Gastric mucosal disease
Liu, Y.

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Chapter 5

Gastric Endocrine cells

Yi LIU \textsuperscript{1,2}, Guido NJ Tytgat\textsuperscript{3}, Shu-dong Xiao\textsuperscript{2} and Fiebo JW Ten Kate\textsuperscript{1}

Department of Pathology \textsuperscript{1} and Gastroenterology \textsuperscript{2}, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and Shanghai Institute of Digestive Disease, Shanghai Second Medical University, Shanghai, The People’s Republic of China \textsuperscript{2}.

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One of the unique properties of the mammalian stomach is its ability to secrete large quantities of hydrochloric acid. This secreting process is highly regulated by central and peripheral events. The peripheral regulation is defined as neural, endocrine and paracrine pathways, which either up-regulate or down-regulate acid secretion by the parietal cells. In this review, the regulation and effect of endocrine cells on gastric acid secretion and their pathologic situation will be discussed.

**General Aspects**

The gastric mucosa is endowed with a rich array of endocrine cell types. At least seven distinct endocrine cells have been identified based on ultra-structural features: the enterochromaffin (EC) cell, the ECL cell, the D cell, the gastrin (G) cell, the A cell, the P cell and the X cell. As a group, they represent approximately 2% of the cells in the fundic mucosa of the rat whereas in man they are somewhat less numerous (0.5-1%). In total, they constitute an endocrine organ approximately equal in size to that of the endocrine pancreas.

The name of enterochromaffin (EC) cells was introduced by Ciaccio in 1906. It was Masson who first proposed the putative endocrine nature – argentaffinity or their silver-reducing power, and their morphological and functional independence of adrenal chromaffin cells. In human, EC cells are found in the antrum and oxyntic mucosa. Their main secretory products are 5-hydroxytryptamine (5-HT). It is this monoamine which reduces silver and chromium, constituting the argeneffin and chromaffin reaction respectively. However, the gastric mucosa of the rat was found also to be rich in
endocrine cells lacking 5-HT and consequently being non-chromaffin and non-argentaffin. Instead they could be demonstrated by silver staining only when an external reducing agent was added (argyrophilia)\textsuperscript{13}. The argyrophile staining demonstrates both argentaffin (EC) and non-argentaffin (non-EC) endocrine cells. Non-EC cells, identified by their argyrophilia, are referred to as enterochromaffin-like (ECL) cells because they have a morphology similar to the EC cells but without serotonin production\textsuperscript{14}. The ECL cell is a type of ultra-structurally characterized cell restricted to oxyntic glands in all species investigated, including man\textsuperscript{15-19}. D cells secrete somatostatin and are distributed throughout the antral and oxyntic mucosa but are more numerous in the antrum. They display argyrophilic staining and may be labeled immunohistochemically using anti-somatostatin antibodies. Gastrin producing G cells are located in the antrum. They are argyrophilic and may be labeled using antibodies against gastrin. The X cells, the function of which remains unknown, are found almost exclusively in the oxyntic gastric mucosa. D1 cells are so named because upon electron microscopy they display granules resembling those found in D cells. Similarly, P cells have granules, which resemble those of pulmonary endocrine cells. Both of these cell types are found in the antral and oxyntic mucosa in man, and their biological function remain to be elucidated\textsuperscript{20-21}. The nature of gastric endocrine cells and their distribution are given in table 1.

It was known that there are two main types of glandular mucosa in the stomach – the acid-secretory oxyntic mucosa of the body and fundus, and the mucus gland mucosa of the antrum. The endocrine cells of the oxyntic gland epithelium lie along the basal lamina, thus facing the lamina propria and are separated from the glandular lumen by
intervening cytoplasmic extensions of non-endocrine epithelial cell. This characteristic is termed as “closed” type \(^{22-23}\). This location of endocrine granules within the epithelial cells is functionally significant. They are not influenced by physio-chemical stimuli related to the gastric content but rather they are involved in paracrine regulatory mechanisms, acting as mediators of the stimuli originating from nerves and blood vessels \(^{24-26}\). In contrast, most endocrine cells in the antral mucosa belong to the “open” type \(^{22}\), each being provided with an apical cytoplasmic extension with short microvilli that projects into the glandular lumen and has abundant pinocytotic vesicles. The “open” type represents the anatomical basis for the cell response to physical/chemical variations of the gastric contents.

