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ORIGINAL RESEARCH

Reduced secretion of epidermal growth factor in duodenal ulcer patients with *Helicobacter pylori* infection

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Abstract

AIM: To investigate the concentration changes of epidermal growth factor (EGF) in duodenal ulcer patients with *Helicobacter pylori* (*H. pylori*) infection.

METHODS: Immunoreactive concentration of somatostatin, gastrin and epidermal growth factor of gastric and saliva juice in healthy volunteers, and chronic gastritis and duodenal ulcer patients with *H. pylori* infection were measured by radioimmunoassay.

RESULTS: Gastrin concentration of gastric juice in *H. pylori*-positive chronic gastritis ($P > 0.05$) and duodenal ulcer patients ($P < 0.01$) was higher than that of healthy volunteers ($P < 0.05$), whereas som atostatin concentration of gastric juice in chronic gastritis ($P < 0.05$) and duodenal ulcer patients ($P < 0.01$) was lower than that in healthy volunteers. Furthermore, EGF levels of gastric and saliva juice in duodenal ulcer patients with *H. pylori* infection ($n = 10$, 272.0 ng/L ± 96.3 ng/L and 8.3 ng/L ± 2.4 ng/L, respectively) were significantly lower than that in healthy volunteers ($n = 12$, 405.6 ng/L ± 35.6 ng/mL and 22.0 ng/L ± 17.0 ng/L, respectively) and in *H. pylori*-positive chronic gastritis patients ($n = 25$, 423.0 ng/L ± 104.0 ng/L and 22.0 ng/L ± 11.1 ng/L, respectively ($P < 0.05$).

CONCLUSION: A lower secretion of EGF may be a causative factor in the pathogenesis of *H. pylori*-positive duodenal ulcer.

Key words: Duodenal ulcer; *Helicobacter pylori*; Gastritis epidermal growth factor; Gastrins; Somatostatin

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INTRODUCTION

Increasing evidence suggests that *Helicobacter pylori* (*H. pylori*) may play a role in the pathogenesis of duodenal ulcer although the mechanism remains unsolved[1-3]. More than 90% of patients with duodenal ulcer are concomitant with *H. pylori* infection in gastric antrum which leads to chronic active gastritis. *H. pylori*-positive patients with duodenal ulcer are known to have a high gastric acid output, an increased parietal cell mass and a raised basal as well as a bombesin/gastrin releasing peptide and meal stimulated gastrin secretion[4-6]. The patients also have a decreased somatostatin level in gastric juice and antral mucosal tissue[7]. Eradication of *H. pylori* may decrease hypergastrinemia, enhance antral somatostatin secretion, and then reduce gastric acid secretion[8-10]. However, hypergastrinemia and decreased antral somatostatin secretion cannot explain the relation between *H. pylori* and duodenal ulcer, because there was no consistent relationship between chronic *H. pylori* infection and acid secretion (either basal or stimulated) observed [11,12].

Epidermal growth factor (EGF) is a polypeptide of 6000 daltons containing 53 amino acid residues[13]. The peptide has been proved to have an action to inhibit the gastric acid secretion in several species including humans, prevent the gastric mucosa from damage, and promote the healing of experimental

gastric ulcers in rats[14-16]. Sialoadenectomy in rats damages the integrity of gastric mucosa[16,17]. Mucosal ulceration can induce a novel EGF secreting cell lineage in human gastrointestinal stem cells[18]. These evidences suggested that EGF may play an important role in the pathogenesis of duodenal ulcer.

The present study was to determine the changes of basal acid output, the secretion of gastrin, somatostatin and EGF in normal subjects, and in patients with chronic gastritis and duodenal ulcer due to *H. pylori* infection, so as to elucidate the possible role of EGF in the pathogenesis of duodenal ulcer.

MATERIALS AND METHODS

Subjects

Thirty-nine *H. pylori*-positive patients and 14 healthy volunteers were studied. None of them had taken steroids, nonsteroidal anti-inflammatory drugs, antibiotics, anticoagulants, or any investigational medication during the previous 4 wk. Exclusion criteria included the history of chronic gastrointestinal and other

active illnesses. Eligible patients gave informed written consent before enrolment. They were assigned to two groups based on the endoscopic results: Chronic gastritis group, consisting of 10 men and 17 women (mean age 38.5 years) and duodenal ulcer group, including 5 men and 7 women (mean age 32.8 years). Healthy group included 4 men and 10 women (mean age 37.4 years).

Endoscopy and basal acid output measurement

Gastroduodenoscopy was performed using an Olympus endoscope with standard biopsy forceps. Four fragments from the lesser curvature of the antrum at 1-2 cm from the pylorus and 2 fragments from the greater curvature of the corpus were obtained. The biopsy forceps were disinfected with 70% ethanol after each use. Before the biopsy, sampling of gastric juice as much as possible was obtained. The basal acid output was measured by titration of gastric juice in one hour with 10 mmol/L NaOH.

