Immunocytochemical and morphometric studies of gastrin-, somatostatin- and serotonin-producing cells in the stomach and duodenum of patients with acid peptic disorders

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WR YACOUB, ABR THOMSON, P HOOPER, LD JEWELL. Immunocytochemical and morphometric studies of gastrin-, somatostatin- and serotonin-producing cells in the stomach and duodenum of patients with acid peptic disorders. Can J Gastroenterol 1996:10(6):395-400. Gastric and duodenal biopsies from 90 patients with various acid peptic disorders – reflux esophagitis (n=24), gastric ulcer (n=13), duodenal ulcer (n=47) and nonulcer dyspepsia (n=6) – were examined. Seven patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum served as controls. Immunoperoxidase staining for gastrin-producing G cells, somatostatin-producing D cells and serotonin-producing EC cells was carried out on fundic, antral and duodenal biopsies, and was quantified using a Zeiss MOP Videoplan using the peroxidase-antiperoxidase technique of Sternberger. In the gastric antrum, a G:D:EC cell ratio of approximately 1.6:1:1 was observed. In the duodenum the corresponding ratio was 1:1:2.4. No significant differences were observed within any of the major diagnostic categories. Patient age, sex, duration of symptoms, smoking habits, alcohol consumption and nonsteroidal anti-inflammatory drug use had no effect on endocrine cell densities. Reduced G cell density in the descending duodenum was observed in the presence of mild duodenitis in four patients. In four patients with evidence of antral intestinal metaplastic changes, a significant increase in duodenal G cell densities was found. These results suggest that a change in the number of G, D or EC cells does not play a primary role in the pathophysiology of acid peptic disorders in the majority of patients.

Key Words: *Acid peptic disorder, D cells, EC cells, G cells, Immunohistochemistry*

Examen immunocytochimique morphométrique des cellules productrices de gastrine, de somatostatine et de sérotonine dans l'estomac et le duodénum de patients souffrant de maladies gastro-duodénales acides

RÉSUMÉ : Les biopsies gastriques et duodénales de 90 patients souffrant de diverses affections acides, oesophagite de reflux (n = 24), ulcère gastrique (n = 13), ulcère duodénal (n = 47) et dyspepsie non ulcéreuse (n = 6), ont été examinées. Sept patients souffrant de symptômes dyspeptiques mineurs et présentant un estomac et un duodénum normaux à l'endoscopie et à l'histologie ont servi de témoins. La coloration à l'immunoperoxydase pour le dépistage de cellules G productrices de gastrine, des cellules D productrices de somatostatine et de cellules EC productrices de sérotonine a été effectuée sur des

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biopsies fundiques, antrales et duodénales et a été quantifiée à l'aide du Vidéoplan MOP de Zeiss à partir de la technique de peroxydase-antiperoxydase de Sternberger. Dans l'antre gastrique, on a observé un ratio de cellules G:D:EC d'environ 1,6:1:1. Dans le duodénum le ratio correspondant était de 1:1:2,4. Aucune différence significative n'a été notée à l'intérieur de l'une ou l'autre des catégories diagnostiques. L'âge, le sexe, la durée des symptômes, les habitudes de tabagisme, de consommation d'alcool et d'AINS n'ont exercé aucun effet sur les densités cellulaires endocriniennes. La densité moindre de cellules G dans le duodénum descendant a été observée en présence de duodénite légère chez quatre patients. Chez quatre patients présentant des signes d'anomalies métaplasiques intestinales antrales, une augmentation significative des densités de cellules G duodénales a été observée. Ces résultats donnent à penser qu'un changement du nombre de cellules G, D et EC ne jouent aucun rôle primordial dans la physiopathologie des troubles gastro-duodénaux acides chez une majorité de patients.

Peptic ulcer disease is thought to result from an imbalance of aggressive and defensive factors (1-3). Peptides and amines contained in and secreted by endocrine cells play various roles in modulating these factors. For example, gastrin, the peptide stored by and released from the G cells, has an established role in gastric acid stimulation (4-7). Somatostatin, the peptide stored by and released from the D cells, is a candidate hormone for inhibition of gastric acid secretion (8-11). The role of these gastrointestinal peptides and amines in acid peptic disorders is related to possible increased stimulation of parietal cells by gastrin (12-15), somatostatin deficiency, or dysfunction of G cells, D cells or both (16-19). The present investigation examines the distribution and ratio of gastrin-secreting G cells, somatostatin-secreting D cells and serotonin-secreting EC cells in the stomach and duodenum of patients with acid peptic disorders.

