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Review Articles

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THE ROLE OF *H. PYLORI* INFECTION IN THE PATHOPHYSIOLOGY OF DUODENAL ULCER DISEASE

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The discovery of *H. pylori* infection and the recognition of its effects on gastric physiology has significantly advanced our understanding of the pathophysiology of ulcer disease, In DU patients *H. pylori* gastritis is mainly confined to the antral mucosa. It stimulates increased release of gastrin by the antral mucosa and this is accompanied by high acid output by the oxyntic mucosa. This high acid response to gastrin stimulation by the oxyntic mucosa in DU patients is due to the combination of a high parietal cell mass and the fact that the function of these parietal cells is not impaired by any body gastritis. The increased acid secretion results in an increased duodenal acid load with the development of gastric metaplasia within the duodenal bulb and then actual ulceration. The reason why only some subjects develop this antral predominant pattern of *H. pylori* gastritis and associated acid hypersecretion is unclear but may be explained by a premorbid high acid output protecting the oxyntic mucosa form *H. pylori* gastritis.

K e y w o r d s: *ulcer disease, gastritis, gastrin, cholecystokinin, gastrin releasing peptide*

INTRODUCTION

H. pylori infection is now accepted as the most important acquired factor in the pathogenesis of duodenal ulcer disease. More than 95% of patients who develop duodenał ulcer disease have *H. pylori* infection and eradicating the infection markedly reduces the ulcer relapse rate. For many years it has been recognised that duodenal ulcer disease is related to excessive gastric acid secretion and has therefore been controlled by the use of anti-secretory medication or acid-lowering surgical procedures. Recent studies have indicated that in a subgroup of subjects *H. pylori* infection stimulates excess gastric acid secretion and this is likely to be a key mechanism by which it results in duodenal ulceration.

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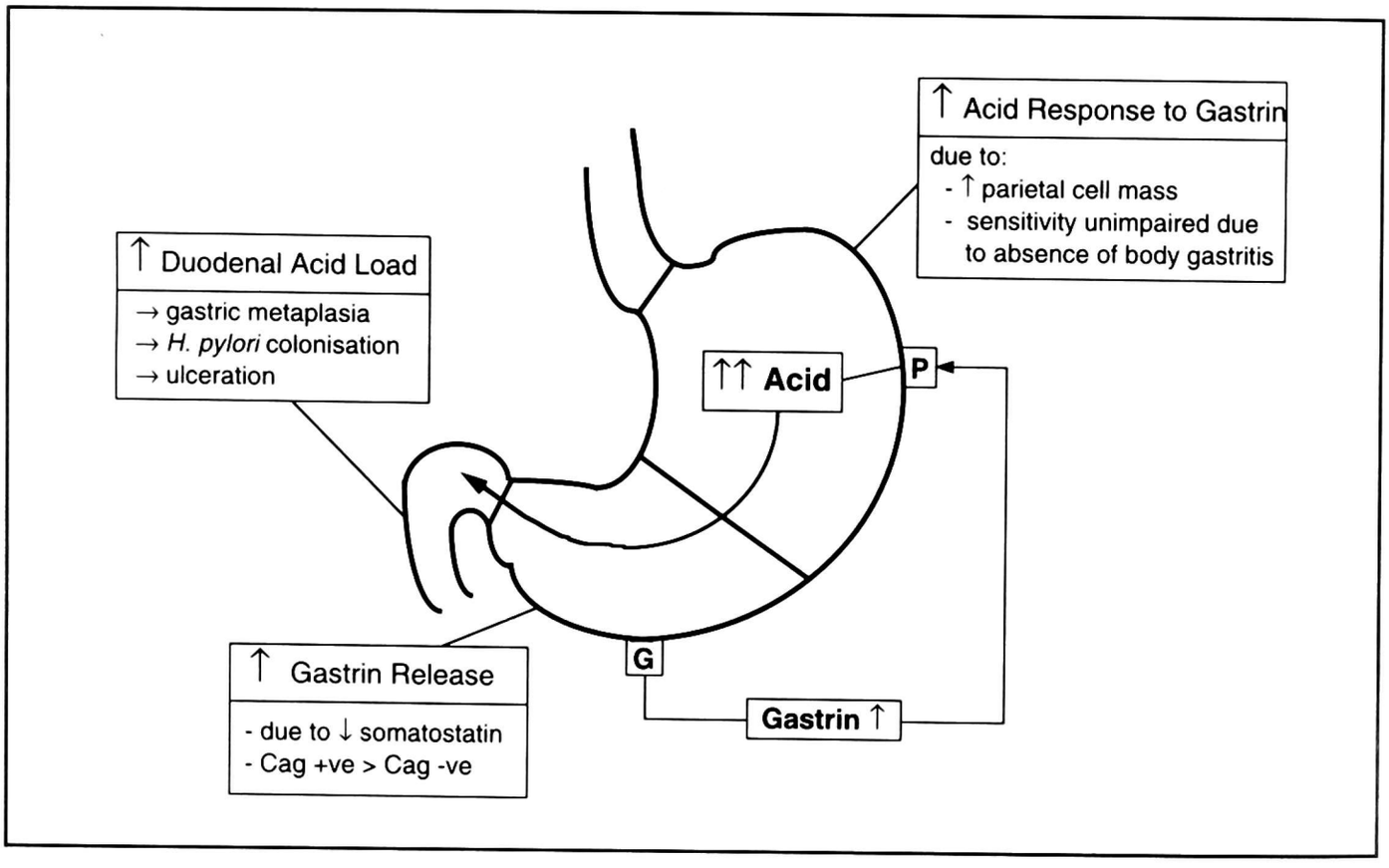

