Anatomy and Physiology of the Stomach and Pylorus

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Anatomy of the Stomach

The stomach is an organ of digestion situated in the abdomen between the termination of the esophagus and the beginning of the duodenum. The stomach develops from the caudal portion of the embryonic foregut during the 5th week of gestation, as a primitive structure located within the ventral and dorsal mesenteries [1]. Due to the rotation of the gut, the left vagal trunk ends up in an anterior location, and the right vagal trunk ends up in a posterior location. Due to the movement of the foregut toward the embryo's left side, the stomach ends up occupying most of the left upper quadrant of the abdomen.

In the adult, the stomach rests between the 10th thoracic and the 3rd lumbar vertebral segments, and it is suspended and fixed by four ligaments despite its intraperitoneal location: (1) gastrosplenic or gastrolienal (from the stomach to the spleen), (2) gastrophrenic (from the stomach to the diaphragm), (3) hepatogastric or lesser omentum (from the stomach to the liver), and (4) gastrocolic or greater omentum (from the stomach to the transverse colon). The borders of the stomach are (1) the liver (superiorly and laterally to the right), (2) the spleen (laterally to the left), (3) the pancreas (posteriorly), and (4) the transverse colon inferiorly.

The stomach is divided into four segments that are important guides when planning a surgical resection: (1) the *cardia*, (2) the *fundus*, (3) the *corpus* or *body*, and (4) the *antrum* (Fig. 3.1). The *cardia* is the most proximal part of the stomach located immediately after the gastroesophageal junction. The *fundus* is the region of

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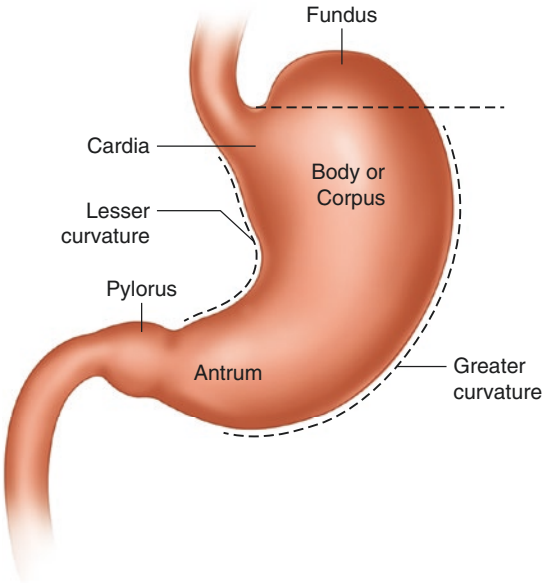

Fig. 3.1 Stomach segmental division

the stomach that extends above the gastroesophageal junction. The *corpus* or *body* lies between the fundus and the antrum and is marked distally by the *angularis incisura*, a notch on the lesser curvature of the stomach located near to the pyloric end. The last segment is the *antrum*, which extends from the corpus or body to the pyloric sphincter, a thick muscular valve that separates the antrum from the duodenum [1]. Each of these segments has histologic differences and is involved in unique roles in the process of digestion [2].

The stomach has four layers from the outermost to the innermost: (1) the *peritoneum* or *serosa*; (2) the *muscularis propria*, also known as *muscularis externa* that is composed of three layers of muscles (longitudinal, circular, and oblique) (Fig. 3.2), which contains the myenteric plexus of Auerbach; (3) *the submucosa*, which represents the strongest layer of the stomach; and (4) the *mucosa*, which is subdivided into muscularis mucosae, lamina propria, and surface epithelium.

Arterial Blood Supply and Venous Drainage of the Stomach

Five major sources contribute to the rich vascular supply of the stomach, all of which arise from the celiac trunk forming multiple anastomoses that protect the stomach from ischemic events. In a clockwise matter, the *left gastric artery* (a direct branch from the celiac trunk) supplies the upper portion of the lesser curvature of the stomach; the *vasa brevia* or *short gastric arteries* (direct branches from the splenic artery) supply the fundus and upper portion of the corpus; the

