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Antral gastrin-producing G-cells and somatostatin-producing D-cells in peptic ulcer

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Summary. The number of G cells and D cells per area unit and the G cell/D cell ratio was studied in control subjects and patients with duodenal or gastric ulcer. A great inter-individual variation in the population density of both types of cells was observed in the three groups studied. G cell density was significantly decreased in both duodenal and gastric ulcer patients, when compared with controls; whereas no difference in G cell density was seen between duodenal ulcer patients and gastric ulcer patients. However, D cell density was significantly decreased in duodenal ulcer patients when compared with control subjects and gastric ulcer patients. In this latter group, D cell density was also lower than in control subjects. A significant positive linear correlation between G cell number and D cell number was found in the three groups studied. The G cell/D cell ratio was significantly increased in duodenal and gastric ulcer patients when compared with controls. This was mainly due to a decrease in D cell numbers. It is concluded that a local deficit in antral D cells in patients with peptic ulcer may favor the pathogenesis of ulcer disease.

Key words: Gastrin – Somatostatin – Peptic ulcer

Introduction

Since its original isolation from ovine hypothalami (Brazeau et al. 1973), somatostatin has been found in many organs and tissues: central nervous system, pancreas, gastrointestinal tract, thyroid gland etc. In the gastric mucosa somatostatin has been localized within the D cell (Polak et al. 1975) of both the antral and fundic glands. In these areas, D cells are in close vicinity to G cells, parietal cells and principal cells (Larsson et al. 1979).

These morphological findings, together with the fact that somatostatin secretion depends in great part on the endoluminal pH (Uvnas-Wallensten et al. 1981) suggest a major significance for the paracrine control that somatostatin exerts on neighbouring G cells. Somatostatin greatly inhibits chlorhydropeptic and gastrin secretion (Bloom et al. 1974; Gomez-Pan et al. 1975; Schwarting et al. 1983).

Thus, it is possible that an altered number or distribution of D cells in the gastric mucosa may influence the physiopathological disorders that favor the development of peptic ulcer disease. The present work shows the results obtained in the study of the number of D cells and G cells per area unit, and the G cell/D cell ratio in human antral mucosa samples of control subjects and patients with peptic ulcer.

Material and methods

Antral mucosa samples from 21 duodenal ulcer patients, 14 gastric ulcer patients, and 20 control subjects were used. Prior to the collection of the samples all the subjects gave their written consent after being informed of the aims and risks of the study.

The average age of the control subjects (9 males, 11 females) was 48 years (range: 26–70), of duodenal ulcer patients (14 males, 7 females) 42 years (range: 26–70) and of gastric ulcer patients (9 males, 5 females) 52 years (range: 33–72).

None of the control subjects had abnormalities in the gastroduodenal mucosa or gastrointestinal disease. The peptic ulcer patients were diagnosed by means of gastroduodenal study using barium and endoscopy. None of them received antiulcer medical treatment for at least 10 days prior to the beginning of the study.

Antral mucosa samples were obtained either through endoscopy of fasted, non pre-medicated subjects, using an Olympus GIF-Q gastroduodenoscopy or during surgical resections

