Helicobacter pylori-Induced Changes in Gastric Acid Secretion and Upper Gastrointestinal Disease

Adam J. Smolka and Mitchell L. Schubert

Abstract Appropriate management of *Helicobacter pylori* infection of the human stomach is evolving and remains a significant clinical challenge. Acute infection results in hypochlorhydria, whereas chronic infection results in either hypo- or hyperchlorhydria, depending upon the anatomic site of infection. Acute hypochlorhydria facilitates survival of the bacterium and its infection of the stomach. Interestingly, most patients chronically infected with *H. pylori* manifest a pangastritis with reduced acid secretion due to bacterial virulence factors, inflammatory cytokines, and various degrees of gastric atrophy. While these patients are predisposed to develop gastric adenocarcinoma ($\sim$1%), there is increasing evidence from population studies that they are also protected from gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC). Eradication of *H. pylori*, in these patients, may provoke GERD in predisposed individuals and may be a contributory factor for the rising incidence of refractory GERD, BE, and EAC observed in Westernized societies. Only $\sim$10% of chronically infected patients, mainly the young, manifest an antral predominant gastritis with increased acid secretion due to a decrease in somatostatin and increase in gastrin secretion; these patients are predisposed to develop peptic ulcer disease. *H. pylori*-induced changes in acid secretion, in particular hypochlorhydria, may allow ingested microorganisms to survive transit through the stomach and colonize the distal intestine and colon. Such perturbation of gut microbiota, i.e. dysbiosis, may influence human health and disease.

A.J. Smolka (✉)
Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, USA
e-mail: smolkaaj@musc.edu

M.L. Schubert
McGuire Veterans Administration Medical Center, Richmond, VA 23249, USA

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1 Gastric Acid Secretion

1.1 Introduction

Helicobacter pylori is a Gram-negative bacterium that infects about half the world's population, colonizing the gastric epithelium and inducing chronic inflammation. Most of those infected persons are asymptomatic, but ~10% develop peptic ulcer disease, and ~1% progress to gastric adenocarcinoma (Polk and Peek 2010). The severity and pathological sequelae of diffuse acute and later chronic inflammation are determined by bacterial virulence, host genetics and environmental factors. One function of the stomach, to regulate and sustain acid secretion at levels sufficient to sterilize ingested nutrients, is impaired in the setting of mucosal inflammation. In chronic infection, the degree of impairment and whether acid secretion is increased or decreased depends on the predominant anatomic focus of the infection (Dixon et al. 1996). Infection of the gastric antrum (i.e., pyloric mucosa) is associated with acid hypersecretion that is driven by an increase in gastrin secretion as well as effects of cytokines derived from infiltrating proinflammatory neutrophils and macrophages. Infection of the gastric body and fundus (i.e., oxyntic mucosa) is associated with acid hyposecretion that is driven by *H. pylori*-induced suppression of H,K-ATPase (the parietal cell proton pump) expression as well as effects of cytokines. *H. pylori*-induced changes in gastric acid secretion can have deleterious as well as beneficial clinical consequences in humans. Deleterious outcomes include duodenal ulcer disease, autoimmune and atrophic gastritis, intestinal metaplasia, and gastric adenocarcinoma. Beneficial outcomes include protection from gastroesophageal reflux disease (GERD), Barrett's esophagus (BE),

esophageal adenocarcinoma (EAC), and rebound hypersecretion after acute cessation of proton pump inhibitors (PPIs) (Reimer et al. 2009; Backert and Blaser 2016).

1.2 Physiology of Gastric Acid Secretion

1.2.1 Neural, Hormonal, and Paracrine Regulation

The major physiological stimulants of acid secretion are histamine, secreted from oxyntic enterochromaffin-like (ECL) cells (paracrine pathway); gastrin, secreted by antral G cells (hormonal pathway) (Beales et al. 1997; DelValle et al. 1987); and acetylcholine, secreted from oxyntic and antral intramural postganglionic neurons (neural pathway). The parietal cell expresses specific receptors for each of these secretagogues (H_2, gastrin or CCK_2, and M_3, respectively). However, it is currently thought that gastrin, the main hormonal stimulant during meal ingestion, activates acid secretion mainly by releasing histamine from ECL cells. Histamine H_2 receptors are coupled predominantly to adenylate cyclase which catalyzes generation of adenosine 3′,5′-cyclic monophosphate (cAMP). However, in rat hepatoma-derived cells transfected with canine histamine H_2 receptor, histamine also elicits concurrent transient elevation of intracellular calcium ($[Ca^{2+}]_i$) with generation of inositol trisphosphate (IP_3) (DelValle et al. 1992). Gastrin, acting via CCK_2 receptors (formerly termed gastrin receptors) coupled to an increase in $[Ca^{2+}]_i$, stimulates the parietal cell directly and, more importantly, indirectly by releasing histamine from ECL cells. Acetylcholine stimulates parietal cells directly through M_3 subtype muscarinic receptors coupled to an increase in $[Ca^{2+}]_i$ and indirectly by inhibiting somatostatin secretion via M_2 and M_4 receptors. The principal inhibitor of acid secretion is somatostatin, released from oxyntic and antral D cells. Oxyntic (gastric body and fundus) somatostatin cells are anatomically and functionally coupled to ECL and parietal cells, whereas antral (pyloric) somatostatin cells are anatomically and functionally coupled to G cells. During the basal state, somatostatin exerts a tonic restraint on acid secretion from the parietal cell, histamine secretion from the ECL cell, and gastrin secretion from the G cell. Removing this restraint (i.e., disinhibition) by activation of cholinergic neurons is an important physiological mechanism for stimulating acid secretion (Fig. 1).

