Mucosal peptic activity during *Helicobacter pylori* infection in pediatric patients

J Yahav, G Oderda, A Diver-Haber, N Keller, A Jonas

Abstract

Intramuscular peptic activity may participate in the genesis of acute and chronic superficial gastritis. The proteolytic activity of homogenates of gastric mucosa (antrum and body) and duodenum were measured at pH 2.0 (total peptic activity) after exposure to pH 8.0 (pepsinogen) and the activated pepsinogen (pepsin) was calculated in pediatric patients investigated for the presence of *Helicobacter pylori* (H pylori). 122 antral, 77 stomach body, and 74 duodenal biopsies were examined in 43 H pylori positive patients, 51 controls, and 28 H pylori negative gastritis patients. Activated pepsinogen was significantly reduced in the stomach of H pylori positive patients only. Pepsinogen values were similar in all the anatomical areas tested in all patients. In 13 H pylori positive patients reinvestigated three months after antibiotic therapy, antral mucosal activated pepsinogen activity increased significantly (mean pretreatment 1.56 (1.0) U/mg protein versus mean post-treatment 2.72 (1.7) U/mg protein) and reached values comparable with controls. The decreased activated pepsinogen activity in association with normal pepsinogen content observed in the antrum of H pylori positive gastritis patients indicate local pepsin inactivation or alternately enhanced removal into the gastric lumen or backflow into the circulation.

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Accumulating evidence supports the concept that *Helicobacter pylori* infection plays a causative role in gastric inflammation in children. On the grounds of epidemiologic studies, based on specific serum antibodies, H pylori was considered to be uncommon in childhood and to increase progressively with age. The reduced colonisation rate of children compared with adults disappears when patients with primary antral gastritis are considered specifically. Although studies have shown a striking correlation between the presence of H pylori and classic inflammation of the antral mucosa, the exact mechanism of tissue injury remains obscure.

In this study the peptic activity was determined in gastric mucosa obtained from children with H pylori infection compared with non-infected patients with evidence of gastritis and with those with normal gastric histology.

**Methods**

**PATIENTS**

During the period June 1989 to June 1990 children undergoing endoscopy for various reasons in both medical centres (Tel Hashomer and Tel Aviv) were prospectively tested for the presence of *H pylori* infection. Endoscopy was carried out after sedation, using an Olympus GIF-10 fibroptic endoscope. Biopsy specimens were obtained from the gastric body, antrum, and duodenum for the following procedures: routine histology, *H pylori* culture (antrum only), urease test (antral only), and peptic activity determination. Not all procedures were done in every patient. Biopsies for histological preparation were fixed in Bouin’s solution, sectioned, stained with haematoxylin and eosin, Giemsa and Gram stain and examined for the presence of *H pylori* and signs of inflammation. Mucosal inflammation was identified by the presence of increased numbers of acute or chronic inflammatory cells. The classification of gastritis was made without knowing the results of the Giemsa staining, urease test or pepsinogen determination. Antral biopsies cultured for *H pylori* were inoculated onto blood agar and Skirrow’s medium and incubated at 37°C in anaerobic environment for seven days. Urease test used the Christensen formulation without agar. Change of medium colour was tested after 24 hours. The criteria for *H pylori* infection were based on the presence of histopathological evidence of gastritis and of typical bacilli on staining, a positive urease test and or culture.

Biopsy specimens for peptic activity determination were immediately homogenised in 1 ml H2O using Ultra Turax T25 homogeniser (Ianko and Kunkel). Homogenates were stored at −20°C in 10% glycerol solution. The peptic activity of mucosal homogenates was determined in an assay at pH 2.0 by the method of Anson and Mirsky and expressed as specific activity (IU/mg protein); aliquots of mucosal homogenates assayed by this method were considered as representing total peptic activity. Separate aliquots of the same mucosal homogenates were assayed for peptic activity after being exposed to pH 8.0 by alkalisation using 1N NaOH. The peptic activity obtained in these aliquots was considered to represent pepsinogen concentra-

**TABLE 1** Specific activity of total peptic activity, pepsinogen and activated pepsinogen in antral biopsies

<table>
<thead>
<tr>
<th>Group</th>
<th>Total peptic activity [IU/mg protein]</th>
<th>Pepsinogen [IU/mg protein]</th>
<th>Activated pepsinogen [IU/mg protein]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (43)</td>
<td>1.81 (1.15)</td>
<td>0.52 (0.56)</td>
<td>1.34 (1.03)</td>
</tr>
<tr>
<td>Group II (28)</td>
<td>2.39 (0.83)</td>
<td>0.36 (0.12)</td>
<td>2.04 (0.87)</td>
</tr>
<tr>
<td>Controls (51)</td>
<td>3.03 (1.25)</td>
<td>0.49 (0.45)</td>
<td>2.54 (1.29)</td>
</tr>
</tbody>
</table>

*p* Values of group I v controls; **p** value of group I v group II.

Obtained by Student’s t test. Results are given as mean (SD).

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<table>
<thead>
<tr>
<th>Table II</th>
<th>Specific activity of total peptic activity, pepsinogen and activated pepsinogen in stomach body biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total peptic activity IU/mg protein</td>
</tr>
<tr>
<td>Group I (30)</td>
<td>3.89 (1.63)</td>
</tr>
<tr>
<td>Group II (11)</td>
<td>5.13 (2.34)</td>
</tr>
<tr>
<td>Controls (36)</td>
<td>4.47 (1.56)</td>
</tr>
<tr>
<td>*p = &lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

*p Values of group I vs controls, obtained by Student’s t test. Results are expressed as mean (SD).