PATIENTS AND METHODS

Patient population: Mucosal biopsy specimens were obtained from the gastric antrum, body and fundus, descending duodenum and duodenal bulb of 90 persons with dyspepsia or acid peptic disorders and seven controls. There were 55 males and 42 females. The study group comprised 47 patients with endoscopically verified duodenal ulcers (DU); 13 with gastric ulcers (GU); 24 with esophagitis due to gastroesophageal reflux disease (GERD); six with nonulcer dyspepsia (NUD), ie, patients with symptoms suggestive of peptic ulcer disease in whom endoscopic and histological examinations revealed gastritis and/or duodenitis without ulceration; and seven controls, ie, persons with various gastrointestinal disorders (eg, Crohn's disease, irritable colon) and minimal dyspeptic symptoms in whom the stomach and duodenum were endoscopically and histologically normal. Patient characteristics are listed in Table 1.

Immunohistochemistry: Two biopsies were obtained from each of the duodenum (bulb and descending), antrum and body/fundus. These were fixed in Bouin's fluid and embedded in paraffin in the usual manner, cut 4 to 6 μm and stained for G, D and EC cells by a peroxidase-antiperoxidase technique (20) using the following antisera: rabbit antihuman gastrin (Incstar Corp, Minnesota), rabbit antisynthetic somatostatin (Dimension Laboratories Inc) and guinea pig antisynthetic serotonin (Arnel Products, New York).

Morphometric studies: The MOP videoplan image analysis computer system (Zeiss Kontron Elektronik Gruppe, Kontron Bildanalyse, Germany) was used for the morphometric studies. The instrument was calibrated by measuring a series of small objects of known area. Mucosal surface areas were traced using the x1 objective. Results were expressed as the number of cells/mm^2 mucosal surface area.

Every cell, regardless of its shape or whether a nucleus was present, was identified as a G, D or EC cell if a dark brown granular reaction was present within cytoplasm. Images were projected into the computer monitor via a video camera mounted over the microscope, and the number of positively stained cells and the mucosal area were determined. Only sections that were adequately oriented and contained the full thickness of the mucosa were included.

Statistical analysis: All analyses were based on the square roots of the cell counts. A theoretical argument suggested that on this scale the variance would remain nearly constant as the mean changed. Plots of the data showed that the distributions of the root counts were fairly symmetric. How the G, D and EC square root counts and their ratios varied among the six different sites and for each primary diagnosis was determined. Point estimates were examined and tests of significance were done. Paired Student's *t* tests tested for the significance of differences in the mean values of the root counts and Wilcoxon signed-rank tests tested for the significance of differences in the ratios. The nonparametric test was used in the latter instance because the ratio distribution appeared to be skewed.

TABLE 1
Patient characteristics

	Controls	NUD	DU	GU	GERD
Sex					
Males (n=55)	3	4	29	3	16
Females (n=42)	4	2	18	10	8
Mean age (years)	32	54	47	52	54
Age range (years)	22-62	30-69	24-71	43-64	24-76
Mean duration of dyspeptic symptoms (months)	9	81	87	106	81
Range (months)	<1-60	3-240	< 1-360	1-300	1-480
Positive family history of PUD (%)	50	–	26	54	33
Smokers (%)	14	33	49	39	42
Alcohol consumers (%)	100	33	62	46	74
NSAID ingestion (%)	57	50	38	46	52

Controls Patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum; DU Duodenal ulcer; GERD Gastroesophageal reflux disease; GU Gastric ulcer; NSAID Nonsteroidal anti-inflammatory drug; NUD Nonulcer dyspepsia; PUD Peptic ulcer disease

Multivariate analysis of covariance was done to examine whether the mean root counts for the G, D, and EC cells in the six sites depended on the primary diagnosis. An additive model was first considered, but no significant effects were found. Given the number of significance tests carried out during the study, there is some doubt that the observed interaction reflected a real effect.

RESULTS

G, D and EC cell distribution in the stomach and duodenum: G, D and EC cell density distribution findings in all patients are summarized in Table 2. G cell densities were higher in the antral than in the duodenal sites (P=0.000). No significant differences in G cell densities were detected between the descending duodenum and duodenal bulb or between the biopsied antropyloric sites. No G cells were seen in either the gastric body or fundus.

