

MINI-REVIEW

Proton Pump Inhibitors and *Helicobacter Pylori*-Associated Pathogenesis

Tadashi Hagiwara, Ken-ichi Mukaisho*, Takahisa Nakayama, Takanori Hattori, Hiroyuki Sugihara

Abstract

The fact that long-term use of proton pump inhibitors (PPIs) aggravates corpus atrophic gastritis in patients with *Helicobacter pylori* infection has been proven clinically and experimentally. Corpus atrophic gastritis is a known risk factor for gastric cancer. Therefore, gastric neoplasia might be associated with the long-term use of PPIs. One of the causes of worsening corpus atrophic gastritis, leading to the development of adenocarcinoma, might be bacterial overgrowth under conditions of hypochlorhydria. The production of potentially carcinogenic N-nitrosocompounds by nitrosating organisms under conditions of hypochlorhydria might be associated with carcinogenesis. Interactions between bile acids, pH, and *H. pylori* might also contribute to carcinogenicity, especially in patients with gastro-esophageal reflux disease (GERD). The concentration of soluble bile acids, which have bactericidal or chemorepellent properties toward *H. pylori*, in gastric contents is considerably higher in patients undergoing continuous PPI therapy than in healthy individuals with normal acid production. Under these circumstances, *H. pylori* might colonize the stomach body rather than the pyloric antrum. Hypergastrinemia induced by PPI administration might promote the development of gastric cancer. Because the main cause of corpus atrophic gastritis is *H. pylori* infection, and not PPI administration, *H. pylori* infection should be eradicated before starting long-term PPI therapy.

Keywords: *Helicobacter pylori* - proton pump inhibitors - gastric cancer - corpus atrophic gastritis - GERD - gastrin

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Introduction

Helicobacter pylori (*H. pylori*) is a microbial species that specifically colonizes the gastric epithelium (Polk et al., 2010). *H. pylori* infections are probably acquired in childhood and adolescence (Kuipers et al., 1993). Infected individuals develop coexisting gastritis, which typically persists for decades, coupling *H. pylori* and its human host into a dynamic and prolonged equilibrium (Polk et al., 2010). In a study conducted by Graham et al., healthy volunteers deliberately infected with a well-characterized laboratory strain of *H. pylori* developed inflammation of the acute infectious phase in both the proximal and distal stomach mucosa (Graham et al., 2004). When colonization becomes persistent, infection results in chronic gastritis lasting for many years, possibly life-long. *H. pylori* is the strongest known risk factor for gastric cancer. It has been estimated that *H. pylori* colonization increases the risk of gastric cancer by approximately 10-fold, and *H. pylori* has been designated a class I carcinogen by the World Health Organization (IARC Monographs on the Evaluation of Carcinogen Risk to Humans, 1994). Intestinal-type adenocarcinoma, the more prevalent form of gastric cancer, is believed to develop via a series of histological

steps. The cancer progresses from chronic gastritis to atrophic gastritis, intestinal metaplasia, and dysplasia (Correa et al., 1975). Uemura et al. demonstrated that *H. pylori*-infected patients who have corpus-predominant atrophic gastritis with intestinal metaplasia have a high risk of developing adenocarcinoma (Uemura et al., 2001).

The use of proton pump inhibitors (PPIs) to treat peptic ulcers and gastro-esophageal reflux disease (GERD) has increased substantially over the past two decades. Furthermore, widespread use of non-steroidal anti-inflammatory drugs in populations at a risk for gastro-duodenal side effects is another common indication for PPI therapy (Torgownik et al., 2008; Hawkey et al., 1998). It has been widely accepted that long-term use of PPIs aggravates corpus atrophic gastritis in patients with *H. pylori* infections (Kuipers et al., 1995; Kuipers et al., 1996; Garcia et al., 2006). Although the exact mechanism underlying this effect has not been determined, long-term PPI therapy in *H. pylori*-infected patients has been suggested to increase the risk for gastric cancer. Thus, a potential association might exist between gastric neoplasia and long-term use of PPIs.

In this review, we discuss the mechanism underlying corpus-predominant gastritis, which leads to gastric cancer

related to PPI therapy in *H. pylori*-positive patients, including in those with GERD.

Relationship between acid-suppressive therapy and corpus atrophic gastritis

In the 1970s, corpus atrophic gastritis was observed in duodenal ulcer patients undergoing vagotomy (Meikle et al., 1976). Although *H. pylori* had not yet been identified as the causative organism, most of these patients were probably infected with *H. pylori*, as evidenced by the presence of refractory duodenal ulcers. Subsequently, aggravation of corpus atrophic gastritis was reported in many *H. pylori*-infected GERD patients undergoing long-term PPI therapy. Kuipers et al. evaluated GERD patients from two separate cohorts; one group was treated with omeprazole (OPZ) and the other group, with a fundoplication. The incidence of corpus atrophic gastritis was very low in both patient groups in the absence of *H. pylori* infection. However, a significantly higher number of *H. pylori*-infected patients undergoing OPZ therapy developed corpus atrophic gastritis than *H. pylori*-infected patients treated with a fundoplication, over an average period of 5 years (Kuipers et al., 1996). Long-term use of lansoprazole, as well as OPZ, aggravates corpus atrophic gastritis in *H. pylori*-infected patients (Geboes et al., 2001).

