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G- and D-Cell Populations, Serum and Tissue Concentrations of Gastrin and Somatostatin in Patients with Peptic Ulcer Diseases

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Background: *Gastric acid is the most important pathophysiologic determinant in the development of peptic ulcer diseases, and gastrin and somatostatin are believed to be physiologic hormonal regulators in gastric acid secretion. The aim of this study is to investigate patterns of these peptides, both in serum and in tissue, and to correlate with numbers of their secretory cells in the antral and the duodenal bulb mucosa.*

Methods: *The study population was made up of 256 patients with peptic ulcer (duodenal ulcer, 127; gastric ulcer, 74) and 55 patients with non-ulcer control subjects. Serum and mucosal concentrations of G17, G34 and somatostatin were measured by radioimmunoassay technique and peptides producing cells were identified immunohistochemically using peroxidase-antiperoxidase staining technique.*

Results: *Serum G17 concentration was significantly decreased in duodenal ulcer patients (93.4±36.0 pg/ml) and G34 were more than twice as high as G17 both in patients with gastric and duodenal ulcer (210.6±50.6 pg/ml and 202.7±48.1 pg/ml vs 103.8±41.8 pg/ml and 93.4±36.0 pg/ml). Antral G17 (19.9±14.8 mcg/g, tissue) and G34 (26.6±18.5 mcg/g, tissue) were increased in duodenal ulcer patients and duodenal G17 (12.5±9.5 mcg/g. tissue in Gu and 8.5±7.4 mcg/g. tissue in DU) and G34 (15.7±12.6 mcg/g. tissue in GU and 13.9±12.0 mcg/g. tissue in DU) concentrations were found to be increased in both gastric and duodenal ulcer patients than in non-ulcer subjects (G17: 5.3±4.9 mcg/g. tissue. G34: 6.5±4.4 mcg/g. tissue). Only the antral somatostatin concentration was significantly increased in duodenal ulcer patients (5.3±5.9 mcg/g. tissue).*

Numbers of the antral G-and D-cell were lowest in GU patients (48.1±47.4 and 7.9±12.3) and numbers of both cells decreased proportionately with the severity of atrophic gastritis and/or intestinal metaplasia of the gastric mucosa. D/G cell ratio between non-ulcer subjects and DU patients was similar (1 : 4 and 1 : 5) but slightly increased in GU patients (1 : 7). There was no correlation between numbers of each peptide-producing cells and serum or mucosal concentration of gastrin and soamtostatin.

Conclusions: *Patients with duodenal ulcer had decreased level of serum G17 in the fasting state while mucosal concentrations of G17 and G34 were increased in the antrum and the duodenal bulb. Patients with garic ulcer had increased levels of G17 and G34 only in the duodenal bulb mucosa. Only the antral soamtostatin concentration was significantly increased in duodenal ulcer patients. Patients with gastric ulcer had lowest numbers of G- and D-cells in the antrum and numbers of both cells decreased proportionately with the degree of chronic atrophic gastritis and/or intestinal metaplasia of the gastric antrum. Numbers of G- and D-cells were not correlated with the serum or mucosal concentrations of each peptide.*

Key Words: *G17, G34, Somatostatin, G-Cell and D-Cell*

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INTRODUCTION

Of gut peptides, gastrin and somatostatin have been considered as important pathogenic factors in developing the peptic ulcer disease. In duodenal ulcer (DU) patients, there is a significantly higher increase in serum gastrin after a protein rich meal[4,5], insulin hypoglycemia[6] or sham feeding[7], than in healthy controls. The exaggerated gastrin response of DU patients may result from an increased number of antral and/or duodenal G-cells, an increased antral and/or duodenal gastrin content or increased release of higher molecular-weight gastrin components characterized by a longer half-life.

In the stomach, somatostatin is a powerful inhibitor of gastrin and gastric acid secretion. This inhibitory action in the stomach suggests that somatostatin may play a role in diseases when there is abnormal gastric secretion. In the normal antrum, somatostatin-secreting D-cells are located in the mid-zone of the antral mucosa, adjacent to gastrin-secreting G-cells. In normal conditions, there are eight times as many G cells as there are inhibitory D cells in the antrum. In most subjects with DU. the normal ratio (D : G) of 1/8 remains unchanged but, in certain cases, relative somatostatin deficiency could be present, and this condition could explain the over-reactivity of G-cells to their releasing stimuli in these patients[8].

