, gastric acid secretion may be only moderately reduced and Hp eradication even in patients with some degree of atrophy can augment acid secretion [Tari *et al.* 2007]. In patients with pan-gastritis and oxyntic atrophy, Hp may

not be detectable [Karnes *et al.* 1991]. It is presumed that Hp cannot live under these conditions. Hp may have been replaced by other microorganisms which can live in this situation in the stomach, or alternatively, NH_3 production by Hp urease creates a local milieu too alkaline for the agent itself in a stomach without acid [Marshall *et al.* 1990]. The role of acid for Hp to thrive is also demonstrated by the effects of acid inhibition in combination with antibiotics in eradication of Hp [Unge *et al.* 1989], as well as the possible oral spread in the stomach during treatment with inhibitors of gastric acid secretion [Logan *et al.* 1995]. Interestingly, the new inhibitor of gastric acid secretion, vonoprazan, belonging to potassium-competitive acid blockers, and probably more efficient in inhibiting acid secretion than proton-pump blockers, seems to be more efficient in combination with antibiotics in eradicating Hp compared with proton-pump inhibitors [Murakami *et al.* 2016].

Conclusion

It may be concluded that Hp is dependent on temporal hypoacidity or anacidity for its primary infection, but acidity to survive for a long time. Hp infection in the antral mucosa causes duodenal ulcers induced by increased gastric acid secretion secondary to slight increased gastrin release from the G cells, probably due to NH_3 production provoked by urease. When infecting the oxyntic mucosa causing inflammation, the functions (mucous and HCO_3^- production) of the superficial cells are reduced, predisposing for gastric peptic ulcer. Long-term infection of the oxyntic mucosa causes atrophy and marked reduced gastric acid secretion, leading to gastric hypoacidity and marked hypergastrinemia that probably predisposes for gastric cancer. HP does not survive in a too acidic (patients with gastrinoma) or in an anacidic stomach.

The interactions between Hp and the stomach are very complex, but we now understand the pathogenesis of most of the diseases in the stomach and duodenum, since Hp plays a central role in most of these conditions.

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Conflict of interest statement

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