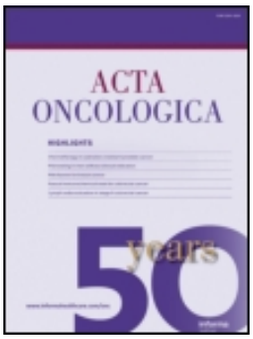

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THE ENTEROCHROMAFFIN-LIKE (ECL) CELL

Physiological and pathophysiological role

HELGE L. WALDUM, ARNE K. SANDVIK, UNNI SYVERSEN and EILIV BRENNA

Histamine has a central role in the regulation of gastric acid secretion. This histamine is produced by and released from the enterochromaffin-like (ECL) cell which accordingly has a key-regulatory role in the oxyntic mucosa. Gastrin and the vagal nerves stimulate the formation and release of histamine from the ECL cell. Moreover, gastrin and the vagal nerves also stimulate the proliferation of the ECL cell. An increased ECL cell density may partly explain the increased acid secretion in patients with duodenal ulcer, particularly in patients with Zollinger-Ellison syndrome. The reduced potency of histamine-2 blockers in patients with Zollinger-Ellison syndrome is probably due to increased histamine release by an elevated ECL cell mass. Prolonged and profound hypergastrinemia may lead to ECLomas. Moreover, a proportion of diffuse gastric carcinomas may originate from ECL cells.

Neuroendocrine or enterochromaffin cells were first described in the stomach of the rabbit and dog by Heidenhain (1) and such cells were shortly afterwards also found in other parts of the gastrointestinal tract (2). The enterochromaffin cells of the gut are heterogeneous morphologically (3, 4) as well as histochemically and immunocytochemically (5). According to the ultrastructural morphology of the secretory granules, the neuroendocrine cells of the oxyntic mucosa of the stomach may be classified into at least six types (4, 6).

The enterochromaffin-like (ECL) cell

The ECL cell is quantitatively the most important neuroendocrine cell in the oxyntic mucosa in man (6) and especially in the rat (7). The ECL cell was originally described by Håkanson & Owman (8) who demonstrated the presence of histamine histochemically in an oxyntic mucosal cell with staining properties resembling the enterochromaffin cell of the intestine, and accordingly they named the cell the enterochromaffin-like or the ECL cell. The presence of a histamine producing non-mast cell had shortly before been shown by Thunberg (9). Besides in rodents, histamine was not found in the ECL cell of other species including man (10). Consequently, the ECL cell was recognized as the cell producing histamine participating in the regulation of acid secretion in the rat, and the mast cell was assumed to have this function in other species (11). Some years ago, however, Håkanson et al. (12) using immunohistochemistry demonstrated the presence of histamine in the ECL cell in most species. In contrast to mast cells there is also an inverse relationship between the ECL cell density and the potency of histamine as gastric acid secretagogue (13). Furthermore, physiological regulators of acid secretion, like gastrin and somatostatin, influence the histamine release from ECL cells in man (14), rat (15, 16) and rabbit (17). It therefore seems justified to conclude that the ECL cell is the cell producing and releasing the histamine being involved in the regulation of gastric acid secretion (18). Moreover, the gastrin stimulation of gastric acid secretion may be solely explained by the stimulation of histamine release in rat (19) and man (20) and probably in other species as well (19).

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Accordingly, the ECL cell has a gastrin receptor, whereas from a functional point of view it is not necessary to postulate such a receptor on the parietal cell (18, 19, 21). Particularly in the dog, the presence of a gastrin receptor on the parietal cell has been claimed to be proved (22). However, even in this species gastrin elicits a brisk stimulation of histamine release (23, 24), and it should also be realized that histamine is a very potent gastric acid segretagogue in the dog (25). In contrast to the other two major gastric secretagogues, acetylcholine and histamine, gastrin only weakly stimulates the acid secretion in isolated parietal cells assessed by the O_2 consumption or the accumulation of the weak base aminopyrine (26–28). This discrepancy between in vivo and in vitro effect of gastrin may best be explained by an indirect effect on the parietal cell by gastrin (29). Studies claimed to exclude any role of histamine in the gastrin stimulation of secretion in isolated parietal cells (30, 31) have not taken into consideration the fact that the released histamine is not instantaneously distributed to the whole incubation medium. To inhibit any effect of histamine released via gastrin stimulation, the rather weak histamine antagonist cimetidine has been used in a concentration insufficient to prevent the stimulation by histamine of parietal cells in close proximity to histamine-releasing ECL cells (19, 32).