Recently, the interaction of gastrin and somatostatin in the gastric antrum has gained interest and several studies on their concentrations and on the patterns of G- and D-cell have been carried out[9~12].

In this report, we have measured serum and mucosal concentrations of the molecular forms of gastrin and somatostatin, and then made a comparison between these peptides concentrations and G- and D-cells populations in the antral and duodenal bulb mucosa in patients with peptic ulcer and in non-ulcer control subjects.

MATERIALS AND METHODS

1. Patients

The study populations were consisted with 256 patients of whom 127 patients were DU (96 male patients; average age 37.3 years, range 18-64 years. 31 female patients; average age 46.6 years, range 18-73 years) and 74 patients were GU (60 male patients; average age 41.4 years, range 20-63 years. 14 female patients; verage age 49.7 years, range 19-65 years). Non-ulcer control subjects were made up of 18 male patients (average age 35. 1 years, range 20-63 years) and 37 female patients (average age 34.5 years, range 16-66 years) (Table 1).

2. Methods

Active ulcer craters were confirmed by endoscopy in each patient and the benignancy was proved by the histopathological examination of each biopsy specimen in cases with GU. Before performing endoscopy, a sample of blood was taken in each patient for the measurement of serum concentrations of gastrin-17 (G17), gastrin -34 (G34) and somatostatin. All samples were centrifuged immediately and serum were stored below-20°C until the assay. Gastro-duodenal endoscopy was performed after an overnight fast with the Olympus P10 (Japan) endoscope.

1) Tissue Sampling

During the time of endoscopy, specimens of antral or duodenal bulb mucosa were obtained by forceps biopsy. Usually, four biopsy specimens were obtained from the normally appearing gastric antrum and the duodenal bulb. Antral mucosa were taken from the lesser curvature site of the antrum, approximately 5 cm proximal to the pyloric ring. The average weight of the forceps biopsies was as follows: antral mucosa 8.4 ± 0.7 mg(range 4.6-14.6); duodenal mucosa 7.2 ± 0.5 mg (range 3. 5-11.2). The samples were either fixed immediately for histological investigation or frozen with liquid nitrogen gas and then homogenized with 0.5 to 1. 0 ml of distilled water and stored in a deep-freeze (-70°C) until peptides assay.

2) Measurement of G17, G34 and Somatostatin Concentrations

Serum and tissue concentrations of each peptide were determined by a radioimmunoassay technique using Gastrin-17 ^{125}I, Gastrin-34 ^{125}I and Somatostatin ^{125}I RIA kit (INCSTAR Inc. USA). Antisera against G17, G34 and somatostatin were highly specific showing that each antiserum had less than 0.01% of cross-reactivity with any other peptide belonging to the same peptide family. Tissue homogenates were quickely thawed in a water bath at 27°C, centrifuged and G17, G34 and somatostatin levels were determined in the supernatant in a series of dilution from 1 : 100 to 1 : 10, 000.

3) Immunohistology

Tissue samples were immediately fixed in sodium phosphate-buffered formalin solutions of pH 7.0 and embedded in paraffin wax. Sections, 5 micron thick, were cut vertically to the mucosal surface. Immunohistochemical identification of the gastrin and the somatostatin cells was carried out by peroxidase-antiperoxidase staining technique using K 546 and K 512 DAKO-PAP Kit, system 20 (DAKO A/S, Denmark). For the staining of gastrin and the somatostatin cells, sections were deparaffinized, rehydrated and treated with 3% hydrogen peroxide solutions and were followed by an incubation with normal swine serum. Sections were allowed to react with rabbit anti-gastrin and/or anti-somatostatin antiserum. After a rinse, sections were covered with swine anti-rabbit immunoglobulin. The sections were again washed and incubated for another 20 minutes with the soluble horseradish peroxidase-rabbit antihorseradish peroxidase complex and rinsed. Finally, a substrate solution consisting of hydrogen peroxide and aminoethylcarabzloe was added. The sections were counterstained with hematoxylin and all the responsible peptide-producing cell numbers were counted under the low-power field of a microscope.

RESULTS

1. Molecular Froms of Serum Gastrins

Fasting serum concentrations of G34 were more than twice as high as G17 both in patients with GU and DU (210.6±50.6 pg/ml and 202.7±48.1 pg/ml vs 103.8±41.8 pg/ml and 93.4±36.0 pg/ml, respectively), but the difference between GU and DU patients was not significant. G17 concentration in fasting state was lowest (93.4±36.0 pg/ml) in patients with DU and was statistically significant, comparing between two ulcer groups. ($p<0.05$) (Table 2).

