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REVIEW

Physiological and clinical significance of enterochromaffin-like cell activation in the regulation of gastric acid secretion

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Abstract

Gastric acid plays an important role in digesting food (especially protein), iron absorption, and destroying swallowed micro-organisms. H+ is secreted by the oxyntic parietal cells and its secretion is regulated by endocrine, neurocrine and paracrine mechanisms. Gastrin released from the antral G cell is the principal physiological stimulus of gastric acid secretion. Activation of the enterochromaffin-like (ECL) cell is accepted as the main source of histamine participating in the regulation of acid secretion and is functionally and trophically controlled by gastrin, which is mediated by gastrin/CCK-2 receptors expressed on the ECL cell. However, long-term hypergastrinemia will induce ECL cell hyperplasia and probably carcinoids. Clinically, potent inhibitors of acid secretion have been prescribed widely to patients with acid-related disorders. Long-term potent acid inhibition evokes a marked increase in plasma gastrin levels, leading to enlargement of oxyntic mucosa with ECL cell hyperplasia. Accordingly, the induction of ECL cell hyperplasia and carcinoids remains a topic of considerable concern, especially in long-term use. In addition, the activation of ECL cells also induces another clinical concern, i.e., rebound acid hypersecretion after acid inhibition. Recent experimental and clinical findings indicate that the activation of ECL cells plays a critical role both physiologically and clinically in the regulation of gastric acid secretion.

Key words: Enterochromaffin-like cell; Gastrin; Gastric acid; Gastric carcinoid; Rebound acid hypersecretion

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INTRODUCTION

One of the main functions of the stomach is to produce hydrochloric acid, which plays an important role in protein digestion, iron absorption and particularly in destroying swallowed micro-organisms[1,2]. The stomach is rich in neuroendocrine cells[3-5]. At present, at least six endocrine cells have been described in the stomach: G cells, D cells, enterochromaffin-like (ECL) cells, A-like cells, D1/P cells, and enterochromaffin (EC) cells. In the stomach, G cells are found only in the antral mucosa, while A-like and ECL cells are confined to the oxyntic mucosa[4]. D and D1/P cells are found in both the antral and oxyntic mucosa. These endocrine cells constitute approximately 2% of the oxyntic mucosal cells in rodents. The ECL cell was originally described by Hakanson *et al*[6] and Capella *et al*[7] respectively. However, its physiological function was also long disputed, except for in rat where it was initially recognised as the major histamine producing cell of the stomach[8]. It is now recognized that the ECL cell is the dominant endocrine cell in the oxyntic mucosa of all mammals studied so far. Localization within the glands differs from one species to another. In rodents, they are mainly located in the basal third of the oxyntic mucosa. Gastric acid is produced by the parietal cell in the oxyntic mucosa[9], and the production of acid is regulated by neurons, hormones and paracrine substances[10,11].

Gastrin released from the antral G cells, histamine from the oxyntic ECL cells and acetylcholine (Ach) from postganglionic cholinergic neurons are the main stimuli of acid secretion[9]. The ECL cell is under the control of gastrin. Gastrin-ECL cell axis activation has been found to be important physiologically and pathophysiologically. In this mini-review, we will summarize the physiological and clinical significance of ECL cell activation in regulating gastric acid secretion.

THE PHYSIOLOGICAL SIGNIFICANCE OF ECL CELL ACTIVATION IN REGULATING GASTRIC ACID SECRETION

Gastrin is a potent stimulus of gastric acid secretion by stimulating the release of histamine from ECL cells[12-16]. The gastrin-ECL cell axis plays a critical role in regulating acid secretion from parietal cells. In the totally isolated vascularly perfused rat stomach model, gastrin induces an immediate and concentration-dependent histamine release from the ECL cell[12]. With concomitant administration of the histamine-2 (H2) receptor antagonist, ranitidine, together with gastrin, the acid secretion in the isolated stomach model is reduced to baseline level. Thus, the stimulation of acid secretion by gastrin occurs most likely *via* histamine release from the ECL cells *via* gastrin/CCK-2 receptors[17-20]. This finding was supported by studies using isolated ECL cells *in vivo*[21-23]. Not only histamine release but also the synthesis of histamine in the ECL cell is regulated by gastrin[24-26]. Administration of exogenous gastrin, at a dose giving concentration in the physiological range, can evoke a significant increase in histidine decarboxylase (HDC) activity[13], as well as an increase in HDC mRNA abundance[24-26]. HDC catalyses the formation of histamine from histidine. Endogeneous hypergastrinemia after potent acid inhibition can induce a similar increase in HDC activity[13,27]. Histamine release from ECL cells is considered to be a limiting step in gastrin-stimulated maximal gastric acid secretion[12,28]. Now it is generally accepted that the gastrin-histamine sequence is the main pathway for gastrin stimulation of gastric acid secretion. Recently, the role of gastrin precursors (glycine-extended gastrin and progastrin) in stimulating acid secretion was also postulated[29,30]. It was found that a high dose infusion of glycine-extended gastrin into isolated stomach can activate histamine release from ECL cells and acid secretion, which could be blocked by antagonists of H2 receptors and gastrin/CCK-2 receptors[31,32]. This supported the activation of ECL cells as mediating the main pathway of glycine-extended gastrin acid secretion stimulation. Moreover, the role of glycine-extended gastrin in preserving parietal cell density was found. Coexpression of glycine-extended gastrin with gastrin in transgenic mice reduced long-term hypergastrinemia induced parietal cell loss. Thus, an important physiological role of gastrin precursors was postulated[30].

