H pylori

Mechanisms of increased acid secretion after eradication of *Helicobacter pylori* infection

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Eradication of *Helicobacter pylori* infection leads to recovery of gastric acid secretion in some individuals but the mechanism is not fully understood. In the short term, there is an impressive increase in expression of H⁺/K⁺-ATPase pumps without an increase in the number of parietal cells. Longer follow up studies are needed to see if the parietal cell mass eventually recovers

Gastric acid secretion represents an important non-immunological first line of defence against ingested microbes. Almost all vertebrates produce acid in their upper gastrointestinal tracts, suggesting that this physiological process has a fundamental survival advantage. The ability to produce acid allowed vertebrates to ingest more complex diets, but more importantly, it protected them against microbes that gained access through the gastrointestinal tract. It seems that a pH of 4 or less is crucial in protecting the host against ingested bacteria and any therapy or disease that raises the intragastric pH above 4 will allow bacterial overgrowth to occur.¹ Perhaps the most important consequence of loss of gastric acid secretion is the increased risk of developing gastric cancer. This complication develops after decades of severe destructive inflammation, and usually in the context of *Helicobacter pylori* induced chronic gastritis. Understanding the mechanism by which inflammation, *H pylori* induced or otherwise, leads to loss of acid secretion is therefore crucial to understanding the pathogenesis of gastric neoplasia.

The effect of *H pylori* infection on gastric acid secretion depends on the severity and distribution of gastritis. Antral inflammation is associated with increased production of gastrin, which in turn increases the drive for acid secretion by parietal cells in the gastric corpus. If the corpus is affected by severe inflammation, the host's ability to respond to the increased gastrin is greatly attenuated. Thus subjects with severe corpus inflammation have reduced capacity to secrete acid, and this may initially be due to functional inhibition of parietal cells by either products of *H pylori* itself or more likely

products of the inflammatory process.² In time and with sustained chronic inflammatory injury, the gastric glands atrophy and it is debatable whether loss of acid secretion in this context ever recovers. Permanent loss of parietal cells, resulting in achlorhydria, is a very strong risk factor for gastric cancer, especially if combined with sustained chronic inflammatory activity. This is no doubt related to the risk of bacterial overgrowth and colonisation of the gastric milieu by nitrosating bacteria that produce carcinogenic nitrosamines.³ In order to understand the effects of *H pylori* induced gastritis on acid secretion, it is important to consider its effects on parietal cells and the acid secretory machinery within these cells.

EFFECT OF *H PYLORI* ON PARIETAL CELLS AND ACID SECRETION

Parietal cells are derived from anchored stem cells in the isthmus of the oxyntic pit-gland units. They migrate bidirectionally along the pit-gland axis so that in time they appear in the pit in an outward direction and also in the neck in an inward direction and continue until they reach the base of the gland.⁴ Interestingly, there seems to be functional heterogeneity in the parietal cell population along the pit-gland axis such that younger cells in the isthmus and neck are more active than older cells in the pit and base regions.⁵ Preparietal cells develop from tissue derived stem cells and go through a number of stages during which they acquire an increase in the surface area of the apical plasma membrane forming numerous long microvilli. They then acquire a few cytoplasmic H⁺/K⁺-ATPase containing tubules and vesicles and their apical membrane invaginates to form a canaliculus. Full maturation is heralded

by expansion of the canaliculi and increase in cell size.⁴ Turnover time of parietal cells in humans is not certain but is thought to be approximately 54 days in mice,⁶ which clearly means that it is considerably longer in humans. There is surprisingly very little information on the life cycle of a human parietal cell. One report suggests the lifespan of a parietal cell is thought to be between 150 and 200 days, in contrast with the average surface epithelial cell (four days).⁷ This issue is important for understanding the potential for recovery of parietal cell function following removal of chronic inflammatory stimuli (for example, following *H pylori* eradication). It is patently evident however that it would take a considerable time for parietal cells to regenerate in humans, and this has to be reflected in the design of studies assessing recovery of parietal cell numbers or function.

