The Biology and Pathobiology of the ECL Cells

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The enterochromaffin-like (ECL) cells represent the predominant endocrine cell population in the acid-producing part of the stomach of both experimental animals and man. These cells actively produce and store histamine in addition to an anticipated but as yet unidentified peptide hormone and are under the control of gastrin. An acute gastrin stimulus causes exocytosis of the cytoplasmic granules/vesicles (and release of histamine and activation of the histamine-forming enzyme, histidine decarboxylase), while a more sustained gastrin stimulus causes first hypertrophy and then hyperplasia of the ECL cells in the rat (at most, a fivefold increase in the cell number). These effects can be demonstrated following infusion of gastrin or following an increase in the concentration of circulating gastrin of endogenous origin. The growth of the ECL cells reflects an accelerated self-replication rate. As studied in the rat, the self-replication rate is accelerated quite soon after induction of hypergastrinemia (blockade of acid secretion), the rate is maximally elevated within two weeks and then declines to control values at ten and 20 weeks despite the sustained hypergastrinemia. Lifelong hypergastrinemia in rats is associated not only with ECL-cell hyperplasia but also with an increased incidence of ECL-cell carcinoids. Recently, we could show that α-fluoromethylhistidine, which is a suicide inhibitor of histidine decarboxylase, effectively depletes the ECL cells of histamine and that the histamine-depleted ECL cells respond to gastrin with hyperplasia in a manner identical to normal ECL cells. Other factors beside gastrin seem to participate in the control of ECL-cell function and proliferation. Although exogenous somatostatin is known to suppress the activity of the ECL cells, we have failed to obtain evidence that the somatostatin cells in the oxyntic mucosa play a role in the physiological control of the ECL cells. The vagus, however, is important for the ability of the ECL cells to respond to gastrin. This conclusion is based on the observation that vagal denervation suppresses the hyperplastic response of the ECL cells to gastrin. Porta-cava shunting, on the other hand, greatly enhances the responsiveness of the ECL cells to gastrin. The mechanism behind this effect is unknown.

INTRODUCTION

It is perhaps not widely known that not only the antrum but also the acid-producing part of the stomach is rich in endocrine cells. Most of the endocrine cells in the latter region remain unidentified in functional terms. Interest in these cells increased greatly with the observation that long-term treatment with effective inhibitors of gastric acid secretion (proton pump inhibitors and histamine H_2-receptor antagonists) caused hyperplasia of one of the endocrine cell populations in the acid-producing mucosa, the so-called enterochromaffin-like (ECL) cells, and

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Abbreviations: α-FMH: α-fluoromethylhistidine ECL: enterochromaffin-like (cells) ECLoma: ECL-cell tumor(s) LI: labeling index PCS: porta-cava shunting

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that there were reasons to believe that carcinoids could develop from these cells in response to lifelong hypergastrinemia.

Thus, the ECL cell of the stomach has moved from relative obscurity to fame, if such a word can be used to describe the fascinated but somewhat bewildered interest that this cell has attracted for the last five years or so. The fascination can be accounted for by the tendency of the ECL cell to generate tumors in situations characterized by hypergastrinemia, and the bewilderment reflects our ignorance of its normal functional significance. The present paper reviews the current evidence that seems to indicate that the ECL cells represent an important endocrine cell system and that they are under the control of gastrin.