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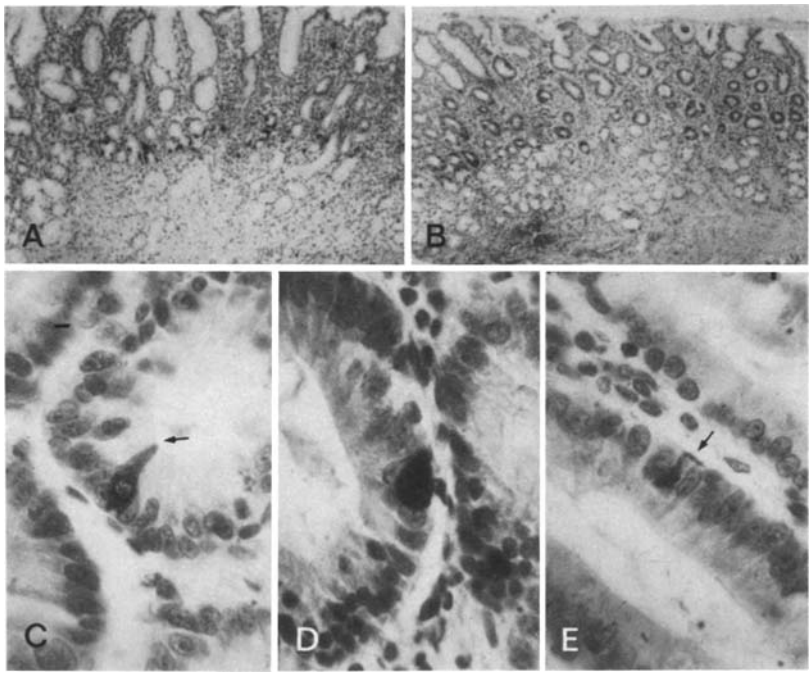

Fig. 1 A–E. Morphological features of G and D cells of antral human mucosae. Both D (**A**) and G (**B**) cells are preferentially distributed in the medial zone of the mucosae. Two kinds of D cells can be found: "open-type" (**C**) and "close-type" (**D**). Cytoplasmic processes in close relationship with neighbouring cells are observed in D cells (**E**)

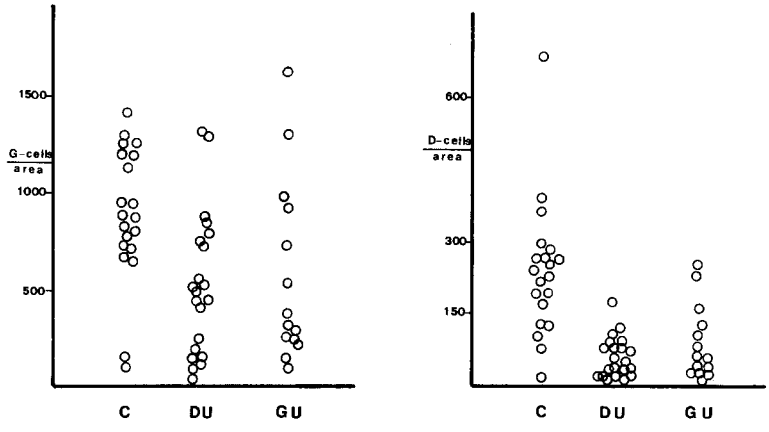

Fig. 2. Antrum G- and D-cells per area unit in 20 control subjects (*C*), 21 patients with duodenal ulcer (*DU*), and 14 subjects with benign gastric ulcer (*GU*). A great inter-individual variations was observed

performed in ulcer patients. Three to four samples were taken in each individual at 3–4 cm over the pylorus (posterior side) and independently of those samples taken to confirm the benignity of the ulcer lesions. An histological control using haematoxilin-eosin was performed in every biopsy in order to discard those samples lacking the entire thickness of the mucosa or showing intestinal metaplasia or severe inflammatory infiltrates in the lamina propria since these two factors can be related to gastric endocrine cell population. Thus, we only admitted to this study those cases with minor grade of superficial chronic gastritis.

Tissue samples were immediately fixed in Bouin's fluid and embedded in paraffin wax. Five μ thick sections were cut vertical to the mucosa surface, deparaffinized, and stained for gastrin and somatostatin immunoreactivity using the PAP technique (Sternberger 1974). Rabbit anti-somatostatin antiserum (Immunonuclear Corp.) and rabbit anti-gastrin antiserum (Calbiochem Behring Corp.) were diluted at 1/200 and 1/20, respectively. These antisera did not cross-react with any structurally related peptides. Unlabeled sheep antirabbit IgG and the peroxidase-antiperoxidase (PAP) complex were purchased from Dakko Patt (Copenhagen).