H pylori can damage the gastric epithelial layer through direct and indirect mechanisms. The organism can directly induce apoptosis of gastric epithelial cells through production of numerous molecules, including cytotoxin (VacA), lipopolysaccharide, monochloramine, and nitric oxide.⁸ This proapoptotic effect is dependent on activation of nuclear factor κB.⁹ *H pylori* organisms are capable of attaching to gastric epithelial cells and are responsible for triggering the production of proinflammatory cytokines such as interleukin (IL)-8, IL-1β, and tumour necrosis factor α (TNF-α). The ensuing inflammatory activity can also damage epithelial cells, including parietal cells, and this could have an effect on acid secretion. However, the presence of these cytokines has a direct inhibitory effect on acid secretion per se. Indeed, IL-1β is the most powerful acid inhibitor known and TNF-α also has acid inhibitory properties, albeit weaker than IL-1β.¹⁰⁻¹³ The acid inhibitory effect of IL-1β is thought to be mediated through IL-1 receptors on parietal cells.¹⁴ IL-1β also causes sustained functional impairment of ECL cells, which also express IL-1 receptors.¹⁵

EFFECT OF *H PYLORI* ON THE GASTRIC H⁺/K⁺-ATPASE

The H⁺/K⁺-ATPase is an ion motive ATPase that belongs to the P2 subfamily of ATPases and consists of alpha and beta subunits. It forms an integral part of the apical membranes of parietal cells. It transports its cations as a cycle of phosphorylation and dephosphorylation of the transport protein. When parietal cells are stimulated the pumps are translocated from the cytoplasmic tubulovesicles into the membrane of the secretory canaliculus, to form microvilli

lining the canalicular space, and a KCl pathway is activated to allow K^+ to access the external surface of the ATPase and secretion of Cl^- .^{16,17} The H^+/K^+ -ATPase actually pumps hydronium ions (H_3O^+) rather than H^+ ions and is able to release H_3O^+ at a concentration of 160 mM, which is equivalent to an external pH of 0.8 and a 4 million-fold gradient across the surface of the parietal cell. The H^+/K^+ -ATPase pumps are involved in the final stages of gastric acid secretion and are stimulated to secrete acid by intracellular signals from H_2 receptors, muscarinic M_3 receptors, and gastrin receptors on parietal cells.¹⁷

There is evidence that *H. pylori* infection exerts inhibitory effects on the human gastric H^+/K^+ -ATPase α subunit. Gööz *et al* showed that *H. pylori* inhibits α subunit gene expression via intracellular pathways involving protein kinases A and C and protein tyrosine kinase.¹⁸

WHAT IS THE EFFECT OF ERADICATION OF *H. PYLORI* ON GASTRIC ACID SECRETION?

The answer relies entirely on the extent to which the corpus mucosa is affected by inflammatory activity. Thus if the corpus is relatively healthy with an antral predominant pattern of gastritis, the net effect of eradication will be a reduction in the degree of hypergastrinaemia, which in turn may lead to a reduction in acid secretion. If on the other hand the corpus is severely inflamed, eradication will remove at least the functional inhibition of the parietal cells and this will be associated with an increase in acid secretion.¹⁹ We know that acid secretion recovers within a very short period after initiation of antibiotic therapy, which suggests that the inflammatory process exerts some functional inhibition on acid secretion that could easily be reversed by reducing the acute inflammatory component and associated array of acid inhibitory cytokines, such as IL-1 β and TNF- α .²⁰ Acid recovery also continues well after successful eradication, suggesting perhaps recovery in parietal cell numbers also but it is generally accepted that the onset of gastric atrophy and intestinal metaplasia heralds a less reversible stage with very little recovery in acid secretion.