OCCURRENCE, TOPOGRAPHY, AND ULTRASTRUCTURAL FEATURES OF THE ECL CELL

The ECL cells represent one of several different endocrine cell populations that have been identified in the acid-producing part of the gastric mucosa [1–8]. It should be pointed out that the endocrine cells in the acid-producing gastric mucosa are quite numerous (constituting 1 and 2 percent by volume in man and rat, respectively) and that consequently this part of the stomach represents a quantitatively impressive endocrine organ. As such, the acid-producing part of the stomach remains largely unexplored. On the basis of their histochemical features and ultrastructure, it can be assumed that the different endocrine cell populations produce peptide hormones, although very little is known about the nature of these anticipated hormones. While four different endocrine cell types have been demonstrated in the oxyntic mucosa of the rat, at least five endocrine cell populations have been identified in man [4,5,8]. In all species studied, the ECL cells form the predominant endocrine cell population [8–10], and in all species they seem to be restricted to the oxyntic mucosa. In man, they make up 35 percent of the total number of endocrine cells in the oxyntic mucosa [11,12]; in the rat, the corresponding figure is 65 percent [8]. The ECL cells, which are usually small and elongated, or irregularly shaped, are characterized by the presence of numerous large electron-lucent vesicles in the cytoplasm [2,5,6,10,13] (Fig. 1). Some of these vesicles have an electron-dense core, and, in a few of these vesicles, the core is so predominant that the organelle should probably be referred to as a granule rather than a vesicle. There seems to be some species variation in the appearance of the vesicles; in man, for instance, most of them have an electron-dense core. The ECL cells can be demonstrated by the fact that they produce and store histamine [14], which can be visualized immunocytochemically by the use of antibodies to histamine [9] (Fig. 2) or to the histamine-forming enzyme [15]. ECL cells or ECL-cell equivalents seem to occur in the acid-producing gastric mucosa of a variety of species, from cartilaginous fish to man [9]. They are particularly numerous in the rat and chicken, and they are relatively few in dog, monkey, and man. Their topographic distribution within the acid-producing mucosa differs among different classes of animals. In mammals, they occur in the basal third or basal half of the glands; in birds, they are found in the periphery of the spherical compound glands that make up the mucosa of the proventriculus. In amphibia and lizards, they occur at the base of the foveolae in the neck region, and, in fish, they are often found within the surface epithelium [9].
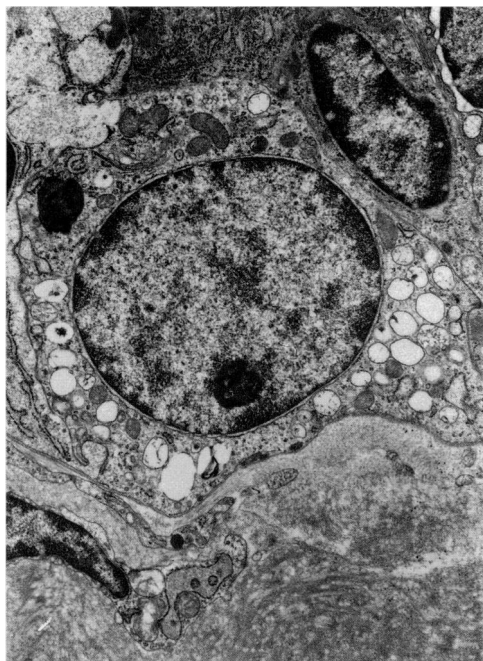
FIG. 1. Electron micrograph of an ECL cell in rat stomach with the characteristic vesicular-type cytoplasmic granules, some of which display a small electron-dense core, ×6,000.

THE ECL CELL RESPONSE TO GASTRIN

In all species that have been studied so far, the ECL cells have been found to respond to gastrin. This process has been studied in detail in the rat [16–19]. The response is manifested in several ways (Fig. 3). Elevated circulating gastrin concentration is reflected in prompt histamine release and increased histidine decarboxylase activity. If the gastrin stimulus is sustained, the ECL cells will respond with hypertrophy; this response is manifested within a few days of gastrin challenge [13]. They respond also with hyperplasia; this response requires weeks to months to develop [19]. These responses of the ECL cells have been demonstrated in experimental animals that have been subjected to treatments that either lower or raise the circulating concentrations of gastrin. In addition, gastrin stimulates growth of the oxyntic mucosa, and lack of gastrin is associated with atrophy of the oxyntic mucosa.
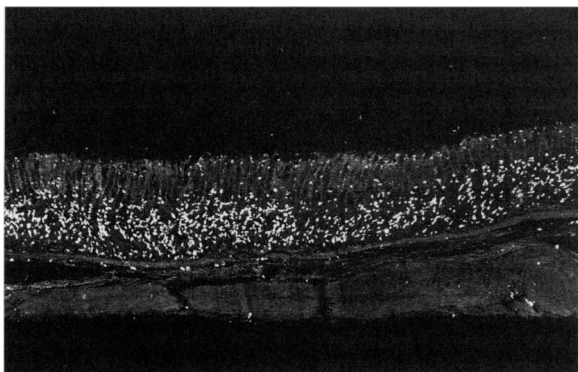

FIG. 2. Histamine-immunoreactive ECL cells in the acid-producing part of the rat stomach (transverse section, mucosal surface upward). Mast cells are relatively few and located at the mucosal surface and in the submucosa and muscle coat. The ECL cells are located basally in the glands. The immunoreactive cells are demonstrated by dark-field microscopy following peroxidase-antiperoxidase staining, ×100.