The histamine release is influenced not only by gastrin (33, 34) but also by vagal stimulation (35) and cholinergics (24, 36) as well as by somatostatin (37) and prostaglandins (38). Histamine from the ECL cells being mainly located at the base of the glands (7), may reach the parietal cell not only by the paracrine route but also via the capillaries (18). Thus, the ECL cell via histamine release plays a central role in the regulation of gastric acid secretion (Figure).

The ECL cell may also produce other mediators. Håkanson et al. (39) have presented data suggesting that a gastric calcitoninlike peptide is produced in the ECL cell (39). Until now, however, they have not succeeded in purifying any peptide from the ECL cell with an effect on the calcium metabolism. On the other hand, chromogranin A (40), alpha chain of the glycohormones (41) and calbindin (42) have been found in the ECL cell by immunocytochemical methods. Any physiological or pathophysiological role of these peptides from the ECL cells has, however, not been shown. Histamine not only stimulates the acid secretion, but also induces a vasodilatation (43), as well as an increase in capillary permeability (44). Thus, by releasing histamine, gastrin stimulates both the acid secretion and the mucosal blood flood.

Histamine has hitherto been thought not to have any trophic effect on the oxyntic mucosa (45, 46) but, we could show that the dose of histamine used in a previous study (45) gave a histamine concentration in serum much lower

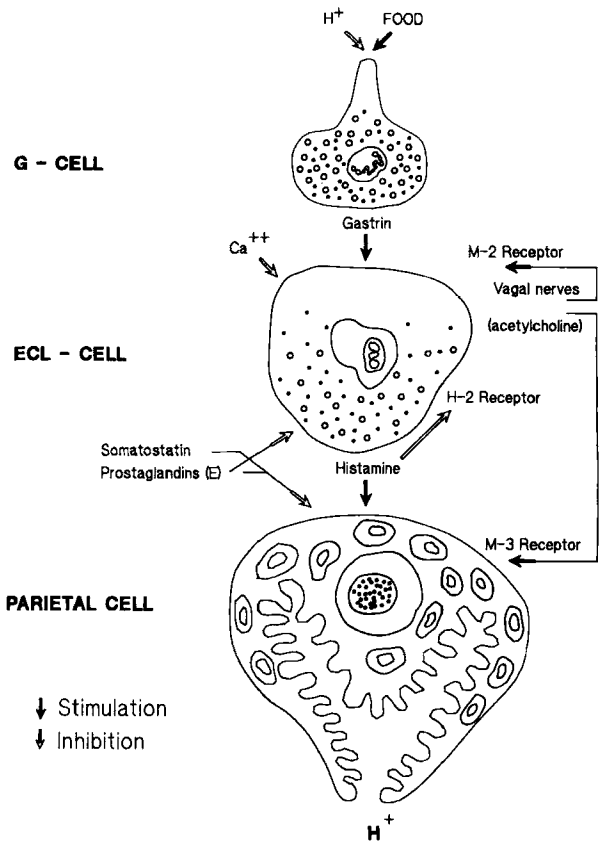

Figure. The ECL cell plays a central role in the regulation of gastric acid secretion.

than that found in the oxyntic mucosal vascular bed during gastrin stimulation (47). Accordingly, it is not ruled out that locally released histamine may have a growth regulatory effect (47). The general trophic effect of gastrin on the oxyntic mucosa (45, 48) may, like the stimulation of acid secretion, be a secondary one (47). Histamine-1 blockade does not, however, affect the general trophic effect of gastrin on the oxyntic mucosa (49). On the other hand, in contrast to omeprazole, long-term histamine-2 blockade with loxtidine resulting in secondary hypergastrinemia did not affect the weight of the oxyntic mucosa, suggesting a positive trophic effect of histamine via a histamine-2 receptor (50). The parietal cell numerical density was also reduced in loxtidine-treated rats (50) which agrees with a previous study showing parietal cell atrophy after long-term treatment with the long-acting H-2 antagonist tiotidine (51). The malignant ECLomas occurring spontaneously in the African rodent mastomys are surrounded by a zone with parietal cell hyperplasia (52), suggesting that a paracrine trophic substance is released from these ECL tumor cells. Since the ECL cell also in the mastomys produces histamine (53), this suggests that histamine may indeed have a local trophic effect.