D cell densities were higher in the gastric fundus than in the body (P=0.000). D cell densities were similar in the gastric fundus, antrum and proximal duodenum.

EC cell densities were higher in the descending duodenum than in the duodenal bulb (P=0.000). Antral EC cell densities were higher than in the gastric body and fundus (P=0.007). No differences were observed between the gastric body and fundus, or between the antropyloric sites.

Because no significant differences were found in the G and D cell densities in the descending duodenum and duodenal bulb, the results are reported as a single value for each of the G and D cell densities in the duodenum. EC cell densities are reported separately for the descending duodenum and duodenal bulb. Because G, D and EC cell densities showed no statistically significant differences in the biopsied antral sites, these values are reported as a single value for the cell density in the antrum. D cell densities were significantly different in the gastric body and fundus, and are therefore reported separately. Because no significant difference was found in the EC cell densities in the latter two sites, one value is reported for the combined sites.

In the antrum, the proportions of G, D and EC cells were 40%, 31% and 28%, respectively, with a G:D:EC ratio of approximately 1.6:1:1. In the duodenum EC cells prevailed, followed by the D and G cells, with a G:D:EC ratio of approximately 1:1:2.4. The D cells were more numerous than EC cells in the gastric body and fundus. The cell ratios are given in detail in Table 3.

G, D and EC cell densities in acid peptic disorders and controls: G, D and EC cell densities showed a considerable overlap in patients with NUD, DU, GERD and controls in all the biopsied sites. The numbers of each of three cell types studied in the various anatomical sites are illustrated in Figure 1. No significant differences were observed among any of the major diagnostic categories. For further analysis, ratios rather than individual cell numbers were explored because the ratios are less subject to interindividual variations. No significant differences in the gastric and duodenal G:D, G:EC and D:EC ratios were detected between patients with acid peptic disorders and controls (Table 4).

TABLE 2
Comparison of the mean (square root) of G, D and EC cell densities in the stomach and duodenum

	Mean G density	Mean D density	Mean EC density
Descending duodenum	–	–	4.927*
SD	–	–	1.339
Duodenal bulb	–	–	4.059
SD	–	–	1.472
Descending duodenum and duodenal bulb	2.827	2.893	–
SD	0.945	0.827	–
Antrum	4.469†	3.491‡	3.172§
SD	2.329	1.603	1.498
Body	N/D	2.702	–
SD		1.442	–
Fundus	N/D	3.723‡	–
SD		1.745	–
Body and fundus	N/D	–	2.394
SD		–	0.960

**Significantly higher EC density than in duodenal bulb (P=0.000); †Significantly higher G density than in duodenum (P=0.000); ‡Significantly higher D density than in gastric body (P=0.000); §Significantly higher EC density than in gastric body and fundus (P=0.007). N/D None detected*

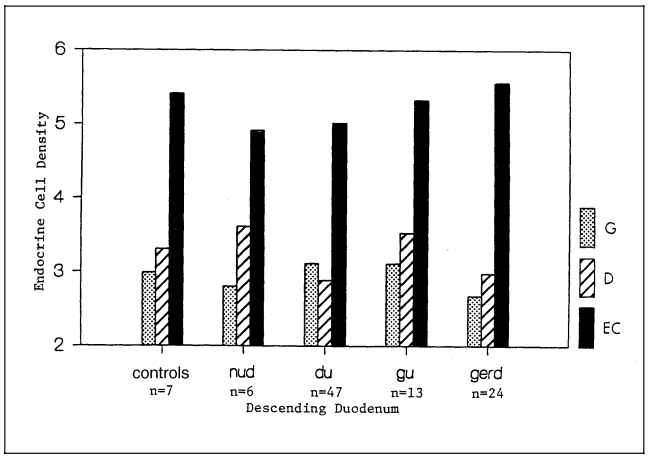
TABLE 3
Median of square roots of cell ratios in the stomach and duodenum