Fig. 1. Role of *H. pylori* infection in the pathophysiology of DU disease.

H. PYLORI AND INCREASED ANTRAL GASTRIN RELEASE IN DU DISEASE

In patients with duodenal ulcer disease, *H. pylori* infection and the accompanying gastritis predominantly involve the antral region of the stomach (1). The antral mucosa plays an important role in the regulation of gastric acid secretion due to its production of the hormone gastrin. After being synthesised and released by G cells within the antral mucosa, the hormone enters the systemic circulation and then stimulates the parietal cells in the body of the stomach to secrete acid. In duodenal ulcer patients *H. pylori* infection stimulates increased release of gastrin and this is seen during fasting periods as well as following stimulation with food or gastrin releasing peptide (GRP) (2, 3). The increased circulating gastrin associated with *H. pylori* is mainly due to an increase in Gastrin-17 (6). This form of gastrin originates mainly from the antral mucosa and its selective increase is consistent with the infection predominantly affecting this region. Gastrin-17 is also the main form of the hormone which rises in response to eating and this is consistent with *H. pylori*-associated hypergastrinaemia being most pronounced post-prandially (2). Eradication of *H. pylori* results in resolution of the increased gastrin levels and the fall in gastrin occurs within 2—14 days of commencing the anti-*H. pylori* therapy (7, 8).

The mechanism by which *H. pylori* infection stimulates increased gastrin release in DU patients remains incompletely understood. The release of gastrin

by the antral mucosa is under physiological inhibitory control in order to prevent excessive gastric acid secretion. Gastrin release is suppressed when antral luminal pH falls below 3, (9). In addition, there is inhibitory control exerted on gastrin release by cholecystokinin and other enterogastrones released from the small intestine (10, 13). The inhibition of gastrin release exerted by both gastric acid and cholecystokinin is mediated mainly via the release of somatostatin by D cells within the antral mucosa (10, 14—16). These D cells lie in close proximity to the G cells and the somatostatin they release exerts paracrine inhibitory control on both gastrin synthesis and release. Several studies have now demonstrated lowered concentrations of somatostatin within the antral mucosa of subjects with *H. pylori* (17—22). In addition, somatostatin mRNA concentrations are lowered indicating a reduced synthesis of this inhibitory hormone. These findings are consistent with *H. pylori*-related hypergastrinaemia being partly or entirely secondary to a deficiency of antral somatostatin and thus loss of the normal inhibitory influence this hormone exerts on gastrin release.

If the *H. pylori* induced hypergastrinaemia in DU patients is due to impaired somatostatin-mediated inhibitory control then defective inhibitory control of gastrin release should be apparent in studies of gastric secretory studies. Several studies have confirmed this to be the case. Tarnasky *et al.* have demonstrated impaired acid-mediated inhibition of gastrin release and acid secretion in *H. pylori*-positive subjects (23). Further evidence of impaired inhibitory control of gastrin release is provided by the studies of Konturek *et al.* employing the cholecystokinin A receptor antagonist loxiglumide (24, 25). Cholecytokinin exerts tonic inhibitory control on gastrin release. This is mediated by the hormone activating CCK A receptors on antral D cells and thereby stimulating somatostatin release which inhibits gastrin release. Konturek *et al.* found that the CCK A antagonist increased the gastrin and acid response to a test meal in healthy controls but not in duodenal ulcer patients (24). In a separate study they found that eradication of *H. pylori* infection restored the physilogical response to CCK A blockade in duodenal ulcer patients (25). These findings are again consistent with *H. pylori* impairing somatostatin mediated inhibitory control of gastrin release.