Pathophysiological role of the ECL cell

Role in duodenal ulcer disease and Zollinger-Ellison syndrome

Recently, D'Adda et al. (54) described an increased ECL cell density in patients with duodenal ulcer disease. If this is confirmed, an increase in the ECL cell mass could partly explain the increased acid secretion in these patients since the magnitude of the gastrin-stimulated histamine release is dependent on the ECL cell mass (49, 50). Patients with duodenal ulcer disease have also an increased sensitivity towards gastrin as gastric acid secretagogue (55, 56) which is compatible with an increased ECL cell mass. Furthermore, experimental hypergastrinemia induces an increase in maximal acid secretion which cannot be explained by the increase in the parietal cell mass (57). Even patients with Zollinger-Ellison syndrome have an increased maximal acid secretion out of proportion with the increase in the parietal cell mass. Those patients have, however, a marked increase in the ECL cell density (58) which could be the most important factor behind the increase in maximal acid secretion in Zollinger-Ellison syndrome (59). It should be realized that the acid secretion even in patients with Zollinger-Ellison syndrome may be completely inhibited by H-2 blockers, although at a very high dose (60). The reduced potency of H-2 blocker in patients with Zollinger-Ellison syndrome simply indicates that there is an increased histamine release in these patients, which is best explained by the increased ECL cell mass (61). It is also important to note that the maximal gastrin-stimulated acid secretion is lower than the maximal histamine-stimulated acid secretion in the isolated rat stomach, and that gastrin does not affect maximal histamine-stimulated acid secretion in this model which is completely without a gastrin background stimulation (62). This indicates that, due to a general toxicity, histamine cannot in vivo be given in a dose giving maximal acid secretion. Therefore, in vivo, maximal gastrin-stimulated and histamine-stimulated acid outputs are apparently similar (63, 64).

Gastric ECLomas

Quantitatively, the ECL cell is the most abundant endocrine cell in the oxyntic mucosa (6). Gastric carcinoids are also most often of the ECL cell type (65). Gastrin has a specific trophic effect on the ECL cell (66) and, not surprisingly, ECL cell carcinoids occur after long-term hypergastrinemia in man (67, 68) as well as in the rat (69, 70, 71). The acid secretion does not seem to play any significant role in the pathogenesis of the ECLomas since such tumors occur in patients with hypergastrinemia combined with hypersecretion of acid (68), in those with anacidity and secondary hypergastrinemia (67), and in rats after drug or surgically induced hypo/anacidity (69–72). Atrophic gastritis itself has been claimed to be a separate factor in the ECL cell tumorigenesis (73). This seems, however, not likely since patients with Zollinger-Ellison syndrome also develop ECLomas (68). Gastric ECLomas in connection with Zollinger-Ellison syndrome occur especially in patients with multiple endocrine neoplasia type 1 (MEN-1) (74, 75) and it has therefore been speculated that these carcinoids could as well reflect a general tendency towards endocrine neoplasia in these patients. However, endocrine tumors occurring in patients with MEN tend to be less malignant than those developing spontaneously, and since the gastrinomas in patients with MEN often are multiple, they are not surgically removed (76, 77). Therefore, patients with Zollinger-Ellison syndrome as a part of MEN-1 would be expected to live longer with hypergastrinemia than those with spontaneous gastrinomas, and thus have a longer life time with hypergastrinemia and a greater risk to develop ECLomas (78). The risk of the development of ECLomas in man depend on the level of hypergastrinemia up to a certain level of gastrin around 500 pM (79), which is approximately the same level of hypergastrinemia giving maximal trophic effect on the ECL cell in the rat (80). Besides the level of hypergastrinemia, the duration of hypergastrinemia seems to be important for the ECL cell tumorigenesis (79).

If the ECL cell tumorigenesis simply reflects the degree of ECL cell proliferation, even moderate hypergastrinemia will in the long run be expected to increase the incidence of ECLomas (78). ECL cell carinoid is, however, a rather rare tumor in humans. On the other hand, dedifferentiated neuroendocrine tumors may be difficult to distinguish from dedifferentiated adenocarcinomas (81). Thus, the malignant ECLomas, occurring spontaneously in mastomys, (82) were originally thought to be adenocarcinomas (83). The tumors found in rat after lifelong treatment with the unsurmountable H-2 blocker loxtidine were first classified as adenocarcinomas (84) and later reclassified as ECL cell carcinoids (71) after the description of similar tumors found to be ECL cell carcinoids in rats treated with omeprazole (70). Similarly in man, when doing retrospective studies, some of the tumors, originally assumed to be dedifferentiated adenocarcinomas, have been reclassified as malignant neuroendocrine tumors (81, 85).

