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The antral gastrin-producing cells in duodenal ulcer patients

An ultrastructural study before and during treatment with cimetidine

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Summary. Ultrastructural examination of the antral G cells has been carried out on 11 patients with chronic duodenal ulcer, before and after treatment with a histamine H-2 – receptor antagonist (cimetidine 1 g/day) for 8 weeks. The study demonstrated an increased area of the Golgi complex, rough endoplasmic reticulum and electron-dense granules, indicating increased G cell activity during treatment. An increased number of lysosomes was a constant feature during treatment. As an hypothesis we suggest that these lysosomes may participate in the secretory mechanism of human G cells, by destroying superfluous (Gastrin) components produced during hyperactivity.

Key words: Cimetidine – Duodenal ulcer – Gastrin producing cells – Ultrastructure

The treatment of chronic duodenal ulcer by selective vagotomy or histamine H-2 – receptor antagonists is followed by 1) inhibited basal, pentagastrin and food stimulated gastric acid secretion (Richardson et al. 1976; Feldman et al. 1979; Ørnsholt et al. 1983), 2) ultrastructural signs of decreased parietal cell activity (Aase and Roland 1977; Nielsen et al. 1980c), 3) elevated levels of basal and food stimulated serum gastrin (Saik et al. 1977; Buchanan et al. 1978; Forrest et al. 1979); and 4) hyperplasia of the antral gastrin-producing cells (G cells) (Nielsen et al. 1980b). Experimental studies, performed on rats, have shown that changes in the gastric acid secretion are followed by ultrastructural G cell changes (Alumets et al. 1979; Alumets et al. 1980; Håkanson et al. 1982). As there is a possibility that a species difference exists, the results of these studies cannot be applied directly to human patients.

The ultrastructure of G cells has been studied in the present investigation in duodenal ulcer patients before and during treatment with a histamine H-2 – receptor antagonist, cimetidine.

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Materials and methods

The material comprises 11 patients (9 males and 2 females), all of whom had a history of chronic duodenal ulcer disease. Their median age was 41 years (range 35–61). The presence of active ulceration was confirmed by endoscopic examination in all 11 patients. They were treated with cimetidine 1 g daily for eight weeks. None of the patients had been given a histamine H-2 – receptor antagonist earlier, although antacids were permitted up to the day of study.

Four biopsies (a sufficient number for G-cell quantitation, Nielsen et al. 1980a) were taken 2 cm proximally to the pyloric ring during gastroscopy (performed after 8 hours of fasting) before and after 8 weeks of treatment. The biopsies were immediately fixed in 5% cold glutaraldehyde buffered at pH 7.4 by means of 0.2 M Na-cacodylate. The specimens were post-fixed in 1% osmium tetroxide, dehydrated and embedded in epon. Thick sections (4 μm) from each biopsy were stained with toluidine blue for orientation. The number of thick sections was so large that at least one area from each biopsy included the luminal, middle and basal part of the mucosa, the areas subsequently selected for the ultrathin sections. Any areas exibiting intestinal metaplasia were excluded. The ultrathin sections (60–80 nm) were counter-stained with lead citrate and Zn-uranyl acetate, and examined in a Philips EM 201C electron microscope. At least 50 ultrathin sections were examined from each biopsy, all the endocrine cells were identified and photographed.

Results

The endocrine cells were found in the deeper part of the mucosa. Five different types could be identified: G-, EC-, D-, D-1- and gastric P cells (Solcia et al. 1980). All of the cells, apart from the EC cells, were in contact with the antral lumen and displayed microvilli. G cells were most numerous, although both EC and D cells were present in substantial numbers; there were very few D-1 and gastric P cells. No difference was observed in the number of the various types of cells nor of the ultrastructure of EC-, D-, D-1- or gastric P cells following treatment with cimetidine.

The G cells were found in groups of 3 to 7 cells or as single cells. Contact between G cells and other types of endocrine cell was regularly observed, D cells in particular, were frequently found in the neighbourhood of G-cells.