Suitable animal models to study the histological changes induced by *H. pylori*

Animal models may be used to understand the pathogenesis of human diseases. Several murine models for *H. pylori* infection have been reported in the literature. Initially, long-term colonization of the murine stomach by *H. pylori* was difficult to achieve. However, in the 1990s, some researchers reported that *H. felis* and *H. pylori* strain SS1 could colonize the mouse stomach and cause lymphocytic gastritis but not peptic ulcers or gastric cancer (Lee et al., 1990; Lee et al., 1997). In 1991, Yokota et al. (1991) demonstrated that *H. pylori* could colonize the stomach of Mongolian gerbils. Subsequently, some researchers reported that the gastric pathology of *H. pylori*-infected Mongolian gerbils was similar to that of human patients exhibiting peptic ulcers, atrophic gastritis, intestinal metaplasia (Matsumoto et al., 1997; Honda et al., 1998a), and gastric adenocarcinoma (Honda et al., 1998b; Wang et al., 1998; Watanabe et al., 1998; Franco et al., 2005). Therefore, Mongolian gerbils are excellent model organisms to study *H. pylori* infection, because the gross and histological findings mimic the lesions induced by *H. pylori* infection in the human gastric mucosa.

Omeprazole (OPZ) administration promotes corpus atrophic gastritis in Mongolian gerbils infected with *H. pylori*: a study by our group

In a previous study, we successfully demonstrated that long-term PPI administration promotes corpus atrophic gastritis in Mongolian gerbils with *H. pylori* infection

(Hagiwara et al., 2011). Briefly, we divided the gerbils into four groups: *H. pylori* (ATCC43504) was inoculated into the OPZ (omeprazole)+Hp (*H. pylori*) and Hp groups, a PPI (OPZ) was administered to the OPZ+Hp and OPZ groups and the control group received no treatment. At the end of the 6-month experiment, corpus atrophic gastritis and adenocarcinomas were significantly more common in the OPZ+Hp group than in the other groups. However, one of the important findings of this study was that long-term OPZ administration in the absence of *H. pylori* infection did not induce corpus atrophic gastritis. In another experiment using male rats, neither corpus atrophic gastritis nor neoplastic lesions developed after administration of OPZ over a period of 1 year (Hagiwara et al., 2007). These findings suggested that *H. pylori* infection, and not long-term PPI administration, was the direct cause of corpus atrophic gastritis leading to the development of adenocarcinoma (Fox et al., 2011; Hagiwara et al., 2011; 2012).

Intragastric pH and the gastric microbiota

Conventional wisdom espoused the dogma that the stomach was a sterile organ. This was attributed to the acidic conditions (pH<4) prevalent in the stomach (Hill et al., 1985). However, over the last 30 years, with the discovery of *H. pylori* (Marshall et al., 1984; Warren et al., 1983), it has been established that the stomach supports a bacterial community with hundreds of phylotypes (approximate species-level taxa) (Bik et al., 2006; Andersson et al., 2008; Li et al., 2009). Drug-induced inhibition or reduction of gastric acid secretion due to parietal cell loss caused by *H. pylori* infection can lead to hypochlorhydria or even achlorhydria, thereby increasing the risk of bacterial overgrowth and possible detrimental infections throughout the gastrointestinal tract (Martinsen et al., 2005; Cover TL et al., 2009). Bacterial overgrowth under conditions of hypochlorhydria (pH>4) might be responsible for the worsening corpus atrophic gastritis observed in patients with *H. pylori* infection undergoing long-term treatment with PPIs.

Possible mechanism of gastric carcinogenesis under conditions of hypochlorhydria

H. pylori infection and the associated changes in the stomach alter the ecological niche inhabited by the gastric microbiota. However, the gastric microbiota also competes with *H. pylori* for a gastric niche, and therefore, it might play an important role in the progression of the disease (Sheh et al., 2013). Before the discovery of *H. pylori* infection, Correa proposed that gastric carcinogenesis is the result of a chain of events triggered by the onset of hypochlorhydria and the colonization of the stomach by nitrosating bacteria (Correa, 1984; Correa, 1992). Nitrosating organisms can produce potentially carcinogenic N-nitrosocompounds by combining nitrite and other organic nitrogen compounds present in the gastric juice. These N-nitrosocompounds are known to cause malignancies of the digestive tract (Xu et al., 1993;

Ziebarth et al., 1997).