Morphometric analysis was performed by counting all the positive cells present in the totality of the cut of a particular sample, over a given histological section. Those stained areas not carrying a nucleus were not taken as positive. The counting was done in all cases using a 40 × lens (with 10 × oculars and a binocular modification factor of 1.25). The counting was always made by the same investigator who did not know the diagnosis of the sample under study.

The total number of G and D cell was related to the actual area of the lamina propria expressed in mm^2. This measurement was taken from a drawing of the sample section using a quantitation apparatus (Kontrol Messgeräte Gmbh) and corrected for the magnification factor used in the study. The number of G or D cells per mm^2 is thus obtained. Later, the G cell/D cell ratio per surface unit can be established.

Results are shown as means ±SEM. An analysis of variance was first used to look for significant differences followed by a non-paired Student's *t* test to establish statistical signifi-

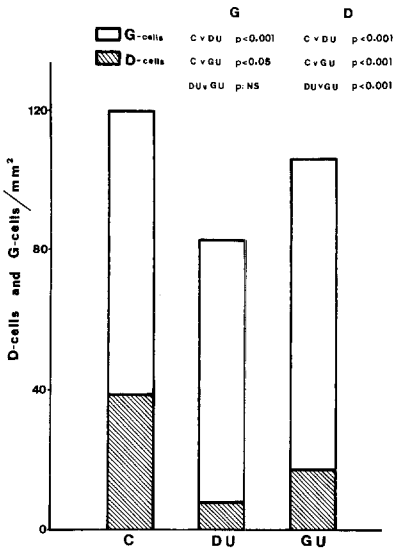

Fig. 3. Comparison of G and D cell numbers per mm^2 in antral mucosae of control subjects (*C*) ($n=20$), patients with duodenal ulcer (*DU*) ($n=21$), and subjects with benign gastric ulcer (*GU*) ($n=14$)

cances. A linear regression analysis was used to determine a possible correlation between G and D cell numbers.

Results

Figure 1 shows the morphological characteristics of G and D cells of the antral mucosa. Both types of cells are preferentially located to the medial zone of the antral mucosa (Fig. 1, A and B). Two different types of D cells could be observed: one that reaches the glandular lumen (Fig. 1 C) and another that do not (Fig. 1 D). Some D cells show cytoplasmatic processes that seem to be in contact with neighbouring cells (Fig. 1 E).

Figure 2 illustrates the great inter-individual variation observed in the G and D cell numbers in both the control group and patients with duodenal or gastric ulcer. These variations were found both in samples obtained from endoscopic biopsies and in samples taken during surgery.

However, a significant difference in G and D cell density per mm^2 was seen between the various groups studied (Fig. 3). G cell density is significantly decreased in patients with duodenal or gastric ulcer when compared with control subjects, while no significant difference is seen when comparing G cell density of patients with duodenal ulcer with that of patients with gastric ulcer ($p>0.05$). D cell density is significantly decreased in patients with duodenal ulcer when compared with both control subjects ($p<0.001$) and gastric ulcer patients ($p<0.001$). In patients with gastric ulcer,