1.2.2 H,K-ATPase: The Parietal Cell Proton Pump

The final step in gastric acid secretion is mediated by the enzyme H,K-ATPase which is expressed in cytoplasmic tubulovesicles and canalicular membranes of parietal cells (Forte et al. 1989; Sachs 1987). Functional H,K-ATPase is a heterotetrameric ($\alpha_2\beta_2$) assembly of catalytic α subunits (HKα) and glycosylated β subunits (HKβ). HKα and HKβ mRNAs are translated on endoplasmic

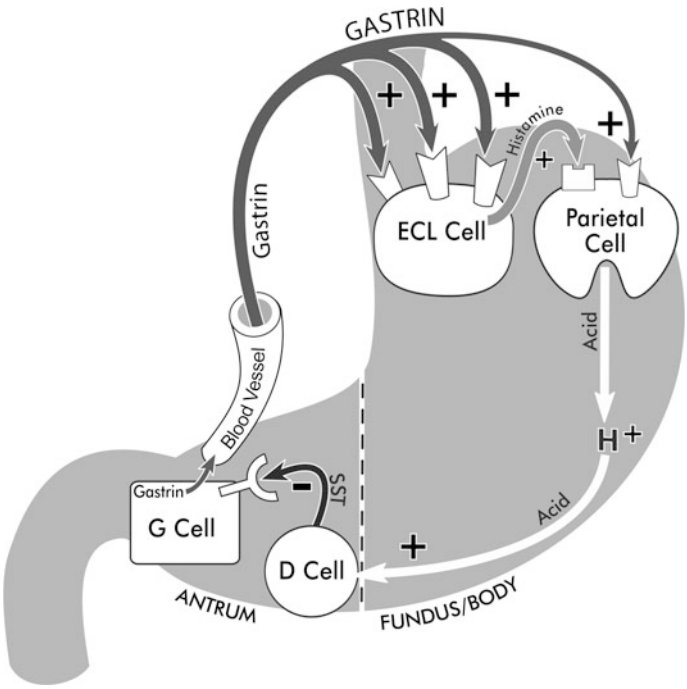

Fig. 1 Regulation of gastrin and acid secretion in health and disease. (i) Between meals, acid secretion is inhibited by somatostatin (SST)-secreting D cells on adjacent gastrin-secreting G cells. This inhibition is complemented by unbuffered luminal acid which also stimulates SST. (ii) During a meal, food buffers the secreted acid and the increased pH inhibits SST, stimulating gastrin secretion. Distension and nutrient protein also stimulates gastrin. Gastrin stimulates parietal cell acid secretion and mediates histamine release from ECL cells. Gastrin also stimulates proliferation of ECL cells, which also occurs during long-term PPI treatment, particularly at high dose. (iii) Most patients chronically infected with *H. pylori* manifest a pangastritis and are hypochlorhydric, due in part to gastric atrophy. In such patients, *H. pylori* may protect against GERD, Barrett's esophagus, and esophageal adenocarcinoma. Eradication of *H. pylori*, especially in patients on long-term PPIs, may lead to acid hypersecretion caused by hypergastrinemia-induced increase in ECL mass. (iv) About 10% of patients with chronic *H. pylori* infection exhibit hyperchlorhydria, have antral predominant inflammation, and are vulnerable to duodenal ulcer disease. The increased acid secretion is due to reduced antral SST secretion and increased basal and stimulated gastrin secretion

reticulum-bound ribosomes into integral membrane polypeptides that are targeted to cytoplasmic tubulovesicles. HKα subunits carry out the transport function of the enzyme, whereas HKβ subunits mediate assembly of functional H,K-ATPase, delivery of the complex to the tubulovesicular and canalicular compartments, and protect the enzyme complex from degradation (Asano et al. 2000; Bakkelund et al. 2010; Spicer et al. 2000). In the absence of luminal K^+, the enzyme complex is inactive. Enzyme activity is stimulated by secretagogue-mediated increases in intracellular cAMP (e.g., histamine) and activation of calcium-dependent signaling

pathways (e.g., acetylcholine) that activate downstream protein kinases, ultimately leading to fusion of tubulovesicles with collapsed invaginations of the parietal cell apical membrane which expand into the extensive microvillous secretory canalicular network characteristic of actively secreting parietal cells. Potassium channels in the canalicular membrane (KCNQ1, its β-subunit KCNE2, and Kir4.1) supply and regulate flow of cytoplasmic K^+ to luminal K^+-binding sites on the HKα catalytic subunit, thereby initiating electroneutral 1:1 exchange of luminal K^+ for cytoplasmic protons (Roepke et al. 2006; Song et al. 2009b, 2011). Under maximal secretory drive, H,K-ATPase activity establishes a million-fold proton gradient across the canalicular membrane (Black et al. 1980; Smolka et al. 1983; Soroka et al. 1993).

PPIs such as omeprazole, lansoprazole, rabeprazole, and esomeprazole are substituted benzimidazoles that potently inhibit acid secretion by covalently binding to luminally exposed cysteine residues on the HKα subunit. PPIs have revolutionized the treatment of GERD, peptic ulcer disease, and Zollinger-Ellison syndrome (gastrinoma). More recently, the potassium-competitive acid blocker Vonoprazan, a lipophilic, weak base pyrrole derivative that accumulates in parietal cell canaliculi and prevents proton pump activation by competing with K^+ on the luminal surface of HKα, offers the potential for more potent and sustained acid suppression with more favorable pharmacokinetics and toxicological profile than conventional delayed-release PPIs (Hunt and Scarpignato 2015; Otake et al. 2016).