<table>
<thead>
<tr>
<th>Table III</th>
<th>Specific activity of pepsin pepsinogen and activated pepsinogen in duodenal biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total peptic activity IU/mg protein</td>
</tr>
<tr>
<td>Group I (30)</td>
<td>0.95 (1.05)</td>
</tr>
<tr>
<td>Group II (10)</td>
<td>0.81 (0.62)</td>
</tr>
<tr>
<td>Controls (36)</td>
<td>0.82 (0.75)</td>
</tr>
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<tr>
<th>Table IV</th>
<th>Antral biopsies specific activity pre v post treatment in 13 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total peptic activity IU/mg protein</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>1.76 (1.0)*</td>
</tr>
<tr>
<td>Post treatment</td>
<td>3.03 (1.12)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.006</td>
</tr>
</tbody>
</table>

*p Values of pre v post treatment patients, obtained by Student’s t test.
Individual values of activated pepsinogen in antral mucosae before and after treatment.

Decreased peptic activity was present not only in the antral mucosa but also in the less affected mucosa of the gastric body. *H. pylori* is classically associated with inflammation of the antrum but not exclusively so. Significant degrees of colonization were found in gastritis located in the body of the stomach when this was specifically sought after, especially in the early stage of the disease. The dynamics and importance of *H. pylori* reduced altered mucosal peptic activity is far from being clarified. The only report investigating and supporting our finding of reduced gastric peptic activity in *H. pylori* infection comes from an unusual case report which followed the natural history of *H. pylori* infection in a volunteer.

The peptic activity of *H. pylori* infected mucosa was significantly reduced in comparison with normal mucosa as well as that of patients with gastritis not associated with *H. pylori* infection. We were unable to determine the aetiology of the gastritis in every patient of this latter group; histology failed to detect features of secondary gastritis, but additional sites of inflammation of the gastrointestinal mucosa were found in most of these patients. Twelve of these children received previous antibiotic therapy for various reasons, with possible inadvertent effects on the diagnosis of *H. pylori*. The results of other studies in children confirm the existence of *H. pylori* negative antral gastritis in 30% of children, especially of a younger age group.

The decreased peptic activity observed in our patients with *H. pylori* infection was the result of decreased activated pepsinogen (pepsin) activity, while pepsinogen, determined after alkalisation of mucosal homogenates, remained comparable with control.

The gastric peptic activity derives from a diversity of intracellular enzymes whose activity depends on the rate of secretion and the ambient pH. Peptic activity is pH dependent and pepsin is irreversibly denatured at alkaline pH. By exposing mucosal homogenates to pH 8-0 pepsinogen remains stable but inactive and will regain full activity when reexposed to pH 2-0, the pH conventionally used in pepsin assays in vitro.

The relation between total gastric pepsinogen secretion in vitro and the peptic activity in vivo is not fully understood. An effort to correlate mucosal pepsinogen accumulation with total peptic activity and peptic cell mass shows good correlation between these parameters in normal and inflamed gastric mucosa. In this study, patients with superficial gastritis showed significant reduced pepsinogen content and secretion in the presence of a reduced chief cell mass. No clinical data regarding the aetiology of superficial gastritis in these patients are given.

The fact that *H. pylori* infected gastric mucosa has normal pepsinogen activity indicates adequate zymogen production and storage. Pepsinogen synthesis has been found closely linked to secretion and depletion of stores by a well regulated feedback mechanism under in vitro conditions. The decreased activated pepsinogen activity is possibly the result of local inactivation of secreted pepsin by bacteria or their metabolites or alternately, backflow into the circulation through an epithelium with altered permeability. Supporting this concept is the fact that serum pepsinogen I activity has consequently found to be raised in both adults and children with *H. pylori* associated antral gastritis and these concentrations return to normal in most patients after successful therapy. An alternative possibility for reduced total peptic activity and activated pepsinogen in the antral musoca of *H. pylori* gastritis may be the utilisation of these proteins as energy substrate by the bacteria colonising the stomach.

The mechanism by which *H. pylori* causes reduced peptic activity is unknown. The organism induces decreased acid secretion, at least in the early phase of the disease but this may persist for weeks or even months. Suppression of acid secretion seems to be directly associated with the presence of the organism overlying the gastric mucosa and to be reversed by antibiotic therapy in the course of the disease. Similarly, our data confirm the direct relationship between active disease and decreased peptic activity as well as normalisation of the activity after antibiotic therapy and eradication of the infection.

The efficacy of metronidazole and amoxicillin has recently been assessed in a group of 32 children with non-specific abdominal pain and *H. pylori* gastritis. Thirty of 32 (94%) children were cleared of *H. pylori* after a six week treatment and nine of 12 (75%) of these still remained free of *H. pylori* after six months. These results support the 100% eradication in the 13 patients re-investigated in this study. Glupczynski and Buret in their recent review article also suggest...
that combination therapy of a bismuth salt and an antibiotic, or two different antibiotics alone, will improve the eradication rate of H pylori and reduce the risk of resistance development.20

Experimental inhibition of 14C aminopyrine accumulation of rabbit parietal cells in vitro by whole organisms or sonicated bacteria isolated from patients with H pylori infection suggest the existence of an inhibitory protein.21 The protein was further shown to inhibit cAMP release of gastric fundic biopsies and to prevent its stimulation by histamine.22 In this regard the adrenergic stimulated pepsinogen secretion mediated by cAMP,23 may become an alternate pathway of bacteria induced decrease of peptic activity.

Reduced peptic activity in consonance with achlorhydria may favour opportunistic infection located in or in transit through the upper gastrointestinal tract of these patients. The relationship between these alterations, hypergastrinaemia and chronic ulcer disease has also been suggested.24

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