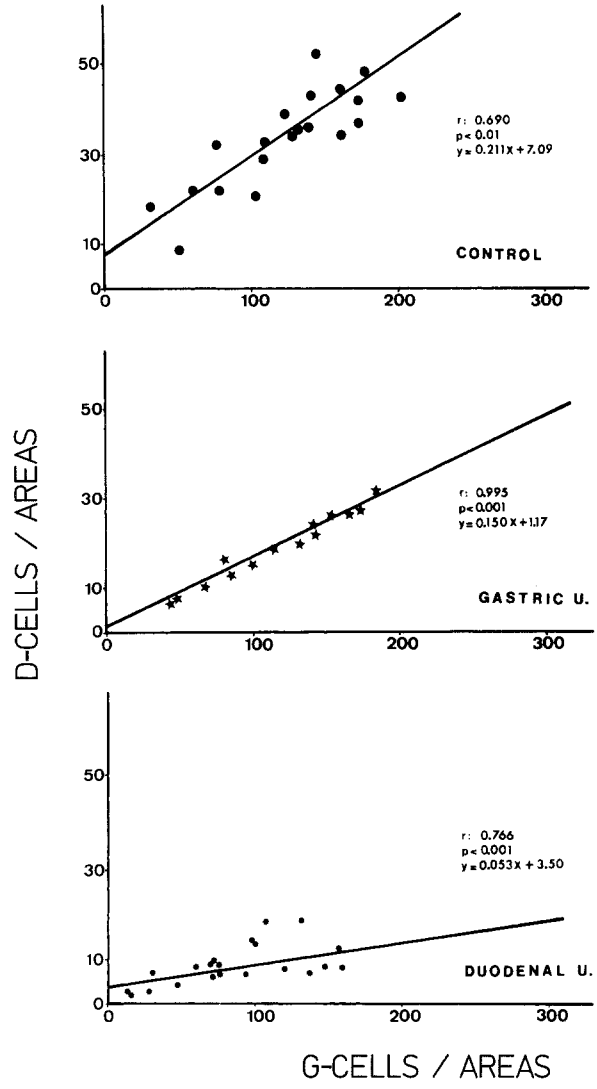

Fig. 4. Correlation of G-cell density with D-cell density estimated in samples taken from the antrum in 20 control subjects, 21 patients with duodenal ulcer, and 14 patients with benign gastric ulcer

D cell density is also significantly diminished when compared with controls ($p<0.001$).

A significant positive linear correlation between D cell number and G cell number per surface unit was found in the three groups studied (Fig. 4).

G cell/D cell ratio: Table 1 summarizes the results obtained in the study of the G cell/D cell ratio per surface unit. The analysis of variance showed a significant difference at least between two of the groups studied ($F=23.661$, $p<0.001$, $n=55$, 3 groups).

Duodenal ulcer patients have a significant increase in the G cell/D cell ratio when compared with control subjects ($p<0.001$) and patients with

Table 1. G/D cell ratio in antral mucosa of control subjects (*C*). patients with duodenal ulcer (*DU*), and patients with benign gastric ulcer (*GU*)

N°	*C*	*DU*	*GU*
1	3.60/1	13.14/1	6.49/1
2	2.78/1	6.31/1	6.43/1
3	5.69/1	16.98/1	6.01/1
4	3.73/1	8.75/1	6.23/1
5	4.39/1	11.24/1	5.83/1
6	5.71/1	12.00/1	6.10/1
7	3.70/1	7.23/1	5.68/1
8	3.64/1	8.63/1	5.77/1
9	2.75/1	7.61/1	6.45/1
10	4.08/1	7.29/1	5.01/1
11	3.66/1	11.40/1	5.40/1
12	3.58/1	8.78/1	6.20/1
13	5.47/1	6.28/1	7.34/1
14	3.52/1	17.30/1	6.60/1
15	3.64/1	6.73/1	
16	2.87/1	7.78/1	
17	3.85/1	7.32/1	
18	6.15/1	6.47/1	
19	4.10/1	21.08/1	
20	4.29/1	8.72/1	
21		13.37/1	
$\bar{X}\pm$SEM:	4.06±0.27	10.21±0.97	6.11±0.10

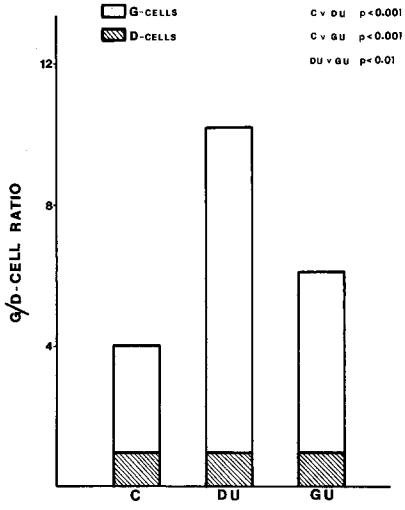

Fig. 5. Comparative G/D-cell ratio in antrum of 20 control subjects (*C*), 21 patients with duodenal ulcer (*DU*), and 14 patients with gastric ulcer (*GU*)

gastric ulcer ($p<0.01$) (Fig. 5). In patients with gastric ulcer, a significant increase in the ratio G cell/D cell is also found ($p<0.001$) when compared with controls.