All endocrine cells in the antral mucosa are of the “open” type with the exception of EC cells, the quantitatively and functionally most important endocrine cell types in this region present the advantage of being all identifiable with specific immunostaining in routine preparation. In contrast with the antral mucosa, neither immunostaining method is specific for a given cell type in the oxyntic mucosa. Electron microscopy is the most reliable technique for identifying the specific endocrine cell types of the oxyntic glands, primarily on the basis of the ultra-structural characteristics of the secretory granules \(^{25-27}\).

**Gastric Endocrine Cells**

The major groups of endocrine cells known to play an important role in acid secretion are the gastrin (G) cell of the antrum, the somatostatin (D) cells of the fundus and antrum, and ECL cell of the fundus \(^{2.4-6,20,28-29}\).

**Gastrin and G cell**
Gastrin is released into the circulation from the G cells which are located exclusively in the gastric antrum after stimulation by food and strongly stimulate the ECL cells and the parietal cells in the corpus to secrete acid. The two main forms of gastrin in plasma are gastrin–34 (G34) and its C terminal fragment gastrin-17 (G17). About 95% of antral gastrin is G17, whilst duodenal gastrin is about 60% G34. Gastrin shares an identical pentapeptide amide with CCK, which results in relatively similar binding to the CCK 2 receptor. Since the G cells of the gastric antrum are of “open” type with their apical surfaces reaching the glandular lumen, luminal contents (protons, amino acid, NH₃) may be able to directly modulate G cell activity and the release of gastrin. Upon stimulation, gastrin is released into the extracellular fluid and then diffuses into the circulation and reaches the gastric corpus to stimulate acid secretion. It stimulates the parietal cells directly and/or by releasing histamine from adjacent ECL cells. Gastric also has a trophic effect on the gastric epithelium and particularly on the ECL cells.

1. Regulation of functional G cells

pH The most effective event to modulate the release of gastrin is the pH of the antral lumen, which at values < 3 completely suppresses gastrin release. This serves to terminate gastric digestion. If the antral luminal pH remains elevated in the presence of continuing stimulation, hypergastrinemia results. Achlorhydria, secondary to either atrophic gastritis or pharmacological suppression of acid, is the most powerful stimulant of G cell secretion and proliferation. A reduction in acid secretion, for example following the administration of proton pump inhibitors inhibits D cells and so up-regulates G cells.
**Food** The primary event responsible for the physiological release of gastrin from the G cells is the presence of the food in the stomach. The mechanism involved in this process comprises at least three stimulatory pathways, which include central neural activation, distension of the antrum and specific chemical components in the food. When food enters the stomach, the protein component stimulates G cells situated in the antral region to release gastrin which circulates and again stimulates the ECL/parietal cells in the body region to secrete acid. Therefore, food in the stomach maintains acid secretion by activating both neural (local and vago-vagal) and endocrine pathways. Fasting causes a decrease in the number of G cells, which is rapidly reversed by feeding induced proliferation.

**GRP (Gastrin Releasing Peptide)** GRP is another important, powerful stimulant of gastrin secretion. It is localized in enteric gastric nerve fibers, where it is responsible for gastrin release and in the fundus where it may be related to GRP regulation of motility. Infusion of GRP normally exerts a mixture of stimulatory and inhibitory effects on acid secretion. GRP directly activates G cells but also indirectly stimulates D cells via gastrin release in the gastric antrum and through neural reflexes in the gastric fundus. GRP stimulates Ca\(^{2+}\) signaling in an isolated G cell preparation. The GRP receptor belongs to the G protein coupled superfamily and appears to be coupled to phospholipase C activation in other cells. Plasma gastrin concentration is elevated during infusion of GRP.