There is now, therefore, substantial morphologinal and physiological evidence that the increased release of gastrin caused by *H. pylori* is secondary to the infection depleting antral somatostatin. The mechanism by which *H. pylori* results in depletion of antral somatostatin has still to be elucidated, but there are at least three potential mechanisms. The first is that *H. pylori* raises mucosal surface pH by virtue of its high urease activity and ammonia synthesis (3). Low antral pH is an important physiological stimulus to the synthesis and release of antral somatostatin. Studies have been performed to see whether altering the rate of *H. pylori* ammonia production affects gastrin release.

However neither increasing *H. pylori* ammonia production by the intragastric infusion of urea (26) or inhibiting it by acetohydroxamic acid (27) or completely suppressing it with 24 h of triple antibacterial therapy (7) was found to alter serum gastrin. However, this lack of effect of acute alterations in ammonia production on serum gastrin does not exclude a role of long-term *H. pylori* ammonia production in disrupting the regulation of gastrin release. It has been shown that pH induced adaptive changes in antral D cells occurs at a slow rate (28). It is possible that elevation of antral surface pH by ammonia leads to atrophy of antral D cells by blocking the chronic trophic stimulus exerted by gastric acid.

The second mechanism by which *H. pylori* infection might be altering G and D cell function is *via* its stimulation of various cytokines by antral mucosal cells. The infection upregulates the local production of various cytokines (25). Recent *in vitro* studies indicate that some cytokines stimulate gastrin release though it is difficult to know whether this can be extraploated to the *in vivo* situation (30). It is possible that *H. pylori* produces biogenic amines which could modify antral D and G cell function. There is a single report that the bacterium produces N alpha-methylhistamine and if confirmed by other studies could be of physiological importance (31). This amine is a potent agonist of H_3 receptors and activation of such receptors on human antral D cells inhibits somatostatin release.

There is recent evidence that the degree of disturbance of antral gastrin release is related to the strain of *H. pylori*. Subjects with *H. pylori* infection who develop DU disease are much more likely to be colonised by a Cag positive strain of the organism than a Cag negative strain. In contrast, subjects with *H. pylori* infection who do not develop DU disease are equally likely to be colonised by a Cag positive or Cag negative strain. Recent studies have shown that the degree of increase in gastrin release is more marked in subjects with Cag positive strains (32). This more marked increase in gastrin release stimulated by Cag positive strains may explain their stronger association with DU disease.

H. PYLORI AND INCREASED GASTRIC ACID SECRETION IN DU DISEASE

It is now firmly established that the increased gastrin release stimulated by *H. pylori* infection results in increased gastric acid secretion in patients with duodenal ulcer disease. Basal acid output is increased several fold in DU patients compared to normal controls (i.e. *H. pylori*-negative healthy volunteers) (33—36). Eradication of *H. pylori* infection in these subjects results in a fall in both basal gastrin levels and the accompanying increased basal acid output (33—16). Duodenal ulcer patients with active *H. pylori* infection also have a markedly increased acid output in response to stimulation with gastrin

releasing peptide (GRP) (33, 34, 36). This neuropeptide stimulates antral gastrin release which then circulates and stimulates acid secretion by the oxyntic mucosa. Compared to normal controls, *H. pylori*-positive DU patients have a five-fold increased acid response to GRP stimulation. Following eradication of *H. pylori* infection, both the increased GRP stimulation gastrin release and increased acid secretion largely or fully resolve (33, 34, 36).

The increased acid secretion associated with *H. pylori* infection in DU patients is not usually seen in *H. pylori* infected subjects without DU disease. Though *H. pylori* positive healthy volunteers have increased basal and stimulated gastrin concentrations these are not accompanied by increased gastric acid secretion (37). Thus, a characteristic which distinguishes *H. pylori* infected subjects with DU disease from *H. pylori* infected subjects without DU disease is the greater acid response to gastrin stimulation in the former.