The granules of the G cells were mainly located to the basal part of the cell. Various ultrastructural patterns of granules were observed in the same cell. Some granules had dense cores with closely applied membranes, while others were vesicular, containing a loose core of floccular or filamentous material (intermediate type of granules) or were vesicular and electron lucent. Most cells, before treatment, contained granules of the intermediate and vesicular electron lucent types (Fig. 1). No signs of exocytosis were observed.

The following changes in the ultrastructure of the G cells were observed after 8 weeks of treatment with cimetidine: 1) the number of electron lucent and intermediate type granules were reduced in the apical and paranuclear cytoplasm (Fig. 2), and the electron dense granules comprised a greater proportion of the total granule population. 2) The granular endoplasmic reticulum was considerably increased (Fig. 3). The ribosome studded profiles of endoplasmic reticulum were distended and contained a fine granular

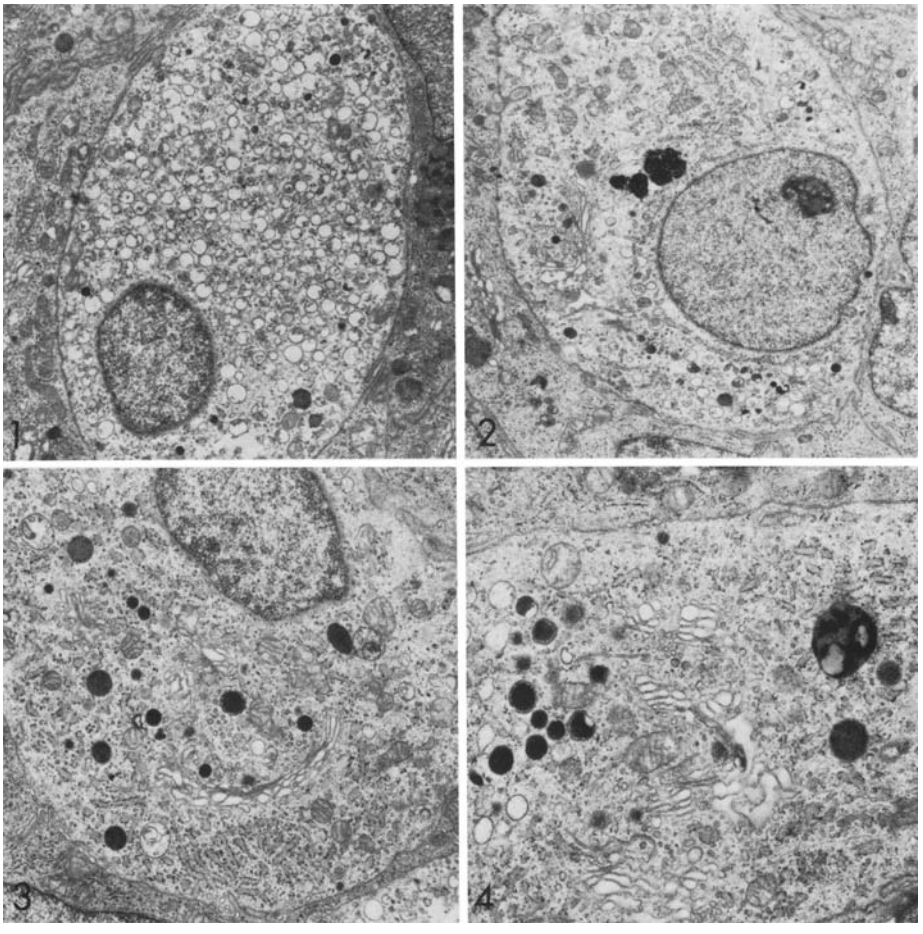
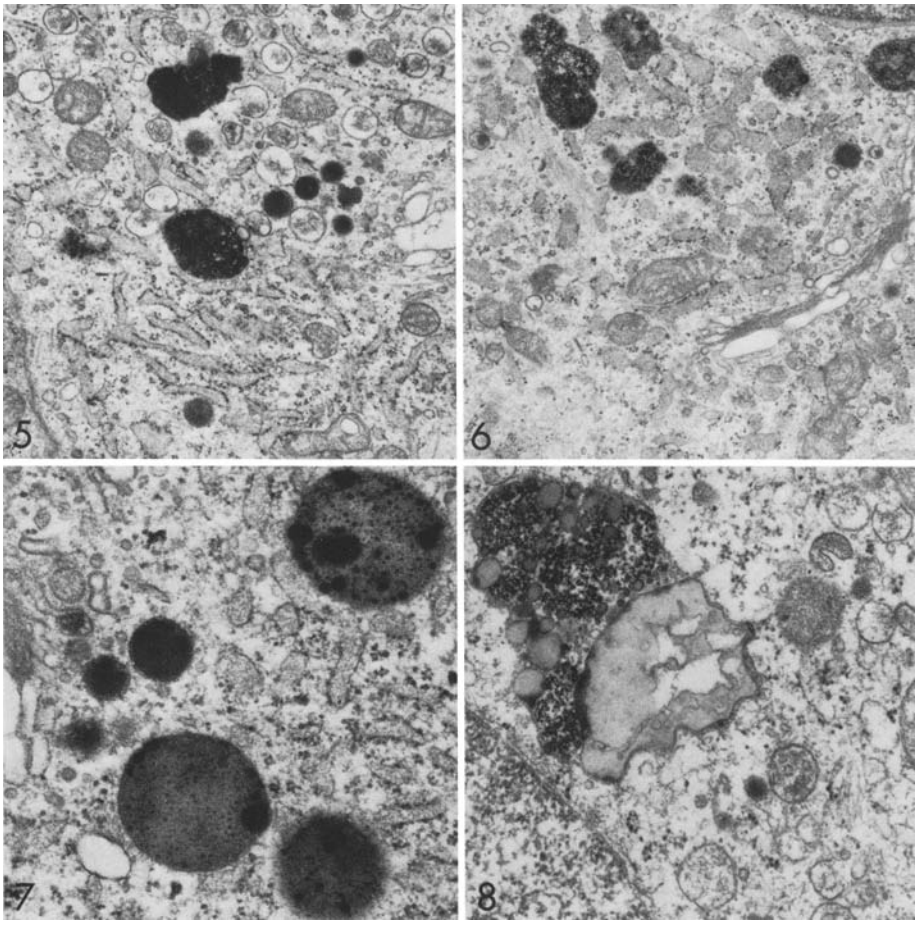