2. G17 and G34 Concentrations in Antral Mucosa

Mucosal G17 and G34 concentrations were varied considerably both in non-ulcer subjects and in peptic ulcer patients. As in the results of serum, antral mucosa contained larger amounts of G34 than G17 both in non-ulcer subjects and in peptic ulcer patients. Antral G17 and G34 were significantly increased in patients with DU (G17 : 19.9±14.8 mcg/g. tissue. G34 : 26.6±18.5 mcg/g. tissue) than in those of non-ulcer subjects (G17 : 12.7±9.4 mcg/g. tissue. G34 : 16.9±11.1 mcg/g. tissue) and of GU patients (G17 : 17.3±11.9 mcg/g. tissue. G34 : 21.5±13.7 mcg/g. tissue). ($p<0.05$) Differences in G17 or G34 levels between non-ulcer subjects and gastric ulcer patients and between patients with GU and DU were not significant. ($p<0.05$) (Table 3).

3. G17 and G34 Concentrations in Duodenal Bulb Mucosa

Duodenal bulb also contained higher levels of G34 than G17 in all patients. Both G17 and G34

Table 1. Charateristics of the Study Population

	Sex	No. Patients	Age (years)	
			Range	Average
Non-Ulcer Subjects	Male	18	20-63	35.1
	Female	37	16-66	34.5
Gastric Ulcer	Male	60	20-63	41.4
	Female	14	19-65	49.7
Duodenal Ulcer	Male	96	18-64	37.3
	Female	31	18-73	46.6

Table 2. Concentrations of Serum G17 and G34 in Non-Ulcer Subjects and Patients with Peptic Ulcer

	No. Patients (M/F)	G17 (pg/ml)	G34 (pg/ml)
Non-Ulcer Subjects	37/0	117.7±36.4*	—
Gastric Ulcer	38/20	103.8±41.8	210.6±50.6
Duodenal Ulcer	73/34	93.4±36.0*	202.7±48.1

Values: Mean±SD * : $p<0.05$

Table 3. Concentrations of G17 and G34 in Antral Biopsies in Non-Ulcer Subjects and Patients with Peptic Ulcer

	No. Patients (M/F)	G17 (mcg/g. tissue)	G34 (mcg/g. tissue)
Non-Ulcer Subjects	29/26	12.7± 9.4	16.9±11.1
Gastric Ulcer	27/26	17.3±11.9	21.5±13.7
Duodenal Ulcer	24/37	19.9±14.8	26.6±18.5

Values: Mean±SD
G17 : Non-Ulcer vs DU: $p<0.05$, GU vs DU: $p<0.05$
G34: Non-Ulcer vs DU: $p<0.05$, GU vs DU: $p<0.05$

Table 4. Concentrations of G17 and G34 in Duodenal Biopsies in Non-Ulcer Subjects and Patients with Peptic ulcer

	No. Patients (M/F)	G17 (mcg/g. tissue)	G34 (mcg/g. tissue)
Non-Ulcer Subjects	29/30	5.3±4.9	6.5± 4.4
Gastric Ulcer	26/34	12.5±9.5	15.7±12.6
Duodenal Ulcer	37/41	8.5±7.4	13.9±12.0

Values: Mean±SD
G17: Non-Ulcer vs GU; $p<0.05$, Non-Ulcer vs DU; $p<0.05$
G34: Non-Ulcer vs GU; $p<0.01$, Non-ulcer vs DU; $P<0.01$

Table 5. Antral and Duodenal Somatostatin Concentrations in Non-Ulcer Subjects and Patients with Peptic Ulcer

	No. Patients (M/F)	Somatostatin (mcg/g. tissue)	
		Antrum	Duodenal bulb
Non-Ulcer Subjects	22/23	1.6±1.6*	4.3±5.1
Gastric Ulcer	21/22	3.2±3.4	4.8±4.5
Duodenal Ulcer	23/18	5.3±5.9*	5.5±5.5

Values: Mean±SD *: $p<0.01$

concentrations were significantly increased in GU patients (G17 : 12.5±9.5 mcg/g. tissue. G34 : 15.7±12.6 mcg/g. tissue) and DU patients (G17 : 8.5±7.4 mcg/g. tissue. G34 : 13.9±12.0 mcg/g. tissue) then in non-ulcer subjects (5.3±4.9 mcg/g. tissue. G34 : 6.5±4.4 mcg/g. tissue). ($p<0.05$ and $p<0.01$) But the differences between patients with GU and DU were not significant ($p>0.05$) (Table 4).