One of the major unanswered questions in this field has been the mechanism of recovery of acid secretion after eradication of *H. pylori*. In this issue of *Gut*, Osawa and colleagues²¹ report on the effects of eradicating *H. pylori* infection on expression of H^+/K^+ -ATPase mRNA, in addition to expression of other genes involved in acid secretion, including H_2 receptors, muscarinic M_3

receptors, and anion exchanger 2, which is involved in basolateral base exit during acid production (see page 152). They also assessed expression of IL-1 β expression, due to its role as a powerful proinflammatory cytokine and a potent inhibitor of acid secretion. The key question that Osawa *et al* asked was whether recovery of acid secretion after eradication of *H. pylori* is due to recovery in expression of the proton pump or an increase in parietal cell numbers. The answer was unequivocally in favour of upregulation of H^+/K^+ -ATPase mRNA. There was an impressive 250-fold increase in expression of the pump mRNA but no significant change in the number of parietal cells, at least over the three month follow up period for this study. Interestingly, upregulation of expression of the pump mRNA was seen even in patients with severe atrophic gastritis. The change in H^+/K^+ -ATPase mRNA was accompanied by a significant reduction in IL-1 β levels but no major change in the other studied genes.

The findings of Osawa *et al* mirror those of Furuta *et al*, who found similar increases in H^+/K^+ -ATPase mRNA expression one month following successful eradication of *H. pylori* infection.²² Osawa *et al* extend the work by looking at the changes over a longer period (three months) and by showing that the increase was not due to any changes in parietal cell numbers. The work by Furuta *et al* however included the crucial demonstration of recovery in acid secretion in the same patients. Taken together, it is reasonable to conclude that the initial recovery in acid secretion is most likely due to release of inhibition on expression of the H^+/K^+ -ATPase. It remains an open question whether the parietal cell mass does recover with the passage of time. This issue needs to be addressed by much longer follow up studies that should last years rather than months.

What about future directions in this field? There are many questions that have been asked over the past two decades; some have been answered while the majority remain the subject of much research. Is acid inhibition reversible? Is gastric atrophy reversible? Will eradication of *H. pylori* infection lead to normalisation of acid secretion and recovery of parietal cell numbers? What is the exact mechanism of recovery of acid secretion? If acid secretion recovers fully or partially, will this reduce the risk of gastric cancer? Should we use eradication therapy as a strategy for reducing the risk of gastric cancer, and should this be carried out universally, or only in populations at risk? What is the optimal stage for intervention and does the

recovery in acid secretion have any potential harmful effects?

Perhaps the most pertinent question is whether there is a point of no return in the multistage process of gastric carcinogenesis. These are very valid questions that have occupied workers in the field for a considerable time. However, it is immediately obvious that this is a very worthwhile scientific pursuit, for at stake here is the potential for eliminating the world's second commonest cause of cancer death, namely gastric cancer. Indeed, providing the full answers to these questions will not only help in eliminating gastric cancer, it will also provide a paradigm for understanding other cancers where there is a sustained chronic inflammatory insult. Cancers of the colon, oesophagus, pancreas, gall bladder, head and neck, prostate, urinary bladder, lung, and many others share a similar theme.

The most exciting news for us gastroenterologists came on 3 October 2005 with the announcement that Warren and Marshall have been awarded the Nobel Prize for physiology/medicine for their discovery of *H. pylori*. The award was largely in recognition of the role of *H. pylori* in peptic ulcer disease and the near total disappearance of this previous cause of major morbidity and mortality. However, in my humble opinion, *H. pylori*'s legacy will prove more in the field of cancer, and this will by no means be restricted to gastrointestinal malignancies. The next decade promises to be even more exciting than the last.