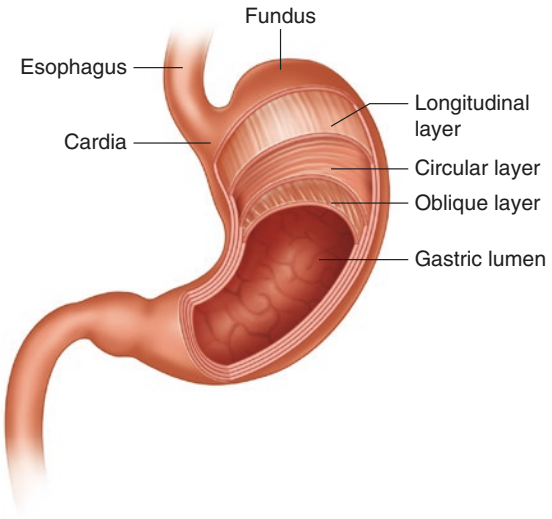

Fig. 3.2 Outermost to the innermost muscular layer division of the stomach

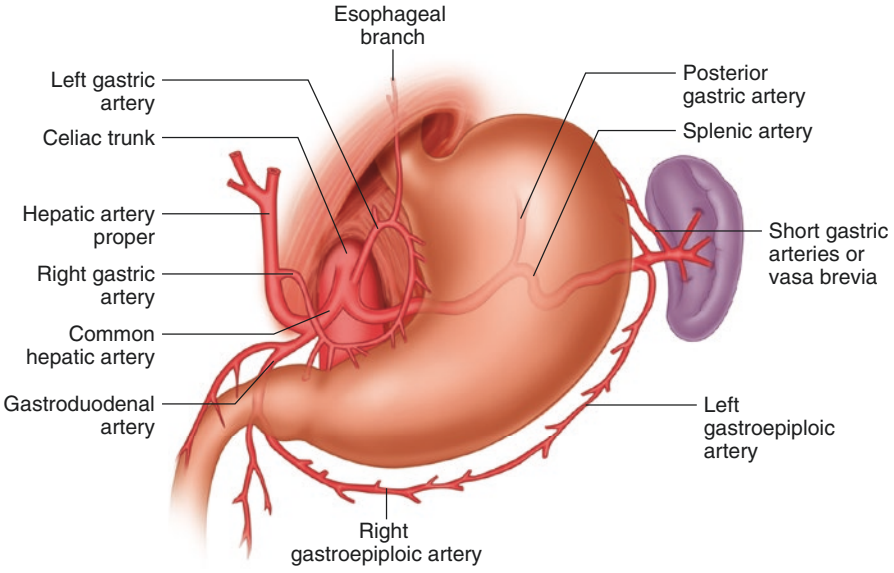

Fig. 3.3 Arterial blood supply to the stomach

left gastroepiploic artery (branch from the splenic artery) supplies the upper corpus; *the right gastroepiploic artery* (branch from the gastroduodenal) supplies the lower corpus and the antrum; and the *right gastric artery* (branch from the common hepatic artery) supplies the lower portion of the lesser curvature (Fig. 3.3) [2].

The venous drainage of the stomach parallels the arterial blood supply. The short gastric veins and left gastroepiploic, via the splenic vein, drain to the portal vein. The right gastroepiploic, via the superior mesenteric vein, drains to the portal vein. Lastly, both right and left gastric (coronary vein) veins drain directly to the portal system [1]. The vein drainage of the stomach is important to understand the pathophysiology of portal hypertension and its complications [3].

Innervation

The stomach has both parasympathetic and sympathetic innervation. Sympathetic nerves are in charge of transmitting pain via the greater splanchnic nerve and celiac plexus. Parasympathetic innervation is characterized by afferent signals of the two anterior and posterior vagal trunks that descend laterally through the esophageal hiatus of the diaphragm, adherent to the muscularis of the esophagus. The right vagal trunk runs posteriorly between the aorta and the esophagus, gives off a celiac branch, and continues its way through the lesser curvature of the stomach (*posterior nerve of Latarjet*), innervating the posterior wall of the stomach. Near the gastroesophageal junction, there is a branch known as the *criminal nerve of Grassi*. Its identification during a truncal vagotomy is very important, as it is thought to be related to recurrent symptoms (Fig. 3.4) [2]. The left vagal trunk runs anteriorly through the esophagus, gives off a hepatic branch, and continues its way throughout the anterior lesser curvature of the stomach (*anterior nerve of Latarjet*), innervating the anterior wall of the stomach and pylorus.