**Somatostatin** Somatostatin is secreted from antral D cells when luminal pH falls below 3.5. The infusion of somatostatin at doses sufficient to inhibit acid secretion fails to inhibit gastrin secretion. Presumably the effect of infused somatostatin on the ECL cell
occurs more readily than on the G cell. Somatostatin therefore acts only as a paracrine agent to suppress gastrin secretion. There are 5 known subtypes of somatostatin receptor and the subtype on the G cell is probably the type 2 (see later).

**Amino acids and amines** Given the fact that the G cell is open to the gastric lumen, chemical effectors can bind to the apical membrane or become internalized by the G cells to influence the gastrin secretion. The amino acids phenylalanine and tryptophan appear to have the greatest gastrin-releasing activity. More recent studies argue for independent stimulation of gastrin release by amino acids and the corresponding amines. However, the amines were found to produce a consistently greater increase in gastrin release at equimolar concentration.

**Vagal regulation** The neural pathways involved in gastrin secretion including both cholinergic and non-cholinergic pathways. The activation of a bombesin neuron by vagal stimulation may lead to the activation of the G cell, leading to gastrin release. Vagal stimulation inhibits somatostatin secretion, and this "antibraking" effect leads to an increase in gastrin secretion.

It is likely that other effectors such as adenosine and galanin play a role but their physiological significance is doubtful.

**2. Influence and possible mechanisms of Helicobacter pylori infection on gastric acid secretion**

The first report on the relationship between Hp infection and plasma gastrin concentrations was proposed by Levi et al. in 1989. Those authors reported that gastrin levels were significantly higher in Hp positive patients compared with Hp negative ones. Their data clearly demonstrated that Hp infection induced hypergastrinemia that was
followed by an increase in basal and stimulated acid secretion. Several investigators have demonstrated that elevated acid secretion decreases after Hp eradication, with simultaneous reduction of serum gastrin. A number of investigators have shown that Hp infected patients with duodenal ulcer and Hp positive healthy volunteers have higher basal serum gastrin levels compared with uninfected controls. Examination of antral biopsies from Hp infected individuals has shown that gastrin synthesis is increased. Our results are consistent with the finding that the total amount of G cells is significantly increased. In Hp infected subjects, G17 is the predominant form released by a meal or following GRP infusion. Eradication of Hp reduced the output of G17 with no effect on G34. The mechanisms leading to exaggerated gastrin secretion in Hp infected subjects are unclear. But some possibilities have been suggested:

1. Ammonia generated by Hp urease may produce an alkaline environment in the vicinity of G cells, thus stimulating gastrin releasing. Acid inhibits gastrin release, probably by stimulating D cells to release somatostatin, so that local alkalization might have the opposite effect.

2. Cytokines released by inflammatory cells may evoke gastrin release. Hp infection increases the mucosal expression of many cytokines including: interleukins (IL), tumor necrosis factor (TNF-α), interferon – γ (IFN γ) and platelet-activating factor (PAF). Calam et al found that TNF α and IFN γ release gastrin from the canine antral endocrine cells in primary culture. Immunoblockade of somatostatin, if anything, enhanced the effect, suggesting that the cytokines were not acting via D cells.
**Somatostatin and D cell**

Somatostatin is released from D cells located both in the antral mucosa in close proximity to G cells and fundic mucosa in the vicinity of parietal cells, and play a major inhibitory role within the gastric mucosa. It has two biologically active forms -SST28 and SST14. Chromatographic studies have shown that the predominant form of SST in the human stomach to be SST14. However, both forms have high affinity for the various receptors SSTR1-5. But SSTR2 is most involved in the physiological inhibition of acid secretion, since mice in which the SSTR2 gene has been deleted exhibit increased basal and stimulated acid secretion. It is difficult to measure the response of gastric D cells in patients because somatostatin is released in many organs, but acts and is degraded locally. Recently it has been possible to define the D cells in the mixed endocrine cell population by immunostaining with anti-somatostatin antibody. In the antrum, D cells are more frequent than in the fundus and have apical membranes that are exposed to the lumen ("open" type). In the fundus, the D cells are of the "close" type; they are not exposed to the luminal surface of the mucosa.

