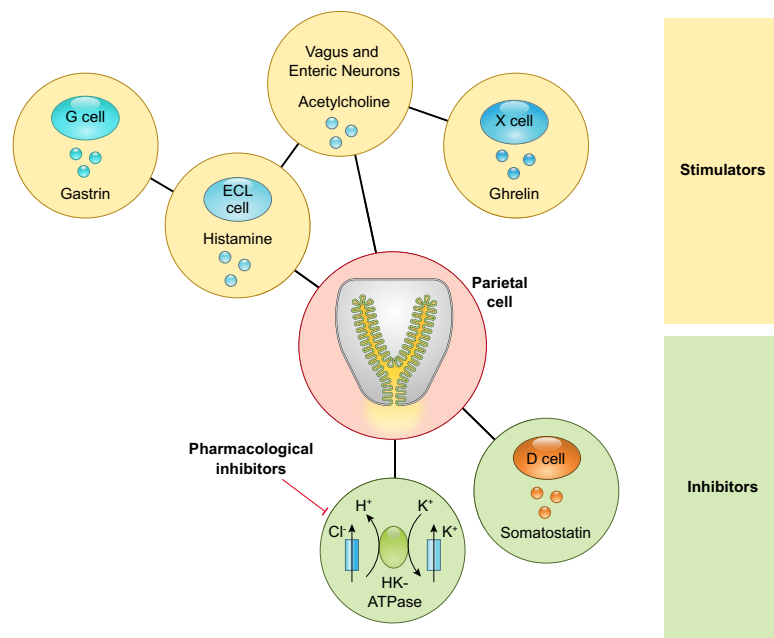# THE PHYSIOLOGY OF THE GASTRIC PARIETAL CELL

GRAPHICAL ABSTRACT

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KEYWORDS

acid secretion; growth factors; mucosal homeostasis; parietal cell; stomach

CLINICAL HIGHLIGHTS

This review summarizes the complex literature related to the physiology and cell biology of gastric parietal cell acid secretion and the impact of directed pharmacology in the therapeutic manipulation of acid secretion. In addition, the article addresses the role of gastric parietal cells as sources of growth factors and regulators of gastric mucosal homeostasis.

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THE PHYSIOLOGY OF THE GASTRIC PARIETAL CELL

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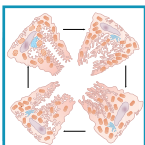
Engevik AC, Kaji I, Goldenring JR. The Physiology of the Gastric Parietal Cell. *Physiol Rev* 100: 573–602, 2020. First published October 31, 2019; doi:10.1152/physrev.00016.2019.—Parietal cells are responsible for gastric acid secretion, which aids in the digestion of food, absorption of minerals, and control of harmful bacteria. However, a fine balance of activators and inhibitors of parietal cell-mediated acid secretion is required to ensure proper digestion of food, while preventing damage to the gastric and duodenal mucosa. As a result, parietal cell secretion is highly regulated through numerous mechanisms including the vagus nerve, gastrin, histamine, ghrelin, somatostatin, glucagon-like peptide 1, and other agonists and antagonists. The tight regulation of parietal cells ensures the proper secretion of HCl. The H^+-K^+-ATPase enzyme expressed in parietal cells regulates the exchange of cytoplasmic H^+ for extracellular K^+. The H^+ secreted into the gastric lumen by the H^+-K^+-ATPase combines with luminal Cl^- to form gastric acid, HCl. Inhibition of the H^+-K^+-ATPase is the most efficacious method of preventing harmful gastric acid secretion. Proton pump inhibitors and potassium competitive acid blockers are widely used therapeutically to inhibit acid secretion. Stimulated delivery of the H^+-K^+-ATPase to the parietal cell apical surface requires the fusion of intracellular tubulovesicles with the overlying secretory canaliculus, a process that represents the most prominent example of apical membrane recycling. In addition to their unique ability to secrete gastric acid, parietal cells also play an important role in gastric mucosal homeostasis through the secretion of multiple growth factor molecules. The gastric parietal cell therefore plays multiple roles in gastric secretion and protection as well as coordination of physiological repair.

acid secretion; growth factors; mucosal homeostasis; parietal cell; stomach

This review summarizes the complex literature related to the physiology and cell biology of gastric parietal cell acid secretion and the impact of directed pharmacology in the therapeutic manipulation of acid secretion. In addition, the article addresses the role of gastric parietal cells as sources of growth factors and regulators of gastric mucosal homeostasis.

I. HISTORICAL PERSPECTIVE ON ACID SECRETORY PHYSIOLOGY AND PATHOPHYSIOLOGY

The pursuit of an understanding of gastric acidity has been a central focus of gastrointestinal medicine and physiology through the ages. Acid-peptic disease has been a consistent cause of morbidity and mortality throughout human history. Early physicians such as Galen and Vesalius recognized the caustic nature of gastric secretions in many animals including humans (402). Nevertheless, it was not until the 18th century that physiologists systematically sought to determine the chemical nature of gastric secretion. The insights into the composition of gastric juice began with the studies involving dubious ethics by William Beaumont who studied the effluent from a gastric-cutaneous fistula in a soldier wounded in the French and Indian War (31). These studies allowed Beaumont to determine a number of meal-related stimuli to the flow of gastric juice. While many believed that lactic acid accounted for the acidity in the stomach, in 1823, Prout determined definitively that the highly caustic nature of the gastric juice was due to HCl (258). This recognition of HCl secretion led to investigation of how neurons and humoral regulators control the secretion of acid from parietal cells. Similarly, the drive to understand acid secretion as a cause of ulcer disease led to extensive physiological studies beginning in the late 19th century focusing on identifying ways to moderate acid secretion and ameliorate acid-peptic disease. Latrajet (220) was the first to detail the innervation of the stomach, and Pavlov (289)

expanded these insights to define neuronal regulation of acid secretion. The studies of Latrajet and Pavlov led to the development of acid suppressive surgery by Dragstedt, first through vagotomy and later through vagotomy and antrectomy (80). These operations, based on concepts of regulation of physiology, dominated the treatment of duodenal ulcer disease through most of the 20th century until the introduction of H_2-histamine receptor blockers in the 1970s and the recognition in the 1980s of *Helicobacter pylori* infection as the predominant cause of duodenal ulcers.

II. THE CELLULAR ANATOMY OF THE STOMACH

The human stomach is separated into three anatomical regions: the cardia, the corpus, and the antrum. The corpus represents the largest portion of the stomach and is populated by oxyntic glands. The oxyntic glands contain large numbers of acid-secreting parietal cells and an isthmal progenitor zone near the top quarter of the glands. Foveolar surface Muc5AC-expressing mucous cells migrate towards the lumen from the isthmus, while parietal cells migrate towards the base (188, 189). The oxyntic glands also show Muc6-expressing mucous neck cells that migrate towards the base and subsequently redifferentiate into pepsinogen-secreting chief cells (190). The position of the progenitor zone near the lumen is the result of differing lifetimes of corpus gland lineages. Thus surface mucous cells, which migrate towards the lumen, live 5–7 days (189). In contrast, the parietal and chief cell lineages that migrate towards the base live 90–120 days (187, 190, 417). The oxyntic glands are also defined specifically by the presence of ghrelin-secreting enteroendocrine cells and harbor histamine-secreting enterochromaffin-like (ECL) cells, somatostatin-secreting D cells, and a few serotonin-secreting enterochromaffin (EC) cells (77, 239) **(FIGURE 1)**.

In contrast, the antral or pyloric glands contain foveolar surface mucous cells and Muc6-expressing deep mucous cells. The presence of gastrin-expressing G cells defines the antrum, and these glands also show D cells and some EC cells (77). It is important to note that while the discrete separation of corpus oxyntic glands from mucus-secreting antral glands is very sharply demarcated in rodent and rabbit stomach, the human antrum usually contains a mixture of oxyntic- and antral-type glands. The oxyntic-type glands in the antrum do contain parietal cells and chief cells, but at significantly reduced numbers compared with corpus glands (77, 385). It is not clear whether the presence of parietal cells in the human antrum has consequences on the prevalence of duodenal ulcer disease.

The cardia region in humans as well as rabbits resides adjacent to the gastroesophageal junction and has variable size ranging from a few glands to 20–30 glands. Cardia glands are characterized by an absence of parietal cells and chief cells and have overall characteristics more similar to antral glands. All mammals studied possess a unique first gland directly after the squamo-columnar junction that has unique characteristics including Lgr5-positive stem cells, a general absence of endocrine cells or parietal cells, and an abundance of sensory tuft cells (182, 277). It remains controversial whether larger numbers of cardia glands in humans represents an expansion of the gland populations from the first gland. It should be noted that rodents do not have a real cardia. Rather rodents possess a large squamous epithelia-lined forestomach. Nevertheless, they still show a characteristic first gland at the squamo-columnar junction (277).

III. REGULATION OF GASTRIC ACID SECRETION

A. Neurohumoral Regulation of Parietal Cell Secretion

Hydrochloric acid secreted from gastric parietal cells generates the strongly acidic environment of the gastric lumen (pH <2) (305), which kills food-derived bacteria, facilitates food digestion, and promotes absorption of minerals including phosphate, calcium, and iron. High levels of acid secretion also represent a potentially harmful substance to the integrity of the gastric mucosa. Thus the gastric mucosa must maintain a balance between acid secretion and mechanisms for mucosal protection. The extrinsic and intrinsic neuroendocrine system of the stomach balances the influences of agonist and antagonist to maintain a safe range of acid secretion. Below we highlight the present knowledge of how the physiological balance between stimulatory and inhibitory pathways is integrated within the gastric mucosa **(FIGURES 2 AND 3)**.

