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Ascorbic acid secretion in the human stomach and the effect of gastrin

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Abstract

AIM To investigate the changes of gastric mucosal ascorbic acid secretion in patients with nonulcer dyspepsia and the effect of gastrin on it, and to relate any observed changes to *H. pylori* infection and mucosal histology.

METHODS Ascorbic acid secretions in patients were examined by collecting continuously gastric juice for one hour after having aspirated and discarded fasting gastric juice. Using the clearance rate (mL/min) of ascorbic acid from blood to gastric juice represented ascorbic acid secretion in the gastric mucosa. Ascorbic acid concentrations in plasma and juice were measured by ferric reduced method.

RESULTS Gastric ascorbic acid secretions in *H.pylori*-positive patients (1.46**mL/min, range** 0.27-3.78**) did not significantly differ from those in *H.pylori*-negative patients (**1.25**mL/ min,** 0.47-3.14**) (*P*>**0.05**). There were no significant differences in ascorbic acid secretions between patients with mild (**1.56**mL/ min,** 0.50-3.30**), moderate (**1.34**mL/min,** 0.27 -2.93**) and severe (**1.36**mL/ min,** 0.47-3.78**) inflamm ation (*P*>**0.05**). There were no significant differences in ascorbic acid secretions between patients without activity (**1.45**mL/min,** 0.27-3.14**) and with mild (**1.32 mL/min,** 0.61-2.93**), moderate (**1.49**mL/min,** 0. 50-3.78**) and severe (**1.43 **mL/min,** 0.51-3.26**) activity of chronic gastritis either (*P*>**0.05**). Ascorbic acid secretions in patients with severe atrophy (**0.56**mL/min,** 0.27-1.20**) were markedly lower than those in patients with out atrophy (**1.51**mL/min,** 0.59-3.30**) and with mild (**1.43**mL/min,** 0.53-3.78**) and moderate (**1.31**mL/min,** 0.47-3.16**) atrophy (*P*<**0.005**). There was a significant negative correlation between ascorbic acid secretion and severity of atrophy (correlation coefficient = -**0.43, *P*<**0.005**). After administration of pentagastrin, ascorbic acid secretions were markedly elevated (from** 1.39**mL/min,** 0.36-2.96 **to** 3.53**mL/min,** 0.84-5.91**) (*P*<**0.001**).**

CONCLUSION Ascorbic acid secretion in gastric mucosa is not affected by *H. pylori* infection. Gastric ascorbic acid secretion is markedly related to the severity of atrophy, whereas not related to the severity of inflammation and activity. Gastrin may stimulate gastric ascorbic acid secretion . A decreased ascorbic acid secretion may be an important factor in the link between atrophic gastritis and gastric carcinogenesis.

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INTRODUCTION

Ascorbic acid, a powerful antioxidant, is potentially important for the prevention of gastric cancer. It may be able to protect against gastric cancer by scaven ging nitrite and preventing the formation of carcinogenic N-nitroso compounds within gastric juice[1-5]. In addition, it is capable of scavenging reactive oxygen metabolites[6-8] that may damage gastric mucosal DNA[7] and play a role in the development of experimental gastric carcinoma and precancerous lesions induced by N-methyl N-nitro N-nitrosoguanidine[9] whereby it may also protect against gastric cancer. Various epidemiological studies have clearly shown that high dietary vitamin C intake may reduce the risk of gastric cancer[10-12]. *H. pylori* infection has been associated with gastritis, peptic ulcer and an increased risk of gastric cancer[13-17], but its precise role in gastric carcinog enesis is still unknown[18]. Some previous studies have shown that asco rbic acid is present in the gastric juice of healthy subjects in concentrations considerably higher than those in plasma[19-21]. This high ratio of gastric juice to plasma ascorbic acid implies active secretion of ascorbic acid by gastric mucosa. It has been recognized recently that gastric juice ascorbic acid concentrations are decreased markedly in subjects with *H. pylori* infection[22-27] and chronic

