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Long-term Effects of *Helicobacter pylori* Infection on Acid and Pepsin Secretion

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Chronic *Helicobacter pylori* infection causes a slight postprandial hypergastinemia, generally referred to as exaggerated or inappropriate gastrin release. This can be ablated by eradication of this infective agent. The expectations that this would further unravel the mysteries of the pathogenesis of peptic ulcer disease have not been fulfilled. It is now well established that of conventional acid secretory patterns such as basal acid secretion, maximum gastrin-stimulated acid secretion, and of sensitivity of the parietal cell to gastrin, only basal acid is modified by chronic *H. pylori* colonization. This particularly relates to basal secretion in duodenal ulcer patients, as basal secretion of otherwise healthy, chronically *H. pylori*-infected subjects appears to be affected in only a small proportion of subjects. It is of particular interest, however, that chronic *H. pylori* infection supplies a solid explanation why acid inhibitory pathways are deficient in duodenal ulcer disease, since this is reversible following *H. pylori* eradication as demonstrated by elegant studies with gastrin-releasing, peptide-stimulated acid secretion. Furthermore, it has gradually become apparent that exaggerated gastrin response is probably no more than an innocent bystander of chronic *H. pylori* infection. Paradoxically, in a small subset of patients, hypo-or anacidity accompanying chronc *H. pylori* infection can be reverted by *H. pylori* eradication, for currently unknown reasons.

The question remains open whether enhanced pepsin release from the chief cell, which characterizes duodenal ulcer disease and is also reversible following *H. pylori* eradication, has any direct implication in ulcer expression in duodenal ulcer patients.

INTRODUCTION

The aim of this paper is to review current knowledge of the effect that chronic *Helicobacter pylori* (HP)[c] infection exerts on chief and parietal cells with comparison to the respective acute effects as extensively reviewed by Cave in this issue (Page 91). Attempts are made to reconcile these findings with long-established changes in pepsin and acid secretion of patients suffering from chronic peptic ulcer disease.

Cave has well demonstrated and elucidated the mechanisms involved through which HP effector molecules induce *in vitro* effects on parietal and chief cells. His observations on increased pepsin release from the chief cell of isolated gastric glands of rabbits can easily be reconciled with the previously established fact that in a substantial proportion of duodenal ulcer (DU) patients, pepsinogen levels are elevated in the blood. This has long been considered a pathognomonic marker of DU disease [1, 2]. Since it has also been shown that this phenomenon is reversible following HP eradication [3], the causative relationship to HP infection is well established.

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[c]*Abbreviations:* HP, *Helicobacter pylori*; DU, duodenal ulcer; GRP, gastrin-releasing peptide.

It is considerably more difficult, however, to reconcile the *in vitro* findings obtained in the parietal cells with the acid secretory pattern found in patients suffering from chronic peptic ulcer disease or in otherwise healthy subjects who are chronically infected with HP. The observation that acute HP infection blocks acid secretion *in vivo* can explain the temporary hypo- or achlorhydria found in subjects who volunteered to be infected or in those subjects who were accidentally infected with HP [4-6]. It also supplies a putative explanation for observations made long before the pathogenic role of HP was established, that histamine or gastrin-resistant achlorhydria can occasionally occur in young people in the absence of atrophic gastritis [7]. The hypo- or achlorhydria observed following acute HP infection must generally, however, be a temporary phenomenon since peptic ulcer disease is largely associated with normal or increased gastric acid production despite widespread and undisputed association with HP infection. The molecular mechanisms through which the parietal cells overcome the property of the potential HP effector molecule to block acid secretion remains unknown. Furthermore, it is not established whether the acid secretory capacity of the individual cell returns to preinfection values or whether up or down regulation may occur in some subjects.

The association between peptic ulcer disease and gastric acid has been well recognized since Schwarz [8] established the dictum "no acid, no ulcer." This fundamental recognition has, however, provoked a widespread overestimation of the pathogenic role of gastric acid and led to an erroneous belief that all peptic ulcer patients produce acid in excess. Soon after the introduction of the maximum acid secretion test, which allows quantitative assessment of acid production under standardized conditions, it was established that this generalization was not appropriate. While DU patients on average secrete more acid than healthy controls, this only holds true for a small proportion of patients suffering from gastric ulcer, mainly those with prepyloric ulcers. A substantial proportion of patients with gastric ulcers produce even less acid than healthy subjects. Even in DU disease, the overlap with acid secretory patterns of healthy subjects is considerable, as only one-third of DU patients have a maximum acid output above those values observed in healthy controls [9]. Another often overestimated abnormality of DU-associated acid secretion is the increased sensitivity of the parietal cell to gastrin [10], which again affects only a fraction of DU patients [11].