ECL CELL   Time scale:

| Histamine release | minutes |
| Activation of histidine decarboxylase | hours |

GASTRIN

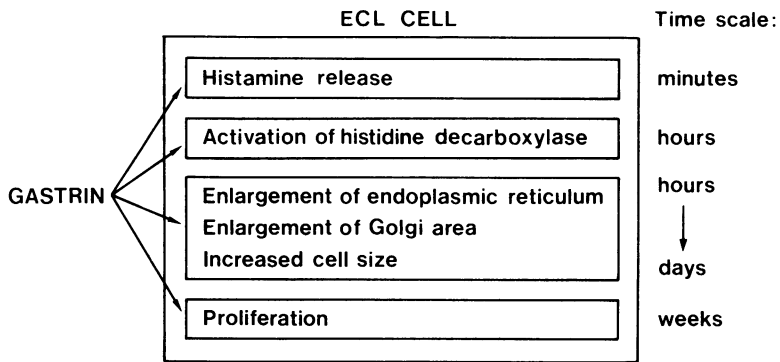| Enlargement of endoplasmic reticulum
Enlargement of Golgi area
Increased cell size | hours
↓
days |

| Proliferation | weeks |

FIG. 3. A schematic outline of some recognized effects of gastrin on the ECL cells, with an approximate time scale indicating how long the hypergastrinemia has to be sustained in order for the various effects to become manifest.

The induction of endogenous hypergastrinemia by antrum exclusion [20] or by partial removal of the acid-producing part of the stomach (fundectomy or corpectomy) [21] resulted in an increased ECL-cell density, whereas hypogastrinemia induced by antrectomy had the reverse effect [22,23]. Administration of effective inhibitors of acid secretion, such as H_2-receptor antagonists like ranitidine or proton pump inhibitors like omeprazole [23–25], raised not only the level of circulating gastrin but also the ECL-cell number (Fig. 4). Also, hypergastrinemia induced by
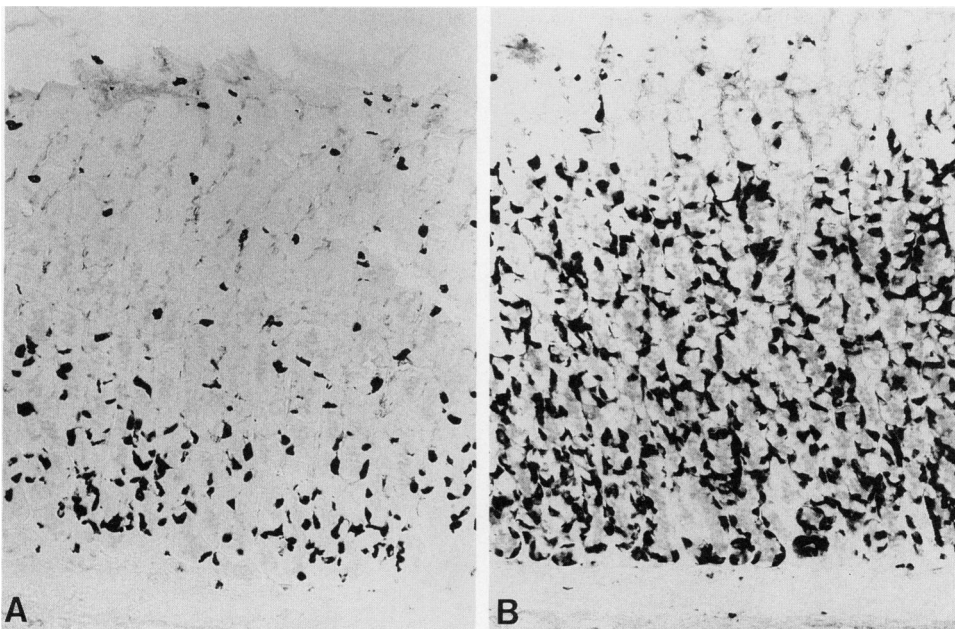

FIG. 4. ECL-cell hyperplasia following ten weeks of daily administration of large doses of omeprazole.   Control rat, A.   Omeprazole-treated rat, B. The ECL cells are visualized by histamine immunostaining (peroxidase-antiperoxidase), ×200.

continuous infusion of exogenous gastrin for 28 days in the rat resulted in ECL-cell hyperplasia [26].