B. Stimulatory Mediators

1. Vagus nerve/acetylcholine

Extrinsic nerves densely innervate the upper gastrointestinal mucosa and regulate gastric acid secretion through afferent and efferent signals **(FIGURE 2)**. The importance of the vagus nerve in stimulating acid secretion was first elaborated by Pavlov (289). Since vagotomy decreases basal and distension-induced acid secretion (136), this surgery was a mainstay of peptic ulcer treatment for decades (80). Afferent nerves processes from neural bodies in nodose ganglia consist of ~80% of vagus nerve fibers, implicating the importance of sensory function in the gastrointestinal mucosa. Sensory function for vagal components may be critical for luminal sensing and coordination of acid secretion and other functions including cell lineage homeostasis. Powley et al. (302) demonstrated the afferent terminals running
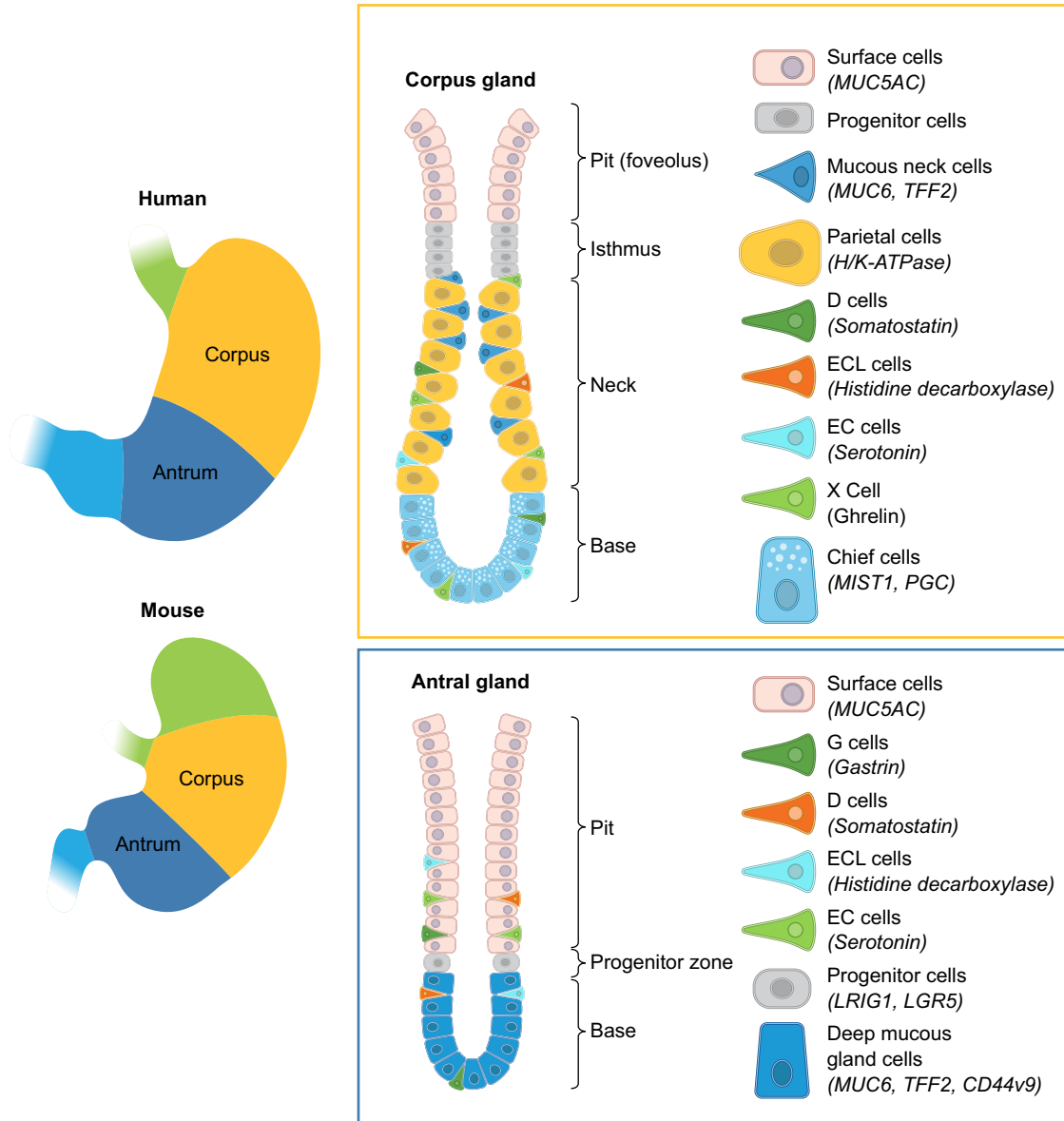
FIGURE 1. Cellular anatomy of the stomach. The human stomach is composed of three distinct regions: the cardia, the corpus, and the antrum. The gastric cardia resides in the most proximal portion of the human stomach. The corpus contains the oxyntic glands that harbor an isthmal progenitor region and contains the majority of acid-secreting parietal cells and pepsinogen-secreting chief cells. Corpus glands uniquely contain ghrelin-secreting X cells. The antral glands are predominantly mucus secreting glands and uniquely harbor the gastrin expressing G cells. It is important to note that, in the human stomach, the antrum contains a mix of oxyntic and antral glands; however, the oxyntic-type glands in the antrum have significantly fewer chief cells and parietal cells compared with corpus glands (77).

close to epithelial cells of antral glands and duodenal villi and glands. However, they did not directly contact the lumen, suggesting that afferent nerves indirectly monitor luminal signals. Afferent nerve terminals and varicosities contain the neuropeptide calcitonin gene-related peptide (CGRP), released by local activation to stimulate ghrelin and somatostatin secretion from gastric X and antral D cells, respectively (98, 241, 446). Mechanical and chemical stimuli in the stomach activate a subset of vagal afferent neurons expressing glucagon-like peptide 1 receptor (GLP-1R) shown by in vivo ganglion imaging in reporter protein transgenic mice (422). The same study demonstrated that intraduodenal chemicals activated another subset of nodose neurons, which express GPR65, a proton sensing receptor (346, 422). Neuronal tracer studies in rats precisely mapped the afferent innervation and showed that right and left nodose afferents line antral mucosa, while left nodose predominantly innervates the duodenum (411). Unilateral vagotomy may alter the gastrointestinal response to intraduodenal foods. Afferent signals through nodose neurons are transduced to the nucleus tractus solitarius (NTS) in the medulla, which is influenced by postprandial circulating
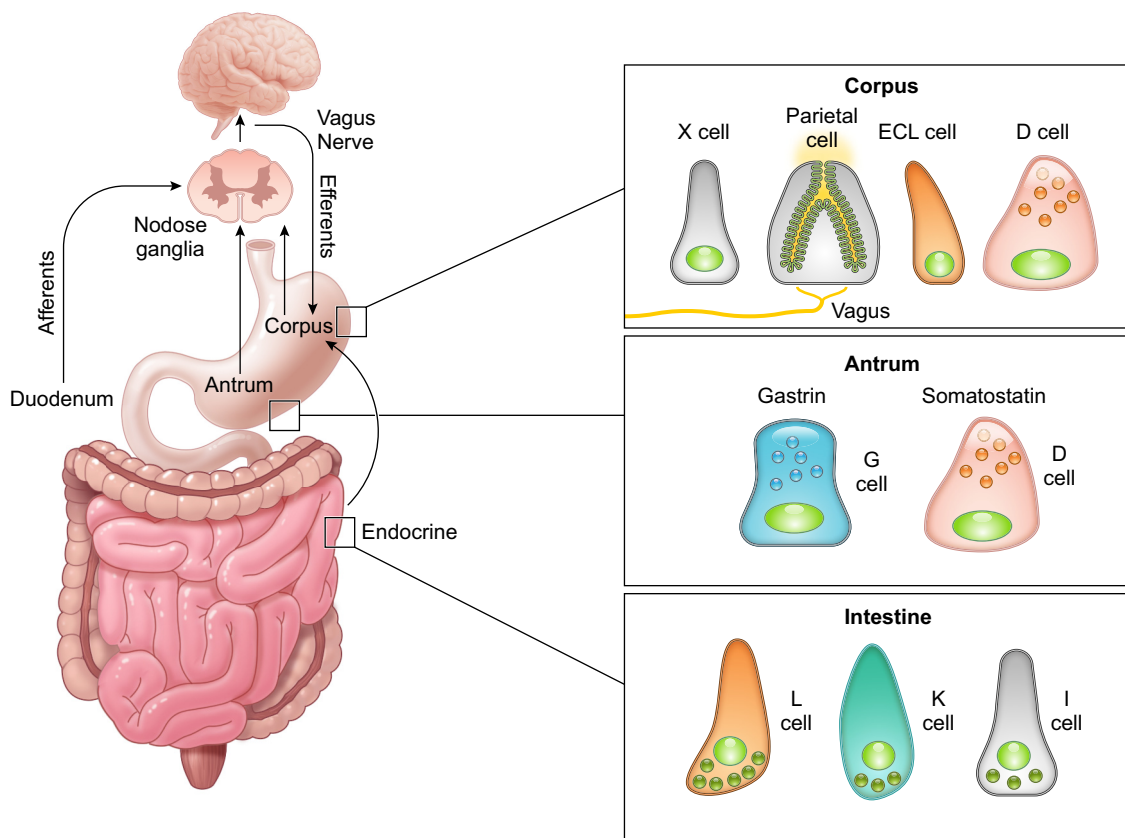
FIGURE 2. Neurohumoral regulation of gastric acid secretion. Multiple pathways are involved in the regulation of gastric acid secretion, including the neuronal and endocrine pathways mediated by the enteric nervous system and enteroendocrine cells in the gastrointestinal mucosa. Histamine-producing enterochromaffin-like (ECL) cells and ghrelin-producing X cells are found in the corpus, while somatostatin-producing D cells are distributed throughout the stomach. Gastrin-producing G cells are specifically localized in the antrum. Small intestinal enteroendocrine cells have some overlapping expression of gastric peptides including ghrelin and somatostatin (93, 185).

hormones and nutrients by the blood-brain barrier, which is relatively leaky to these molecules. NTS neurons contact dorsal motor nucleus (DMN), where the efferent nerves of the vagus originate. Electrical activation of DMN increases gastric acid secretion in cats (429). Vagal efferent nerves connect to gastric myenteric ganglia in the enteric nervous system (ENS), and the final vagal neurotransmitter is acetylcholine (ACh). Gastric mucosal nerves originating from intrinsic (submucosal and myenteric) ganglia predominantly contain ACh (15). Gene deletion of the neurturin receptor GFRα2 in mice causes a loss of mucosal cholinergic nerves, although basal and histamine-stimulated acid secretion as well as plasma gastrin level is similar to levels detected in wild-type mice (211). Unstimulated gastric acid output in GFRα2 knockout (KO) mice is reduced by the muscarinic antagonist atropine to the same extent as in wild-type mice (211), suggesting that a non-neural ACh source in gastric mucosa may exist to maintain the basal constitutive activity of muscarinic receptors.

Electrical stimulation of the cervical vagus nerve increases gastric acid secretion (41, 361). Vagal activation-induced acid secretion is reduced by atropine by 70% and abolished by the combination of atropine with ganglionic ACh receptor antagonist hexamethonium in anesthetized rats (347), suggesting the predominant contribution of the muscarinic pathway. The ACh analogue carbachol increases intracellular Ca^{2+} ($[Ca^{2+}]_i$) in isolated parietal cells, some ECL cells, and G cells to activate secretion (268, 439, 449). Distinct G protein-coupled muscarinic ACh receptors (M_1R-M_5R) differentially regulate gastric acid secretion. Selective antagonists for M_3R increases inositol phosphate and $[Ca^{2+}]_i$ in isolated parietal cells from rats and rabbits (296, 421). The deletion of each muscarinic receptor subtype in transgenic mice demonstrated that M_3R mediates the greatest influence on stimulating acid secretion, with an additional contribution of M_5R, but not M_1R (8, 9). In addition, M_4R activation suppresses somatostatin release from D cells, further enhancing gastric acid secretion (377).

2. Gastrin/G cell/CCK₂ receptor

A gastric acid-stimulating hormone, gastrin, produced in the antrum was proposed in 1906 (92). Classic physiological experiments using isolated antrum with Heidenhain pouch in dogs demonstrated the presence of this humoral
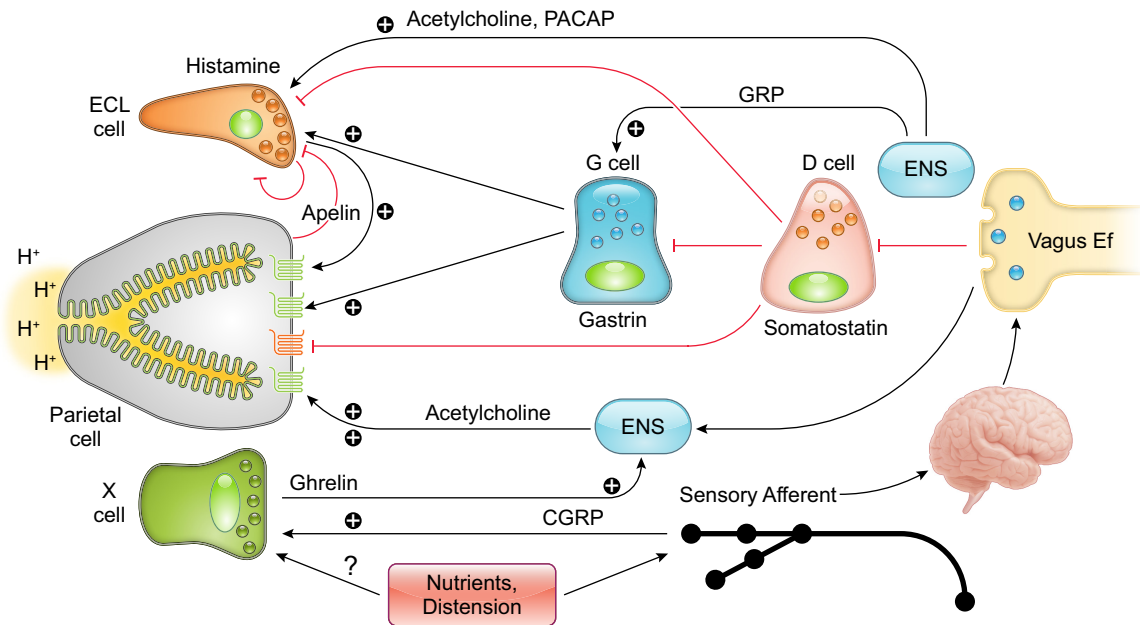
FIGURE 3. Cellular components that control gastric acid secretion. Numerous cell types regulate gastric acid secretion. Enterochromaffin-like (ECL) cells through histamine and X cells that secrete ghrelin activate parietal cells via paracrine and neural pathways, respectively. Gastrin secreted from G cells binds directly on parietal cells or stimulates acid secretion mediated by histamine release from ECL cells. Vagal efferent mediated by the enteric nervous system (ENS) stimulates G cells through gastrin-releasing peptide (GRP) and acetylcholine (ACh) and stimulates ECL cells through pituitary adenylate cyclase-activating peptide (PACAP). The cholinergic signal can also inhibit somatostatin release from D cells, accelerating acid secretion. Additionally, calcitonin gene-related peptide (CGRP) released from vagal afferent terminals activates X cells to enhance the acid secretory pathway. Somatostatin directly inhibits gastric acid secretion from parietal cells as well as indirectly through its action on ECL cells and G cells. Histamine suppresses ECL cell activity as a negative feedback system. Apelin, produced by parietal cells, exerts inhibitory or stimulatory effects on ECL cells.