gastritis[19-21,26]. This change of gastric juice ascorbic acid concentrations in *H. pylori*-infected patients may be an important factor in the link between *H. pylori* infection and gastric carcinogenesis. However, these studies only observed the changes of ascorbic acid concentrations in gastric juice. The changes of ascorbic acid secretion in gastric mucosa have rarely been studied. The purpose of this study is, therefore, to investigate the changes of ascorbic acid secretion in gastric mucosa, to assess their relationships to *H. pylori* infection and mucosal histology, and to explore the effect of gastrin on ascorbic acid secretion.

SUBJECTS AND METHODS

Subjects

Fifty-five consecutive cases shown nonulcer dyspepsia by endoscopy and type B ultrasonography were studied. None of them had undergone upper gastrointestinal surgery, nor had taken any drugs over the previous two weeks.

Methods

Collection of samples All patients were studied at the same time (6:00 am) after a 10-hour overnight fast. A 2mL sample of venous blood was withdrawn into a heparinised tube for measurement of plasma ascorbic acid concentration. Then a nasogastric tube was inserted into the patient's stomach. Gastric juice was continuously collected for one hour by a constant suction pump after having aspirated and discarded fasting gastric juice. One hour later, 20 consecutive patients of them were immediately given pentagastrin (6μg/kg) intramuscularly and followed by collecting gastric juice for one hour again. Each gastric sample was analyzed for volume and ascorbic acid concentration.

Ascorbic acid measurement Venous blood and gastric juice sam ples were immediately stored at 4℃ after being collected. Ascorbic acid conce ntrations in the plasma and gastric juice were measured by ferric reduced method[28] within 10 hours. This method is based on the quantitative rapid reduction of ferric to ferrousion by ascorbic acid and the colorimetric measurement of the ferrousion through its formation of a colored complex with bathophena nthroline. Briefly, the venous blood samples were centrifuged at 3000×*g* for 20min and gastric juice for 40min before ascorbic acid assay. Then 0.2 mL aliquots of the gastric juice and the plasma supernants were mixed with 0.75mL of 5% tricloroacetic acid to precipitate protein, which were then removed by centrifugation at 3000 *g* for 20min. Subsequently, 0.5mL of the further supernants were mixed with 1.0mL of acetate buffer, 2.0 mL of bathophenanthroline solution, 0.5mL of ferric chloride solution, and 0.2mL of phoshporic acid solution. Finally, the concentration was determined with a spectrophotometer at 536nm against standards. Ascorbic acid secretion in gastric mucosa was estimated by clearance rate of ascorbic acid from blood to gastric juice (mL/min), which was calculated by the formula: clearance rate = GV/Bt, where V is the volume of gastric juice collected over t min (mL), G the concentration of ascorbic acid in gastric juice (μmol/L), B the concentration of ascorbic acid in plasma (μmol/L), t = 60min.

***H.pylori* detection and histopathological examination** Three antral biopsies were obtained from every patient for *H.pylori* detection and histopathological examination. One biopsy from the lesser curvature was used for a rapid urease test. Other two biopsies (one from the lesser curvature and another from the greater curvature) were used for Warthin-Starry stain for *H.pylori* and hematoxylin-eosin stain for histopathological examination. Patients were considered to be *H. pylori* positive if one of the two tests was positive, whereas to be *H. pylori* negative if all negative. The severity and extent of gastric inflammation, activity and atrophy were graded on a scale of mild, moderate and severe according to the Sydney System[29].

Statistical analysis The data in the text were expressed as median values with ranges. Statistical analysis was carried out using non-parametric Mann-Whitney U test. The Spearmen rank correlation test was used to calculate correlation coefficients. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

Among the 55 patients studied, 31 were *H. pylori* positive and 24 negative. According to the histological division of the Sydney System, 14 had mild inflammation, 17 moderate inflammation, and 24 severe inflammation; 16 had no activity, 11 mild activity, 14 moderate activity and 14 severe activity; 17 had no atrophy, 16 mild atrophy, 12 moderate atrophy and 10 severe atrophy.