2 *H. pylori* Infection of the Stomach

2.1 Colonization of Favored Gastric Niches

The human stomach is an inhospitable environment for microorganisms, including bacteria. High acidity (160 mM hydrochloric acid or pH 0.8), in combination with pepsin and lipase, kills ingested microorganisms. In order to establish gastric colonization, *H. pylori* must minimize its exposure to lethal concentrations of acid (i.e., low pH). Bacterial urease catalyzes the hydrolysis of ambient gastric urea into carbon dioxide and ammonia (Hidaka et al. 2001). Basic ammonia (NH_3) neutralizes protons diffusing into *H. pylori*'s periplasmic space via conversion to ammonium (NH_4^+), thereby maintaining the bacterial microenvironment at a pH compatible with optimal growth and survival. The efficiency of this process is such that *H. pylori* is able to sustain proton motive force across its inner membrane, essential for ATP synthesis, at external pH ranging from 3.5 to 8 (Meyer-Rosberg et al. 1996). The local increase in pH also effects a gel-sol transition in the 200-μm-thick gastric mucus layer that overlies the mucosal epithelium (Bansil et al. 2013; Celli et al. 2009), allowing *H. pylori* to penetrate the mucus gel by virtue of its spiral morphology and flagellar activity. Surface epithelial cells actively secrete bicarbonate, establishing a pH gradient across the mucus gel, although there is little

evidence that mucus itself poses a significant diffusion barrier to hydrogen ions (Schubert and Kaunitz 2015; Tanaka et al. 2002). Within this extracellular niche, immediately adjacent to surface epithelial cells and their tight junctions with neighboring cells, *H. pylori* is well situated to (i) evade humoral and cellular immune defenses and (ii) modulate gastric acid secretion. *H. pylori* inhibits acid secretion directly by interfering with parietal cell proton pump expression, and indirectly by activating neural pathways coupled to stimulation of somatostatin and inhibition of histamine and acid secretion. Other constituents and products of the bacterium [e.g., acid inhibitory factor, vacuolating cytotoxin, and lipopolysaccharide (LPS)] as well as proinflammatory cytokines (interleukin-1β, interleukin-2, tumor necrosis factor-α, and interferon γ) are also capable of directly inhibiting parietal cell secretion (Beales and Calam 1998, 2001; Gooz et al. 2000; Hoffman et al. 1995; Kobayashi et al. 1996; Padol and Hunt 2004; Saha et al. 2010a; Schepp et al. 1998). In rat oxyntic mucosa mounted in Ussing chamber, acute perfusion of the mucosal surface with *H. pylori* derived from humans with duodenal ulcer activates intramural calcitonin gene-related peptide (CGRP) sensory neurons coupled to stimulation of somatostatin and thus inhibition of histamine and acid secretion (Zaki et al. 2013). Activation of neural pathways may explain how initial patchy colonization of the superficial mucosa by the bacterium can acutely and profoundly inhibit acid secretion.

Gastric *H. pylori* colonization is usually accompanied by inflammation, the severity of which is correlated with *H. pylori* density (Alam et al. 1992; Khulusi et al. 1995). Although *H. pylori* can be detected throughout the stomach, the antrum is initially more susceptible to infection and inflammation than the body (Bayerdorffer et al. 1989, 1992; Louw et al. 1993; Satoh et al. 1991). The determinants of *H. pylori* colonization of particular anatomic regions of the stomach are not fully understood, but may include chemosensing of localized gastric epithelial cell secretion of urea, mediated by the bacterial chemoreceptor TipB (Huang et al. 2015). Gastric acid secretory status also plays a role in colonization. The efficiency of *H. pylori*'s defenses against low pH notwithstanding, the organism favors colonization of the antrum, whose mucosal branched glands lack parietal cells and consequently do not secrete acid. Antral predominant infection is associated with a decrease in antral somatostatin content and a corresponding increase in gastrin and acid secretion; such patients are predisposed to duodenal ulcer disease. The decrease in somatostatin secretion may be mediated by proinflammatory cytokines derived from the inflammatory infiltrate (e.g., interferon γ and tumor necrosis factor-α) (Calam 1998). Hypergastrinemia may not only be mediated by decreased somatostatin secretion, but there is evidence that certain cytokines (e.g., interleukin-8 and platelet activating factor) are capable of directly stimulating gastrin as is CagL, an *H. pylori* protein considered to be a component of its type IV secretion system (T4SS) (Beales 2001; Cover 2012; Wiedemann et al. 2012).

With time, exacerbated by the use of antisecretory medications, *H. pylori* infection with inflammation migrates proximally from antrum to the oxyntic mucosa (body and fundus) of the stomach. Most patients chronically infected with *H. pylori* manifest a pangastritis and produce less than normal amounts of acid.

Reduced acid secretion initially is due to suppression of parietal cell H,K-ATPase expression by products of *H. pylori* as well as the inflammatory infiltrate. Subsequently, an advancing front of atrophic gastritis ensues with loss of parietal cells and multifocal areas of intestinal metaplasia. It is upon this background of atrophic pangastritis with intestinal metaplasia that gastric cancer develops (Plottel and Blaser 2011; Spicer et al. 2000; Zavros et al. 2005).

2.2 Immune Response

H. pylori resides in proximity or attached to surface epithelial cells but can penetrate deeper into gastric pits and glands, ultimately breaching tight junctions to gain access to basolateral membrane receptors. The gastric immune response to *H. pylori* is necessarily complex (Hunt et al. 2015) as it serves as much to provide an hospitable environment for continued colonization and infection as it does to protect the host from the more damaging potential sequelae of *H. pylori*'s delivery of virulence factors into gastric epithelial cells. The immune response includes both innate (epithelial, neutrophil, macrophage, dendritic cell) and adaptive (B and T cell) components. The innate responses are particularly relevant to acid secretory regulation as *H. pylori*-induced secretion of IL-8 from epithelial cells mediates chemotactic recruitment of neutrophils and macrophages into glandular mucosa where their release of IL-1β (Cullen et al. 2015) potently inhibits acid secretion (Beales and Calam 1998; Wallace et al. 1991). Ingestion of *H. pylori* or its cellular debris by antigen-presenting cells in the lamina propria promotes activation of the adaptive response which leads to diverse cytokine production by helper T cells (Th), including interferon-γ (Th1 cells) and interleukin-17 (Th17 cells), while regulatory T cells (Tregs) mediate tolerance. The Th cytokines stimulate epithelial cell production of chemokines which drive neutrophil and macrophage secretion of reactive oxygen and nitrogen species (ROS and RNS). Hydroxyl radicals enhance IL-8-induced gastrin-stimulated acid secretion (Yakabi et al. 2003), and exposure of gastric epithelial cells to hydrochloric acid itself induces mitochondrial superoxide production, which then triggers cellular lipid peroxidation and apoptosis (Matsui et al. 2011). Production of these mediators of gastritis, which would otherwise promote an unfavorable environment for continued *H. pylori* colonization, is counteracted by anti-inflammatory responses conferred by *H. pylori*-induced activation of a subset of Tregs that express FOXP3, a transcription factor that regulates Treg development (Fontenot et al. 2005) and increase mucosal levels of IL-10 and TGF-β1 (Arnold et al. 2011; Kabisch et al. 2014; Kandulski et al. 2008). These and other cytokines are now understood to play an important role in persistence of *H. pylori* infection (Harris et al. 2008; Rad et al. 2006; Koch et al. 2015). Interestingly, ROS production has been reported to promote glucose-stimulated somatostatin secretion in rat gastric primary D cells, thereby inhibiting acid secretion and favoring *H. pylori* persistence (Li et al. 2010).