This increased G cell/D cell ratio in patients with peptic ulcer is mainly due to a decreased D cell number. When compared with controls the number of G cells is decreased by 44.5% in duodenal ulcer patients and by 22.9% in patients with gastric ulcer. The number of D cells is decreased by 79.5% in duodenal ulcer patients, however, and by 55.2% in gastric ulcer patients.

Discussion

Both the endoscopic samples and those obtained after surgery were suitable for the analysis of the distribution of antral G and D cells since no differences in the results obtained by using either kind of sample has been observed. A similar usefulness has been widely established by other investigators (Crivelli et al. 1977; Hobbs and Polak 1978).

Our results show a marked inter-individual diversity in G and D cell density of antral mucosa in control subjects as well as in patients with peptic ulcer. This confirms previous observations on the irregular distribution of G cells (Stave and Brandtzaeg 1976; Keuppens et al. 1978; Voillemot et al. 1978) and D cells (Polak et al. 1976; Polak et al. 1978) in human antral mucosa. These variations were seen in mucosal samples in which inflamatory changes were scarce since we previously discarded those cases of severe chronic gastritis and/or intense intestinal metaplasia. Several authors have related these two factors to disorders in the gastric endocrine cell population (Keuppens et al. 1978; Sloan et al. 1979; Solcia et al. 1979; Bordi and Ravazzola 1979).

Stereological analysis can render two types of results, absolute and relative ones. Relative results are related to area or volume tissular fractions. Quantification of both types of results is in close relationship with tissue processing because the different fixatives and embedding procedures produce different artefactual contraction in tissues. So our results are difficult to compare in absolute terms to those found by other authors, since a considerable methodological difference regarding the counting technique exists. Thus, we have counted the totality of the histological cut, following the procedure of Willems et al. (1976); and Bertrand and Willems (1980) in rat gastric specimens and Keuppens et al. (1978) in human gastric biopsies. The latter authors, however, introduced in their studies a retraction coefficient and expressed their results in relation to mucosal surface and not to lamina propria area on section as we did. Other authors did not count all the histological cut, using field counting (Crivelli et al. 1977) or using a superimposed quadricle (Voillemot et al. 1978) with an arbitrarily taken surface unit (Stave and Brandtzaeg 1976) or a relationship with the muscularis

mucosae length and the mucosal surface (McIntyre and Piris 1981). However, to our knowledge, nobody has established the relation between endocrine gastric cells and area of the lamina propria expressed in mm^2.

A significant decrease in G cell number per surface unit found by us in peptic ulcer patients is consistent with findings previously reported by Crivelli et al. (1977) and Barbara et al. (1978) in duodenal ulcer patients. However, other authors have reported an increase in antral G cells of duodenal ulcer patients when compared with controls (Polak et al. 1972; Friesen et al. 1972; Royston et al. 1978). Ganguli et al. (1974) reported a remarkable increase in antral G cells of some ulcer patients, defining a new clinical entity: antral G cell hyperplasia or "antral gastrinosis". This could constitute either the higher limit of the ulcer patient population or an isolated clinical entity of different aetiology and physiopathology. An increased number of G cells from the proximal side up to the distal part of the antrum has been reported by Stave et al. (1976) in patients with duodenal ulcer when compared with gastric ulcer patients. Other authors found no differences in G cell number between control subjects, patients with duodenal ulcer, and patients with gastric ulcer (Creutzfeldt and Arnold 1978; Arnold et al. 1982). However, a significant increase in antral gastrin content in duodenal ulcer patients had been previously reported by some of these authors (Creutzfeldt et al. 1976).