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REFERENCES

- Williams C. Occurrence and significance of gastric colonization during acid-inhibitory therapy. *Best Pract Res Clin Gastroenterol* 2001;15:511-21.
- McColl KE, El-Omar E, Gillen D. Helicobacter pylori gastritis and gastric physiology. *Gastroenterol Clin North Am* 2000;29:687-703.
- Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;52:6735-40.
- Karam SM. Lineage commitment and maturation of epithelial cells in the gut. *Front Biosci* 1999;4:D286-98.
- Karam SM, Yao X, Forte JG. Functional heterogeneity of parietal cells along the pit-gland axis. *Am J Physiol* 1997;272:G161-71.
- Karam SM. Dynamics of epithelial cells in the corpus of the mouse stomach. IV. Bidirectional migration of parietal cells ending in their gradual degeneration and loss. *Anat Rec* 1993;236:314-32.

- 7 Okabe S. Hypothesis—origin of the parietal cell: microorganism? *J Clin Gastroenterol* 1997;**25**(suppl 1):S141–8.
- 8 Xia HH, Talley NJ. Apoptosis in gastric epithelium induced by *Helicobacter pylori* infection: implications in gastric carcinogenesis. *Am J Gastroenterol* 2001;**96**:16–26.
- 9 Neu B, Randlkofer P, Neuhofer M, *et al.* *Helicobacter pylori* induces apoptosis of rat gastric parietal cells. *Am J Physiol Gastrointest Liver Physiol* 2002;**283**:G309–18.
- 10 Wallace JL, Cuccala M, Mugridge K, *et al.* Secretagogue-specific effects of interleukin-1 on gastric acid secretion. *Am J Physiol* 1991;**261**:G559–64.
- 11 Beales IL, Calam J. Interleukin 1 beta and tumour necrosis factor alpha inhibit acid secretion in cultured rabbit parietal cells by multiple pathways. *Gut* 1998;**42**:227–34.
- 12 Wolfe MM, Nompleggi DJ. Cytokine inhibition of gastric acid secretion—a little goes a long way. *Gastroenterology* 1992;**102**:2177–8.
- 13 El-Omar EM. The importance of interleukin 1 beta in *Helicobacter pylori* associated disease. *Gut* 2001;**48**:743–7.
- 14 Schepp W, Dehne K, Herrmuth H, *et al.* Identification and functional importance of IL-1 receptors on rat parietal cells. *Am J Physiol* 1998;**275**:G1094–105.
- 15 Prinz C, Neumayer N, Mahr S, *et al.* Functional impairment of rat enterochromaffin-like cells by interleukin 1 beta. *Gastroenterology* 1997;**112**:364–75.
- 16 Wallmark B, Stewart HB, Rabon E, *et al.* The catalytic cycle of gastric (H⁺ K⁺)-ATPase. *J Biol Chem* 1980;**255**:5313–19.
- 17 Sachs G, Shin JM, Munson K, *et al.* Review article: the control of gastric acid and *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2000;**14**:1383–401.
- 18 Gööz M, Hammond CE, Larsen K, *et al.* Inhibition of human gastric H⁺(+)-K⁺(+)-ATPase alpha-subunit gene expression by *Helicobacter pylori*. *Am J Physiol Gastrointest Liver Physiol* 2000;**278**:G981–91.
- 19 El-Omar EM, Oien K, El Nujumi A, *et al.* *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997;**113**:15–24.
- 20 Gutierrez O, Melo M, Segura AM, *et al.* Cure of *Helicobacter pylori* infection improves gastric acid secretion in patients with corpus gastritis. *Scand J Gastroenterol* 1997;**32**:664–8.
- 21 Osawa H, Kita H, Ohnishi H, *et al.* *Helicobacter pylori* eradication induces marked increase in H⁺/K⁺-adenosine triphosphatase expression without altering parietal cell number in human gastric mucosa. *Gut* 2006;**55**:152–7.
- 22 Furuta T, Baba S, Takashima M, *et al.* H⁺/K⁺-adenosine triphosphatase mRNA in gastric fundic gland mucosa in patients infected with *Helicobacter pylori*. *Scand J Gastroenterol* 1999;**34**:384–90.

Visceral sensitivity

Can modulating corticotropin releasing hormone receptors alter visceral sensitivity?