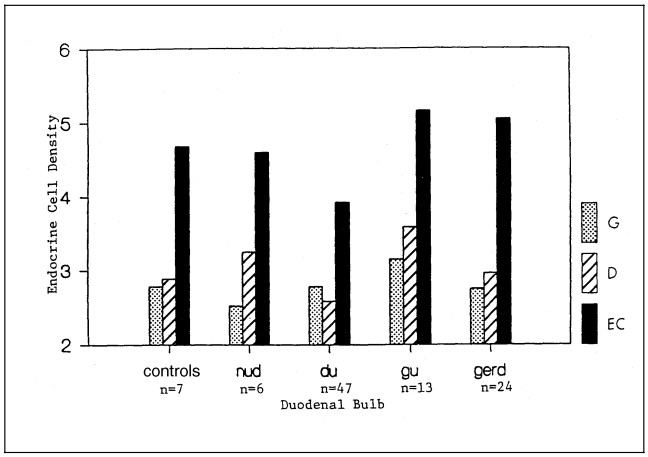
	Median G:D	Median G:EC	Median D:EC
Descending duodenum	0.956	0.613	0.589
Duodenal bulb	0.99	0.609	0.673
Antrum, anterior	1.319*	1.373†	1.111‡
Antrum, posterior	1.312	1.257	1.103
Body	–	–	1.140‡
Fundus	–	–	1.444‡ § ¶

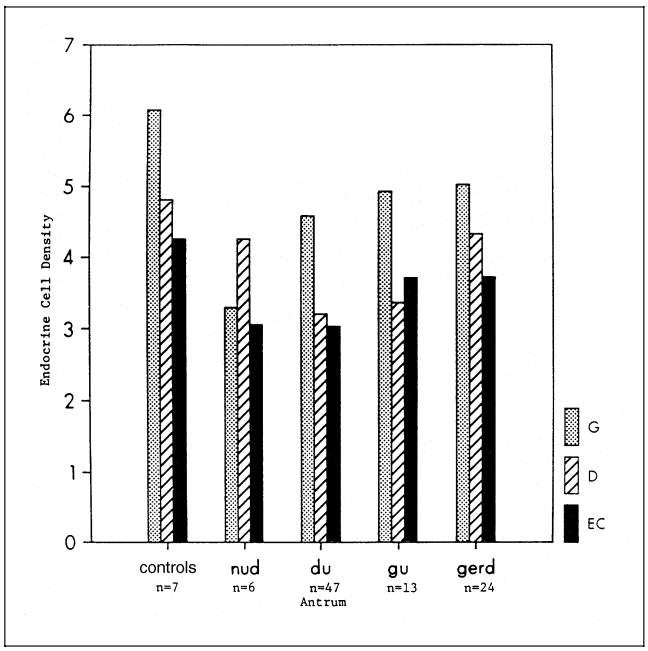
**Significantly higher median G:D ratios than in the duodenum (P=0.000); †Significantly higher median G:EC ratios than in the duodenum (P=0.000); ‡Significantly higher median D:EC ratios than in the duodenum (P=0.000); §Significantly higher median D:EC ratios than in the antrum (P=0.000); ¶Significantly higher median D:EC ratios than in the gastric body (P=0.000)*

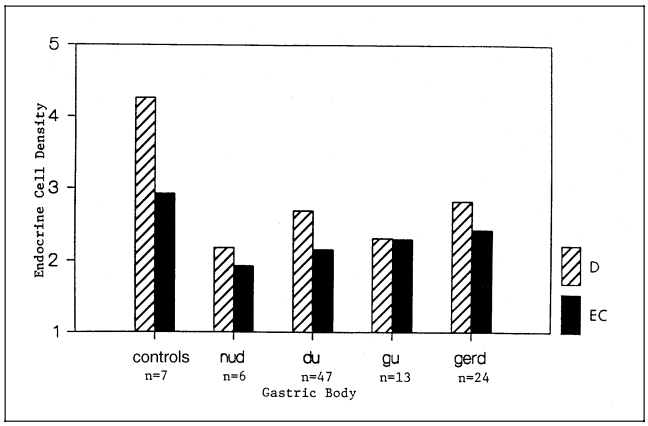
Effect of patient characteristics on G, D and EC cell densities: Multivariate ANOVA showed no significant effect of patient age, sex, duration of symptoms, smoking habits, alcohol consumption and nonsteroidal anti-inflammatory drug (NSAID) use on the G, D and EC cell densities in the stomach and duodenum. A history of peptic ulcer disease showed some evidence of an effect on G, D and EC cell densities when added to the patients' primary diagnosis and treatment in one-way layout. However, considering the P values for all covariates together, this difference may be attributable to chance.