H. pylori diagnosis

The presence of *H. pylori* in the antrum and corpus was evaluated by microbiologic methods including culture[19], rapid urease test (commercial kits from Sanqing Biological Reagents Co, Fuzhou, China) and Warthin starry or Giemsa stains[20]. At least two of these tests should be positive in patients with *H. pylori infection*. *H. pylori* identified by Warthin Starry or Giemsa stains was graded as[21]: 0, null; 1+, a small number of bacteria (up to 20/gastric pit) presenting in a few of gastric pits; 2+, a large number of bacteria (more than 20/gastric pit) presenting in several gastric pits or a small number of bacteria in many gastric pits; 3+, a large number of bacteria presenting in nearly all gastric pits.

Histology

Biopsy fragments taken from the antral and oxyntic mucosa were fixed in 10% buffered formalin (pH7.4), dehydrated and embedded in paraffin, and stained 5 μm thick with hematoxylin and eosin for histological evaluation. All sections were examined by one of the investigators (R.Z.R.), who was unaware of the previous histologic results, endoscopic findings, rapid urease tests and culture results.

Extract and assay of somatostatin, gastrin and EGF from gastric and saliva juice

Samples from gastric juice and saliva juice were boiled in water for 10 min, centrifuged, and pH adjusted to 7.0-7.5 by 10 mmol/L NaOH titration, then transfered to plastic tubes, and frozen with 500 KU/mL trasylol at 30 ℃. Gastrin, somatostatin and EGF were measured using radioimmunoassay kit from National Institute of Atomic Energy, Beijing, China, and Beijing Hai-Ke-Ri Biotech Centre, Beijing, China, respectively. Somatostatin, gastrin and EGF concentrations of gastric or saliva juice were expressed as ng/L.

Statistical analysis

Data of somatostatin, gastrin and EGF were expressed as mean ± SD and analyzed using one-way ANOVA (SNK test). The differences were considered significant when $P < 0.05$.

RESULTS

H. pylori status, gastric histology, and basal acid output were investigated in 27 gastritis patients, 12 duodenal ulcer patients, and 14 volunteers. *H. pylori* were found in 2 of 14 healthy voluteers, 25 of 27 patients with chronic active gastritis, and 10 of 12 duodenal ulcer patients, and in none of those with normal gastric mucosa (Table 1). Presence of *H. pylori* in chronic active gastritis patients was more common than in duodenal ulcer patients. In addition, active inflammatory infiltration tended to attack corpus mucosa in chronic gastritis patients (14/27), and those who had low basal acid output. Four of 12 duodenal ulcer patients had corpus inflammation and high basal acid output. Table 2 summaries the concentration of somatostatin, gastrin and EGF of gastric and saliva juice in *H. pylori*-positive patients and *H. pylori*-negative healthy volunteers. Gastrin concentration of gastric juice in duodenal ulcer was significantly higher than that in control group ($P < 0.01$). There were no significant differences in gastrin concentration between the chronic gastritis group and the control group. On the other hand, the somatostatin concentration of gastric juice in chronic gastritis and duodenal ulcer group was lower than that in the control group ($P < 0.05$ or 0.01). In *H. pylori*-positive chronic gastritis group, the levels of EGF in saliva juice and gastric juice were 423.0 ng/L ± 104.0 ng/L, and 22.0 ng/L ± 11.1 ng/L, with no differences as compared with those in the control group (405.6 ng/L ± 35.6 ng/L and 22.0 ng/L ± 17.0 ng/L, respectively), ($P > 0.05$). However, the levels of EGF in saliva and gastric juice in chronic gastritis group and control group were both significantly higher than those in the duodenal ulcer group (272.0 ng/L ± 96.3 ng/L and 8.3 ng/L ± 2.4 ng/L, respectively), ($P < 0.05$).

DISCUSSION

This study showed for the first time that the levels of EGF in duodenal ulcer patients with *H. pylori* infection were much lower than those of the healthy volunteers and chronic gastritis patients with *H. pylori* infection, and also confirmed the previous fingings that *H. pylori* infection can enhance gastrin secretion and lower somatostatin level, which can cause abnormal secretion of gastric acid[4,7-10].

A strong association between *H. pylori* and diseases of upper gastrointestinal tract has been reported[1,2]. The causal relationship between *H. pylori* and chronic superficial gastritis is well established, but that between *H. pylori* and peptic ulcer is rather difficult to establish on the basis of the available data[1]. The suggested mechanisms in antral organism cause a duodenal lesion including bacterial colonization of gastric metaplasia in the duodenum[22], secondary changes in gastric acid or duodenal bicarbonate secretion[23,24], or the changes caused by the infected organism and/or the inflammatory response to the host[25,26]. Recently, the changes in gastric acid caused by *H. pylori* infection have drawn more attention, for inhibition of gastric acid secretion promoted duodenal ulcer healing even in the presence of *H. pylori* and inflammation of gastric antrum[27].