Realizing the difficulties of correct classification of malignant neuroendocrine gastric tumors and the fact that patients with pernicious anemia have an increased risk of gastric carcinomas (86, 87) we did a retrospective study of gastric carcinomas using various markers for ECL cells (88). We found tumor cells with ECL cell staining properties in up to 40% of the tumors classified as diffuse according to Laurén (89), but in none of the tumors classified as gastric carcinoma of the intestinal type (88). This study elicited discussion (90), but it should be realized that there probably is a spectrum of neuroendocrine tumors in the stomach (91) as in the lung (92), which like the

stomach embryologically is derived from the foregut. Malignant ECLomas have been described previously (93, 94) and interestingly also in a patient with pernicious anemia (94). Moreover, Waldenström et al. (95) as early as in the fifties reported a patient with a peculiar flush, hyperhistaminemia and a malignant gastric tumor which they described as an argentaffinoma. This patient probably had a malignant histamine-producing ECLoma. A few other patients with malignant gastric tumors and a peculiar rash have also been described (96, 97). Interestingly, one of the patients in our series who died of a malignant gastric tumor with ECL cell characteristics (88), had for some years been treated for meal-induced urticaria. Accordingly, some of these malignant ECLomas may have retained the ability to produce histamine. Histamine may stimulate angiogenesis and this effect, as well as an increase in the vascular permeability due to histamine (44), could facilitate the growth and the spread of the tumor (98). It is worth emphasizing that the consequences of an increase in the mass of a peculiar cell type may vary according to the mediator, normally produced by that cell (98).

Interestingly, gastric carcinomas of the diffuse type induce a thickening of the nearby mucosa (99) which makes it more difficult to obtain tumor tissue in biopsies taken during endoscopy (100). This growth of the mucosa, covering the gastric carcinomas of the diffuse type, suggests a trophic effect of paracrine substances from the tumor (99). Similarly, the occurrence of mixed tumors with well-defined parts with carcinoid and gastric carcinoma (101) could be explained by a paracrine trophic effect of the carcinoid tumor on the glandular elements, finally leading to gastric carcinoma as well (78). In this context it should be recalled that the mucosa covering the spontaneous malignant and histamine-producing ECLomas in mastomys (82) may show glandular hyperplasia (52) as well as dysplasia (82). By producing and releasing substances with growth-stimulatory effects, the ECL cell could thus play a role not only in gastric carcinomas of the diffuse and mixed types, but also in the carcinogenesis of gastric carcinoma of the intestinal type (78). The role of mitogens in carcinogenesis has been increasingly realized during the recent years (102).

In his classification of gastric carcinomas, Laurén (89) noted that in individual patients gastric carcinomas did not change from one type to the other during the course of the disease. There are also other differences like sex and age occurrence between the two types of carcinomas (89). Altogether, this suggests different histogenesis of the two types of gastric carcinomas (78). Tumors are normally classified according to the most differentiated tumor cells. In the classification of gastric carcinomas and of other tumors, neuroendocrine tumor cells have been regarded as a redifferentiation of dedifferentiated cells. Such a view is only valid if the neuroendocrine cells originate from the common endodermal stem cell giving rise to the other epithelial cells in the mucosa. Based on chimeric studies, the common stem cell hypothesis has been the accepted theory during the last decade (103). However, Pearse (104) initially proposed that the neuroendocrine cells were derived from the neural crest, and recent studies showing that the growth of these cells are separately regulated (105, 106) do not favour the unitarian theory for the origin of the neuroendocrine glandular cells (78, 105). Intracellularly PAS-positivity at histochemistry has been thought to be a specific method to demonstrate mucus-producing, exocrine glandular cells. However, PAS-positivity is not a specific staining method for mucus substances (107). Even more important, PAS-positivity has also been described in carcinoid tumor cells (108, 109). Therefore, neuroendocrine tumors not only in the stomach but in other organs as well, have probably been misclassified (78). The neuroendocrine cells may thus play an important role in the carinogenesis, not only in the lung (92) but probably in the stomach (78) and in other organs. A classification of tumors based on the histogenesis is important, since it may give rise to specific therapeutic approaches. Thus, stimulatory gastrin receptors have been found only in gastric carcinomas of the diffuse type (78). With the development of peptide hormone analogues (110) correct tumor classification based upon histogenesis and mapping of the receptors of the different cell types may give rise to therapeutic progress in cancer diseases.

To conclude, the ECL cell plays a central role in the regulation of gastric acid secretion, and may also have a paracrine regulatory effect on the growth of the oxyntic mucosa. The ECL cell probably gives rise to a significant proportion of gastric carcinomas of the diffuse type, and can also indirectly play an important role in the carcinogenesis of tumors of the intestinal type.

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