Effect of histopathology on G, D and EC cell densities: Reduced G cell densities (P=0.002; multivariate test statistics, P=0.00) were found in the presence of mild duodenitis in the descending duodenum of four patients. However, a reduction of G cells in the antrum of duodenum must be interpreted carefully because inflammatory changes such as a









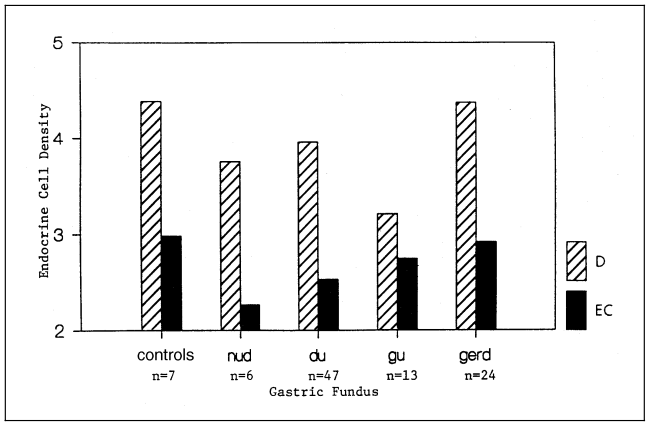


Figure 1) *G (G), D (D) and EC cell (EC) densities in the biopsied sites of acid peptic disorder patients and controls (patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum).* **Top left** *Descending duodenum;* **Middle left** *Duodenal bulb;* **Lower left** *Antrum;* **Top right** *Gastric body;* **Above** *Gastric fundus. DU Duodenal ulcer; GERD Gastroesophageal reflux disease; GU Gastric ulcer; NUD Nonulcer dyspepsia*

cellular infiltrate or an edematous expansion of the lamina propria may result in an apparent reduction in the number of endocrine cells per unit mucosal area.

In four patients (three biopsies obtained from three GU patients and three biopsies from one DU patient) the presence of intestinal metaplasia detected in the antrum was significantly associated with increased G cell densities in the duodenum (P=0.001; multivariate test statistic, P=0.00) (Table 5). The same results were obtained when analysis included only one biopsy from the DU patients (P=0.008; multivariate test statistic; P=0.00). None of the remaining histopathological findings appeared to exert an effect on the G, D and EC cell densities in the stomach and duodenum.

DISCUSSION

There was no evidence of any diagnosis causing statistically significant alterations in the cell densities in the biopsied sites. In DU and GU, our antral G and D cell counts agree with those reported by Gutierrez et al (21), Arnold et al (22), Piris and Whitehead (23), Royston et al (24) and Creutzfeldt et al (25), but not with those reported by Grivelli et al (26) and Torres et al (17). Furthermore, Domschke and colleagues (27) did not find a somatostatin deficit in either the antral or fundic mucosa of DU patients. Grivelli and co-workers (26) reported significantly lower antral G cell counts in DU patients compared with controls.

Torres et al (17) reported lower antral G and D cell densities in both DU and G patients compared with controls. The lower counts may be attributed to differing methods of morphometric analysis.

There was a large interindividual variation in endocrine cell densities among patients within the same diagnostic group, leading to a wide overlap between cell counts in acid peptic disorders and controls. The distribution was not influenced by patient age, sex, duration of symptoms, smoking habits, alcohol consumption, NSAID use or family history of peptic ulcer disease. G cell distribution confirms previous reports (23,28-31).

A gradual increase in serotonin-containing EC cell densities was observed from the gastric to the duodenal sites; the lowest EC density was found in the gastric fundic and body regions, with significant increments distally, and the highest in the descending duodenum. This EC cell distribution is consistent with possible serotonin involvement in the motility of this gastrointestinal tract segment, as well as possible inhibition of gastric acid secretion (32-34).

The proportion of G, D and EC cells in the antrum was approximately 40%, 31% and 29%, respectively. These values closely agree with those described by Solcia et al (35) and Own (36). In the present study, the antral G:D:EC ratio was approximately 1.6:1:1 and the duodenal G:D:EC ratio was approximately 1:1:2.4. The median antral G:D ratio (1.6) observed in this investigation is in close agreement with the 1.8 ratio reported by Gutierrez et al (21). However, this ratio is lower than the previously reported higher G:D ratios of 4:1 (17,22), 7:1 (22) and 8:1 (19). This diversity is probably due to the different methods used in the various studies.