factor (139, 426, 427). Gregory and Tracy (135) extracted gastrinlike peptides from pig antral mucosa and determined its amino acid sequence. Subsequently, human gastrin was isolated as a heptadecapeptide with only one amino acid difference from pig gastrin (37). The gastrin gene was cloned from pig antrum in 1982 (440) and human in 1983 (50, 192). The gastrin-producing enteroendocrine cell (G cell), which has an apical brush border with direct access to the lumen, was first identified by Solcia et al. (364) in guinea pig antrum. Yalow and Berson (434) developed a radioimmunoassay with highly specific human gastrin antisera and showed that intragastric HCl decreased plasma gastrin level within a few minutes in pernicious anemia (autoimmune gastritis) patients, who have hypergastrinemia. The G cell was the first physiologically and histologically identified enteroendocrine cell and inspired further characterization of other enteroendocrine cell populations as gut nutrient sensor cells (112). Bioactive amidated gastrin has two major forms, G34 (big gastrin) and G17 (little gastrin), which share COOH-terminal polypeptides and are released into circulation after a meal (215). Most stored gastrin in human antrum is G17 (181, 310). G34 has a longer half-life and causes long-lasting acid stimulation (410), suggesting that the processing mechanism can regulate gastrin efficacy. Several G_q-coupled receptors for digested protein (peptone and amino acids) are found in G cells, such as CaSR, GPCR6A, and LPAR5 (102, 144, 309, 311). These chemical sensors are likely a mechanism of amino acid-induced gastrin secretion, subsequently stimulating acid secretion from parietal cells (100). A recent study, using CaSR agonists and the synthetic antagonist NPS2143, showed that CaSR activation stimulates gastrin release from dissected pig antral glands and that aromatic amino acids together with extracellular Ca^{2+} trigger this pathway (430).

The gastrin receptor, also designated as CCK_2R by the International Union of Basic and Clinical Pharmacology (IUPHAR)/British Pharmacological Society (BPS) "Guide to Pharmacology" (gene name: *CCKBR*; $IC_{50} = 1$ nM), was cloned in several animals including humans as an identical receptor in the stomach and brain (205, 298, 415). In human stomach, CCK_2R immunoreactivity is localized on the basolateral membrane in the majority of parietal cells and some chromogranin-A containing ECL cells (210, 341). Histamine H_2-receptor antagonists inhibit CCK_2R-activated acid secretion in vivo (1, 46) and in parietal cells (71, 122), suggesting that gastrin indirectly stimulates acid secretion through histamine release from ECL cells. Although CCK_2R is present on parietal cells, direct effect of gastrin on acid secretion in humans is likely minor. Synthetic G17

infusion increases acid secretion in fasted men, and this response is reduced >70% by atropine and abolished by famotidine (451). The primary pathway of gastrin-induced acid secretion in humans is likely paracrine release from ECL cells of histamine, which directly activates parietal cells. Additionally, gastrin-CCK_2R signaling potentiates cholinergic input on parietal cells (117). CCK_2R is also essential for parietal cell differentiation and maturation. Germline CCK_2R-deficient mice demonstrate gastric mucosal atrophy and decreased parietal cell and ECL cell numbers, resulting in increased basal gastric pH and plasma gastrin level (216, 264). Likewise, gastrin-deficient mice have few parietal cells and low basal and stimulated acid secretion in vivo (110). However, isolated parietal cells from gastrin KO mice show higher Ca^{2+} responses than wild-type cells (163), suggesting that gastrin influences parietal cell characteristics and balances the receptor expression levels. Furthermore, gastrin is required for tonic expression of the gastric trefoil factors and parietal cell maturation (199, 285). The gastrin-secreting G cells regulate parietal cell function as a feedback system from the distal part of the stomach.

The CCK_1 receptor (CCK_1R; gene name: *CCKAR*) has 1,000-fold higher affinity to cholecystokinin (CCK)-8 than gastrin, while CCK_2R has similar affinity to both peptides. CCK is produced and secreted by a subpopulation of the enteroendocrine cells of the duodenum in response to luminal fatty acids and digested protein (154, 227). CCK_1R activation inhibits acid secretion in anesthetized rats and healthy humans (230, 338). CCK_1R immunoreactivity is found in both chief cells and D cells, which are CCK_2R negative (341, 343), suggesting that CCK contributes to postprandial acid inhibition likely through somatostatin release.

3. Histamine

Histamine is a bioactive amine and strong acid secretagogue, generated by histidine decarboxylase (HDC) in the ECL cells and mast cells in the corpus gastric glands (145). ECL cells, which are frequently found next to parietal cells, have no direct contact with the gastric lumen (closed type enteroendocrine cells). These ECL cells show long basal processes that are thought to come in apposition with multiple parietal cells (66, 99). Histamine release is directly activated by circulating gastrin via CCK_2R (162) and neuronal pituitary adenylate cyclase-activating peptide (PACAP) via the PAC_1R (447) **(FIGURE 4)**. Histamine release is suppressed by somatostatin via SST_2 and galanin via Gal_1 (448) receptors on ECL cells. Diamine oxidase (DAO) and histamine-*N*-methyltransferase deactivate histamine. The infusion of exogenous DAO made from pig kidney inhibited histamine-induced gastric acid secretion in dogs (138). In a human study, heparin-induced gastric acid inhibition was mediated by endogenous DAO (151).

The H_2 histamine receptor (H_2R) was defined pharmacologically as a mediator of gastric acid secretion through the use of its antagonist, burimamide, in anesthetized rats (46). Acid secretion is insensitive to H_1R antagonists, such as mepyramine. H_2R antagonists inhibit cholinergic- and gastrin-induced acid secretion in vivo and in isolated gastric glands (40, 137). Synthetic H_2R antagonists were the first targeted therapeutics for peptic ulcers and erosive esophagitis (46, 260) before the development of proton pump inhibitors. Parietal cells express G_s-coupled H_2 receptors, which increase intracellular cAMP to stimulate acid secretion directly and potentiate Ca^{2+}-induced acid secretion (40). Histamine induces accumulation of cAMP (238) and activates cAMP-dependent protein kinase in isolated parietal cells (69). H_2R-activated cAMP production is the crucial and rate-limiting trigger of parietal acid secretion. HDC-deficient mice barely respond to carbachol and/or gastrin, but gastric acid secretion is stimulated by the combination of forskolin and carbachol (115). Similarly, H_2R-deficient mice lack the response to gastrin, but basal acid secretion is maintained by M_3R and CCK_2R signaling (114). Transgenic mice with H^+-K^+-ATPase promotor-derived cholera toxin show consistently high intracellular cAMP concentration in parietal cells. These mice have high basal acid secretion and low plasma gastrin, and subsequently develop metaplasia with parietal cell loss by 15 mo of age (231).

Four subtypes of G protein-coupled histamine receptors (H_1-H_4R) have been cloned and identified in different types of cells in the gastrointestinal tract (326). Inhibitory H_3 receptors on ECL cells likely mediate a direct autocrine feedback mechanism in rats and rabbits (166, 304); however, the functional expression of H_3R in humans is still controversial.

4. Ghrelin

Ghrelin, which is an octanoylated 28-amino acid peptide released from the oxyntic mucosa of stomach, was identified by Kojima et al. (202) as a growth hormone secretagogue receptor (GHSR) ligand. Circulating ghrelin levels have a circadian rhythm and are increased by fasting and decreased by feeding in rodents (388) and humans (82). Ghrelin-producing X cells are closed-type enteroendocrine cells (83), which have no direct contact with the lumen and are distributed in corpus oxyntic glands reciprocally with gastrin in the antrum (77). A variety of metabolite and neurohumoral receptors are expressed on X cells. Bitter taste receptor (T2R)-coupling G proteins, such as gustducin and transducin, are colocalized with ghrelin in murine stomach. Bitter compound ingestion increases plasma ghrelin level within 40 min (177). FACS and qPCR techniques revealed that X cell release of ghrelin is inhibited by the activation of FFA2 (short-chain fatty acids), FFA4 (long-chain fatty acids), HCA_1 (lactate), CaSR (extra cellular calcium, amino acids), and SST_{1-3} (somatostatin) receptors, explaining the decreased plasma ghrelin levels after a meal.
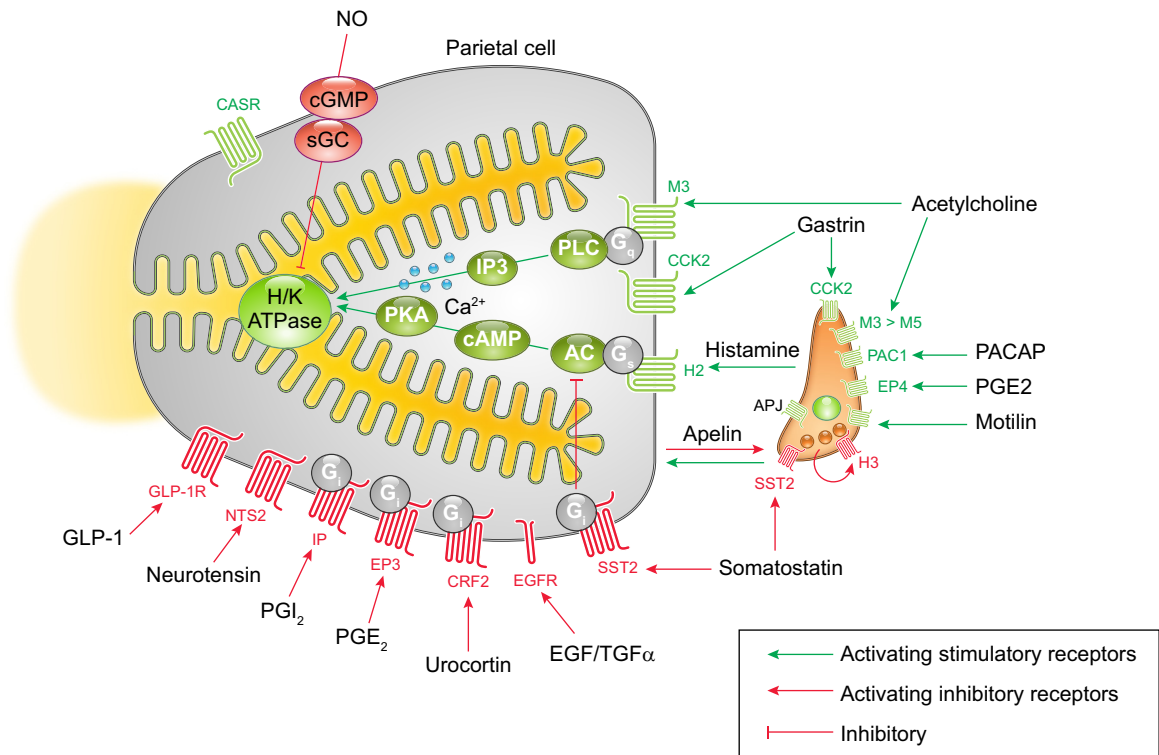
FIGURE 4. Membrane receptors on parietal and enterochromaffin-like (ECL) cells and intracellular signaling pathways that regulate gastric acid secretion. Stimulatory pathways are indicated in green, and inhibitory pathways are indicated with red lines. The parietal cell expresses G protein-coupled receptors (GPCRs) for acid secretagogues, including the muscarinic receptor (M3) for acetylcholine, the gastrin receptor (CCK2), and the histamine receptor (H2). M3 and CCK2 receptors are coupled to G protein G_q that activates phospholipase C (PLC), which leads to intracellular Ca^{2+} release to potentiate acid secretion. Binding of histamine to the H2 receptor activates adenylate cyclase (AC) to generate cAMP through G_s signal, which potently stimulates H^+-K^+-ATPase (H/K) activity via cAMP-dependent protein kinase (PKA). Histamine release from ECL cells is stimulated by a variety of receptors, including CCK2, PAC1, EP4, and the motilin receptors. Several receptors for inhibitors of gastric acid secretion are present on parietal cells including GLP-1R, NTS2, IP, EP3, CRF2, EGFR, and SST2 receptors. The inhibitory G protein (G_i) suppresses AC activities to inhibit cAMP-mediated secretory pathways. Additionally, nitric oxide (NO) inhibits acid secretion through the cGMP pathway. Angiotensin-like peptide receptor (APJ), activated by parietal cell-derived apelin, exerts both inhibitory and stimulatory effects. The H3 histamine receptor, expressed on ECL cells, contributes to negative feedback for histamine release.