Fig. 1. Antral G cell prior to treatment with cimetidine, containing granules, almost all of which are of the electron lucent or intermediate type. × 8,000

Fig. 2–4. Antral G cells after treatment with cimetidine 1 g/day for 8 weeks. **2)** Note the reduced number of electron lucent and intermediate types of granule and the increased proportion of electron dense granules. × 8,000. **3)** Note the increased granular endoplasmic reticulum, especially at the bottom of the picture. × 8,000. **4)** Note the enlarged Golgi area surrounded by electron dense granules in the middle of the picture. × 8,000

material in the lumen. 3) The Golgi complex was enlarged (Fig. 4) with the laminar system of cisternae dispersed over large areas of the apical and paranuclear cytoplasm. Dense cored granules were present in a larger number in the interior of the Golgi complex, and granule formation could be seen. 4) Lysosomes which were rarely observed in the G cells before treatment were a constant feature of the cells during treatment (Figs. 5–8). They were mainly located in the upper perinuclear region of the cell, in the vicinity of the distended granular endoplasmic reticulum (Fig. 5) and



Figs. 5–8. Antral G cells after treament with cimetidine 1 g/day for 8 weeks, showing several morphologically different types of lytic bodies. **5**) Lysosomes in the vicinity of the distended granular endoplasmic reticulum. ×15,200. **6**) Lysosomes, Golgi complex and endoplasmic reticulum. ×15,200. **7**) Dense bodies containing material very similar to the content of secretory granules. ×26,300. **8**) Dense vacuolated bodies containing lipid inclusions. ×26,300.

the Golgi complex (Fig. 6). Several morphological types of lytic bodies were seen, they included dense bodies, multivesciular bodies and autophagic vacuoles (Figs. 7, 8). A material almost identical to the content of secretory granules was observed in the dense bodies (Fig. 7). Vacuolated dense bodies and dense bodies containing lipid inclusions were also observed (Fig. 8). The autophagic vacuoles rarely contained secretory granules, being typically composed of granular endoplasmic reticulum and ribosomes (Fig. 7). Fusion between the membrane of the secretory granules and the lytic bodies was occasionally observed.