4. Antral and duodenal Somatostatin Concentrations

As shown in Table 5, only the patient with DU had significantly higher levels of somatostatin in the antrum. ($p<0.01$) Antral somatostatin concentration in patients with GU disease were similar to those of non-ulcer subjects. Duodenal somatostatin concentrations were also not significantly different between non-ulcer subjects and peptic ulcer patients, and the difference between GU and DU was also insignificant. ($p<0.05$)

5. Distributions of G- and D-Cells within Antral and Duodenal Bulb Mucosa

Mucosal distributions of peptide-producing cells varied considerably between subjects. The concentration of G-cells were significantly lower in the duodenal bulb mucosa than in the antral mucosa, both in non-ulcer subjects and patients with peptic ulcer diseases. But there were slight differences between antral and duodenal bulb distribution of D-cells either in non-ulcer subjects and the peptic ulcer patients. Patients with GU had significantly decreased numbers of both G- (48.1±47.4) and D-cell (7.9±12.3) in the gastric antrum than non-ulcer subjects (G-cell : 82.7±58.8, D-cell 20.7±13.0) and DU patients (G-cell 1 : 87.1±68.8, D-cell 1 : 16.4±20.5). The ratios of antral D/G cells were 1 : 4 in non-ulcer subjects, 1 : 7 in GU, and 1 : 5 in DU patients. There were significant differences between non-ulcer subjects and patients with peptic ulcer in their D/G cell ratios ($p<0.01$)

Table 6. Numbers of G- and D-Cell in Antral Biopsies in Non-Ulcer subjects and Patients with Peptic Ulcer

	No. Patients (M/F)	G-Cell	D-Cell	D/G Ratio
Non-Ulcer Subjects	20/18	81.7±52.8*	20.7±13.0**	1 : 4
Gastric Ulcer	44/43	48.1±47.4*	7.9±12.3**	1 : 7
Duodenal Ulcer	66/65	87.1±68.8	16.4±20.5	1 : 5

Values: Mean±SD
* : $p<0.05$
** : $p<0.01$
Antral D-Cell: GU vs DU; $p<0.01$
Duodenal D-Cell: GU vs DU; $p<0.01$

Table 7. Numbers of G- and D-Cell in Duodenal Biopsies in Non-Ulcer subjects and Patients with Peptic Ulcer

	No. Patients (M/F)	G-Cell	D-Cell	D/G Ratio
Non-Ulcer Subjects	18/19	21.4±21.5	18.7±12.0	1 : 1.2
Gastric Ulcer	38/41	12.7±14.1	12.0±13.2	1 : 1
Duodenal Ulcer	56/57	16.4±17.3	16.4±20.5	1 : 1

Values: Mean±SD

but not between GU and DU patients. However duodenal G-cell and D-cell numbers and D/G cell ratio were within similar range in both non-ulcer subjects and patients with peptic ulcer diseases (Table 6 and 7)

6. Relationship Between G-cell Population, Mucosal Gastrin and Serum Gastrin Concentration

It was very difficult to analyze and assess the significance between G-cell number, tissue gastrin and serum gastrin levels in endoscopic biopsy specimens. Our results showed that antral gastrin concentrations (both G17 & G34) were not correlated with numbers of antral G-cell. Numbers of G-cell of DU patients and non-ulcer subjects were similar, but gastrin concentrations were higher in DU patients. On the contrary, G-cell numbers were lowest in GU patients and antral gastrin concentrations were similar to that of non-ulcer subjects and DU patients or slightly increased. GU patients had lowest numbers of G-cell in the duodenal bulb but gastrin concentrations were higher than those of non-ulcer subjects or DU patients. But antral concentrations, both of G17 and G34, were significantly increased in DU patients.

7. Relationship between D-cell Population and Mucosal Somatostatin Concentration

In this ovservation, we could not find any direct correlation between numbers of somatostatin-producing cells and tissue concentration of this peptide: Antral D-cell numbers were lowest in GU patients but antral somatostatin concentration was lowest in non-ulcer subjects. Duodenal D-cells were lowest in GU patients but tissue levels of somatostatin were not different between non-ulcer subjects, GU and DU patients.