Transgenic insulin-gastrin (INS-GAS) mice, which exhibit hypergastrinemia, develop atrophic gastritis, hypochlorhydria, and gastrointestinal intraepithelial neoplasia upon infection with *H. pylori* (Wang et al., 2000). Gastric atrophy and hypochlorhydria lead to non-helicobacter microbiota overgrowth. Lofgren et al. reported that *H. pylori* monoassociation induced cancer in INS-GAS mice, but the absence of gastric colonization with enteric microbes significantly inhibited the development of gastric cancer in the INS-GAS mice (Lofgren et al., 2011). These findings suggest that microbiota overgrowth might increase the risk of gastric cancer in *H. pylori*-infected patients with gastric atrophy and hypochlorhydria.

Interactions between bile acids, pH, and *H. pylori* in GERD patients

The use of PPIs for the treatment of GERD has increased substantially over the past two decades. We recently proposed that interactions between bile acids, pH, and *H. pylori* might be responsible for exacerbated corpus atrophic gastritis in *H. pylori*-positive patients with GERD undergoing long-term treatment with PPIs. Duodeno-gastric reflux, which is composed of bile, occurs even in healthy individuals, and bile reflux is increased in patients with GERD (Dixon et al., 2001). Diluted human plasma and bile acids have been found to function as potent chemoattractants and chemorepellents, respectively, toward *H. pylori* (Worku et al., 2004). Although only taurine conjugates, with a pKa of 1.8-1.9, are soluble in an acidic environment, glycine conjugates, with a pKa of 4.3-5.2, as well as taurine-conjugated bile acids, are soluble in the presence of PPI (Kuipers et al., 1995; Nair et al., 1971; Stamp et al., 2002). Thus, the concentration of soluble bile acids in the gastric contents of patients with GERD after continuous PPI therapy is considerably higher than that in healthy individuals with normal acid production. In the distal stomach, the soluble bile acids, at high concentrations, function as a bactericide or chemorepellent toward *H. pylori*. In contrast, the mucous layer in the proximal stomach has an optimal bile concentration that forms chemotactic gradients with the plasma components that are required to direct *H. pylori* to the epithelial surface. *H. pylori* may then colonize the stomach body rather than the pyloric antrum, which may explain the occurrence of corpus-predominant pan gastritis after PPI therapy in *H. pylori*-positive patients with GERD (Mukaisho et al., 2014).

Effects of hypergastrinemia on gastric cancer development

Infection with *H. pylori* increases gastrin expression (Shafaghi et al., 2013; Sordal et al., 2013), and acid suppression therapy leads to hypergastrinemia in nearly all patients receiving long-term PPI therapy (Orlando et al., 2007). Gastrin has a trophic effect on the gastrointestinal tract and acts as a growth and differentiation factor

(Tsukamoto et al., 2011). However, it is still unclear whether hypergastrinemia promotes the development of gastric adenocarcinoma. In patients with hypergastrinemia, such as those with Zollinger-Ellison syndrome or pernicious anemia, enterochromaffin-like (ECL) cell hyperplasia occasionally develops but rarely leads to carcinoids. In animal models, INS-GAS transgenic mice, which exhibit hypergastrinemia, with *H. felis* or *H. pylori* (strain SS1) infection develop gastric cancer (Wang et al., 2000; Fox et al., 2003), but this not accompanied by ECL cell hyperplasia (Wang et al., 2000). Hypergastrinemia in rats results in the development of ECL cell carcinoids (Havu et al., 1986; Havu et al., 1990; Mattsson et al., 1991). As mentioned previously, our study demonstrated that the serum gastrin levels were higher in the OPZ+Hp group than in the other groups and that the OPZ+Hp group developed gastric adenocarcinoma (Hagiwara et al., 2011). These findings suggest that hypergastrinemia might promote the development of gastric cancer in patients infected with *H. pylori* undergoing long-term treatment with PPIs. Watson et al. hypothesized that gastrin might not lead to cancer development on its own in humans, but it might function as an important cofactor once pre-malignant changes are triggered (Watson et al., 2006).

Conclusion

In this review, we discussed the possible mechanism underlying the development of atrophic corpus gastritis leading to adenocarcinoma in patients with *H. pylori* infection undergoing long-term PPI therapy. Although many studies initially raised doubts about the safety of long-term PPI administration, several studies have now shown that the main cause of worsening corpus atrophic gastritis leading to the development of adenocarcinoma is not long-term PPI administration, but *H. pylori* infection. Therefore, it is recommended that patients being considered for long-term PPI therapy should be tested for *H. pylori* infection. If infection is detected, the pathogen must be eradicated before commencement of treatment.

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