3 *H. pylori*-Induced Changes in Gastric Acid Secretion

3.1 Acute Hypochlorhydria

Acute infection with *H. pylori* results in hypochlorhydria, whereas chronic infection results in either hypo- or hyperchlorhydria, depending upon the predominant anatomic site of infection. Many clinical studies, including reports of accidental *H. pylori* inoculation through contaminated gastric endoscopes and nasogastric tubes, have associated acute *H. pylori* infection with transient hypochlorhydria. Gastric pH one to four weeks after initial infection was reported to range from 6.4 to 7.6 (Gledhill et al. 1985; Morris and Nicholson 1987; Ramsey et al. 1979; Sobala et al. 1991), with acid secretion returning to baseline levels within a few weeks or months (El-Omar et al. 1997; Gledhill et al. 1985; Graham et al. 1988; Harford et al. 2000; Marshall 1995; Morris and Nicholson 1987; Ramsey et al. 1979; Sobala et al. 1991). The hypochlorhydria associated with acute infection is thought to facilitate survival of the bacterium and its colonization of the stomach (Merchant 2005). Acute *H. pylori*-induced acid inhibition is not caused by parietal cell loss or atrophy as normal numbers of parietal cells are reported in the stomachs of acutely infected Mongolian gerbils as well as gastric biopsies of inadvertently infected patients (Graham et al. 1988; Ramsey et al. 1979; Takashima et al. 2001).

Soon after the discovery of *H. pylori* as an etiologic agent of gastritis and peptic ulceration, in vitro studies showed that interaction of parietal cells with bacteria and/or with secreted bacterial products was sufficient to inhibit acid secretion (Cave and Vargas 1989; Defize et al. 1989; Hoffman et al. 1995). Human gastric mucosal ultrastructural studies revealed the presence of *H. pylori* in the immediate vicinity of parietal cells and even sequestered within parietal cell secretory canaliculi (Bjorkholm et al. 2000; Chen et al. 1986; Tagkalidis et al. 2002; Tricottet et al. 1986). In animal studies, dogs and ferrets became achlorhydric after infection with *Helicobacter* species (Fox et al. 1993; Lee et al. 1992), and acid secretion by isolated rabbit and guinea gastric cells, as measured by [^{14}C] aminopyrine accumulation, was reduced after *H. pylori* infection (Cave and Vargas 1989; Kobayashi et al. 1996). In human parietal cells, *H. pylori* inhibits histamine-, carbachol-, and dibutyryl cyclic AMP-stimulated acid secretion (Jablonowski et al. 1994a, b). The acute inhibitory effects of *H. pylori* on acid secretion are transitory and normal acid secretion can be restored after *H. pylori* is eradicated (Furuta et al. 1999).

H. pylori interferes with transcription of the parietal cell HKα gene. In gastric AGS cells transfected with human or rat HKα 5′-flanking DNA sequence fused to a luciferase reporter plasmid (Gooz et al. 2000), histamine elicits a dose-dependent increase in cAMP, $[Ca^{2+}]_I$, and HKα promoter activity. Addition of *H. pylori* of the transfected cells dose-dependently inhibited basal and histamine-stimulated HKα promoter activity as well as HKα activity induced by phorbol myristate acetate or the diacylglycerol analog 1-oleoyl-2-acetyl-*sn*-glycerol that was sensitive to staurosporine and calphostin C. The data indicate that *H. pylori* inhibits HKα gene expression via intracellular pathways involving protein kinases A and C

(Gooz et al. 2000). Interestingly, the study also showed that a human HKα-*Luc* reporter construct transfected into human gastric epithelial cells was far more sensitive to *H. pylori*-induced repression than the rat HKα reporter, consistent with the fact that, with the exception of non-human primates (Dubois et al. 1994), the human stomach is the only substantial reservoir of *H. pylori*. A later study assessed the biochemical and physiological consequences of *H. pylori*-mediated HKα gene repression (see below) (Saha et al. 2010b). Taken together, the data confirmed that *H. pylori*-induced repression of HKα promoter-reporter constructs in AGS cells is recapitulated in acutely isolated, *H. pylori*-infected human gastric biopsies, where the effects of infection are manifest as significant attenuation of HKα mRNA, virtual disappearance of HKα protein subunit, and concomitant inhibition of gastric acid secretion. The data are consistent to a certain degree with a microarray analysis of parietal cell DNA from germ-free and *H. pylori*-infected mice that showed 5.3-fold down-regulation of H,K-ATPase α-subunit expression by *H. pylori* (Mills et al. 2001). However, the relatively comprehensive *H. pylori*-induced elimination of HKα protein and acid secretory capacity observed in human biopsies (Saha et al. 2010b) suggests that in addition to HKα transcriptional regulation, *H. pylori* also targets posttranscriptional phases of H,K-ATPase synthesis and activation.