Gastric ascorbic acid secretion and H.pylori infection

Gastric ascorbic acid secretions in *H.pylori* -positive patients (1.46mL/min, 0.27-3.78) did not differ significantly from those in *H. pylori* negative patients (1.25mL/min, 0.47-3.14) ($P>0.05$).

Gastric ascorbic acid secretion and gastric inflammation

Gastric ascorbic acid secretions in patients with mild, moderate and severe inflammation were respectively 1.56 mL/min (0.50 - 3.30), 1.34mL/min (0.27 - 2.93) and 1.36mL/min (0.47 - 3.78). There were no significant differences between them ($P>0.05$).

Gastric ascorbic acid secretion and activity of gastritis

Gastric ascorbic acid secretions in patients without activity and with mild, moderate and severe activity were respectively 1.45mL/min (0.27 - 3.14), 1.32 mL/ min (0.61 - 2.93), 1.49 mL/ min (0.50 - 3.78) and 1.43mL/min (0.51 - 3.26). There were no significant differences between them either (P>0.05).

Gastric ascorbic acid secretion and gastric atrophy

Gastric ascorbic acid secretions in patients without atrophy and with mild, moderate and severe atrophy were respectively 1.51 mL/ min (0.59 - 3.30), 1.43 mL/min (0.53 - 3.78), 1.31 mL/ min (0.47-3.16) and 0.56mL/min (0.27 - 1.20). Ascorbic acid secretions in patients with severe atrophy were significantly lower than those in patients without atrophy and with mild and moderate atrophy (P < 0.005). There were no significant differences between patients without atrophy and with mild and moderate atrophy (P>0.05). With the progress of atrophy, ascorbic acid secretion was gradually decreased, with a significant negative correlation (correlation coefficient = -043, P<0.005).

Effect of gastrin on ascorbic acid secretion

In 20 patients given pentagastrin, gastric ascorbic acid secretions rose from 1.39mL/min (0.36-2.96) to 3.53mL/min (0.84 - 5.91). There was very significant difference between them (P<0.001).