1. **Regulation**

The release of somatostatin from D cells, as with the release of gastrin from G cells, is regulated by a complex set of mechanisms, not all of which have been clearly defined.

**Gastrin and CCK** Both gastrin and CCK stimulate somatostatin release from isolated D cells, and this cell type has both CCK-1 and CCK-2 receptors. In contrast to ECL cell, D cell responds to both CCK-1 and CCK-2 stimulation, indicating that cholecystokinin may
play a significant role in inhibition of fundic ECL cell histamine release. 

**Gastrin releasing peptide (GRP)** Three hours infusion of GRP significantly elevates somatostatin mRNA content of antral biopsy specimens from patients infected with Hp, showing that the cells are at least capable of responding. However, the amount of somatostatin mRNA after stimulation remained well below that present in uninfected persons. Schubert ML et al. found that GRP could stimulate somatostatin release, which is mediated by antral gastrin.

**CGRP/VIP** Gastric acid stimulates mucosal nerve endings, releasing CGRP (calcitonin gene-related peptide) and VIP (vasoactive intestinal peptide), which stimulate the release of somatostatin from D cells. Inhibition of acid secretion by injected CGRP must be from to effects on either antral or fundic D cells or both. CGRP inhibits gastric acid secretion whether given centrally or peripherally. The latter is probably due to stimulation of somatostatin release and no effect has been found in isolated rat ECL cells. The subsequent suppression of gastrin release may account for at least some of the ability of such peptides to inhibit acid secretion in vivo.

**Acetylcholine** D cells have inhibitory muscarinic receptors, of either M2 or M4 subtype, in contrast to the M1, M3 or M5 receptors on other gastric cells, allowing the conclusion that vagal stimulation of acid secretion inhibits somatostatin release.

**Food/Acid** Somatostatin is released from the antrum by luminal factors, but also by food. The antral open D cell, unlike those of the fundus, release somatostatin in response to increased acidity in the gastric lumen and thus are capable of detecting chemical food component. Because the apical surface of D cell opens onto the gastric lumen, changes in pH may be sensed directly through chemoreceptors on the apical
membranes. This may represent a mechanism for suppression of gastrin release at low intraluminal pH, a critical factor in the physiological regulation of gastric acidity.

2. **Effect and possible mechanisms in Helicobacter pylori infection**

Several studies have now demonstrated lowered concentrations of somatostatin within the antral mucosa of subjects with Hp antral gastritis \(^{59,62,82-87,89-92}\). In addition, somatostatin mRNA concentrations are lowered, indicating a reduced synthesis of this inhibitory hormone \(^{62,86}\). These findings are consistent with our results (unpublished data) that the amount of D cells was significantly decreased in Hp-infected persons compared with uninfected and normal individuals, while the amount of G cells was elevated significantly. Eradication of infection is associated with an increase in the density of antral somatostatin cells and level of antral somatostatin mRNA \(^{93}\). Therefore, the major defect leading to hyperfunction of gastrin in Hp infected subjects appears to involve disruption of the inhibitory effect of somatostatin on the G cell. The agreement was made that Hp antral gastritis increasing gastrin by creating a deficiency of antral somatostatin and thus preventing normal inhibitory influence this hormone exerts on gastrin release.

It is interesting that H. pylori infection diminishes mucosal somatostatin. Because it explains diminished mucosal somatostatin in DU patients and it offers an explanation for other aspects of Hp pathophysiology, since somatostatin is a potent inhibitor of G cells, ECL cells and parietal cells. However, the mechanism responsible for diminished expression of somatostatin remains unclear. There are several hypotheses:

1. The first proposed by John Calam et al \(^{49}\) is that Hp urease activity produces high concentrations of ammonia. It has been postulated that this may block the acid-
mediated inhibitory control. Elevation of antral surface pH by the ammonia would also remove the trophic effects of acid on antral D cells in Hp infected subjects;

2. Inflammatory mediators associated with antral gastritis might also affect the D cells. Weigert N et al \(^{88}\) suggests that the cytokine TNF-α might be involved; Calam et al also found that the reduced somatostatin mRNA in Hp infection is attributable to the release of TNF-α that inhibit antral D cell function, and incubation of D cells with TNF-α for 24 hours resulted in a 40% diminution in somatostatin release in response to CCK \(^{94}\).