The evidence and mechanistic basis for *H. pylori*-induced interference with HKα gene expression was recently reviewed (Smolka and Backert 2012). Pathogenic *H. pylori* strains that express a T4SS with pilus can inject virulence factors into gastric epithelial cells. Structural T4SS proteins are encoded by a cytotoxin-associated gene (*cag*) pathogenicity island (PAI). The *H. pylori* T4SS protein, CagL, interacts with host cell $\alpha_5\beta_1$ integrin (Kwok et al. 2007; Conradi et al. 2012; Barden et al. 2013) facilitating injection of the oncogenic bacterial protein CagA which can activate multiple signaling pathways including the proinflammatory transcription factors NF-κB (Backert and Selbach 2008) (Fig. 2). *H. pylori* infection of gastric epithelial cells in vitro has been shown to inhibit HKα gene expression by ERK 1/2-mediated NF-κB p50 homodimer binding to HKα promoter (Saha et al. 2008). Acute *H. pylori* infection causes CagL to dissociate ADAM17 from $\alpha_5\beta_1$ integrin, activating ADAM17-dependent, NF-κB-mediated repression of HKα promoter (Saha et al. 2010a). *H. pylori cag*PAI isogenic mutants (Δ*cagE*, Δ*cagM*, and Δ*cagL*) failed to repress HKα, confirming the need for T4SS integrity (Saha et al. 2010b). *H. pylori* is also implicated in posttranslational regulation of HKα expression. *H. pylori* infection has been reported to up-regulate gastric epithelial cell microRNA (miR-1289), which in turn binds to a highly-conserved HKα 3′-UTR binding site, repressing HKα mRNA translation (Zhang et al. 2014). In the same study, CagA and bacterial soluble lytic transglycosylase (SLT) (Hammond et al. 2015; Viala et al. 2004) were also implicated in HKα-specific miR-1289 up-regulation. More recently, virulence factors other than those mediating CagA translocation or IL-8 induction have been reported to participate in HKα repression by activating NF-κB (Hammond et al. 2015). AGS cells transfected with HKα promoter-*Luc* reporter constructs containing an intact or mutated NF-κB binding site were infected with wild-type *H. pylori* strain 7.13, isogenic mutants lacking *cag*PAI genes responsible for CagA translocation and/or IL-8 induction (*cagA*, *cag*, *cag*, *cagZ* and *cagβ*), or deficient in

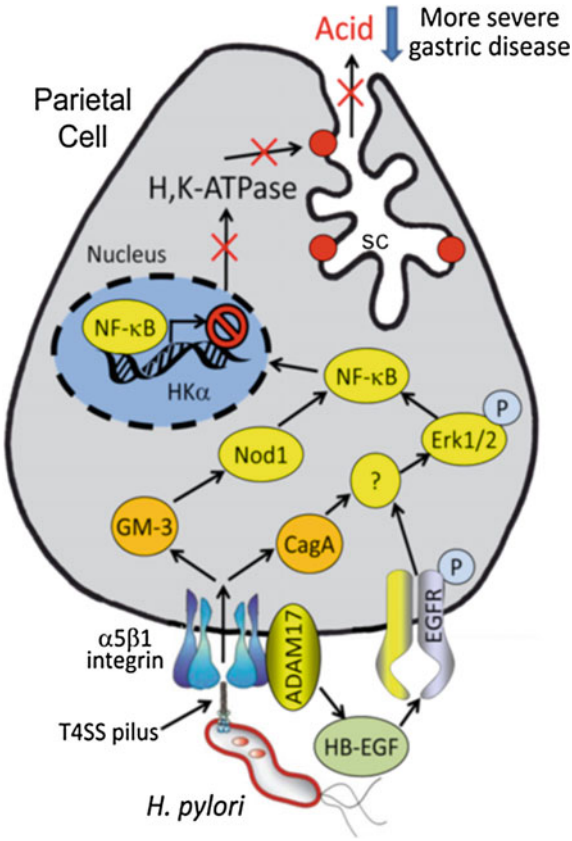

Fig. 2 Mechanistic basis of *H. pylori*-induced acid inhibition. Schematic diagram of a gastric parietal cell showing the *H. pylori* T4SS pilus interacting with α5β1 integrin on the basal lateral membrane to facilitate delivery of CagA and SLT-derived glycosylated tripeptide GM-3 into the parietal cell. Subsequent activation of diverse host signaling pathways mobilizes nuclear factor-κB (NF-κB) p50 homodimers to the nucleus resulting in transcriptional repression of the H,K-ATPase α subunit gene. *H. pylori* interaction with host cell integrin also activates ADAM17, leading to generation and binding of heparin-binding epidermal growth factor (HB-EGF) to EGF receptor (EGFR) and synergistic ERK-mediated mobilization of NF-κB (*sc* secretory canaliculus)

genes encoding two peptidoglycan hydrolases (*slt* and *cagγ*). Measurement of *H. pylori*-induced AGS cell HKα promoter activity, translocated CagA, IL-8 secretion and acid secretion in human oxyntic biopsies showed that HKα repression is independent of IL-8 expression and that CagA translocation together with *H. pylori* transglycosylases encoded by *slt* and *cagγ* participates in NF-κB-dependent HKα repression and acid inhibition (Hammond et al. 2015).

Although virulence factors secreted by *H. pylori* as well as inflammatory cytokines are capable of directly inhibiting parietal cell secretion, such inhibition may be restricted to inter-prandial periods when parietal cells are in a resting state, and bacterial penetration deep into oxyntic glands is not impeded by the relatively

high intraglandular pressures generated during active secretion (Holm et al. 1992). In rat oxyntic mucosa mounted in Ussing chamber, it was shown that acute perfusion with *H. pylori* activates CGRP sensory neurons coupled to stimulation of somatostatin and inhibition of histamine secretion (Zaki et al. 2013). Activation of neural pathways may explain how initial patchy colonization of superficial gastric mucosa can acutely and profoundly inhibit acid secretion.