A decreased D cell number per surface unit in peptic ulcer patients found by us has not previously seen by other investigators. No significant differences in D cell numbers between control subjects and gastric or duodenal ulcer patients have been found by several authors (Creutzfeldt and Arnold 1978; Arnold et al. 1982). Others reported an increase in the number of antral D cells in patients with duodenal ulcer but not in patients with gastric ulcer when compared with controls (Dayal et al. 1979). Finally, Polak et al. (1976) found a 71% decrease in duodenal D-cell numbers of patients with duodenal ulcer.

The G cell/D cell ratio found in control subjects by us is similar to that reported by Creutzfeldt and Arnold (1978) and Arnold et al. (1982), but lower than that seen by Pearse et al. (1976, 1977). Our observations of an increased G cell/D cell ratio in duodenal and gastric ulcer subjects, mainly due to a decrease in D cell number, do not agree with the reports of Creutzfeldt et al. (1978) and Arnold et al. (1982) where no significant difference in the G cell/D cell ratio was seen between these groups of subjects. A slightly increased G cell/D cell ratio was reported by Polak et al. (1978) in duodenal ulcer patients. This increased G cell/D cell ratio goes up to values of 70/1 in patients with antral G cell hyperplasia. Similar results were found by Pearse et al. (1977).

The observation of a positive significant linear correlation between the number of G cells and D cells per area unit in the three groups studied reinforces the existence of a functional relationship between both types of cells. Arnold et al. (1982) have published similar findings in control subjects and duodenal ulcer patients. The gastrin and somatostatin content of antral samples was measured by Dan (1982). This author found a significant correlation between immunoreactive gastrin and somatostatin levels in duodenal ulcer patients but not in control subjects or gastric ulcer patients. Besides this functional correlation, the spatial closeness found between G and D cells and the fact that D cells posses cytoplasmic processes that seem to contact the neighbouring cells reinforces the importance of a local or paracrine control mechanism by which somatostatin exerts an inhibitory action upon gastrin secretion.

A decreased number of D cells per surface unit correlates well with the lower antral somatostatin like-immunoreactivity (SLI) content measured by RIA that has been found both by us (unpublished results) and others (Chayvialle et al. 1978; Dan 1982; Fukushima et al. 1983) in duodenal and gastric ulcer patients. Both the D cell and somatostatin content deficits seem to have only a local effect on the mucosa since no differences have been observed in plasma somatostatin levels of patients with duodenal ulcer when compared with control subjects (Gustavsson et al. 1982; Colturi et al. 1984). In addition, no correlation has been found between antral SLI concentrations and plasma gastrin levels (Arnold et al. 1982). This somatostatin deficit seems to be of a quantitative nature rather than of a qualitative one, since administration of exogenous somatostatin inhibits the secretion of hydrochloric acid, pepsin, intrinsic factor, and gastrin in ulcer patients (Schrumpf et al. 1976; Colturi et al. 1984), even though several authors have pointed out that a lower potency of somatostatin is seen in these subjects, as compared to controls (Konturek et al. 1977).

The mechanism whereby this antral D cell decrease may favor the development of peptic ulcer remains uncertain. An alteration on the inhibitory mechanisms of chlorhydropeptic and gastrin secretion might be elicited by this D cell decrease thus favoring the hyperacidity and/or hypergastrinae-

mia found in these patients. Alternately, a D cell deficit could decrease the local mucosa resistance through a deterioration of the cytoprotective function that somatostatin exerts over it (Johansson and Aly 1982). Schusdziarra (1983) suggested that gastric D cell secretory activity deteriorates with age along with a reduced capacity to secrete chlorhidric acid. These two factors would be responsible of both the wellknown hypergastrinaemia seen in old people and the antral D cell decrease. However, Fukushima et al. (1983) observed that although antral somatostatin levels decrease in control subjects along with age and an increasing degree of gastritis, in peptic ulcer patients this decrease is higher and independent of age and degree of gastritis.

In summary, although there is no current evidence supporting the conclusion that decreased antral D cell number (and thus somatostatin deficiency) is the primary cause of ulcer disease, this alteration might favor the pathogenesis of the disease through a deterioration of the protective physiopathological mechanisms of the gastroduodenal mucosa.

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