3. Unlike other bacteria, Helicobacter pylori possess \(N^a\)-histamine methyltransferase activity and produces an unusual histamine catabolite—\(N^a\) methylhistamine, which is a potent gastric secretagogue and inhibitor of antral somatostatin release \(^{80}\). It was suggested that Hp might induce hypergastrinemia by altering the metabolism of histamine and inhibiting somatostatin expression in the stomach. Vuyyuru et al \(^{81}\) studied the effect of histamine \(H_3\)-receptor stimulation and blockade on the release of gastrin, somatostatin and histamine from extracts of antral mucosa. Stimulation of \(H_3\) receptors decreased release of somatostatin and increased release of gastrin and histamine, whereas \(H_3\) blockade had the opposite effect. These results used the specific \(H_3\) receptor agonist \(N^a\) methylhistamine. The results raise the possibility that less specific agonist \(N^a\) methylhistamine, which Hp produces, might suppress the D cells.

ECL cells and histamine
ECL cells are the predominant and functionally most important endocrine cell type of the oxyntic mucosa. These cells are not in direct contact with the lumen of the stomach (as the closed type), therefore not affected directly by gastric content. They are located in the basal part of the mucosa, as a rule being in close contact with chief cells. The ECL cells can be identified by light microscopy using the Grimelius and Sevier-Munger silver methods or Chromogranin A (CgA) immunostaining, however, none of these is specific. ECL cells display a unique and characteristic ultra-structure. They are irregular in shape with numerous large electron-lucent cytoplasmic vesicles, a few electron-dense granules and a few clear microvesicles.

Histamine is the main product of the ECL cells, which has a crucial role in stimulating acid secretion from parietal cells. Histamine is produced from histidine by histidine decarboxylase (HDC) in gastric ECL cells and perhaps also in gastric mast cells. However the histamine produced and stored in ECL cells is relatively low compared with that found in mast cells. ECL cells react to the antral gastrin by histamine secretion, activation of histamine synthesizing enzyme-HDC and also by cellular proliferation.

Histamine stimulates acid secretion via H₂ receptors on parietal cells. Gastrin stimulates acid secretion by stimulating ECL cells as well as by a direct effect on parietal cells.

The importance of gastric ECL cells as the major histamine pool in the stomach was not fully recognized till the development of proton pump inhibitors as anti-ulcer drug. The stimulation of ECL cells involves activation of gastrin/CCK 2 receptor and the ensuing release of histamine is necessary for further gastrinergic stimulation of the parietal cells (again via gastrin/CCK 2 receptors).

1. Regulation
**Gastrin/CCK** Gastrin has multiple actions on ECL cells. The response of ECL cell to gastrin may be regarded as exhibiting an acute, intermediate and chronic phase relating to histamine secretion, HDC activation and lastly DNA synthesis. The ECL cells are under the control of circulating gastrin that stimulates both their secretion and proliferation by binding CCK-2 receptors located on the basal plasma membrane. The CCK-2 receptor has been cloned from canine parietal cells and rodent ECL cells and shows typical signature sequence for a guanine nucleotide binding protein (G protein) coupled receptors.

**Acetylcholine** Stimulation of ECL cells by acetylcholine results in the release of histamine and is accompanied by characteristic changes of intracellular calcium. However whereas all ECL cells respond to gastrin, only about 10-30% of the cells respond to acetylcholine.