In order to learn whether the mechanism leading to hyperplasia was an increase in the ECL-cell mitotic activity or a passive mechanism such as increased ECL-cell life span or whether the hyperplasia was caused by accelerated stem cell differentiation, specific immunocytochemistry and autoradiography were combined to observe variations in the ECL-cell kinetics. The DNA in rat ECL cells can be radiolabeled using ^{3}H-thymidine [27]. The proportion of ECL cells that become labeled with ^{3}H after a single injection of ^{3}H-thymidine is referred to as the ECL-cell labeling index (LI). In normal rats, the ECL cells display greater LI during the night than during the day, coinciding with the time when rats have high circulating gastrin levels. Nine days after starting a blockade of acid secretion by a high-dose treatment with omeprazole in male rats, which leads to hypergastrinemia, we observed an eightfold increase in the ECL-cell LI, while, at the same time, mitotic figures in ECL cells were quite numerous [27]. Hence, we conclude that activation of self-replication is the mechanism increasing the ECL-cell number in response to omeprazole-evoked hypergastrinemia (see also [28]). In fact, we observed a positive correlation between the ECL-cell proliferation rate (LI) and the circulating gastrin levels in the animals of that experiment [27].

In another study, male rats were submitted to surgery in order to induce endogenous hypergastrinemia through antrum exclusion or hypogastrinemia through antrectomy [29]. A 52 percent increase in ECL-cell number was observed six weeks after antrum exclusion; the number decreased by 17 percent after antrectomy. The ECL-cell LI was doubled following antrum exclusion, while it was reduced to less than 25 percent of its value in control rats after antrectomy. Again, there was a good correlation between the ECL-cell proliferation rate and the circulating gastrin levels.

Sustained endogenous or exogenous hypergastrinemia of comparable magnitude was induced in female rats [30]. The rise in circulating gastrin was induced either through oral administration of 80 μmol/kg of omeprazole once daily or by subcutaneous infusion of 1,200 μmol/kg/day of ranitidine through osmotic mini-pumps. Rat gastrin-17 was administered through subcutaneously implanted mini-pumps at a dose of 60 nmol/kg/day. Previously, antrectomized rats were also given either omeprazole or the solvent. After 12 days, the ECL-cell density as well as the gastrin levels had increased in the groups with an intact antrum receiving antisecretory drugs or gastrin, whereas the number of ECL cells had decreased in the antrectomized groups. Accordingly, treatment with ranitidine as well as with omeprazole or exogenous gastrin increased the proliferative parameters in the ECL-cell population to values reaching four to seven times the control value (see also [31]). In the antrectomized rats, with or without omeprazole, the ECL-cell LI was lower than in the intact rats. Again, a significant correlation was observed between circulating gastrin levels and the proliferative activity of the ECL cells (Fig. 5).

All these experimental results favor the hypothesis that circulating gastrin is a major trophic factor for the ECL-cell population. Whenever hypergastrinemia is induced, regardless of whether acid secretion is stimulated or depressed, there is an increase in the mitotic activity of the ECL cells, followed by the development of ECL-cell hyperplasia. Hence, gastrin appears to play a central role in the kinetic control not only of the oxyntic mucosal stem cells but also of the ECL cells, the major endocrine cell population in this part of the stomach. The results seem to justify the
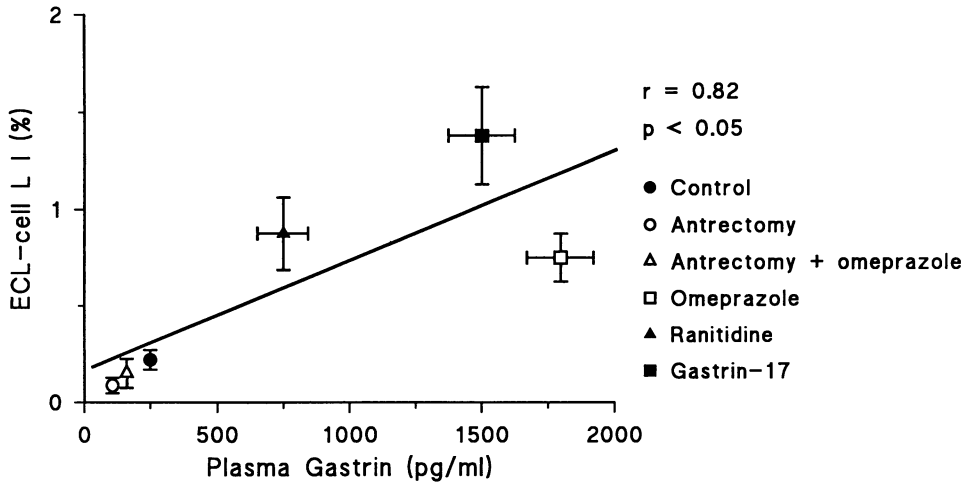
FIG. 5. ECL-cell labeling index (**LI**) as a function of the circulating gastrin level at the time of sacrifice. Antrectomized rats were operated six weeks before entering the study. The rats were treated with omeprazole (80 μmol/kg/day), ranitidine (1,200 μmol/kg/day), rat gastrin-17 (60 nmol/kg/day), or solvent for 12 days. Ten to 11 rats were in each group. The rats were killed between 10 A.M. and noon, one hour after a single intraperitoneal injection of ^{3}H-thymidine (1 mCi/kg). There was a positive correlation ($p < 0.05$) between the ECL-cell LI and the plasma gastrin concentration [30].