The unaltered G:D ratios in acid peptic disorders (Table 4) and the differences associated with major changes in gastric acid secretion observed in Zollinger-Ellison syndrome (12,22), pernicious anemia and postvagotomy support the hypothesis of antral pH regulation of this ratio, as postulated by Arnold and colleagues (22). However, the pathogenetic mechanism(s) underlying the G:D relationship variations in the various secretory states are unknown. For example, is there a defect in D cell function in hypersecretory states? Have D cells become unable to 'cope' with hyperfunctioning/hyperactive G cells (the latter having been observed with electron microscopy) (28,37)? Is there a disturbance in the synthesis and/or processing of somatostatin?

G:EC ratios (Table 4) reflect their respective cell density distribution in the antrum and duodenum. Resnick et al (38) first demonstrated an inhibitory role for serotonin on gastric acid secretion in vivo in humans. More recent studies in humans (39) and animals (32,33) provided further evidence. The mode of action of serotonin in gastric acid inhibition is unknown and the physiological importance of plasma serotonin in humans is unclear (40). The proximity of EC cells to parietal cells suggests a local paracrine mechanism of action. In humans, serotonin may exert a background restraining effect on basal gastric acid secretion without an effect on gastrin release (39). Serotonin interaction with gastrin differs according to species; serotonin inhibited gastrin output in dogs (41) but in rats had a releasing effect (34). Inhibition of gastrin release by serotonin in dogs was attributed to reduced visceral bloodflow rather than to a direct effect on G cells. On the other hand, lower antral EC densities may undermine pyloric defences, since serotonin is known to stimulate mucin production in the mucosa (42) or weaken acid inhibitory processes.

TABLE 4
Comparison of the median cell ratios: effect of primary diagnosis

Ratio	Site	Controls (n=7)	NUD (n=5)	DU (n=42)	GU (n=12)	GERD (n=24)
G:D	Descending duodenum	0.863	0.633	1.072	0.964	0.834
	Duodenal bulb	0.903	0.625	1.075	0.989	0.985
	Antrum, anterior	1.317	0.327	1.559	1.296	1.262
	Antrum, posterior	1.237	0.489	1.353	1.499	1.256
G:EC	Descending duodenum	0.605	0.396	0.646	0.725	0.543
	Duodenal bulb	0.551	0.419	0.739	0.635	0.573
	Antrum, anterior	1.485	0.602	1.648	1.134	1.404
	Antrum, posterior	1.214	0.710	1.273	1.481	1.460
D:EC	Descending duodenum	0.600	0.667	0.571	0.825	0.617
	Duodenal bulb	0.677	0.715	0.667	0.707	0.564
	Antrum, anterior	1.240	1.096	1.126	0.881	1.300
	Antrum, posterior	0.785	1.452	0.949	0.937	1.259
	Body	1.236	0.745	1.207	1.054	1.179
	Fundus	1.445	1.488	1.474	1.221	1.398

Controls Patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum; D D cell; DU Duodenal ulcer; EC EC cell; G G cell; GERD Gastroesophageal reflux disease; GU Gastric ulcer; NUD Nonulcer dyspepsia

TABLE 5
G cell densities in the duodenum and antrum of patients with antral intestinal metaplasia

Duodenal G cell densities			Antral G cell densities	
Mean G cell density	Biopsies with metaplasia	Location of ulcer	Mean G cell density	Biopsies with metaplasia
Controls = 2.885±0.499	4.728	DU	Controls = 6.069±2.110	3.750
	3.574	DU		4.370
	4.692	DU		3.940
DU = 2.857	5.528	GU	DU = 4.319	3.493
GU = 3.155	3.592	GU	GU = 3.969	3.022
	4.635	GU		4.456

Controls Patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum; DU Duodenal ulcer; GU Gastric ulcer

CONCLUSIONS

Considering the postulated inhibitor role for somatostatin and serotonin on gastrin acid secretion and the morphological proximity of D and EC cells to the candidate target cells (G and parietal cells), an interactive, functional relationship

may exist between somatostatin and serotonin and/or their cells. Somatostatin and serotonin may be – separately or synergistically – exerting a background restraining and possibly paracrine effect on fundic parietal cells and antral G cells. The interaction among serotonin, somatostatin and gastrin in the human stomach and duodenum awaits further investigation. Any participation by these peptides and amines in 'ordinary' acid peptic disorders does not appear to be related to altered cell numbers or ratios.

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