It is well-known that the maximum acid secretory capacity of the stomach correlates with the number of parietal cells present in the corpus mucosa [12] and that, on average, DU patients have a two-fold increase in the total parietal cell mass [13]. However, it has also been recognized that gastritis is very widespread in peptic ulcer disease and can vary from mild forms of superficial gastritis to more severe forms. The antrum is generally affected, but extension to the gastric corpus may eventually lead to partial replacement of parietal cells by mucous-secreting cells. Atrophic gastritis within the corpus mucosa has been found to be particularly associated with ulcers in the upper part of the gastric fundus. In this connection, the term pyloro-cardiac extension of gastritis was created and duodeno-gastric reflux was considered by many as the causative factor for both chronic gastritis and gastric ulcer [14].

Soon after it became possible to reliably measure plasma gastrin levels by radioimmunoassay, it also became apparent that patients with gastric, and, to a lesser degree, those with duodenal ulcer disease, had slightly increased gastrin levels, especially in the postprandial phase. This so-called exaggerated or inappropriate gastrin release was explained by a defect in the feedback loop through which gastrin release was inhibited once the antral pH fell below 2.5 [15].

With the known trophic effect of gastrin, it was tempting to attribute the increase of the parietal cell mass observed in DU patients to the growth-promoting effect of gastrin. This hypothesis was indirectly supported by the observation that the vast majority of ulcer

patients are infected with HP and that the inflammatory changes are largely reversible by HP eradication [17]. This was considered by many to suggest that the disregulation of gastrin release may be causally related to ulcer-associated hypersecretion of acid. The large variation of the acid secretory patterns within ulcer patient populations, however, makes it very unlikely that one simple variant such as a relatively modest increase in postprandial gastrin would be the causative agent for ulcer associated changes in acid regulation.

DOES CHRONIC HP INFECTION CAUSE ACID HYPERSECRETION?

Though a large number of studies are available on this subject, the results are controversial [18-29]. Unfortunately, the majority of reported studies provide only cross-sectional data in small numbers of subjects, and some are based on retrospective data. The availability of efficacious regimens to eradicate HP infection has been particularly helpful in elucidating how this infection modifies acid secretion in chronically infected subjects. Important information has also been gained by comparing acid secretion between healthy HP-positive and negative subjects.

Chronic HP infection and basal acid secretion

While the majority of studies indicate there are no differences in basal acid output between HP-positive and negative subjects [18-25], a moderate increase of basal acid output in HP-infected subjects was found in studies of Mullin et al. [26], Moss et al. [27], El-Omar et al. [28], and Levi et al. [29]. The obvious reason for this discrepancy lies in the particularly large individual variation of basal acid secretion. This can be more clearly inferred from the well-designed, longitudinal study by the McColl group [28] where individual values are displayed. Basal acid output was moderately elevated in HP-positive subjects not affected by peptic ulcer disease, although more than 60 percent had values overlapping that of HP-negative controls. It is of particular interest that HP eradication failed to significantly reduce basal acid secretion in the HP-positive group. In their HP-positive DU patients, basal acid secretion was higher than that observed in HP-positive and HP-negative healthy controls, and the overlap with that of both control groups was relatively small. Following HP eradication, values gradually fell reaching the level of the HP-negative controls by the end of the one-year observation period. This indicates there is a considerable lag to the very early ablation of the exaggerated gastrin release. Thus, it appears that chronic HP infection enhances basal acid secretion in only a small proportion of otherwise healthy subjects, although it is responsible for the increased basal acid secretion of a large fraction of HP-positive DU patients. Doubts prevail, however, as to what degree this anomaly contributes to the expression of ulcer disease in the individual chronically HP-infected subject.

Chronic HP infection and maximum gastrin-stimulated acid secretion

With the exception of the study of Levi et al. [29], studies performed on both healthy HP-positive subjects and on those affected by DU have not found that HP colonization increases maximum acid output as induced by gastrin. It is of particular interest that HP eradication fails to lower maximum acid output [18-28] even one year after eradication, despite a much earlier ablation of the exaggerated gastrin release [28]. Similarly, neither maximum acid output nor ED_{50} values, as determined in gastrin dose-response studies, differed between HP-positive and negative subjects [23-25, 27]. Therefore, it appears very unlikely that the increased parietal cell mass in DU disease is related to HP-mediated, exaggerated gastrin release and that genetic reasons are a more likely, albeit speculative, explanation.