following conclusions: *(1)* The ECL-cell density reflects the circulating gastrin concentration. *(2)* Large doses of effective and long-acting inhibitors of acid secretion cause proliferation of ECL cells through the ensuing hypergastrinemia. Also, hypergastrinemia of a moderate degree is associated with hyperplastic manifestations. This fact was demonstrated in obese Zucker rats, who had a two- to threefold increase in the serum gastrin concentration compared to lean rats. At 18 months of age, the obese (but not the lean) rats displayed both linear and micronodular ECL-cell hyperplasia [32].

THE DEVELOPMENT OF ECL-CELL TUMORS: THE GASTRIN CONCEPT

Lifelong administration (two years) of high doses of effective antisecretory drugs to rats is associated with the development of ECL-cell tumors, i.e., ECLoma, gastric carcinoids [33–43]. Changes ranged from a diffuse hyperplasia through focal aggregation of cells to structures of more solid appearance, the latter manifestations occurring after long-lasting treatment only. In view of the known stimulating effect of gastrin on the ECL cells, the so-called gastrin concept was formulated in order to explain the hyperplasia and the development of carcinoids. The gastrin concept maintains that effective inhibition of gastric acid secretion abolishes luminal acid feedback inhibition of the antral gastrin cells, leading to hypergastrinemia, which in turn activates the ECL cells, producing first diffuse and later on focal ECL-cell hyperplasia with micronodules and finally carcinoids [18,19,44] (Fig. 6). The sequence of events described above is not drug-specific, in that many different agents produce it (see, e.g., [45]). The common denominator is that all the drugs produce hypergastrinemia. The view that gastrin is an important causative factor is supported by the fact that partial fundectomy (corpectomy) (25 percent of the acid-producing

Proposed mechanism for the developement
of gastric carcinoids (ECLom) induced
        by acid blockade:

Inhibition of acid secretion

⬇

Hypergastrinemia

⬇

ECL cell hyperplasia
 – diffuse general hyperplasia
 – focal hyperplasia
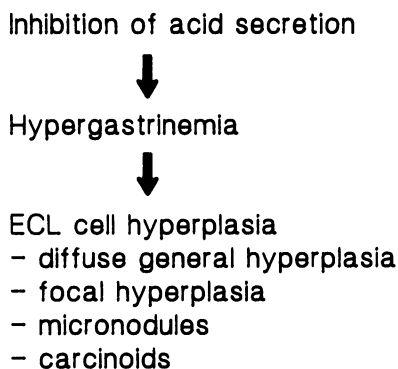 – micronodules
 – carcinoids

FIG. 6. A schematic outline of the proposed sequence of events behind the development of gastric ECL-cell tumors.