The possible hypotheses in explaining the relationship between *H. pylori* infection and duodenal ulcer have been described as "gastrin link"[2,28,29] or "somatostatin link"[10,30], as duodenal ulcer patients with *H. pylori* infection often have hypergastrinemia, which may increase parietal cell mass and reduce somatostatin secretion known to promote the gastric secretion[4-6,27-30]. On the contrary, there was no consistent relationship between chronic *H. pylori* infection and acid secretion observed[11,12,30,31]. Kang *et al*[11] showed that patients with duodenal ulcer or combined gastric and duodenal ulcer had similar gastric acid outputs irrespective of the presence or absence of *H. pylori*. However, gastric ulcer patients with *H. pylori* had higher basal and maximal acid output when compared to patients without *H. pylori*. McColl *et al*[31] have observed that after eradication of *H. pylori* in duodenal ulcer, daytime intragastric pH and nocturnal acid secretion were unchanged, even after 7 mo. Our results showed that hypochlorohydria in chronic gastritis patients and high acidity in duodenal ulcer patients with *H. pylori* infection, both had enhanced gastrin secretion and reduced somatostatin secretion. Low gastric acidity in chronic gastritis may be elicited by the action of "protein inhibitor of gastric acid"[2,32], but it would not be excluded that parietal cells may be damaged or inhibited by active inflammation of oxyntic mucosa because of host's response to *H. pylori*. The above results suggested that "gastrin link" or "somatostatin link" could not elucidate the mechanism of *H. pylori* in the pathogenesis of duodenal ulcer[30], and other factor (s) should be taken into account.

The pathogenesis of peptic ulcer can be considered in terms of aggressive factors overwhelming mucosal defense. EGF should be one of such factors. In the previous studies it was shown that the EGF is localized in the submandibular and Brunner's glands of the rats and humans, and exerts protection of gastric mucosa and inhibition of gastirc acid secretion[14,16]. Olsen *et al*[15] showed that the oral administration of human EGF/URO may benefit the healing of chronic duodenal ulcers in rats. Gastric mucosal integrity in rats of removed submandibular gland to reduce EGF levels in gastric juice was prone to be damaged[16]. Chen *et al*[33] compared patients with

Table 1 Profile of *Helicobacter Pylori* infection and basal acid output

Group	*n*	Symptom duration (> 4 mo)	*H. Pylori* infection				Mucosal active inflammation		Basal acid output (mmol/h)		
			0	+	+ +	+ + +	corpus	antrum	0-9	2-5	> 5
Con	14	0	12	2	0	0	2	0	0	14	0
CG	27	3	2	9	5	10	27	14	13	9	5
DU	12	3	2	8	1	1	12	4	0	1	11

Con: Healthy volunteers; CG: Chronic gastritis; DU: Duodenal ulcer.

Table 2 Concentration of somatostatin, gastrin and epidermal growth factor in *Helicobacter Pylori*-positive patients and *Helicobacter Pylori*-negative healthy volunteers (ng/L)

Group	*n*	Gastrin	Somatostatin	Epidermal growth factor	
		Gastric juice	Gastric juice	Saliva juice	Gastric juice
Con	12	71.2 ± 18.3	105.2 ± 33.5	405.6 ± 35.6	22.0 ± 17.0
CG	25	84.1 ± 24.0	88.6 ± 24.8[a]	423.0 ± 104.0	22.0 ± 11.1
DU	10	109.2 ± 24.5[b]	52.4 ± 13.8[b]	272.0 ± 96.3[b]	8.3 ± 2.4[a]

[a]$P < 0.05$, [b]$P < 0.01$, compared with control group. Con: Healthy volunteers, CG: Chronic gastritis, DU: Duodenal ulcer.

gastric ulcer and duodenal ulcer to healthy subjects and observed that EGF levels of plasma and saliva juice in the former were lower than that in the latter. Their results are similar to ours, but different from those of Hirasawa *et al*[34] who observed that salivary EGF output in patients with gastric, duodenal and gastroduodenal ulcers was higher than that in normal subjects, however, salivary EGF output in refractory peptic ulcer patients was much lower. Therefore, it is reasonable that any factor (s) which reduce or inhibit EGF secretion may be able to promote gastric mucosal damage. Based on the above evidences, we think that reduced EGF secretion may play an important role in the development of duodenal ulcer with *H. pylori* infection.

The secretion of less EGF is postulated to be predominated by genetic factors or effects of eradication of *H. pylori* on the changes of EGF levels in saliva and gastric juice (unpublished data), which showed that EGF levels in 3 of 4 patients became normal and one remained unchanged in one month. We presume that if less EGF secretion is caused by *H. pylori* infection, alternative explanations for the phenomenon are that cytokines or antibodies resulting from the host's defensive response to *H. pylori* infection should be the inhibitor of secretion of EGF.

In conclusion, our study shows that gastric acidity is higher in *H. pylori*-positive duodenal ulcer patients than that in *H. pylori*-positive chronic gastritis and healthy subjects. Contents of gastrin of gastric juice in *H. pylori* positive chronic gastritis and duodenal ulcer patients were higher than in healthy subjects, and the somatostatin concentration was lower in healthy subjects. Levels of EGF of gastric and salivary juice were also lower than those in the chronic gastritis patients and duodenal ulcer patients with *H. pylori* infection. Based on these results, we assume that EGF may play a causal role in the pathogenesis of *H. pylori*-positive duodenal ulcer.

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