Of particular interest is that the McColl group [30] recently reported that HP eradication leads to an increase in maximum acid output in a small subset of non-DU patients

where chronic HP gastritis had been accompanied by profound hypochlorhydria or even achlorhydria, thus mimicking the situation previously only encountered in patients with acute HP infection. This observation demonstrates that chronic HP infection can exert divergent effects in acid secretion in chronically infected patients, whereby no change or an increase in secretory capacity is considerably more common than a decrease. It has been speculated that different bacterial strains or genetic or other environmental influences might be responsible for this divergence [30].

Chronic HP infection and histamine-stimulated acid secretion

Findings obtained with maximum gastrin stimulation and studies performed with maximum doses of histamine interestingly revealed a lower maximum acid output in HP-positive than HP-negative DU patients [31]. The data are difficult to interpret and have been criticized because of the unusually low HP prevalence in the DU patients of that study [32], and a selection bias cannot be fully excluded. This observation, nevertheless, further substantiates the hypothesis that chronic HP colonization reduces maximum acid secretory capacity in a subset of patients.

DOES CHRONIC HP INFECTION INTERFERE WITH PHYSIOLOGIC DOWN-REGULATION OF ACID SECRETION?

Chronic HP infection and acid secretion as stimulated by the gastrin-releasing peptide

New light into the puzzle of changes in the regulation of acid secretion as induced by chronic HP infection has come recently from observations that maximum GRP-stimulated acid output is substantially higher in HP-positive subjects. In the only longitudinal study, El-Omar et al. [28] found a three-fold increase in GRP-induced maximum acid output in HP-positive, healthy subjects and a six-fold increase in DU patients. In both HP-positive healthy subjects and DU patients, this increase was fully reversible following HP eradication. GRP has a considerably more complex function within the gastointestinal tract than can be inferred from its name. In addition to being a potent stimulant of gastrin release, it simultaneously activates neuroendocrine pathways that exert inhibitory control on gastric secretion. This is achieved by stimulation of multiple peptides (including cholecystokinin, secretin, gastric-inhibitory peptide, vasoactive intestinal polypeptide, neurotensin and enteroglucagon) [33-36]. These peptides exert their inhibitory influence by stimulating release of the inhibitory peptide, somatostatin, from D cells within the antral and oxyntic mucosa. GRP thus activates both stimulatory and inhibitory pathways of acid secretion. Several studies have shown reduced somatostatin concentrations and messenger RNA expression in the gastric mucosa of subjects with HP infection, a finding consistent with disruption of inhibitory control at this level [37-39]. Due to stimulation of inhibitory pathways, maximum GRP-induced acid output is considerably smaller than that achieved with gastrin. In HP-colonized subjects, this difference is much smaller than in healthy controls, supporting the hypothesis of a defect in the inhibitory pathway. In DU patients, GRP-induced maximum acid output is reduced towards values observed in healthy HP-negative subjects within one year of HP eradication. Also, the increase in GRP-stimulated maximum acid secretion cannot be fully explained by the exaggerated gastrin release of chronically HP-infected subjects, since the HP-induced, exaggerated gastrin response resolved much earlier than the increase in GRP-induced acid secretion [28].

SUMMARY

It has gradually become apparent that chronic HP infection may be responsible for the increase in basal secretion observed in a relatively small fraction of HP-positive, healthy subjects and that it may be causative for the increase in basal secretion present in

a substantial fraction of patients affected with DU disease. Changes in basal secretion, however, do not appear to be mediated by the exaggerated gastrin release that characterizes chronic HP infection. Similarly, chronic HP infection cannot be made responsible for the increased maximum acid output of DU patients nor does it supply an explanation for the increased parietal cell mass observed in a substantial fraction of DU patients. In a small subset of chronically HP-infected patients, maximum acid has even been found to be reversibly decreased. There is no indication that chronic HP infection can be held responsible for the increase in gastrin sensitivity of the parietal cell observed in some DU patients. All these observations suggest that the exaggerated gastrin response resulting from chronic HP colonization represents no more than an innocent epiphenomenon.

The known defect in acid inhibitory pathway in DU disease seems, however, to be a direct consequence of chronic HP infection. The current knowledge of HP-induced changes in acid secretion does not help to identify patients who are at particular risk to develop peptic ulcer disease.

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