Release of ghrelin from X cells is activated by β1-adrenergic, CGRP, gastric inhibitory polypeptide (GIP), and secretin (SCT) receptors, consistent with in vivo observations that postprandial nutrients and hormones regulate ghrelin release (98). Peripheral (248) and intracerebroventricular (84) administration of ghrelin stimulates gastric acid secretion through the vagus nerve in rats. Furthermore, in rats, coadministration of ghrelin with gastrin synergistically increases acid secretion stimulated through the vagus nerve (113, 433). Although most of human ghrelin cells are located close to parietal cells (99), model animal studies so far show that ghrelin action on acid secretion is predominantly mediated by GHSR on afferent nerves and a vagal reflex **(FIGURE 3)**.

5. Apelin

Apelin was isolated from bovine stomach as an endogenous ligand of an orphan human G protein-coupled receptor (GPCR), angiotensin-like peptide receptor (APJ), with higher affinity for short COOH-terminal fragments (apelin-13 or -17) than long fragments (apelin-35) (381). Rat parietal cells express apelin mRNA, while ECL cells express APJ mRNA in purified rat gastric epithelial cells (214), suggesting a feedback pathway from the parietal cell to the ECL cell. In isolated rabbit gastric glands, 100 nM apelin inhibited $[Ca^{2+}]_i$ responses in ECL cells and gastrin-induced parietal cell activation (214). In contrast, in vivo gastric perfusion experiments in rats showed that 100 μg/kg intravenous apelin-12 enhanced acid secretion through histamine release, independent from muscarinic cholinergic pathways (280). Different lengths of apelin fragments interact differently with APJ and its downstream $G_{i/o}$, inhibiting cAMP production in CHO cell expression systems (142), suggesting that different effects of endogenous apelin are influenced by truncation. Apelin immunoreactivities are broadly found in central and peripheral tissues, including in human mesenteric adipocytes with Crohn's disease (118)

and Kupffer cells in rat liver in addition to gastric parietal cells (382). In a stress-induced gastric lesion model in rats, apelin protein expression was increased, and APJ receptor antagonist delayed the mucosal healing, indicating an important role of apelin-APJ signaling in mucosal protection (43). Those observations suggest that apelin can locally and systemically modulate gastric acid secretion through APJ-histamine-H_2R signaling under physiological and pathological conditions. Further examination of apelin functions in human stomach is needed.

6. Motilin

Motilin, which is in the same peptide family as ghrelin, was identified in pig intestine as a gastric motility activating peptide (52). Duodenal Mo cells release motilin during the interdigestive period by unknown stimuli. High doses (10 μg/kg) of motilin or a coadministration of a low dose (1 μg/kg) of motilin and ghrelin synergistically stimulate gastric acid secretion in anesthetized shrews (131). This peptide-induced acid secretion is mediated by histamine release and is independent from cholinergic pathways. Both motilin and ghrelin are released when the stomach is empty, suggesting that this combination is responsible for endocrine regulation of interdigestive motility-related gastric acid secretion.

7. Glucocorticoids

Glucocorticoids are essential steroid hormones for systemic homeostasis, primarily secreted by the adrenal cortex in a circadian manner and in response to stress. Other organs, including the intestine, also synthesize glucocorticoids, and local functions in immune regulation have been proposed (79). Glucocorticoids stimulate gastric acid secretion in dogs (81) and mice through serum- and glucocorticoid-inducible kinase (SGK_1), which stimulates K^+ channels, such as KCNQ1 (327). Adrenalectomy induces oxyntic atrophy and gastric inflammation through the spontaneous activation of $CXCR2^+$ monocytes in mice, suggesting that glucocorticoids are essential for gastric homeostasis (56). In human studies, glucocorticoids induce hypergastrinemia (308), but do not affect acid secretion (164). Glucocorticoids bind ligand-dependent transcription factors, namely, mineralocorticoid (MR or NR3C2) and glucocorticoid (GR or NR3C1) receptors, that are broadly expressed in gastric cells, including parietal cells (56, 278). The activity of glucocorticoids is regulated by the balance of two subtypes of hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2), which either catalyze production of active glucocorticoids or inactivate them, respectively (63). Because human parietal cells highly express mineralocorticoid receptor and 11β-HSD2, mineralocorticoid-specific effects on parietal cells are suggested, rather than glucocorticoid (193). Yet the function of MR in regulating parietal cell mediated acid secretion remains unknown.

C. Inhibitory Mediators

1. Somatostatin

Somatostatin was identified as a growth-hormone release-inhibiting hormone in the hypothalamus and is found in enteroendocrine D cells in human gastric mucosa (219, 299). In anesthetized dogs, intragastric glucose, fat, and casein hydrolysate stimulates somatostatin release from the corpus to a greater degree than from the antrum (345). Conversely, intraduodenal and intragastric HCl infusion potently stimulates antral somatostatin secretion, but not from the corpus (345), suggesting that D cells throughout the gastric mucosa possess several nutrient receptors expressed at different levels and antral D cells are more sensitive to luminal acid. As oligopeptide and amino acid receptors in the human and pig antrum, immunoreactivities of CaSR, LPA5, and GPRC6A are detected in D cells (144), indicating that antral D cells are stimulated by luminal or circulating nutrients. From the circulation, gastrin and CCK regulate somatostatin secretion in the corpus and antral mucosa to different extents (443). More GPCRs were identified in isolated D cells from reporter mouse gastric tissue and primary cultured gastric epithelial cells using transcriptome techniques (6, 94). Trace amine-associated receptor 1, GLP-1R, GIPR, CGRP receptor subunits, vasoactive intestinal peptide R, adrenomodulin R, melanocortin MC_1, muscarinic M_3, CCK_2, and adrenergic receptors are all stimulators of somatostatin release, whereas long-chain fatty acid receptor FFA4, SST_1, and SST_2 receptors are suppressers of somatostatin secretion (6, 94).

Intravenous somatostatin potently reduces feeding- or gastrin-stimulated acid secretion in conscious cats, dogs, and humans (27, 128, 204, 297). The direct effect of somatostatin on isolated gastric glands and parietal cells from rabbit stomach suggests that histamine secretion from ECL cells and acid production in parietal cells are both inhibited by somatostatin (68).

All of the five subtypes of somatostatin receptors (SST_1-SST_5R) are coupled with inhibitory G protein ($G_{i/o}$) and uniquely distributed in the gastric mucosa (11, 209). A splice variant of SST_2R, $SST_{2a}R$, is predominantly expressed in rat ECL cells and human G cells, while another variant, $SST_{2b}R$, was identified in rat parietal cells (140, 336, 370). SST_2R-deficient mice demonstrated higher basal acid secretion (247), confirming that SST_2R activation suppresses cAMP generation and decreases gastric acid secretion.

2. GLP-1 and PYY/"enterogastrone" effect

A substance from intestinal mucosa, which is released in response to intraluminal fat and inhibition of gastric acid secretion, was first described in 1930 as "enterogastrone"

(206). Deficiency of apolipoprotein A-IV in transgenic mice abolishes the inhibitory effect of duodenal lipid on meal-stimulated gastric acid secretion (419), suggesting that absorption is essential for gastric acid inhibition by dietary lipid. Currently, an intestine-specific proglucagon product, glucagon-like peptide 1 (GLP-1), and peptide tyrosine-tyrosine (PYY), another inhibitory gut peptide causing the "ileal brake," a negative feedback mechanism that slows food transit through the gastrointestinal tract, are considered as the molecular components accounting for enterogastrone. Intravenous GLP-1 or PYY inhibits stimulated gastric acid secretion in humans (141, 337). Plasma levels of GLP-1 and PYY are increased by nutrient perfusion, including lipid and carbohydrate in human ileum, correlating with the inhibition of gastric acid secretion (221, 418). PYY inhibition of histamine release from isolated rat ECL cells is mediated by the $G_{i/o}$-coupled Y_1 receptor (450). PYY expression is detected in isolated D cells from murine stomach and only a small number of human stomach enteroendocrine cells (6, 94, 99), implicating direct PYY effects on gastric cells in a paracrine fashion. On the other hand, the GLP-1 receptor is expressed in rat parietal cells, and its agonists stimulate cAMP and acid production (339, 340). Since human parietal cells express GLP-1 receptors (51), elucidating the direct function of GLP-1 on human gastric glands would be important for understanding the side effects of incretin hormone analogues used in diabetic treatments.

3. Gaseous mediators: nitric oxide and hydrogen sulfide

Nitric oxide (NO) and hydrogen sulfide (H_2S) are known to inhibit gastric acid secretion and enhance mucosal restitution. NO is produced from L-arginine by NO synthase (NOS) in the intramural neurons and gastric epithelial cells (53). Immunoreactivity for endothelial NOS was identified in surface epithelial cells and enteroendocrine cells in human gastric mucosa (38), and neuronal NOS was found in isolated rat parietal cells (303). NO activates soluble guanylate cyclase (sGC) to increase intracellular cGMP (FIGURE 4). The exogenous NO donor nitroprusside reduces histamine-induced acid secretion, and the NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) prevents the inhibition of acid secretion induced by mucosal injury in anesthetized rats (378). Acid production in isolated oxyntic glands from rabbits and healthy human biopsies is inhibited by NO via elevations in cGMP, indicating that NO acts as a paracrine regulator (39, 200).

H_2S is generated from L-cysteine by cystathionine β-synthase and cystathionine γ-lyase, which are expressed in the gastric mucosa as well as in parietal cells (245). The exogenous H_2S donor NaHS increases luminal NO release in anesthetized rats and inhibits gastric acid secretion in response to gastric distension (242). Generation of H_2S in gastric mucosa is increased in ulcerated mucosa and en-

hances mucosal healing independent from NO synthesis, suggesting that H_2S maintains the gastric mucosa through several targets (407).