mucosa remaining), which results in sustained hypergastrinemia, causes ECL-cell hyperplasia [21], followed by the development of gastric carcinoids [46]. The "gastrin concept" provides a rational explanation to account for the development of ECL-cell hyperplasia in the rat in response to treatment with powerful anti-secretagogues. The development of ECLoma in the rat stomach after two years of drug administration is, however, less well accounted for. The stimulus behind the development of the ECLoma is thought to be the hypergastrinemia (rather than the achlorhydria), and there is no evidence that, for instance, ranitidine or omeprazole are directly acting carcinogens or co-carcinogens. One question which has not yet been addressed experimentally is whether gastrin acts directly to cause ECL-cell hyperplasia or whether it does so indirectly, through the mediation of some local growth promoter. Although gastrin, directly or indirectly, may be able to stimulate growth of tumors, it appears unlikely that gastrin per se induces oncogenic transformation. In this context, it may be of interest to note that the ECL-cell density in the rat increases with age. In fact, ECL-cell hyperplasia with micronodules has been reported in aging rats [47], and a few cases of spontaneous ECL-cell tumors are on record [48]. Hence, senescence may be a contributing factor behind the development of ECL-cell tumors in the rat, possibly in combination with high concentrations of circulating gastrin.

An analogous situation exists in patients with achlorhydria as a result of chronic atrophic gastritis. These patients usually have high levels of circulating gastrin. Diffuse or focal hyperplasia of argyrophil cells (which include the ECL cells) is a characteristic feature of many such cases, and there seems to be a correlation between the circulating gastrin concentration and the degree of argyrophil cell hyperplasia [49–56]. Gastric carcinoids, which on the whole are rare tumors, are not uncommon in such patients [53,54,57,58]. They are often multiple and associated with hyperplasia of argyrophil cells in the surrounding tissue. Gastric carcinoids have been found in another category of hypergastrinemic patients: namely, those with a gastrin-producing tumor (Zollinger-Ellison syndrome) [59–61]. Thus, there also seems to be a link between hypergastrinemia and an increased incidence of gastric carcinoids in man. Gastric carcinoids, however, have low malignant potential and are rare in patients, even in situations of massive hypergastrinemia associated with

gastrinoma. There are reports indicating that the ECL-cell hyperplasia, including micronodules, in such patients disappears after antrectomy (or after removal of the gastrinoma), and there is evidence that gastric carcinoids may also disappear [62–65].

When rats are given high doses of omeprazole daily, the ECL-cell LI starts to increase after two days and reaches a maximal level after about nine to ten days, which should be enough to explain the gastrin-evoked ECL-cell growth [27]. If the administration of omeprazole is interrupted after 16 days of administration, the ECL-cell LI is rapidly suppressed, in fact, to levels below those seen in the control rats [66]. In another experiment, omeprazole treatment rapidly raised the serum gastrin concentration to a plateau and progressively raised the ECL-cell density up to 10–20 weeks of treatment; thereafter it reached a plateau, while the ECL-cell LI reached a peak after one to two weeks of omeprazole treatment. The peak in the ECL LI was followed by a decline to values similar to or actually below those seen in normal rats [67], perhaps because of the formation of local anti-trophic stimuli in the mucosa or in the ECL cells themselves. There are several points of interest here. Apparently, it is possible to have a progressive and subsequently maintained ECL-cell hyperplasia without accelerated mitosis frequency, possibly because of a prolonged life span of the cells or, less likely, because of recruitment of ECL cells from stem cells. Second, the fact that the histidine decarboxylase activity was maintained at a very high level throughout the experiment is interesting, because it means that the gastrin-induced activation of the ECL cells is maintained even though the trophic stimulus of gastrin, reflected in the elevated LI, is offset. Perhaps we are dealing with two gastrin receptors, one handling activation of the cell, another the induction of mitosis—or we are dealing with two post-receptor pathways, one functioning at all times, the other being offset with long-term exposure to gastrin. According to the classical gastrin concept, ECLomas develop against a background of first diffuse and then focal ECL-cell hyperplasia as a result of long-standing hypergastrinemia. Previously, it had been assumed that a permanently elevated mitotic index, perhaps in combination with an increased risk of mutation because of old age, could explain the ECL-cell tumor development. Now it seems that an explanation has to be found elsewhere.