No evidence of exocytosis was found either before or after treatment.

Discussion

The elevated level of serum gastrin during treatment and even several weeks after withdrawal of cimetidine (Buchanan et al. 1978; Forrest et al. 1979) must be due to a change in the G cells, either hyperplasia and/or hyperfunction. Antral G cell hyperplasia has been reported after treatment for 8 weeks (Nielsen et al. 1980b). The results of the present study suggest that the cells not only display hyperplasia, but also exhibit signs of hyperfunction with an increased number of electron dense granules, enlargement of the Golgi complex and an increase in the endoplasmic reticulum. Similar changes have been described by Håkanson et al. (1982) when comparing resting and active G cells following the removal of the acid-producing part of the stomach of rats (fundectomy). Our finding of an increased number of electron dense and a decreased number of electron lucent granules following permanent stimulation contrast with those of others (Forssmann and Orci 1969, Track et al. 1978, Bastie et al. 1979) who observed the opposite after acute stimulation. This suggests that G cells react differently to acute and chronic stimulation.

It has been suggested, following animal studies, that other endocrine cells may be of importance as local modulators of gastrin secretion (Uvnas-Wallensten et al. 1977, Gustavsson and Lundqvist 1978). Our observations of contact between G cells and other types of endocrine cell, particularly the D cells, indicate that human gastrin secretion is also under paracrine influence.

The mechanism by which gastrin is released from G cells is unknown. There are three possible methods 1) intracytoplasmic release of hormone stored in the granules, 2) release by exocytosis (emiocytosis), i.e., fusion of the granule membrane to the cell membrane, or 3) direct passage of the gastrin through the cytoplasm from the site of synthesis to and through the cell membrane. The first of these mechanisms was generally accepted after the initial studies of the secretory cycle by Forssman and Orci (1969). However, later studies by Miyagami et al. (1977) and Håkansen et al. (1982) suggest that the mechanism is one of exocytosis, although Creutzfeldt et al. (1975) were inclined to accept the theory that newly synthesized gastrin is released directly from the cytoplasm, by-passing the granule storage stage following the observation of rapid release of newly formed gastrin in the antral mucosa after feeding. No evidence of exocytosis before or during treatment with cimetidine was found in the present study.

The occurrence of lysosomes with engulfed secretory granules in the G cells has been described earlier by Forssmann and Orci (1969), who observed the phenomenon in cats, although only after starvation for more than 24 hours. The occurrence of lysosomes has also been reported in respect of other endocrine cells, such as mammotrophic hormone producing cells after cessation of lactation (Smith and Farquhar 1966) pancreatic A cells in diabetic animals (Orci et al. 1968) and in pancreatic B cells after the inhibition of insulin secretion by diazoxide (Creutzfeldt 1968). The hypothesis has been suggested that the granulolytic lysosomes partcipate in the

destruction of unnecessary secretory products (Orci et al. 1968). If this theory holds true for human G cells also, then our observations conflict with those of the above-mentioned investigators. One is then faced with the question, why do G cells display signs of hyperactivity at the same time as exhibiting sings of hormone destruction? There is the theoretical possibility that the G cells are hyperactive in respect of gastrin production, and produce components (by-products) as a result of this hyperactivity which are not required and that granules containing these by-products are destroyed by the lysosomes. It is known that the proportion of gastrin components changes when resting and stimulated G cells are compared (Håkanson et al. 1982). Further studies, both biochemical and morphological, are needed to clarify the role of lysosomes in the G cells of duodenal ulcer patients.

In conclusion, cimetidine produces an increased secretory activity of the G cells, and granulolytic lysosomes may play a role in the mechanism of gastrin secretion in man by destroying unneeded components.

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