DISCUSSION

Some previous studies have found that gastric ascorbic acid concentrations in *H. pylori*-positive patients and patients with chronic gastritis are markedly lower than those in *H. pylori*-negative patients and healthy controls[19-27]. However, little is known the changes of ascorbic acid secretion in the stomach. It is also uncertain whether low gastric juice ascorbic acid concen trations in *H. pylori* - infected patients are induced by impairing gastric mucosal ascorbic acid secretary capacity or other causes. Some researchers speculate that lower gastric juice ascorbic acid concentrations in *H. pylori*-infected patients are mainly related to the impaired gastric secretary capacity in the presence of gastritis induced by *H. pylori* infection. The reason for this notion is that there is a significant negative correlation between gastric juice ascorbic concentration and grading of polymorphonuclear leucocyte infiltration induced by *H. pylori* infection[22,25]. However, some studies have shown that *H. pylori* can potentiate the polymorphonuclear leucocyte oxidative burst[30,31], which is accompanied by a considerable production of reactive oxygen metabolites. Ascorbic acid in gastric juice may be in itself consumed in the course of scavenging these reactive oxygen metabolites. In addition, some studies on gastric mucosal ascorbic acid levels suggest that gastric mucosal ascorbic acid concentration is not related to *H. pylori* infection[32,33] and presence of inflammation[34]. In order to investigate whether gastric ascorbic acid secretion is affected by *H.pylori* infection and the changes of gastric mucosal histology, we made an investigation on gastric ascorbic acid secretion in patients with *H. pylori* infection and chronic gastritis through collecting continuously gastric juice for one hour after having aspirated and discarded fasting gastric juice. We found that Gastric mucosal ascorbic acid secretions in *H. pylori*-positive patients did not significantly differ from those in *H.pylori*-negative patients. The changes of gastric ascorbic acid secretion were independent of the severity and extent of gastric inflammation and activity. However, gastric ascorbic acid secretions in patients with severe atrophy were significantly lower than those in patients without atrophy or with mild and moderate atrophy. There was a significant negative correlation between gastric ascorbic acid secretion and severity of atrophy. The results indicate that gastric ascorbic acid secretion is not influenced by *H. pylori* infection. *H. pylori* infection might lower ascorbic concentration in gastric juice through other mechanisms. A number of reasons could be responsible for low gast ric juice ascorbic acid concentration induced by *H. pylori* infection. In addition to potentiating polymorphoonuclear leucocyte burst described above, one study has shown that the cytochrome c-like water soluble oxidant of *H.pylori* may destroy ascorbic acid in the gastric juice of infected patients[35]. *H. pylori* can also secrete many kinds of enzymes which have higher enzyme activity[36]. It has been shown that *H. pylori* markedly influences the metabolism of certain endogenous organic molecules[36-38]. These enzymes and the local biochemical alterations induced by *H. pylori* might influence the metabolism of ascorbic acid and lower the ascorbic acid concentration in gastric juice. Ascorbic acid is a powerful antioxidant and is potentially important for the prevention of gastric cancer. It may protect against gastric cancer by either preventing the formation of carcinogenic N-nitroso compounds in gastric juice[1-5] or scavenging reactive oxygen metabolites that may damage gastric epithelium[6-8]. Various studies have shown that ascorbic acid levels in gastric juice are related to the incidence of gastric cancer[39-41]. Blood ascorbic acid levels in patients with gastric cancer were markedly lowered[42-44]. These studies suggest that the decrease of ascorbic acid in gastric juice can increase the risk of gastric carcinogenesis. Chronic atrophic gastritis is an important precancerous condition and has been associated with an increased

risk of gastric carcinogenes is[45,46]. Previous studies have shown that an environment of hypochlorhydria in atrophic gastritis favors an overgrowth of nitrite-forming bacteria and increasing the formation of nitrite and N-nitroso compounds[47-50]. However, as ascorbic acid is a powerful antioxidant, it may react with nitrite to form dehydroascorbic acid and nitrous oxide and prevent the formation of carcinogenic N-nitroso compounds. Only when the nitrite in gastric juice is in excess of reduced capacity of ascorbic acid in gastric juice, are carcinogenic N-nitroso compounds available. In the present study, it has been found that gastric ascorbic acid secretions in patients with severe atrophy are markedly decreased. There is a significant negative correlation between gastric ascorbic acid secretion and severity of atrophy. We speculate that this change of gastric ascorbic acid secretions in patients with atrophy may be an important factor in the link between atrophic gastritis and gastric carcinogenesis. Some studies have shown that the supplementation of ascorbic acid may elevate the ascorbic acid concentration in gastric juice[34,51,52], so the diet rich in vitamin C may decrease the risk of gastric cancer in patients with gastric atrophy.

The mechanism whereby gastric mucosa secretes ascorbic acid is unclear. Some studies on the rats have shown that gastric ascorbic acid secretion is physiolog ically regulated not only by muscarinic receptor-associated cholinergic stimul ation[53] but also by CCK receptor-associated humoral stimulation[54]. Our study found that gastric ascorbic acid secretion was markedly elevated after given pentagastrin. The result indicates that gastrin may also stimulate gastric ascorbic acid secretion. In the present study, it was observed that the changes of gastric ascorbic acid secretion were related to the severity of atrophy, whereas not related to the severity of inflammation and activity . As the histologic alteration of atrophy is the loss of specialized gland, we speculate that gastric glands may participate in the secretion of ascorbic acid. However, the detailed mechanism about gastric ascorbic acid secretion will be further investigated.

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