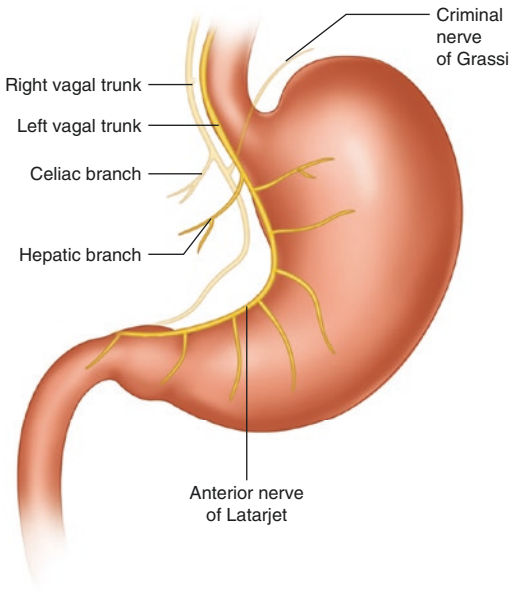

Fig. 3.4 Vagal innervation of the stomach

Lymphatic Drainage

The lymphatic drainage of the stomach also runs near the arterial blood supply. The anatomical importance of lymphatic drainage and the location of the gastric lymph nodes (LNs) relies on its relationship with gastric cancer and gastric metastasis [4]. The anatomical description of lymph node stations has been defined by the Japanese Gastric Cancer Association [5]. The lymph node stations in closer proximity to the stomach that correspond to N1 and N2 lymph node metastasis of the TNM classification include (1) right paracardial LNs, (2) left paracardial LNs, (3) lesser curvature LNs, (4) left and right greater curvature LNs, (5) suprapyoric LNs, and (6) infrapyloric LNs (Fig. 3.5). However, due to the extensive lymphatic communications, metastatic disease can bypass primary lymph node groups [5].

Gastric Physiology

The main function of the stomach is to prepare the ingested food for digestion and absorption. The solid food components need to be broken down to its basic metabolic components in order be absorbed. Thus, the stomach serves as a storage organ to enable this process that takes approximately 3–4 h (transit time). This process

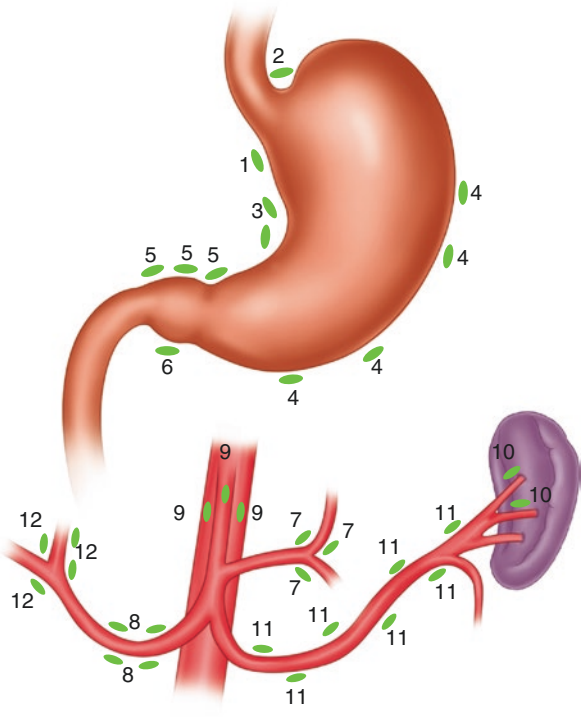

Fig. 3.5 *Lymphatic node stations of the stomach according to the Japanese Gastric Cancer Association 2011. 1 = right paracardial lymph nodes; 2 = left paracardial lymph nodes; 3 = lesser curvature lymph nodes; 4 = greater curvature lymph nodes; 5 = suprapyloric lymph nodes; 6 = infrapyloric lymph nodes; 7 = lymph nodes along the trunk of the left gastric artery; 8 = lymph nodes along the common hepatic artery; 9 = celiac artery lymph nodes; 10 = splenic hilar lymph nodes; 11 = distal splenic artery lymph nodes; 12 = hepatoduodenal ligament lymph nodes*

also involves the release of hydrochloric acid and other peptides from the gastric glands that mixed with the food content (*chyme)* passes from the stomach to the first portion of the small intestine, through the pyloric sphincter to be absorbed.

The stomach contains a glandular epithelium divided into two functional areas: the oxyntic area that corresponds to 80% of the stomach and the pyloric area. The oxyntic area is located in the fundus and corpus (Fig. 3.1). This area is characterized by gastric glands (the acid-secreting unit of the mucosa) (Fig. 3.6) that contain (1) mucus neck cells; (2) parietal cells, in charge of the production and secretion of hydrochloric acid and intrinsic factor; (3) chief cells, in charge of the production of pepsinogen; and (4) enterochromaffin-like cells (ECL cells) that express the enzyme in charge of the production of histamine (histidine decarboxylase). The pyloric area is located in the antrum of the stomach and is mainly composed of G cells that secrete gastrin. Somatostatin releasing cells (D cells) are present in both oxyntic and pyloric glands, and its function is to inhibit gastrin and acid release. Endoscopically, the acid-secreting cells area and the non-acid-secreting cells area are relatively distinguished by the rugal pattern. In the antrum, the rugae are linear and aligned with the long axis of the stomach. In the corpus, the rugae are oriented obliquely and have a convoluted pattern [2].