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Activation of corticotropin releasing hormone (CRH) receptor 2 (CRH-R2) reduces visceral sensitivity induced by colorectal distension in conscious rats. This finding is relevant to the increased interest in the potential use of therapeutic agents that act on CRH receptors in the treatment of irritable bowel syndrome

Clarifying the adverse effects of stress on bodily function is a crucial paradigm for medical research. Evidence that psychosocial stress aggravates digestive diseases has been accumulating and stress induced exacerbation of symptoms in patients with functional gastrointestinal disorders is well recognised.¹ Corticotropin releasing hormone (CRH), a 41 amino acids peptide produced mainly in the paraventricular nucleus of the hypothalamus, is considered to be a major mediator of the stress response.² Indeed, stress is known to induce release of hypothalamic CRH, resulting in pituitary secretion of adrenocorticotrophic hormone (ACTH). In addition, stress related activation of CRH receptors has been reported to alter gastrointestinal functions.³ Moreover, physical or psychological stress is known to delay gastric emptying,⁴ accelerate colonic transit,⁵ and evoke colonic motility⁶ in rats.

Two major G protein coupled receptors for the CRH have been identified, CRH receptor 1 (CRH-R1) and receptor 2

(CRH-R2).^{7–9} CRH-R1, which is highly expressed in the anterior pituitary, neocortex, hypothalamus, hippocampus, amygdala, locus coeruleus, and cerebellum, has been reported to mediate stress induced physiological changes, including stimulation of the hypothalamo-pituitary-adrenal axis, elevation of plasma levels of catecholamines, increased colonic motility,¹⁰ and exaggerated stress related behaviour, especially anxiety.^{11, 12} In addition, stimulation of this receptor is believed to activate adenylate cyclase, an enzyme that catalyses the formation of cyclic AMP (cAMP).^{7–9}

We have previously reported increased colonic motility and visceral perception in response to administration of CRH in patients with irritable bowel syndrome (IBS).¹³ In addition, earlier studies have indicated that gastrointestinal dysmotility¹⁴ and visceral hypersensitivity¹⁵ are major events in the pathophysiology of IBS. Moreover, patients with IBS have been reported to suffer from a variety of chronic or acute psychiatric conditions, including

depression, generalised anxiety, panic, social phobia, and somatisation.¹⁶ Various studies have suggested a relationship between stress induced changes in colonic motility and CRH action in the paraventricular nucleus of the hypothalamus.¹⁷ Accordingly, it has been shown that intracerebroventricular injection of CRH stimulates gastrointestinal motility in a way similar to that induced by stress¹⁸ and that intraperitoneal injection of CRH induces defecation and clustered spike bursts longer than basal spike bursts in rats.¹⁰

CRH-R1 antagonists have been shown to prevent stress-like gastrointestinal motor responses following central or peripheral injection of CRH.¹⁰ In addition, it has been reported that CRH-R1 deficient mice show impaired response to stress, as indicated by absence of increased ACTH and corticosterone levels following exposure to stress, as well as less pronounced anxiety related behaviour.^{11, 12} From these findings, it is reasonable to assume that CRH mediates gastrointestinal and behavioural responses to stress via CRH-R1. Actually, in a recent study,¹⁹ we have shown that administration of an α -helical CRH or CRH-R1 antagonist attenuates hippocampal noradrenaline release and reduces the frequency of abdominal contractions induced by acute colorectal distension in rats. We have also shown that the CRH-R1 antagonist used in that study¹⁹ reduced plasma ACTH and anxiety after acute colorectal distension but not after chronic colorectal distension, probably due to habituation. Another important finding of our previous study¹⁹ is that pretreatment with the CRH-R1 antagonist blocked chronic colorectal distension induced increase in rats faecal pellet output. Because the CRH-R1 antagonist used in our previous study¹⁹ is an agent that crosses the blood-brain barrier, both central CRH-R1 and