4. Neurotensin/xenin

Neurotensin and its related peptide, xenin, are neuropeptides that are produced in the central nervous system as well as from enteroendocrine cells in the distal and proximal intestine, respectively. Plasma concentrations of these peptides are elevated after a meal and influence gastrointestinal functions via high-affinity NTS_1, low-affinity NTS_2, and NTS_3 receptors. Intravenous neurotensin or xenin (50 $ng \cdot kg^{-1} \cdot min^{-1}$) potently inhibits gastric acid secretion stimulated by pentagastrin, but not by histamine in dogs (13, 103). Vagotomy abolishes the antisecretory effect of (Gln4)-neurotensin, which has a glutamine residue at position 4 instead of glutamic acid in the natural form (14), and neurotensin-binding neurons were identified in rat nodose ganglia (198), suggesting the remarkable contribution of a vagal reflex. NTS_1R, which is equally activated by neurotensin and xenin, is distributed in sensory neurons (300), and NTS_2R is localized on basolateral membranes of parietal cells in human gastric mucosa (342). Both neuronal pathways and direct effects on parietal cells likely mediate postprandial antisecretory effects of neurotensin-related peptides.

5. Corticosterone releasing factor

Corticosterone releasing factor (CRF), a neuropeptide identified in the hypothalamus, and the related peptides urocortin (Ucn)1, Ucn2, and Ucn3 (400) are involved in stress-induced gastrointestinal dysfunctions through the G protein-coupled receptors CRF_1R and CRF_2R. CRF_1R has high affinity for CRF and Ucn1, but not for Ucn2 or Ucn3. CRF_2R prefers Ucn1, Ucn2, and Ucn3, but interacts poorly with CRF (156). Intracisternally or intravenously injected CRF inhibits gastrin-induced gastric acid secretion through vagal pathways, indicating the localization of CRF_1R within the nervous system (374, 375). Immunoreactivity for CRF_2R, but not CRF_1R, was found in parietal cells and enteroendocrine cells in the oxyntic glands (65), and all urocortins are present in the gastric mucosa, including in gastric parietal cells (64, 208). These observations suggest local gastric acid regulation by urocortins-CRF_2R signaling, but further studies are needed to clarify when urocortins are released and whether CRF_2R contributes to physiological acid secretory function.

6. Prostaglandins

Prostaglandins are arachidonic acid metabolites, generated by cyclooxygenase (COX)-1 (Gene name: *PTGS1*) and COX-2 (*PTGS2*) in many types of cells in the normal gastric mucosa, including parietal cells, macrophages, and myofi-

broblasts (176). Major prostaglandins in human gastric mucosa are PGE_2 and PGI_2. In experimental animals, exogenous PGE_2 and PGI_2 suppress gastric acid secretion (237, 314, 420). However, the results in humans are controversial (32, 36), probably due to the different level of endogenous prostaglandins in different experimental paradigms. COX inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) augments acid secretion (224) and induces gastric mucosal lesions under fasted conditions. In isolated human parietal cells, PGE_2 potently inhibits histamine-induced acid production, as assessed by aminopyrine uptake (178). Cultured gastric mucosa as well as isolated parietal cells generate PGE_2 (283, 363), indicating that PGE_2 functions as an autocrine feedback regulator suppressing gastric acid secretion and promoting mucosal protection. PGE_2 activates four subtypes of membrane GPCRs ($EP_{1-4}R$) with an affinity order of $EP_3 > EP_4 > EP_2 > EP_1$, coupling with distinct secondary messengers (4). Histamine- or forskolin-induced cAMP accumulation is inhibited by PGE_2 (<1 μM) in isolated canine or rat parietal cells, indicating a G_i-coupled pathway (89, 365). In vivo gastric perfusion in anesthetized rats revealed that EP_3R agonist inhibits pentagastrin- or histamine-stimulated acid secretion through the inhibition of parietal and ECL cells, whereas high concentrations of PGE_2 (>100 μM) or G_s-coupled EP_4R agonist enhances histamine release from ECL cells (194). High concentrations of PGE_2 also stimulate bicarbonate secretion via EP_1R to counteract histamine-up-regulated acid secretion (379), suggesting that gastric pH is balanced by PGE_2 production. EP_3R is distributed on the basolateral membrane of gastric epithelial cells, and EP_4R expression is weak in the epithelium but abundant in lamina propria mononuclear cells in human stomach, as shown by immunohistochemistry (376). Although expression of both isoforms of COX enzymes is increased in inflamed gastric mucosa, COX-1 predominantly mediates gastric acid inhibition through EP_3R as well as IPR, a PGI_2 receptor in isolated parietal cells (26, 176, 267, 272). Constitutive production of PGE_2 and PGI_2 at physiological concentration protects the gastric mucosa.

7. Adenosine

Extracellular adenosine inhibits histamine-induced acid secretion in isolated parietal cells from dogs and guinea pigs, likely through A_1 receptors (123, 161). Rabbit parietal cells express A_{2B} receptors, which stimulate adenylate cyclase activity and acid production (17, 18), suggesting species difference in direct adenosine function. A_1 receptors are found in G cells as an inhibitory mechanism of acid secretion (438). Somatostatin release is enhanced by high concentration of adenosine via A_{2A} receptor activation, while somatostatin release is inhibited by low concentrations of adenosine through an A_1 receptor in mouse stomach (435). Thus the adenosine concentration in the microenvironment is likely important for acid secretory regulation through both direct and paracrine pathways.

8. Impact of Helicobacter pylori

Association between gastric colonization by *Helicobacter pylori* and gastric ulcer disease was discovered by Marshall and Warren (244). Research over the past three decades has demonstrated that chronic infection with different strains of *H. pylori* can lead to either hypersecretion or hyposecretion and their attendant pathological sequelae (95). Hyposecretion and corpus-predominant gastritis are related to the risk of gastric cancer, whereas hypersecretion and antrum-predominant gastritis are associated with duodenal ulcer (95, 243). Well-studied strain-specific virulence factors include the cytotoxin-associated gene pathogenicity island (*cag*PAI) gene, which encodes ~30 proteins of the type IV secretory system (T4SS) forming pili of bacterial outer membrane, and a variety of genotypes of vacuolating cytotoxin (*vacA*) gene (269, 276). Hypochlorhydria and mucosal inflammation are consistently observed with *H. pylori* colonization for a few days to few weeks after acute infection. *H. pylori* inhibits acid secretion by repressing H^+-K^+-ATPase α-subunit transcription and by augmented somatostatin release, enhancing microbial adhesion (130, 186, 261). Once attached to the epithelial cells, *H. pylori* can induce damage through secretion of the pore-forming protein VacA, resulting in apoptosis, disrupted tight junctions, and gastric inflammation. Infection of T4SS-expressing *H. pylori* strains increases the transcription factor nuclear factor (NF)-κB, binding the promoter region of the gastric H^+-K^+-ATPase to repress its transcription (149). A secreted oncoprotein CagA is the 3'-terminal product of *cag*-PAI and is transferred into host cells to induce epithelial hyperproliferation and parietal cell apoptosis, resulting in a high risk of gastric cancer (270, 290, 324). Histamine- or carbachol-induced acid production in human parietal cell culture is acutely inhibited by incubation with a sonicated suspension of *H. pylori* (175). In addition, accumulation of *H. pylori* metabolites, such as fatty acids, suppresses parietal cell activities (35). Short-term (20 min) exposure of Ussing chambered rat gastric mucosa to *H. pylori* or its culture supernatant inhibits histamine release and stimulates somatostatin secretion via CGRP release from mucosal sensory nerves (442). Nevertheless, hyposecretion of acid and atrophic gastritis induced by chronic *H. pylori* infection may also be influenced by host characteristics including interleukin (IL)-1β polymorphisms (96).

Despite a number of mechanisms that can lead to hyposecretion and eventually atrophic gastritis associated with certain strains of *H. pylori*, it is likely that other strains are responsible for >95% of duodenal ulcers. Distinct virulence factors have been identified in different strains that are isolated from patients with gastric ulcer or duodenal ulcer (173, 282, 319). Yet the mechanisms of antrum- versus corpus-predominant inflammation have not been fully characterized. Children with duodenal ulcer and infected with *H. pylori* demonstrated elevated acid secretion and elevated basal and meal-stimulated serum gastrin levels

(195). Eradication of *H. pylori* in duodenal ulcer patients causes reduced acid output (155). Since there is no evidence of acute stimulation of acid secretion by *H. pylori*, the hypersecretion in duodenal ulcer patients is likely caused by the alteration of inhibitory factors by chronic infection rather than direct effect on parietal cells. Indeed, the combination of increased gastrin and acid hypersecretion appears related to decreases in the secretion of somatostatin in the antrum (95, 133, 254, 261), although the precise mechanism for this deficit in somatostatin remains unclear.

9. Growth factors and cytokines

NSAID- or *H. pylori*-induced gastritis involves the production of proinflammatory cytokines, such as IL-1β, IL-6, and IL-8 in human gastric antrum, indicating that those cytokines are upstream of COX activation (148). Intravenous or intraperitoneal injection of IL-1β inhibits acid secretion through the central nervous system and PGE$_2$ production in rat stomach (315, 328, 406). Consistent with those in vivo observations, IL-1β stimulates PGE$_2$ generation in isolated rat ECL cells (228), consequently inhibiting acid secretion. In isolated mouse gastric glands, IL-2 and interferon-γ, but not IL-1β, suppress acid secretion, suggesting that a Th1 type immune response predominantly mediates direct acid inhibition (284). The IL-1 receptor type 1 (IL-1R1) was identified in rat and mouse parietal cells (335), and IL-1β suppresses sonic hedgehog expression in murine parietal cells in an IL-1R1-dependent manner (405). On the other hand, IL-1β as well as tumor necrosis factor (TNF)-α decrease basal and secretagogue-stimulated acid production in cultured rabbit parietal cells (29). Cytokine-mediated regulation of gastric acid secretion may vary among animal species, and the direct antisecretory effect of IL-1R1 in human parietal cells remains to be evaluated.

Transforming growth factor-α (TGF-α) is expressed throughout the gastrointestinal tract and is abundant in parietal cells (30). Epidermal growth factor (EGF) is secreted into salivary fluid (207), although whether breaches in the lumen can lead to access to basolateral EGF receptors in physiological conditions remains unclear. TGF-α and EGF share amino acid homology and a common receptor, namely, ErbB (EGFR), which is predominantly expressed on the basolateral membranes of parietal cells and is weakly detected in mucous neck cells and chief cells in healthy humans (3). EGF and TGF-α inhibit histamine-induced acid production in isolated rabbit, pig, and rat parietal cells (183, 203, 225, 348, 362, 412). ErbB ligands may regulate the physiological activity of parietal cells as autocrine and paracrine mediators. Other EGF family members, such as amphiregulin and heparin-binding EGF-like growth factor (HB-EGF), but not Cripto are produced by human gastric parietal cells (3, 263). The EGF level in the gastric lumen is lower in patients with *H. pylori* infection or Sjögren's disease compared with healthy subjects, suggesting that loss of luminal EGF signal is linked to chronic gastritis (10, 233).

In an experimental gastric injury model in rats, luminal or serosal EGF enhances mucosal restitution as measured by mucosal potential difference (255). In vivo gastric ulcer studies in rats also showed the therapeutic effect of oral EGF combined with an anti-ulcer drug, sucralfate (174). Since low levels of luminal EGF and chronic gastritis are correlated, luminal EGF may reach basolateral receptors and enhance restitution when the mucosa is damaged. Collectively, these findings suggest that EGFR ligands may play a dynamic role in regulating acid secretion and mucosal homeostasis in the gastric mucosa.

D. Luminal Sensing and the Regulation of Acid Secretion

Luminal contents also regulate acid secretion. Dietary proteins stimulate acid secretion, while dietary lipids suppress acid secretion (313). Nevertheless, little is known concerning the mechanisms that regulate luminal sensing in the gastric mucosa. Following the identification of gustatory signal transduction molecules, some of the taste sensor molecules were identified in gastric enteroendocrine cells (143, 401, 428) and parietal cells (67). Further characterization of orphan GPCRs revealed the molecular basis of chemical sensors in afferent nerves and enteroendocrine cells, which recognize food ingredients and regulate gastric physiological functions. Acid-sensing mechanisms have been proposed in the antrum and duodenum (129). However, exact pH sensing molecules and sensor cells are still unknown in the oxyntic mucosa. Since extracellular calcium receptor CaSR is activated by acidic extracellular pH (306) and is identified in parietal cells (67, 90), this GPCR-mediated signal is implicated as an acidity sensor in oxyntic mucosa. Rapid and local regulatory mechanisms of parietal cell activation by sensing microenvironmental pH might be important to maintain the basal tone of acid secretion independently from the central nervous system or systemic humoral control.