**PACAP /VIP** Histamine release from isolated ECL cells is also stimulated by PACAP as effectively as gastrin via elevating intracellular calcium. Lindstrom et al found that isolated ECL cells are able to respond with secretory activation of PACAP and VIP to release histamine. Sacha et al also observed that subtype -27 and -36 of PACAP have an identical function and dosage in stimulating histamine, while VIP had no effect till giving in a high dose compared with PACAP, which indicates that these cells possesses a functional PACAP I receptor subtype. It was reported that the CCK-2 and PACAP receptor appear to be functionally most important in terms of stimulation of histamine release from the ECL cell, the former endocrine, the latter neural.
**TGF-α** TGF-α is expressed by ECL cells of rat\textsuperscript{101-102} and possibly of man\textsuperscript{103}. Its autocrine trophic function is indicated by the TGF-α-induced increase in ECL cell in vitro and by the ECL cell expression of EGF receptor that specifically binds TGF-α.\textsuperscript{101}

**Somatostatin** Somatostatin is the predominant inhibitory regulator of gastric acid secretion with several distinct cellular targets including the ECL cells. It acts via a somatostatin 2-receptor subtype, by inhibiting both histamine release and calcium signaling. This result indicates that somatostatin acts through SSTR2 to block gastrin induced calcium entry into the ECL cells. Since mucosal D cells, both in antrum and fundus, possess elongated basal processes, somatostatin released locally may function as paracrine regulator. The function of antral and fundic somatostatin in gastric acid regulation was described in detail earlier. This somatostatin pool is probably responsible for inhibition of ECL function.

**Histamine** In addition to somatostatin, the release of histamine from ECL cells is inhibited by histamine itself. Only after ECL cell did respond appropriately to H\textsubscript{3} agonists and antagonists, down-regulation of gastric acid secretion occurred by histamine acting at H\textsubscript{3} receptor\textsuperscript{104,106}. This suggests an autocrine feedback regulation of ECL function but this has not been shown physiologically.

**PYY** PYY is a peptide released from intestinal endocrine cells and has been found to be an effective inhibitor of calcium signaling and histamine release in isolated rat ECL cell preparations\textsuperscript{105}. PYY interacts with three receptors—Y1, Y2 and Y3. The ECL cell contains the Y1 receptor subtype, histamine release and calcium signaling are inhibited by PYY.

2. *effects and possible mechanisms in Hp infection*
Mucosal concentrations of histamine are diminished in Hp induced gastritis \(^{108}\), which probably reflects diminished synthesis because mucosal levels of HDC are also diminished \(^{104}\).

The possible mechanisms related to altered ECL function in Hp infection might be:

1. **Gastrin**: It is known to stimulate ECL cells to proliferate and to release gastrin.

2. **IL-1β**: It was reported by Prinz et al \(^{108}\) that IL-1β first stimulates, then profoundly inhibits histamine release from ECL cells and postulated that this effect might cause suppression of ECL cells in Hp induced gastritis.

3. **N\(^a\)-methylhistamine**: Stimulation of H\(_3\) receptors on ECL cells also inhibits histamine release \(^{104}\), therefore, production of the H\(_3\) agonist N\(^a\)-methylhistamine by Hp \(^{104,107}\) might contribute to suppression of these cells. Infected mucosa contained much more N\(^a\)-methylhistamine and the synthetic enzyme N\(^a\) histamine methyltransferase than did non-infected mucosa. Infected mucosa showed a lower capacity to bind \([^{3}\text{H}] \text{N}^a\)-methylhistamine and lower indices of ECL function: histamine itself and HDC.

**Pathology**

The pathologic condition of the endocrine cells is traditionally divided into those resulting from excessive or deficient production of a given hormone. With respect to the stomach, no conditions resulting from deficiency of a digestive hormone have been clearly identified up to now. The endocrine pathology of the stomach consists of a few example of endocrine cell hyperplasia and a variety of tumors. Both hyperplasia and tumors may or may not be associated with clinical manifestation of hyperfunction of the

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cells. Hyperplasia can be defined anatomically as an increased cell mass of the type. The mechanisms resulting in hyperplasia and tumors are not at all understood.

**Hyperplasia**

Gastrin-producing cell hyperplasia is generally defined as G cell hyperplasia. It is observed as a secondary change in chronic atrophic gastritis with severe, long-standing achlorhydria, as typically found in pernicious anemia\(^ {109} \), and as apparently primary change in hyperchlorhydria and peptic ulcer with or without Hp gastritis\(^ {110} \). While Holle et al. also found D cell hyperplasia in the stomach\(^ {111} \).