3.2 Chronic Hypochlorhydria

Most patients chronically infected with *H. pylori* manifest a pangastritis with hypochlorhydria. Reduced acid secretion is mainly due to functional inhibition of parietal cell secretion by products of the bacterium as discussed above, and/or the inflammatory infiltrate, specifically the cytokine IL-1β. Polymorphisms in the promoter region of the host *IL-1B* gene significantly increase neutrophil production of IL-1β in the lamina propria of *H. pylori*-infected gastric mucosa, leading to more profound inhibition of acid secretion. Such prolonged inhibition, coupled with the permanent loss of acid secretory capacity because of chronic inflammatory damage to parietal cells, leads to corpus atrophy with loss of parietal cells and reduced acid secretion (Furuta et al. 2002). This progression to chronic hypochlorhydria may be entirely or partly reversible with eradication of the organism, particularly if atrophy is incomplete. The proinflammatory genotypes of the *IL-1B* gene have been shown to reduce the risk of GERD and complications of erosive esophagitis, an association whose mechanistic basis may be induction of gastric atrophy with reduced acid secretion (Ando et al. 2006).

3.3 Hyperchlorhydria

Hormonal (somatostatin and gastrin) and neural (CGRP) mechanisms are understood to underlie gastric hyperchlorhydria induced by chronic *H. pylori* infection of gastric antral mucosa. Gastrin secretion by antral G cells is regulated by a negative feedback pathway predicated on intraluminal pH, such that gastrin secretion is inhibited at low pH (high acidity) and stimulated at relatively high pH (low acidity); the pathway involves somatostatin. High concentrations of acid activate sensory CGRP neurons that, via an axon reflex, stimulate somatostatin secretion and thus inhibit gastrin secretion, whereas low concentrations of acid, for example, by antisecretory medications such as PPIs or gastric atrophy, fail to stimulate or inhibit somatostatin secretion, and patients develop hypergastrinemia (Brand and Stone 1988; Manela et al. 1995; Schubert et al. 1988). It is conceivable that *H. pylori*'s capacity to alkalinize its immediate environment by virtue of urease hydrolysis of gastric urea creates a localized high pH in the vicinity of antral somatostatin-containing D cells, resulting in decreased somatostatin and increased gastrin

secretion; the latter driving parietal cell trophism and increased acid secretion (Levi et al. 1989). In addition, *H. pylori*-mediated release of proinflammatory cytokines is capable of inhibiting somatostatin secretion and stimulating gastrin secretion (Zavros et al. 2002; Moss et al. 1992; Odum et al. 1994). Finally, neural involvement in *H. pylori*-induced hyperchlorhydria was inferred from a study in which the inhibitory effect on gastric acid secretion induced by antral distension was absent in chronically *H. pylori*-infected patients whether or not they had duodenal ulcer disease (Olbe et al. 1996).

4 *H. pylori* in Gastric and Esophageal Diseases

4.1 Gastric Atrophy, Intestinal Metaplasia, and Adenocarcinoma

Gastric cancer claimed 723,000 lives globally in 2012, making it the third-highest mortality cancer after lung cancer (1.6 million lives) and liver cancer (745,000 lives) (Ferlay et al. 2015). Currently, four subtypes of gastric adenocarcinoma are recognized based on comprehensive molecular evaluation of tumors: Epstein-Barr virus-positive tumors; unstable microsatellite tumors; genomically stable with diffuse-type histology; and chromosomally unstable with intestinal-type histology (Cancer Genome Atlas Research Network 2014). *H. pylori* infection is necessary, but not sufficient, for the development of non-cardia gastric cancer; infection confers a small, but measurable, ∼threefold risk (Helicobacter and Cancer Collaborative Group 2001; Rugge et al. 2016). For the most part, the rates of infection and gastric cancer are concordant. However, in Africa as well as in coastal Colombia, the rate of infection with *H. pylori* is high, but the frequency of gastric cancer is low (Correa et al. 1976; Holcombe 1992). The etiology of gastric cancer is multifactorial and involves environmental and genetic risk factors. Risk factors include *H. pylori* strain, genetically determined host inflammatory responses, specific interactions between *H. pylori* virulence factors and the host, gender, ethnicity, and cigarette smoking (Amieva and Peek 2016; Ernst et al. 2006; Rugge 2015). It has recently been proposed that *H.pylori*-induced changes in gastric commensal flora might play a role in carcinogenesis.

In susceptible individuals, bacterial T4SS-mediated delivery of the oncogenic protein CagA, expressed by *cag*PAI-positive *H. pylori* strains, into host antral epithelial cells and glandular stem cells, triggers multiple signaling cascades that increase the risk for distal gastric cancer compared with strains that lack this locus (Amieva and Peek 2016; Mueller et al. 2012; Sigal et al. 2015). CagA also reduces epithelial cell apoptosis, reduces signaling through cell junctions, and enhances oncogenic wound healing responses (Amieva and Peek 2016). There is recent evidence that carcinogenesis may be promoted by (i) integration of bacterial DNA into the human somatic genome (Riley et al. 2013) and (ii) dysbiosis, manifest as growth of non-*Helicobacter* bacteria within the hypochlorhydric stomach (Correa

2004; He et al. 2016). In support of the latter, transgenic, insulin-gastrin mice develop atrophic gastritis, achlorhydria, overgrowth of non-Helicobacter microbiota, and intraepithelial neoplasia at a high rate after *H. pylori* infection compared with germ-free controls (Lofgren et al. 2011).