DISCUSSION

It is well known that the basal gastrin concentration is similar or slightly increased in the vast majority of DU patients and significantly higher in most of GU patients than in non-ulcer subjects. With regard to the fasting serum concentration of G17, the result of the present study was quite similar to those of our previous observations[1~3]. A substantial variation of the mucosal gastrin concentration has been observed by different investigators[9,10,13]. Our results also showed considerable inter- and intra-subjects variations in mucosal gastrin concentrations. Several mechanisms have been suggested to explain there variations: initial rapid loss of gastrin in unfrozen tissue or random variation among a small number of tissues[9,13] or an uneven distribution of G-cells in the mucosa[10]. Thus, we have taken multiple biopsies in each subject and the specimen has immediately been frozen with liquid nitrogen gas. Creutzfeldt et al[10] have reported that mucosal immunoreactive gastrin concentration was not changed when the specimen was treated with liquid nitrogen gas.

In a group of 61 patients with DU, significantly higher G17 and G34 concentrations have been

found in the antral mucosa. But the differences in values between non-ulcer subjects and patients with GU, and values between patients with DU and GU, were not significant. This result disagrees with published investigations. Malmström and Stadil[9] compared 12 non-ulcer persons with 28 DU patients and Hughes and Hernandez[14] compared 32 non-ulcer persons with 18 DU patients. The absolute values of the former investigators were higher, but both groups found no difference between non-ulcer persons and DU patients. The disagreement between these results and our findings is difficult to explain, but the values of gastrin, using biopsy specimens, could be measured lower than those in the whole mucosal tissues, which have been tested by these investigators, because of uneven distribution of G-cells and random variation of samples. Dockray et al[15] have examined molecular forms of mucosal gastrins in patients with peptic ulcer and found that, whereas antral and duodenal G17 concentrations were similar in both groups, the concentrations of G34 in both antral and duodenal mucosa were elevated in GU subjects. This result also disagreed with our observations. Concentrations of G17 and G34 in the duodenal bulb were significantly higher in both GU and DU patients than in non-ulcer subjects, but values between GU and DU patients were similar.

The present study showed that antral somatostatin concentration was significantly decreased in non-ulcer subjects but duodenal bulb contained relatively similar levels in each patients. Our result disagreed with those of Myachi Y[23] and Chayvialle JAP[11]. Myachi Y et al. observed that the antral somatostatin concentration was directly related with mucosal histology in non-ulcer subjects; the more severe the atrophic changes of the antrum, the lower in the concentration of somatostatin in non-ulcer subjects, while in DU patients the antral somatostatin was very low irrespective of the degree of atrophic changes. Chayvialle JAP et al. also reported that antral somatostatin level was lower in patients with DU, while those of non-ulcer subjects and GU patients was not different.

As was in mucosal peptides concentrations, there were also significant inter-subjects variations in numbers of G- and D-cell. We have also observed that numbers of both G- and D-cell decreased proportinately with the severity of atrophic gastritis and/or intestinal metaplasia of gastric mucosa.

Contrary to the differences of the gastrin concentrations, numbers of the G-cell, identified by immunohistology in antral and duodenal mucosa, were identical in non-ulcer subjects and DU patients. There have been several reports[10,20,21,22] similar to our result, but others reported that DU patients had more abundant G-cells in the antral mucosa[16,17,18] In normal conditions, there are eight times as many G-cells as there are inhibitory D-cells in the antrum. In most subjects with DU, the normal ratio (D : G) of 1/8 remains unchanged: but in cases which have G-cell hyperplasia this ratio is altered to 1 to 80.

In this report, numbers of G- and D-cell were significantly decreased in patients with GU compared to those of non-ulcer subjects or DU partients. We have also observed that G- and D-cells decreased proportionately to the severity of chronic atrophic gastritis and/or intestinal metaplasia of the antral mucosa. Tahara A et al.[19] suggested that antral D cells were affected more seriously by chronic atrophic gastritis and that its count decreased earlier or more diffusely than that of G cells. Antral D/G ratio was lower in GU patients, while duodenal D/G ratio was not different from controls, GU and DU patients. We could not find any correlation between numbers of peptides producing cells and their tissue concentrations.

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