One issue that has been raised recently is whether histamine in the ECL cells is important for the growth of the ECL cells and/or for the growth of the oxyntic mucosa, implying that the ECL cell and its histamine might mediate the gastrin-evoked trophic response of the mucosa [68]. One way to approach this question is to eliminate all histamine from the ECL cells and observe the consequences. We decided to use α-fluoromethylhistidine (α-FMH), which is a so-called suicide inhibitor of histidine decarboxylase [69] and which effectively blocks the production of histamine in the ECL cells. It could be shown by immunocytochemistry that α-FMH depletes histamine from the ECL cells (Fig. 7) but not from the mast cells, which are few in the oxyntic mucosa of the rat. The result was a loss of more than 80 percent of oxyntic mucosal histamine [70]. The effect of histamine depletion on the trophic responses evoked by omeprazole-induced hypergastrinemia for six weeks was studied. Histamine was predictably lost from the ECL cells in the α-FMH-treated rats, while the concentration of oxyntic mucosal histamine was increased in the rats that received omeprazole alone. The growth-promoting effect of omeprazole-evoked hypergastrinemia on the gastric mucosa and on the ECL cells in particular was
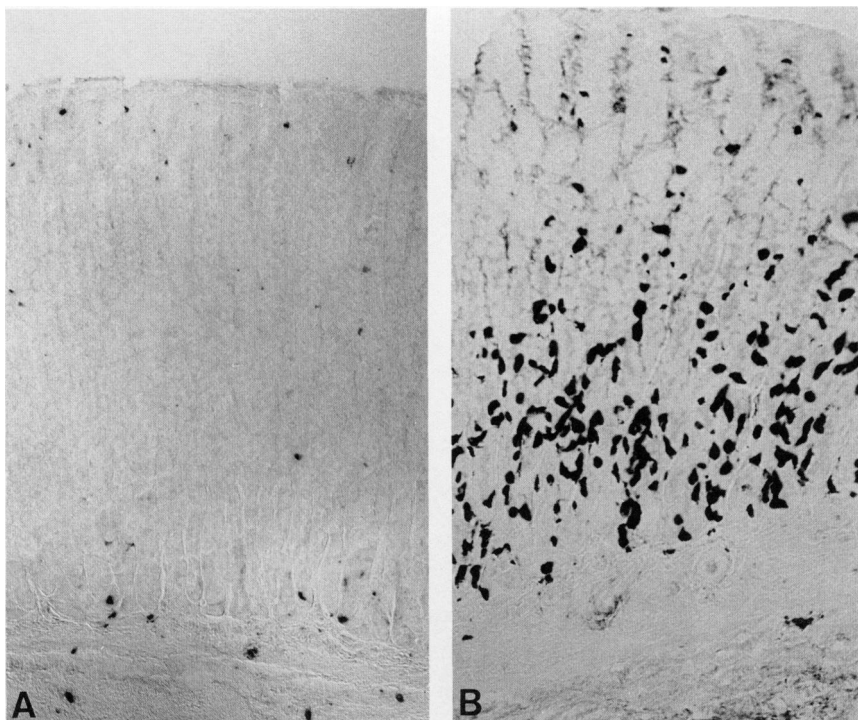
FIG. 7. Histamine immunostaining. Rat stomach, oxyntic mucosa, transverse section. Treatment with α-fluoromethylhistidine prevents the formation of histamine and depletes histamine from the ECL cells (but not from the mast cells) in the rat stomach. This effect is reflected in the loss of histamine immunostaining, **A.** Control rat for comparison, **B,** ×200.

unaffected by α-FMH pre-treatment [68]. In fact, the ECL-cell number was increased by gastrin stimulation to the same degree, regardless of whether the ECL cells contained histamine or not. Hence, it appears that ECL-cell histamine does not play a role in gastrin-evoked growth stimulation; however, the ultrastructure of the ECL cells was greatly affected by α-FMH (Fig. 8). The vesicles were small and greatly reduced in number. The granules remained, apparently unaffected, suggesting perhaps that histamine is located in the vesicles rather than in the granules [70].