Furthermore, the stomach is innervated by different nerves[33] and peptides produced by intrinsic neurons influence stomach functions, including acid secretion[34]. The vagal efferent fibers are preganglionic, and do not directly innervate stomach endocrine or exocrine cells[33]. The targets of these vagal preganglionic neurons are the intrinsic neurons that are located in the myenteric ganglion cells. The intrinsic neurons contain Ach and different peptides[33], such as GRP, VIP, galanin, and PACAP. They innervate the G, D, ECL and parietal cells. The effect of vagal nerves on gastric acid secretion is complex. Ach mainly has a direct effect on acid secretion by acting on a M3 receptor on the parietal cell. *In vivo*, galanin and PYY, for example, have been shown to inhibit histamine release from ECL cells *via* their own receptors[35-39]. VIP induces somatostatin release from D cells, but stimulates histamine release from ECL cells probably *via* a PACAP receptor[35,36,39,40]. PACAP is a potent stimulus of histamine release from ECL cells *via* PACAP-1 receptors[36,39,41,42]. Gastric acid secretion, besides being regulated by the hormonal and neural routes, is also regulated by paracrine factors[11]. Somatostatin, which is a principal paracrine inhibitory factor, can exert its inhibitory effect on gastric acid secretion[17]. The reciprocal paracrine pathway between D and G cells is well known[43], and ECL cells are also in close contact with oxyntic D cells[4]. The antral somatostatin acts on the antral G cells, while the oxyntic somatostatin affects both ECL cells and parietal cells. Thus, somatostatin inhibits acid secretion *via* actions on different cells of the gastrin-ECL cell axis.

THE CLINICAL SIGNIFICANCE OF ECL CELL ACTIVATION IN LONG-TERM GASTRIC ACID INHIBITION

Potent acid inhibitors, such as proton pump inhibitors (PPIs), are highly effective gastric antisecretory agents with long duration[44]. They are intensively used to treat acid related disorders, and are nowadays prescribed even for children[45]. ECL cells are activated during the use of potent acid inhibitors. From a clinical viewpoint, safety concerns for such long-term activation by acid inhibitors have to be considered.

Rebound acid hypersecretion was first described in rats more than 20 years ago after treatment with omeprazole[46]. In humans, rebound acid hypersecretion was found in patients who received long-term acid inhibitors, such as H2 receptor antagonists and PPIs[47-51]. It has been observed that a 3-mo omeprazole treatment, at a dose of 40 mg daily in patients with reflux esophagitis, resulted in a significant (over 50%) increased maximal acid secretion accompanied by remarkable elevated gastrin and histamine levels[48]. This finding was confirmed in our subsequent studies[52,53] and others[50,51], and is due to the fact that gastrin is the most important trophic factor for ECL cell self-replication and that histamine released from ECLs cell is the main stimulator for gastric acid secretion. Long-term acid inhibition induces hypergastrinemia and ECL cell hyperplasia in patients treated with PPIs for various diseases with dyspepsia. The mechanism of rebound acid hypersecretion is likely related to the activation of the gastrin-ECL cell axis caused by drug-induced hypoacidity.

Apart from a stimulatory action on gastric acid secretion, gastrin also has a trophic effect on the oxyntic mucosa[54-56], particularly on ECL cells, which are stimulated to replicate *via* gastrin/CCK-2 receptors expressed in ECL cells[13,19,20]. It has become apparent that rat ECL cells, in response to hypergastrinemia, whether endogenous or exogenous, show hypertrophy within days, hyperplasia within weeks and carcinoids after months through a sequence of diffuse-linear-micronodular hyperplasia to ECL carcinoids[13]. Therefore, there is a causal connection between hypergastrinemia and ECL cell carcinogenesis[13,57-59]. Thus, in patients received long-term

acid inhibiton treatment, another concern is the increased gastric carcinoid risk. In fact, sporadic gastric carcinoid cases have been reported in patients exposed to long-term PPI treatments[60,61]. Long-term safety is still of high concern.

Finally, gastrin was also connected with other types of human cancers; i.e. gastric and colonic adenocarcinoma, and more recently, studying the important role of precursors for gastrin progastrin and glycine-extended gastrin in the carcinogeneiss of gastrointestinal mucosa has been one of the developing research fields. Several outstanding reviews have summarised this topic[62-65]. Thus, whether long-term activation of ECL cells by potent acid inhibition can contribute to increased risk of gastrointestinal adenocarcinoma in humans is still unknown and needs to be studied in the future. In addition, one of the growth factors that regenerates gene proteins, i.e., (Reg)-1, that is mainly released from ECL cells has been found to be a unique growth factor of gastric mucosal cells[66] and may play an important trophic role in the development of gastric cancer[67].

CONCLUSION

It is now generally accepted that ECL cell activation is the most important physiological pathway in the regulation of gastric acid secretion, which is being influenced by both activating and inhibiting stimuli. Furthermore, it has become apparent that the gastrin-ECL cell axis also plays a role in gastric acid disorder, such as rebound acid hypersecretion, and increased risk for gastric tumorigenesis, especially in chronic hypergastrinemic conditions. Therefore, clinicians should be aware that there are important clinical safety issues related to the dose and duration of potent inhibitors of acid secretion.

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