It has been proposed that *H. pylori* infection initiates a series of events starting with chronic inflammation that, over years in susceptible individuals, leads to atrophic gastritis (including autoimmune gastritis with pernicious anemia), intestinal metaplasia (IM), dysplasia, and eventually gastric adenocarcinoma (Uemura et al. 2001). Problems with this multistep model include the relatively poor inter- and intra-observer agreement on the diagnosis of atrophic gastritis as well as the fact that both atrophy and IM are typically multifocal and commonly missed; yields increase with more extensive biopsy sampling (Capelle et al. 2010; El-Zimaity and Graham 1999; Lim et al. 2013). If a sufficient number of biopsies are obtained, virtually all patients chronically infected with *H. pylori* may have histological evidence of some degree of atrophy and IM (de Vries et al. 2010; Lim et al. 2013; El-Zimaity and Graham 1999; Satoh et al. 1998; Sugano et al. 2015). In reality, atrophy and IM usually coexist and IM is often included in the definition of gastric mucosa atrophy (Rugge et al. 2016). Very few practitioners follow the Sydney System recommendation of obtaining five gastric biopsy specimens: antrum, (greater and lesser curvature), incisura, and corpus greater and lesser curvature. Even if followed, these specimens may still be insufficient for an adequate diagnosis of premalignant lesions (El-Zimaity and Graham 1999; Guarner et al. 2003). The presence of extensive IM (and for that matter, extensive atrophy), however, may portend a significantly higher risk of gastric cancer (Cassaro et al. 2000). IM may be defined as replacement of native gastric glands by intestinal-type glands containing enterocytes, goblet cells, and Paneth cells. Pseudo-pyloric metaplasia, currently termed spasmolytic polypeptide-expressing metaplasia, is the replacement of oxyntic glands by mucin-secreting antral-like glands; it is found in virtually all forms of atrophic gastritis (Rugge et al. 2016).

The lifetime risk of acquiring non-cardia gastric adenocarcinoma is ~0.24% for the general population, and modeling suggests that it is only reduced by 0.2% with *H. pylori* screening/treatment (Yeh et al. 2016). Although all individuals chronically infected with *H. pylori* develop gastric inflammation, only a small fraction (<1%) develop gastric adenocarcinoma (Kodaman et al. 2014). In the Netherlands, patients with premalignant histology still have a relatively low annual incidence of gastric cancer: ~0.1% for atrophic gastritis and 0.25% for intestinal metaplasia (de Vries et al. 2008). In the USA, the annual incidence rate of gastric cancer is only 0.07% in patients with IM (Li et al. 2016). Although eradication of *H. pylori* can resolve gastric inflammation, there is insufficient evidence in Western societies with low rates of gastric cancer as well as some Asian societies with high rates of gastric cancer, that eradication of *H. pylori*, once atrophy or IM occurs, can prevent subsequent cancer (Ford et al. 2015; Kawanaka et al. 2016; Lee et al. 2016; Wong et al. 2004). Consequently, present data do not support routine endoscopic surveillance (or for that matter, *H. pylori* eradication) to prevent gastric cancer, at least in the USA. Such practices may be considered in those patients with additional

risk factors such as Hispanics, Asians, extensive IM, or family history of gastric cancer (Choi et al. 2015; Kim et al. 2016). Although *H. pylori* is conceptually easy to treat, antibiotic resistance and patient nonadherence to complex antibiotic regimens are common causes of treatment failure. Standard initial treatment of *H. pylori* infection with triple therapy consisting of a PPI, amoxicillin, and clarithromycin for 10–14 days is presently suboptimal (<80%), mainly due to an increase in prevalence of clarithromycin resistance (Shiota et al. 2015). Due to "indiscriminate" use of antibiotics, the prevalence, in the USA, of resistance to clarithromycin is 16%, to metronidazole is 20%, and to levofloxacin is 31%. Currently recommended empiric therapies consist of complex 14-day regimens of concomitant and bismuth quadruple therapies (Fallone et al. 2016; Graham and Laine 2016). Other adverse effects of antibiotics are dysbiosis (including *clostridium difficile* infection) and emergence of resistance, not only in *H. pylori*, but also in commensal and other pathogenic bacteria.

4.2 Esophageal Gastroesophageal Reflux Disease, Barrett's Esophagus and Adenocarcinoma

GERD is a common malady affecting 25–40% of the population. GERD refers to troublesome symptoms and/or tissue damage that occurs from the backflow of gastric contents, chiefly acid, into the esophagus. GERD can cause inflammation, metaplasia, dysplasia, and cancer of the esophagus. Patients with GERD do not necessarily secrete increased amounts of acid but rather are thought to have increased dwell times in the esophagus due to hiatal hernia, obesity, transient lower esophageal sphincter (LES) relaxation, reduced LES pressure, and impaired esophageal clearance or acid hypersensitivity (Mitchell et al. 2016). The incidence of EAC has increased sharply, more rapidly than any other malignancy in the USA. Most, if not all cases of EAC arise from preexisting BE. BE is thought to develop, in predisposed individuals, when GERD damages the esophageal mucosa and the injury heals through a metaplastic process in which the normal squamous epithelium is replaced by specialized intestinal epithelium. Not only is the incidence of EAC rising coincident with that of BE and GERD, but the incidence of refractory or PPI-unresponsive GERD is rising and now represents ~25% of GERD patients (Vela 2014). Importantly, eradication of *H. pylori* may be a contributing factor in the increasing incidence of routine GERD, refractory GERD, BE, and esophageal adenocarcinoma.