OTHER FACTORS BESIDE GASTRIN CONTROL THE ECL CELLS

Although available evidence suggests that gastrin represents the major stimulus, gastrin is not the only factor of importance for the control of the ECL cells. Somatostatin released from adjacent somatostatin cells could interfere with the ECL cells in a paracrine fashion, and exogenous somatostatin effectively suppresses the activity of the ECL cell and the growth of the ECL cells. We have not been able to demonstrate that gastrin activates the somatostatin cells or causes them to grow, although there is some evidence that they have a gastrin receptor [71]. On the contrary, somatostatin cells in the oxyntic mucosa are reduced in number in hypergastrinemic rats and increased in number in antrectomized rats [72]. The possibility cannot be excluded that gastrin inhibits the somatostatin cells in the oxyntic mucosa, thereby stimulating ECL-cell activity and proliferation. There is
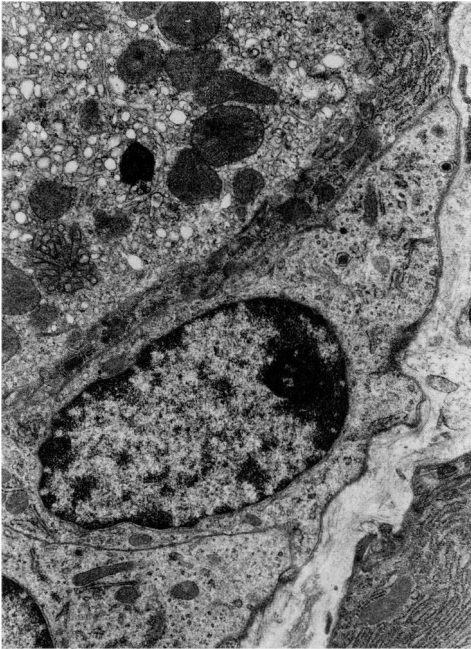
FIG. 8. Effect of α-FMH on the ultrastructure of ECL cells in the rat stomach. Note the relative degranulation and the loss of large vesicular-type granules in the cytoplasm, ×6,000.

some evidence that the somatostatin cells have not only gastrin receptors but also CCK-A receptors [71,73–75]. The ECL cells respond to CCK via an action on gastrin or CCK-B receptors [76]. If the somatostatin cells were to be activated by CCK to release somatostatin to suppress the activity (and growth) of the ECL cells, then CCK-A receptor blockade should enhance the response of the ECL cells to CCK. This hypothesis could not be confirmed. Both gastrin and CCK activated the ECL cells to the same extent, despite CCK-A receptor blockade [76], using maximally effective doses of the CCK-A receptor antagonist devazepide.

The vagus plays a role in the control of the oxyntic mucosal growth, including the ECL cells. This fact can be demonstrated by unilateral vagotomy of rats. If the two sides of the stomach, the denervated and the vagally intact sides, are compared eight to ten weeks after denervation, it is apparent that the vagally denervated side of the mucosa is thinner and that the ECL cells are fewer than on the intact side [77,78]. If unilaterally vagotomized rats are exposed to omeprazole, the serum gastrin concentration is elevated, as in omeprazole-treated control rats, but ten weeks later there is a clear difference in the appearance of the mucosa on the vagally denervated and the intact sides. On the intact side, it is thick and prominent, while, on the denervated side, it is thin and inconspicuous. Not only the mucosa in general but also the ECL cells are affected by the vagotomy. The ECL-cell hyperplasia is much less conspicuous on the denervated side than on the intact side. The results are compatible with the view that an intact vagal innervation is required for a full growth-promoting effect of gastrin. Thus, omeprazole-evoked hypergastrinemia fails to evoke the anticipated growth of the ECL cells and of the mucosa following unilateral vagotomy [79]. It is not known whether these rats are less likely to develop carcinoids than are vagally intact rats. It is also not known whether hypergastrinemic patients would benefit

from vagotomy in terms of lower degree of ECL-cell hyperplasia and lower incidence of gastric carcinoids.

Porta-cava shunting (PCS) is known to increase the ECL-cell density for unknown reasons [22,80]. This operation does not increase the serum gastrin concentration, but antrectomy prevents the effect of PCS, suggesting that, in one way or another, gastrin contributes to the response [80]. In fact, the results suggest that the number of gastrin receptors on the ECL cells are increased severalfold by PCS and that, for this reason, the ECL cells respond to gastrin in an exaggerated manner [80]. The reason for the upregulation of the gastrin receptors is unknown. Omeprazole treatment elevates the serum gastrin concentration in the PCS rats much like that in the sham-operated rats, but ten weeks of omeprazole treatment induces a much-exaggerated ECL-cell hyperplasia and hypertrophy in the PCS rats, compared with sham-operated animals [81]. The reason for this finding is unknown. From these observations, it would seem that gastrin is the major stimulus of the ECL cells and that vagal denervation and PCS alter the way that the ECL cells respond to gastrin.

CONCLUDING COMMENTS

From the observations described above, it is tempting to suggest that the ECL cells represent a gastrin target of major physiological importance. The trophic response of the rat ECL cell to gastrin is spectacular, i.e., a four- to fivefold increase in number as compared with, at most, a 30 percent increase in the oxyntic mucosa as a whole in response to long-term hypergastrinemia [82]. No other endocrine cell type in the oxyntic mucosa seems to respond to gastrin with stimulated growth.

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