IV. CHARACTERIZATION OF THE H⁺-K⁺-ATPase

A. Gastric H⁺-K⁺-ATPase

Secretion of gastric acid by parietal cells is achieved through hydronium ion transport via the H$^+$-K$^+$-ATPase pump. This remarkable enzyme extrudes cytoplasmic protons against a steep concentration gradient while transporting extracellular potassium into parietal cells, resulting in electroneutral ion exchange (321). The H$^+$-K$^+$-ATPase is a P$_2$-type ATPase similar to the Na$^+$-K$^+$-ATPase (78, 301, 373). Gastric H$^+$-K$^+$-ATPase is primarily found in gastric parietal cells and to a lesser degree is expressed in the renal medulla (7, 423). The dynamic membrane trafficking in gastric parietal cells regulates the activity of acid secretion

into the lumen through H^+-K^+-ATPase. In resting parietal cells, gastric H^+-K^+-ATPase is present in tubulovesicles (106, 331). Upon stimulation, H^+-K^+-ATPase containing membranes fuse with the apical secretory canaliculi to form microvilli-like structures with a greatly expanded secretory surface (106, 331). The presence of the H^+-K^+-ATPase in the apical canalicular membrane enables the secretion of hydronium, provided by the H^+-K^+-ATPase enzyme. Debate continues as to the primary K^+ and Cl^- channels that supply the K^+ necessary for the exchange of H^+ and Cl^- in gastric HCl. KCNQ1-KCNE2 likely provides the potassium necessary for exchange by the H^+-K^+-ATPase (213, 316, 399), while evidence suggests that the chloride in gastric HCl may be provided by the putative Cl^- channel Clic6 or parchorin (257, 273, 323).

B. Initial Isolation and Cloning

In 1973, the presence of a K^+-stimulated ATPase in bullfrog gastric mucosa provided evidence for a gastric proton pump (116). Subsequently, in 1976, gastric acid secretion was demonstrated to result from electroneutral ATP-dependent exchange of hydrogen for potassium (321). In this seminal report, Sachs et al. (321) reported that H^+/K^+ exchange was electroneutral in isolated gastric membrane fractions from hogs. This study established a model for acid secretion that required functional H^+-K^+-ATPase in the presence of luminal K^+ to exchange intracellular H^+. Fractionation and electrophoresis of hog gastric mucosal homogenates yielded evidence for the presence of H^+-K^+-ATPase in gastric parietal cells by antibody immunostaining (320). Of the two membrane fractions, one was identified as transporting H^+ and K^+ and originating from the secretory canalicular structure of the parietal cell (320). Isolation of gastric vesicles from stimulated and resting gastric mucosae resulted in cell membrane fractions with profound differences in gastric microsome size, density, and K^+ transport activity (424, 425). Wolosin and Forte (424, 425) postulated that during stimulation there is a transformation from small microsomal vesicles to larger, denser structures that correspond to H^+-K^+-ATPase-rich apical membranes. These studies provided evidence for the theory of morphological transformation of gastric oxyntic cells during stimulation in which an expanded apical membrane is generated by fusion of tubulovesicular membranes (107, 403, 424, 425). Furthermore, they extended our understanding of the localization of the gastric H^+-K^+-ATPase providing important information for future studies targeted at inhibiting gastric acid secretion.

In 1986, Shull and Lingrel (359) were the first to deduce the primary amino acid sequence of the α-subunits of the gastric H^+-K^+-ATPase from the cDNA sequence of rat proton pump. This was soon followed by characterization of the sequence of H^+-K^+-ATPase α-subunits in hog (235), rabbit (23), dog (366), and human (236). The α-subunits of the H^+-K^+-ATPase contain the catalytic sites and are comprised of 1,033–1,034 amino acid sequences with significant homology between species (98%) (24, 235, 236, 359, 366). The H^+-K^+-ATPase α-subunit H^+-K^+-ATPase is also comprised of 8–10 transmembrane spanning segments (23, 25, 253, 262). Originally, only the α-subunit was identified; however, studies demonstrated the presence of a β-subunit in the Na^+-K^+-ATPase, indicating a high likelihood that the H^+-K^+-ATPase similarly had another subunit (235, 246, 358, 359). In 1990, several laboratories confirmed the presence of the β-subunit of the H^+-K^+-ATPase (61, 281, 312, 357, 384). The β-subunit contains 291 amino acids with 6 or 7 N-linked glycosylation sites (312, 355, 357, 384). The α- and β-subunits of the gastric H^+-K^+-ATPase are assembled in the endoplasmic reticulum (ER). Experimental results in *Xenopus* oocytes demonstrated that the proton pump is only properly trafficked and functionally active when the α-subunit is assembled with the β-subunit (19, 33, 34, 121). Expression of the α-subunit of the gastric H^+-K^+-ATPase alone leads to retention in the ER and degradation (34, 201). The β-subunit of the H^+-K^+-ATPase stabilizes the H^+-K^+-ATPase and is required for proper targeting of the enzyme from the ER to the Golgi and the apical membrane, as well as proper maturation of the α-subunit for proton pump function (5, 120, 168, 179). The assembled enzyme, consisting of an α/β-heterodimer, is sorted from the *trans*-Golgi network and trafficked to the plasma membrane as a heterodimeric oligomer (2, 147, 353, 354, 392, 396, 397). In both nonpolarized and polarized cells, sole expression of the β-subunit does not affect its ability to mature and traffic to the plasma membrane (132, 318, 393).

C. Functional Analysis

Parietal cells secrete acid through activation of the H^+-K^+-ATPase. This requires morphological changes in the cell to form the expanded canaliculi resulting from the fusion of tubulovesicles containing H^+-K^+-ATPase with the apical membrane and insertion of the pump into the canaliculi. Hydrolysis of ATP results in conformational changes in the gastric H^+-K^+-ATPase allowing for ion transport. Exchange of H^+ and K^+ results from conformational changes during the cycle of phosphorylation and dephosphorylation, which alters the orientation of the ion binding sites. The H^+-K^+-ATPase enzyme functions as an out of phase oligomeric heterodimer; therefore, if one heterodimer is in the E_1 form, the other is necessarily in the E_2 form (353) **(FIGURE 5)**. The E_1 conformation binds hydronium from the cytoplasmic side at high affinity (ion site in), while the E_2 form (ion site out) has low H^+ affinity and high affinity for K^+ in the lumen. In the E_1 conformation, a hydronium ion (H_3O^+) binds the cytoplasmic region of the H^+-K^+-ATPase enzyme. MgATP phosphorylates the catalytic subunit of the H^+-K^+-ATPase initiating a conformational change. The ion-binding site, which was previously oriented towards the cyto-
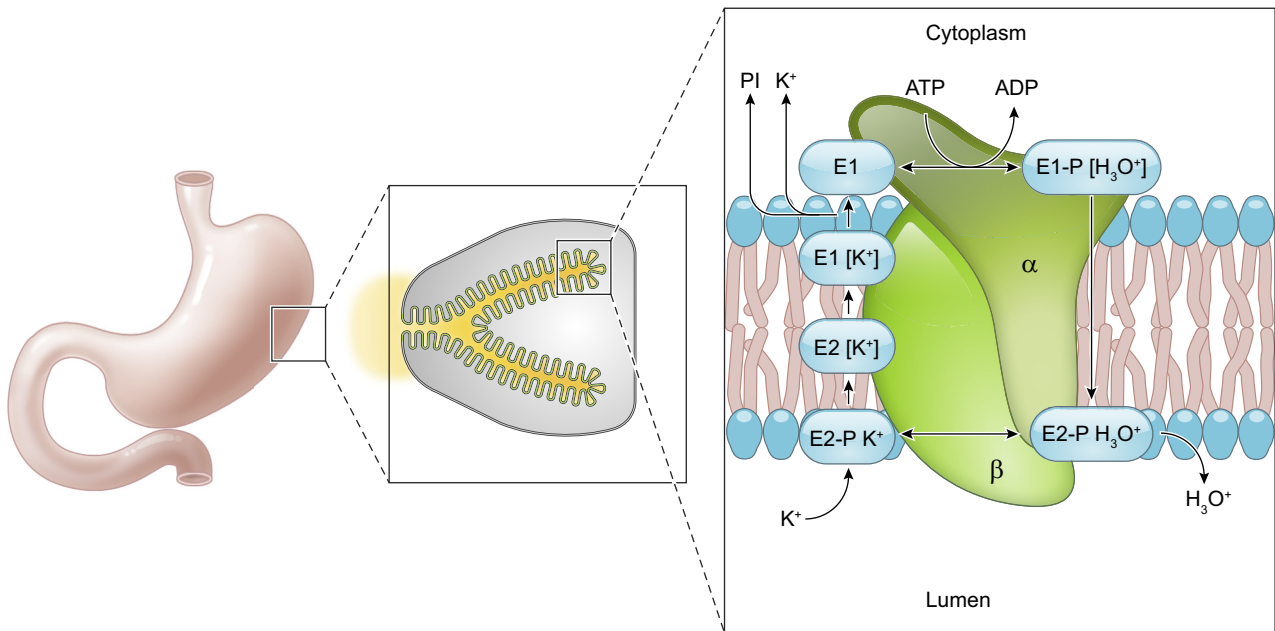
FIGURE 5. Conformational changes of the H^+-K^+-ATPase. Phosphorylation and dephosphorylation of the gastric H^+-K^+-ATPase results in conformational changes facilitating the transport of H_3O^+ out of parietal cells concurrently with influx of K^+. Initially, a hydronium ion binds the cytoplasmic surface of the H^+-K^+-ATPase and MgATP phosphorylates the protein to form the E_1 conformation. In the E_1 form, the ion-binding site faces the parietal cell cytoplasm. Next, the E_1 form undergoes a conformational change to the E_2 form where the ion binding site faces the gastric lumen. In this position the H_3O^+ is released into the gastric lumen. In this E_2 conformation, K^+ binds the ion site where H_3O^+ was previously bound. The enzyme is dephosphorylated, and a conformational change back to the E_1 form results in the ion binding site facing the parietal cell cytoplasm where K^+ is displaced by ATP binding (386, 387). Based on work on the Na^+-K^+-ATPase under physiological conditions, the E_2 to E_1 conformational transition of the unphosphorylated enzyme is postulated to be the rate-limiting step (232).

plasm, alters so that the hydronium ion is exposed to the extracytoplasmic region (the E_2P form). In the E_2P form, the H_3O^+ is released into the gastric lumen. Concomitantly, extracytoplasmic K^+ binds the ion-binding site leading to dephosphorylation of the catalytic subunit to form the E_2K conformation. The E_2K form is converted to E_1K with the potassium site now facing the cytoplasm. K^+ is released from the ion-binding site following MgATP binding (47, 307, 371, 409) **(FIGURE 5)**. The catalytic cycle of the H^+-K^+-ATPase allows for the pumping of hydronium ions out of parietal cells, while facilitating the uptake of K^+ ions.

D. Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are a class of compounds that inhibit gastric acid secretion through covalent binding of the H^+-K^+-ATPase. Timoprazole was the first PPI synthesized in 1975; however, omeprazole (Prilosec) was the first PPI used clinically in 1989. Generally, PPIs have a core structure that consists of substituted pyridylmethylsulfinyl benzimidazoles (101). The PPI timoprazole inhibited gastric acid secretion in vivo regardless of the stimulation pathway (dibutyryl cAMP, histamine, or ACh). However, timoprazole was ineffective in the absence of acid transport by

the H^+-K^+-ATPase, although it could inhibit acid secretion in the presence of acid transport. The findings from these early experiments demonstrated that the initial PPIs were acid activated, an important step in determining the interaction of PPIs with the H^+-K^+-ATPase (408). PPIs were an improvement over H_2-receptor antagonists, since the irreversible covalent binding of the H^+-K^+-ATPase pump results in a longer half-life of inhibition of gastric acid than for H_2 receptor blockers (101, 323, 352, 356). PPIs accumulate in the secretory canaliculus of parietal cells after pyridine protonation. After a second protonation on the surface of the H^+-K^+-ATPase, PPIs are activated and form disulfide bonds with one or more accessible cysteines (351). All PPIs react with cysteine 813 on the α-subunit of the gastric H^+-K^+-ATPase. The reaction of PPIs with cysteine 813 arrests the H^+-K^+-ATPase enzyme in the E_2 configuration. Different PPIs bind additional sites on the extracytoplasmic surface of the gastric H^+-K^+-ATPase α-subunit such as cysteine 892 for omeprazole and cysteine 822 for pantoprazole (42, 322, 350). The luminal exposure of cysteine 813 and 892 of the H^+-K^+-ATPase likely contributes to the reversibility of omeprazole (212). However, the covalent binding of PPIs with cysteine 822 located in the transport domain of the pump near ion binding sites results in inaccessibility to

reducing agents due to the intramembranous location resulting in irreversibility of certain PPIs (42, 322, 350, 356, 394).

PPIs are weak bases. The weak base pK_a of PPIs facilitates accumulation in the high acidity space in the secretory canaliculi of stimulated parietal cells or on the external surface of the H^+-K^+-ATPase pump. This attribute of PPIs is one of the reasons that they are so effective. The concentration of PPIs in the secretory canaliculus, where binding to the H^+-K^+-ATPase occurs, far exceeds the amount present in the blood (356). The initial protonation of pyridines in PPIs is followed by protonation of the benzimidazole moiety. This requirement for a second protonation of PPIs increases their therapeutic value because it allows for the conversion of the pro-drug to the active form in close proximity to the H^+-K^+-ATPase instead of in the lumen of the stomach. The protonation that regulates activation of PPIs results in irreversible binding of PPIs to accessible cysteines of the H^+-K^+-ATPase through disulfide bonds.

E. Potassium Competitive Acid Blockers

While the advent of PPIs was a significant advancement over the use of H_2 receptor blockers, PPIs fail to meet the needs of several acid-related disorders including nonerosive reflux disease, severe erosive esophagitis, extra-esophageal reflux disease, NSAID ulcer, and nonvariceal upper gastrointestinal bleeding (87, 171, 196, 252, 389). Potassium competitive acid blockers (P-CAB) or acid pump antagonists (APAs) represent another type of proton pump inhibitor that may prove a more effective therapeutic for certain gastric acid-related disorders. This class of acid blockers results in a fast, effective, and reversible inhibition of gastric acid secretion (334, 398). P-CABs inhibit acid secretion by binding ionically to the H^+-K^+-ATPase following protonation. The large size of P-CABs likely prevents the access of K^+ cations to their binding site, thus blocking activation of the H^+-K^+-ATPase by K^+ (20, 21, 119, 392, 394, 395). Similar to other PPIs, P-CABs concentrate in the parietal cell canaliculi (119, 150). The accumulation of P-CABs in this highly acidic environment results in instantaneous protonation which facilitates ionic binding to the gastric H^+-K^+-ATPase and inhibition of acid secretion (20, 21, 119, 392, 394, 395). Administration of P-CABs results in a more rapid increase in intragastric pH and inhibits gastric acid secretion to a similar degree as PPIs (119, 441). However, unlike PPIs, P-CAB duration of inhibition of acid secretion is dependent on the level in the blood due to the reversible K^+ competitive nature of P-CABs. While PPIs take repeat doses to reach full effect, P-CABs are fully effective after the first dose (16, 58, 167, 180, 184, 437). Thus P-CABs may represent another generation of gastric acid blockers to add to the compendium of therapeutic PPIs (12).

V. PARIETAL CELL LUMINAL POTASSIUM CHANNELS

Gastric acid secretion is dependent on K^+. Lee et al. (223) were the first to develop an in vivo model that provided evidence for the dependence of acid secretion on the secretion of K^+ into the gastric lumen. KCNQ1 knockout mice exhibit gastric mucosa hyperplasia, hypochlorhydria, and elevated levels of gastrin compared with controls. Moreover, KCNQ1 knockout mice harbored nonfunctional parietal cells, indicating that KCNQ1 was likely required for acid secretion. It was speculated that KCNQ1 maintains low levels of intracellular K^+ through a K^+ efflux channel to allow for exchange of H^+ and K^+ and thus acid secretion (223). Consistent with these findings, inhibition of the KCNQ1 channel in isolated rabbit gastric glands blocked acid secretion to a similar degree as histamine receptor antagonists and H^+-K^+-ATPase inhibitors (213). Thus KCNQ1 likely plays a critical role for K^+ efflux during gastric acid secretion. Functionally, KCNQ1 and its regulatory subunit KCNE2 are proposed to form a luminal K^+ channel (85, 134, 159). The interaction of KCNE2 with KCNQ1 results in a drastic change of KCNQ1 gating properties and current amplitude (383). KCNQ1 and KCNE2 are both highly expressed in parietal cells on the luminal membrane (85, 213). KCNQ1/KCNE2 K^+ channels are stimulated by cAMP, and low extracellular pH was found to increase KCNQ1/KCNE2 current (158, 159). The KCNQ1/KCNE2 channel complex allows for the transformation of the voltage-dependent KCNQ1 current to a voltage-independent current (383). Without its regulatory subunit KCNE2, KCNQ1 is inhibited by a low extracellular pH (109, 159, 293). However, when KCNQ1 is in complex with KCNE2, K^+ conductance increases in an acidic environment (109, 134, 159, 293). The importance of KCNE2 in acid secretion was demonstrated using KCNE2-deficient animals. Similar to KCNQ1 knockout mice, KCNE2 knockout mice showed dramatically decreased parietal cell proton secretion, altered parietal cell morphology, hyperplasia, and hypergastrinemia (316).

The exact localization of KCNE2/KCNQ1 remains controversial. Human KCNE2 and KCNQ1 are recovered on anti-H^+-K^+-ATPase-immunoisolated tubulovesicles (217). In contrast, Nguyen et al. (271) described the distinct localization of KCNQ1 in separate membrane compartments from H^+-K^+-ATPase in unstimulated parietal cells in wild-type mice and mice lacking the tubulovesicular membrane compartment in parietal cells (Atp4b-Y20A). In Atp4b-Y20A mice, the H^+-K^+-ATPase is anchored in the secretory canaliculi, and thus there are no H^+-K^+-ATPase-rich tubulovesicles in these mice. The Atp4b-20A mice demonstrated that the presence of H^+-K^+-ATPase at the secretory canaliculi is not sufficient to regulate acid secretion. Inhibition of KCNQ1 decreased acid secretion in wild-type as well as Atp4b-Y20A mice. These data suggested that trafficking of KCNQ1 to parietal cell canaliculi following stim-

ulation might independently regulate gastric acid secretion. All of these studies and others provide convincing evidence that KCNQ1/KCNE2 form a luminal K^+ channel that provides the extracellular K^+ necessary for proper acid secretion (286, 368).

However, there are data to support a role for another K^+ channel, the Kir family of inwardly rectifying K^+ channels, in the regulation of gastric acid secretion and secretory membrane recycling. Fujita et al. (111) demonstrated that the Kir4.1, an inwardly rectifying K^+ channel, was expressed on the apical membrane of parietal cells in rat gastric mucosa, suggesting a potential role for Kir4.1 in K^+ recycling for proper H^+-K^+-ATPase activity. Other reports confirmed Fujita's findings and demonstrated expression of Kir2.1 in parietal cells as well (197, 213, 240). Kir4.1 was also demonstrated to coprecipitate with H^+-K^+-ATPase from immunopurified tubulovesicles and stimulated secretory membranes (197). Work in Kir4.1-deficient mice demonstrated augmented acid secretion and suggested a role for Kir4.1 in secretory membrane recycling (367). Song et al. (367) suggested a role for parietal cell Kir4.1 channels in balancing rapid K^+ loss via KCNQ1 and K^+ absorption through the slower H^+-K^+-ATPase. Debate still exists as to the degree to which each individual K^+ channel, KCNQ1/KCNE2 and Kir4.1, is responsible for apical K^+ transport, but it appears clear that without functioning of either channel there is a reduction in gastric acid secretion (104, 160). Thus both channels likely play a role in the regulation of gastric acid secretion through distinct mechanisms.

VI. PARIETAL CELL MORPHOLOGICAL TRANSITION: THE MODEL FOR PLASMA MEMBRANE RECYCLING

The unusual cell morphology in the parietal cell was originally documented by Camillo Golgi, who found unusual wandering intracellular membranes, later designated as Muller-Golgi tubules, in silver stains of stomach mucosa (251). Electron microscopy documented the presence of an intracellular canaliculus in parietal cells that ramified within the parietal cell cytoplasm, but was contiguous with the lumen (45, 107). The parietal cell cytoplasm was also noted to have numerous tubulovesicular elements often in apposition to canalicular membranes. More impressive in electron microscopy studies was the morphological transformation that parietal cells underwent following stimulation, with marked expansion and dilation of the secretory canaliculi and the elongation of microvillar-like structures within canaliculi (44, 45, 106). Following acid secretory stimulation, in concert with the expansion of the canalicular network, there was a marked loss of tubulovesicular membranes within activated parietal cells. This morphological alteration is one of the largest reversible membrane alterations in mammalian cells.

The basis for the morphological transformation of parietal cells was contentious for a number of years. Some groups had suggested that the tubulovesicular network in parietal cells was connected to the intracellular canaliculus and that stimulation led to expansion of these elements through activation of the proton pump. In 1977, Forte et al. (105) first suggested a membrane recycling hypothesis to explain the morphological transitions in parietal cells **(FIGURE 6)**. This hypothesis proposed that, in the resting parietal cell, tubulovesicles and the secretory canaliculus were distinct compartments. Forte et al. proposed that stimulation with histamine caused fusion of tubulovesicles with the canaliculus leading to the formation of elongated microvilli-like structures. Upon cessation of the stimulation, tubulovesicular membranes would be retrieved by endocytosis. This hypothesis was the first to suggest the existence of membrane recycling as a physiological process in cells. Rabbit gastric tubulovesicles could be isolated to high purity from resting gastric mucosa and were highly enriched for the α- and β-subunits of the H^+-K^+-ATPase, now designated as ATP4a and ATP4b, respectively (165, 222). One could also prepare rather enriched populations of stimulus-associated (SA) vesicles from stimulated parietal cells that contained the subunits of the H^+-K^+-ATPase along with putative canalicular F-actin (165). Further studies identified canalicular association of the F-actin binding phosphoprotein ezrin (152, 436), which was also enriched in SA vesicles. These latter studies suggested that ezrin defined the canalicular membranes, distinct from tubulovesicles.