A substantial body of data supports the notion that *H. pylori* may protect against GERD/BE/EAC by reducing gastric acid secretion and that eradication of the bacteria may increase acid secretion and promote these conditions in predisposed individuals and make them more difficult to manage. Although acid reflux occurs most commonly after a meal, at a time when nutrient buffering of gastric acidity to a pH > 4.0 is greatest, regional differences in postprandial gastric acidity have been reported (Beaumont et al. 2010; Pandolfino et al. 2007), especially immediately

distal to the cardia where pH = 1.6 has been recorded (Fletcher et al. 2001). Thus, factors that compromise LES function are likely to expose the esophageal mucosa to localized highly acidic gastric refluxate. If gastric acid secretion is inhibited by chronic *H. pylori* infection (or by PPI treatment), the esophageal mucosa is exposed to lower concentrations and volumes of acid, a situation that promotes healing of esophagitis and explains the inverse relationship between *H. pylori* and GERD/BE/EAC reported in numerous population studies (Fischbach et al. 2012; Raghunath et al. 2003; Rokkas et al. 2007). As the prevalence of *H. pylori* infection is decreasing in Caucasian adults in developed countries, there is a parallel increasing incidence of GERD/BE/EAC (Labenz and Malfertheiner 1997). In addition, in those with GERD, *H. pylori*-infected patients have significantly less severe esophagitis compared to uninfected patients (Wu et al. 2000). As discussed earlier, most patients chronically infected with *H. pylori* exhibit reduced acid secretion due to products of the bacteria, inflammatory cytokines, and various degrees of gastric atrophy. After eradication, there is amelioration of inflammation and a partial restoration of gastric acid secretion (>fivefold increase in basal and stimulated secretion) (Annibale et al. 2000). When patients with duodenal ulcer but without reflux esophagitis at the time of *H. pylori* treatment were followed up prospectively for up to three years, the incidence of reflux esophagitis was 26% (n = 244) in those cured of infection versus 13% (n = 216) in those with persistent infection ($P < 0.001$) (Labenz et al. 1997a). Patients who developed GERD after eradication have a more severe body gastritis before cure.

Not only may eradication of *H. pylori* promote GERD in predisposed individuals, but it may make it more recalcitrant to treatment with PPIs. The healing rate of reflux esophagitis at 8 weeks is directly related to the duration that gastric pH is >4 over a 24-h period (Bell et al. 1992). In order to achieve >80% healing of erosive esophagitis, pH must be maintained >4 for at least 15 h of the day; this can only be achieved with PPIs, not histamine H_2-receptor antagonists (H_2RAs). Twenty-four-hour intragastric pH studies were performed in 18 *H. pylori* positive subjects before and after a one week course of a PPI, omeprazole (20 mg daily), and repeated after the infection had been cured (Verdu et al. 1995). During omeprazole treatment, 24-h pH values were ~2 logs higher before cure than after cure of infection (5.4 vs. 2.6); this effect persisted when retested 1 year after cure on infection (Labenz et al. 1997b). Thus, the pH achieved with omeprazole represented the sum of the acid inhibitory effect of the PPI as well as that of *H. pylori*; eradication of the bacteria caused the PPI to be less effective. Similar findings, but less pronounced, were reported during 24 h pH recording during treatment with an H_2RA, ranitidine (300 mg hs), before and 4–6 weeks after cure of *H. pylori* infection (Labenz et al. 1997c). The clinical correlate of the greater increase in intragastric pH during treatment with an antisecretory agent in *H. pylori*-infected versus non-infected individuals is improved overall healing of reflux esophagitis in those infected. In 971 patients with endoscopically verified reflux esophagitis treated with a PPI, pantoprazole (40 mg daily) for 4 weeks, overall healing rates were 87% in those infected with *H. pylori* versus 76% in those non-infected (P = 0.0005) (Holtmann et al. 1999). Thus, eradication of *H. pylori* may be one

factor responsible for the rising incidence of PPI-unresponsive GERD. Preliminary data suggest that *H. pylori* may also protect against developing eosinophilic esophagitis (von Arnim et al. 2016).

In *H. pylori* negative patients, discontinuance of long-term (>8–12 weeks) PPIs may result in rebound acid hypersecretion that may exacerbate GERD, particularly in patients with large hiatal hernias (Gillen et al. 1999; Inoue et al. 2004). The phenomenon is due to hypergastrinemia-induced increases in parietal and ECL cell masses and persists for ~8 weeks (Fossmark et al. 2005). The reason rebound hypersecretion does not occur in *H. pylori*-infected individuals who discontinue PPIs may be due to the fact that the bacteria as well as products of the inflammatory infiltrate inhibit acid secretion and thus mask the phenomenon.

5 Concluding Remarks

As discussed, *H. pylori* clearly modulates gastric acid secretion in multiple ways. Whether the patient develops hypo- or hyperchlorhydria depends on the timeline of infection, the predominant anatomic site of infection, the spectrum of virulence factors expressed by the bacterium, and host genetic and immunologic responses. Since microbiota destined for distal intestinal colonization must first transit the hostile barrier of the stomach, *H. pylori*-induced changes in gastric acid secretion may play a role in gut microbial homeostasis. Perturbation of the gut microbiota (dysbiosis) is increasingly understood to impact human health. Given the overwhelming superiority in bacterial cell and gene numbers compared to human cells (tenfold and 400-fold respectively), the genetic potential of gut microbiota to influence human health and disease is massive (Sommer and Backhed 2013). Dysbiosis may be an etiologic factor in diabetes, obesity, metabolic syndrome, heart disease, allergic disorders, and infections (particularly with *C. difficile*) (Wu and Lewis 2013). Significant associations have been reported between *H. pylori* infection and distal intestinal inflammation, in particular inflammatory bowel disease (IBD) (Lidar et al. 2009; Luther et al. 2010; Song et al. 2009a). Additionally, bacterial species in Crohn's disease, ulcerative colitis, and healthy fecal samples were separately clustered by principal components analysis (Qin et al. 2010), and global microbiome data distinguished IBD patients from healthy controls (Frank et al. 2007). Interestingly, Firmicutes are the most abundant gastric bacterial phylum in the absence of *H. pylori* infection in humans, but Proteobacteria predominate in *H. pylori*-infected humans (Sheh and Fox 2013). Thus, studies of the impact of *H. pylori* gastric infection on the abundance and diversity of the colonic microbiota in humans, and the consequences of such impact in terms of susceptibility and/or resistance to disease, should be accorded high priority.

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