We have recently investigated the mechanism of the different acid response to gastrin in *H. pylori*-positive DU patients and *H. pylori*-positive non-ulcer subjects (37). We did this by performing dose response studies to gastrin stimulation which allowed us to calculate both the maximal acid output (a measure of parietal cell mass) and the sensitivity to gastrin (concentration of gastrin required to achieve 50% maximal acid output). We found that the DU patients had a greater parietal cell mass than either the *H. pylori*-positive non-ulcer subjects or the true normal controls (*H. pylori*-negative healthy volunteers). In addition, we found that the sensitivity to gastrin in the DU patients was similar to that of the normal controls whereas that of the *H. pylori*-positive non-ulcer subjects was decreased compared to either the DU patients or true normals. We also investigated whether there was any defect in somatostatin-mediated inhibitory control of oxyntic mucosal function by comparing the maximal acid response to cholecystokinin versus that to Gastrin-17. There was no evidence of impaired inhibitory control of parietal cell function in the DU patients. These studies therefore indicate that the high acid response to gastrin characteristic of the DU patients is due to an increased number of parietal cells which show normal sensitivity to gastrin stimulation. The reduced acid response to gastrin in the *H. pylori*-positive non-ulcer subjects is due to them having a normal number of parietal cells but which have a reduced sensitivity to gastrin.

The cause of the differences in parietal cell mass and sensitivity to gastrin seen in the DU patients versus infected non-ulcer subjects is unclear. The increased parietal cell mass in the DU patients may be genetic in origin and this is supported by the fact that some *H. pylori*-negative subjects have maximal acid output values equivalent to that of DU patients. It is possible that the increased parietal cell mass in the DU patients is also partly related to the *H. pylori*-induced hypergastrinaemia exerting a trophic influence on the oxyntic mucosa. The reduced sensitivity to gastrin characteristic of the

H. pylori-positive non-ulcer subjects may also be partly genetic but is also probably partly related to *H. pylori* infection. It is recognised that in non-ulcer subjects the *H. pylori* infection induces a degree of body gastritis which impairs the acid response to gastrin. The fact that *H. pylori* gastritis spares the acid secreting mucosa in DU patients leaves their acid response to gastrin unimpaired. In contrast, in non-ulcer subjects the gastritis involves the oxyntic mucosa and impairs its function.

It is possible that subjects premorbid acid secretory status is an important determinant in the pattern of gastritis and accompanying disturbance of acid secretion induced by *H. pylori* infection (38, 39). It is now know that inhibition of acid secretion by proton pump inhibitory therapy in DU patients will transform their pattern of gastritis from an antral predominant/body-sparing to a body predominant gastritis (40). It thus appears that a high rate of acid secretion by the oxyntic mucosa in some way protects it from developing gastritis in response to *H. pylori* infection. In subjects with a premorbid high acid output infection with *H. pylori* will therefore induce an antral predominant gastritis which will have the effect of further increasing their acid secretion. These subjects will have a high risk of developing DU disease. In contrast, subjects with a low premorbid acid secretory status will develop inflammation of both the antrum and body mucosa. Though the *H. pylori* antral gastritis will increase the gastrin levels, this will not result in increased acid secretion as the body gastritis will impair their acid response to the gastrin.

H. PYLORI-INDUCED INCREASED ACID SECRETION AND DU DISEASE

The increased gastrin release and accompanying increased acid output in subjects with an antral predominant gastritis will predispose them to DU disease. This increased acid output results in an increased duodenal acid load. Exposure of the duodenal mucosa to excess acid results in the development of gastric metaplasia within the duodenal bulb (41). *H. pylori* cannot colonise normal duodenal mucosa but is able to adhere to patches of gastric metaplasia. Consequently, the development of gastric metaplasia within the duodenum allows the organism to colonise the duodenum. The duodenal mucosa is now subjected to attack by both an increased acid load and the local production of bacterial cytotoxins. In addition, the infection has been shown to impair the secretion of bicarbonate by the duodenum which will further reduce its ability to withstand the increased acid attack (42). Consequently, the duodenal mucosa becomes ulcerated. Eradication of *H. pylori* infection results in a fall in gastric acid secretion and duodenal acid load and also removal of any local damaging effect of bacterial cytotoxins consequently, eradication of the infection results in cure of the ulcer disease in the vast majority of patients. The sequence of events leading to DU disease are depicted in the figure.

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