In hypergastrinemia there is ECL cell hyperplasia and in extreme cases, the development of ECL cell carcinoid tumors\(^ {112} \)(see below). Hyperplasia of ECL was detectable in patients receiving 5 years omeprazole treatment\(^ {114} \). This effect was due entirely to the hypergastrinemia resulting from inhibition of acid secretion in the face of normal food stimulation of gastrin release from the G cell. Besides secondary change to hypergastrinemia, ECL hyperplasia can also be found in diffuse type A chronic atrophic gastritis with achlorhydria or hypertrophic gastropathy with Zollinger-Ellison Syndrome.

**Neoplastic growth**

with hypergastrinemia due to continuous administration of H2-receptor antagonists or proton pump inhibitors\(^ {114} \).

In the patients with hypergastrinemia from a gastrin-producing tumor, 30% have ECL cell carcinoid tumors\(^ {115} \). 5% of the hypergastrinemia with pernicious anemia secondary to achlorhydria develop ECL cell carcinoid tumors\(^ {112,116} \).

Mutations of the gene encoding Reg 1-α in ECL cell carcinoid tumors have been described\(^ {117} \). Reg 1-α is normally expressed in pancreas and is up-regulated during
differentiation of islet $\beta$ cells. Upregulated reg expression was found in ECL cells of rat during experimental mucosal regeneration. The study of Fukui et al reveals that Reg 1-α is also a growth factor for gastric mucus cells. In both rat and man, it is expressed in ECL cells and its expression is increased with hypergastrinemia.

**Conclusion**

Gastric acid secretion represents the outcome of several regulatory signals. It includes central and peripheral regulation. The latter involves neural, endocrine and paracrine pathways. Gastrin is a major circulating stimulus of acid secretion and a growth factor for parietal cells while the ECL cells are endocrine/paracrine cells that actively produce and secrete histamine. Gastrin stimulates histamine secretion and synthesis in the ECL cells via CCK-2 receptors and that mobilized ECL cell histamine stimulates the parietal cells to secrete HCl via an action on H2 receptors. In contrast, somatostatin has widespread inhibitory effects on endocrine and exocrine cells, including G cells, ECL cells and parietal cells. Expression of somatostatin is maximal when the intragastric pH is low and, during fasting, consistent with an inhibitory role. Both gastrin and somatostatin may exert their effect directly on parietal cells or indirectly via histamine-secreting ECL cells (Fig 1).

There is now a growing recognition that these mechanisms are a component in the pathology of upper gastrointestinal tract, particularly in conditions involving Helicobacter pylori. Infection with H. pylori is associated with a modest rise in plasma gastrin concentration. In part it is likely to be secondary to decreased somatostatin synthesis and the disruption of the inhibitory effect of somatostatin on the G cell.
It is now recognized that the factors which control gastric acid secretion are regulated through complex pathways. Numerous candidates participate in the regulation from Gastrin G cell, ECL cells and somatostatin D cells, but the relative importance and the precise mechanisms by which they affect remain to be clearly defined.

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Abbreviation

CCK: Cholecystokinin
CGRP: calcitonin gene-related peptide
EC cell: enterochromaffin cell
ECL cell: enterochromaffin-like cell
GRP: Gastrin Releasing Peptide
Hp: Helicobacter pylori
IFNγ: interferon-γ
IL: interleukins
HDC: histidine decarboxylase
5-HT: 5-hydroxytryptamine
PACAP: Pituitary adenylate cyclase-activating polypeptide
PAF: platelet-activating factor
PYY: peptide YY
SST: Somatostatin
TGF-α: Transforming growth factor-α
TNF-α: tumor necrosis factor-α
VIP: vasoactive intestinal peptide
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Fig1. Schematic illustration of the regulation of stimulation and inhibition of the three major gastric endocrine cells: ECL cell, G cell and D cell.