The controversy over the role of tubulovesicle fusion in parietal cell morphological transformation was resolved with the identification of vesicle trafficking proteins associated with the canalicular membrane. First, early studies demonstrated the association of Rab small GTPases with rabbit parietal cell tubulovesicle membranes (28, 380). Then application of 3′-rapid amplification of cDNA ends (RACE) to parietal cells revealed a number of unrecognized Rab proteins including Rab11a, Rab25, and Rab14 (126). In particular, further studies on Rab11a revealed that it was highly enriched in parietal cells, and colocalized on tubulovesicles with H^+-K^+-ATPase (59, 127). Rab11a redistributed to the apical canaliculus in concert with the H^+-K^+-ATPase during stimulation (60). Immunoisolation of rabbit tubulovesicles with antibodies against the H^+-K^+-ATPase led to further insights into the association of trafficking proteins, first with the identification of SCAMPs as well as the vesicle SNARE protein VAMP-2 and target SNARE protein syntaxin3 on tubulovesicles and the observation of syntaxin1A on the membranes of the secretory canaliculus (54, 59, 60, 292). Immunoisolation of human tubulovesicles with H^+-K^+-ATPase antibodies confirmed these findings in rabbit membranes and also identified the presence of other vesicle trafficking proteins including VAMP8 and syntaxin7 in association with the proton-pump rich membranes (217). Together, these studies suggested that
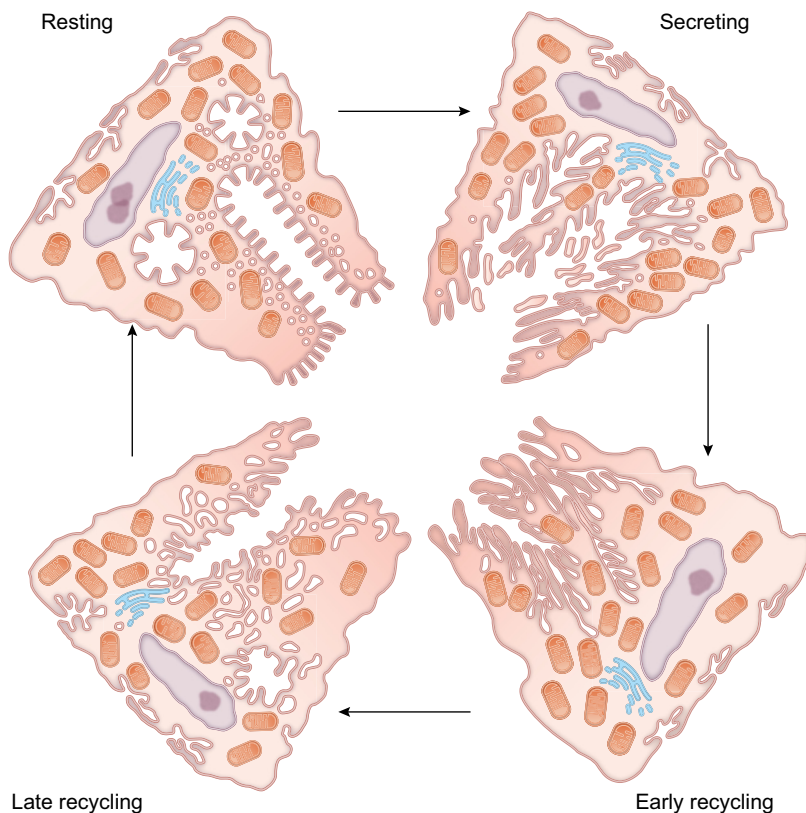
FIGURE 6. Morphological changes in parietal cells that accompany gastric acid secretion. This graphic derived from the hand-drawn figure from John Forte depicts the morphological stages in the course of parietal cell stimulation (105). In the resting state, parietal cells contain many mitochondria, numerous membrane tubulovesicles, and collapsed intracellular canaliculi. Upon stimulation, exocytosis results in fusion of the H^+-K^+-ATPase rich tubulovesicles with the intracellular canaliculus, resulting in an expanded secretory canalicular membrane and the elongation of apical microvilli-like structures. Following stimulation, endocytosis occurs to retrieve the H^+-K^+-ATPase and recycle the membrane to tubulovesicles in the resting state and to prepare for the next stimulus and return.

the tubulovesicular membranes and the secretory canaliculus did indeed represent the model system for large-scale regulated membrane recycling as proposed by Forte et al. Indeed, expression of a dominant negative Rab11a [Rab11a(N141I)] in parietal cells led to inhibition of acid secretion (91). In followup studies, alterations in VAMP2 and syntaxin3 also inhibited the process of H^+-K^+-ATPase translocation to the canalicular membranes (191, 229). It is also possible that other Rab proteins, in addition to Rab11a, are involved in H^+-K^+-ATPase recycling. For example, expression of dominant-negative Rab27b(N133I) can also inhibit parietal cell activation (372).

The recognition of Rab11a and v-SNAREs and t-SNAREs in association with the parietal cell secretory apparatus all supported the paradigm of regulated apical recycling in gastric parietal cells. Indeed, investigations utilizing parietal cell yeast-two hybrid libraries led to the identification of two critical families of Rab11-interacting proteins, the myosin V motors (MYO5A and MYO5B) as well as the Rab11-family interacting protein (Rab11-FIP) family (146, 218). Both Rab11-FIPs and MYO5B are highly expressed in parietal cells, but they were subsequently confirmed as critical regulators of apical recycling in polarized epithelial cells and generalized plasma membrane recycling in nonpolarized cells (22, 62, 146, 218). These findings therefore support the status of the parietal cell as the largest manifestation of apical plasma membrane recycling.

VII. PHYSIOLOGICAL ROLE OF PARIETAL CELLS IN GASTRIC MUCOSAL HOMEOSTASIS

Detailed investigations by Karam and Leblond (187–190) determined the patterns of cell differentiation from isthmal progenitor cells, with short-lived surface mucous cells differentiating towards the lumen and longer-lived parietal cells and mucous neck cells migrating towards the base. Mucous neck cells further redifferentiate into zymogen-secreting chief cells as they reach the gland base (190). While traditionally the focus on parietal cells has related to acid secretion, work over the past decade has brought increased recognition of the function of parietal cells in general mucosal homeostasis. Loss of parietal cells, or oxyntic atrophy, is the pathological finding most associated with gastric cancer (97). Multiple studies have now connected the loss of parietal cells with the development of metaplasia in the corpus mucosa. In part, based on this association, a number of investigators have evaluated roles for parietal cells other than acid secretion.

Loss of parietal cells occurs during infection of the stomach with *Helicobacter* species. The cause of parietal cell loss in the face of *Helicobacter* infection remains unclear. Loss of parietal cells can be replicated in rodent models with chronic infection with either *Helicobacter pylori* or *Helicobacter felis* (108, 291, 349, 413, 414). The loss of parietal cells appears to require the action of T cells, since T cell-

deficient mice do not display oxyntic atrophy in response to *Helicobacter felis* infection (317). More recent studies have suggested that cytokines individually or together may lead to parietal cell death (57, 169). IL-17A induces loss of parietal cells in mouse models (48).

Experimental loss of parietal cells can be induced acutely with parietal cell-toxic drugs (124, 170, 265, 275). In these acute models, the loss of parietal cells is associated with prominent changes in gastric mucosal lineages. Foveolar hyperplasia (the expansion of surface mucous cells) develops rapidly after parietal cell loss, driven to a great extent by elevations in gastrin (275, 291). At the same time, spasmolytic polypeptide-expressing metaplasia (SPEM) develops through transdifferentiation of chief cells into mucous cell metaplasia (170, 265). The exact signals that coordinate these lineage changes remain unclear, and a recent publication indicates that parietal cell loss alone is not sufficient to induce SPEM (55). Interactions of parietal cells with intrinsic immune cells may lead to release of intermediate cytokine regulators (157, 294, 295) that are also required for induction of SPEM.

A. EGF Receptor Ligands

As noted above, EGF receptor ligands, including EGF and TGF-α, are inhibitors of acid secretion (225, 226). Other studies suggested that parietal cells were actually the major source of TGF-α in the gastric mucosa (30). In addition, other studies have demonstrated that parietal cells are also a source for amphiregulin (3) and HB-EGF (263), both potent ligands for the EGF receptor. These findings suggested that EGF receptor ligands were released from parietal cells in part as autocrine inhibitors of gastric acid secretion. Nevertheless, other investigations demonstrated that TGF-α could promote the expansion of surface cell lineages at the expense of glandular lineages such as parietal cells. The greatest impact of these growth factors on lineage derivation is observed in patients with Ménétrier's disease, who show marked overproduction of TGF-α in the gastric mucosa, resulting in massive foveolar hyperplasia as well as loss of parietal cells and other glandular cells (86). Similar results have been reported in metallothionein (MT)-TGF-α transgenic mice following administration of oral zinc to induce TGF-α overexpression (49, 86, 125, 274). More recent investigations have suggested that expression of active Kras in isthmal progenitor cells also induces expansion of foveolar cells at the expense of glandular (parietal cell and chief cell) lineage differentiation (75, 249).

B. Sonic Hedgehog

Members of the sonic hedgehog (Shh) family regulate lineage development in many organs (234). Treatment of isolated dog parietal cells with EGF led to upregulated expression of Shh in parietal cells, and Shh promoted histamine-stimulated acid secretion (369). Later studies suggested that Shh was released from parietal cells in concert with the fusion of tubulovesicles with the apical canaliculus (444), and Shh is processed into an active form by pepsinogen (445). Shh release has been implicated in regulation of stomach cell lineages through feedback regulation of acid sensing (256). Loss of expression of Shh in gastric parietal cells leads to elevations of gastrin and foveolar hyperplasia (432). Similarly, inhibition of acid secretion by proton pump inhibitors or IL-1β decreases the expression of Shh (250, 405) and can be associated with oxyntic atrophy associated with *H. pylori* infection (344). Indeed, Shh appears to play a critical role in regulating mucosal homeostasis in the stomach (88), although the context of these effects appears variable. In mice with deletion of Shh in parietal cells, *H. pylori* infection does not lead to oxyntic atrophy and gastritis (344). Nevertheless, loss of Shh in parietal cells inhibits the resolution of acute acetic acid ulcers in the stomach (431). Overall, expression of Shh and perhaps other hedgehog family members appears critical for mucosal restitution and mucosal protection.

VIII. REMAINING QUESTIONS FOR ACID SECRETORY PHYSIOLOGY

Despite a number of prominent investigations during the past 30 yr, the exact cellular mechanisms that trigger second messenger-regulated acid secretion remain unknown. Although phosphoproteins associated with histamine and cholinergic stimulation have been identified (70, 72–74, 153, 259, 279, 287, 288, 390, 391, 416), the connection of these phosphorylation events to the induction of tubulovesicle fusion with the secretory canaliculus remains solely correlative. Thus alterations in the expression of ezrin or Lasp-1, the LIM and SH3 domain protein, can affect the fusion of tubulovesicles with the canaliculus in parietal cells, but the mechanisms of how these proteins act at a molecular level to promote regulated membrane fusion remain undetermined. No mouse models targeting phosphorylation sites have been characterized, so functional data remain sparse. Of interest, a recent study has demonstrated that a calcium channel resident in tubulovesicles, TRPML1 (ML1), is involved in cAMP-dependent stimulation of tubulovesicle fusion with the canaliculus (325). This finding suggests that discrete targets mediating the process of membrane fusion remain to be definitively identified.

Another question relates to the sensing of luminal pH in the stomach and how this regulates acid secretion. It has previously been assumed that G cells in the antrum or even ECL cells throughout the corpus might be able to sense the gastric lumen and respond to changes in acidity. Thus loss of acid secretion, which leads to increases in gastrin levels, would be triggered through G cells sensing of the lumen pH. Nevertheless, recent identification of classes of tuft cells,

which present a highly specialized sensory apparatus towards the lumen (172, 330), has raised questions of whether tuft cells are a major sensor of luminal contents, including acid. Tuft cells are normally associated with the neck region of the corpus gastric glands and near the progenitor zone in the antrum (329). Importantly, following loss of parietal cells in gastritis models of mice, there is an increase in the number of tuft cells in the gastric mucosa (76, 266, 329). This increase in tuft cell numbers appears to be dependent on gastrin levels (76). Tuft cells can have direct connections with sensory nerves in multiple organs (332, 333), although these direct connections have not been validated in the stomach. Such intrinsic nerve connections could be involved in regulation of gastrin and histamine release from enteroendocrine cells. Tuft cells are known to release IL-25, which may stimulate the release of IL-13 and amphiregulin from intrinsic mucosal immune ILC2 cells (404). IL-13 and amphiregulin may have prominent effects on both lineage derivation and acid secretion in the gastric mucosa (294). Further studies are required to define the role of tuft cell chemosensing to acid secretory physiology.

Finally, the full compendium of growth factors that can be released from parietal cells remains unclear. Because of the long-lived status of parietal cells, it seems likely that this lineage is well placed to perform broad duties in the coordination of lineage maturation in the corpus of the stomach.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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