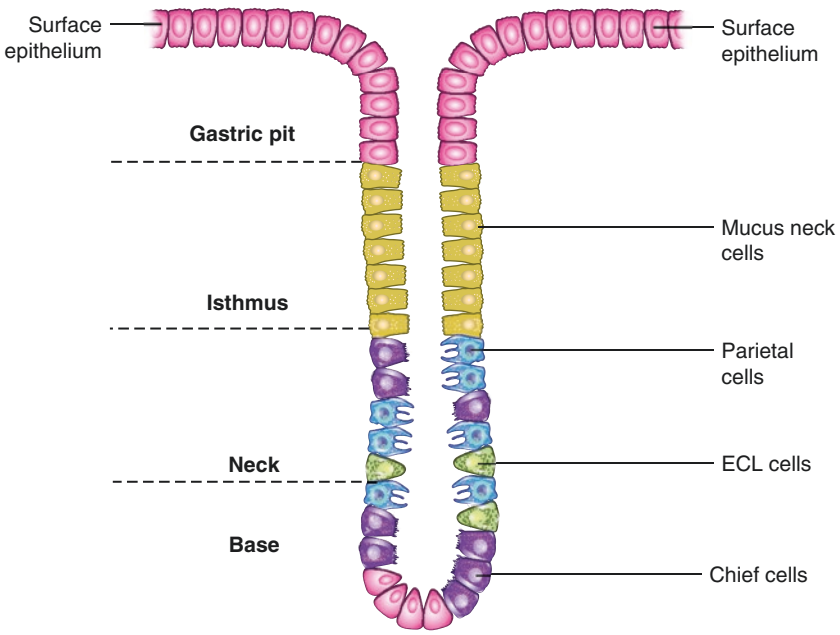

Fig. 3.6 Gastric gland. *ECL enterochromaffin-like cells*

Gastric Acid Secretion

Gastric acid secretion is divided into three phases. First, a *cephalic phase* that originates through sight of food, smell, thought, taste, or swallowing, which accounts for 20–30% of the total acid secretion. This phase is mainly mediated by cholinergic mechanisms. Second, a *gastric phase* stimulated by gastric distention and chemical effects of food in the gastric lumen, which accounts for 60–70% of the total acid secretion. This phase appears to be mainly mediated by gastrin. Finally, a primarily inhibitory *intestinal phase* that is thought to start with the entry of chyme into the first portion of the intestine. However, its mediation is still controversial, and it only accounts for 10% of the total acid secretion [6, 7].

Gastric acid physiologic secretion regulation consists of three stimulating pathways, two inhibitory pathways, and other regulators (Fig. 3.7). The three stimulating pathways in charge of acid secretion in the stomach include (1) acetylcholine, released by cholinergic cells from the vagal trunks; (2) histamine, released by ECL cells; and (3) gastrin, released by G cells [8, 9]. The two inhibitory pathways include extrinsic signals: (1) somatostatin, released by D cells and (2) prostaglandins (E and I) [10]. There have been proposed other types of intrinsic cell signals like the

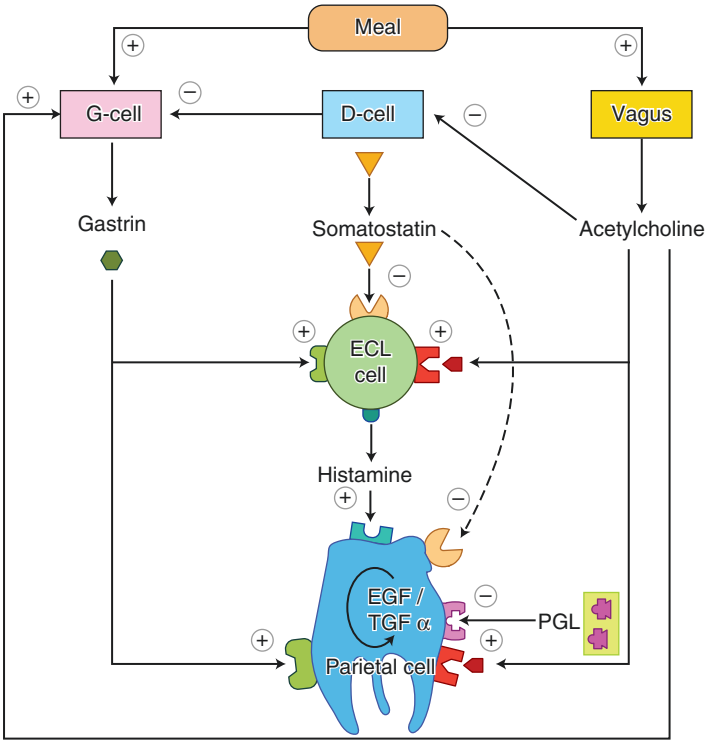

Fig. 3.7 Physiology control of acid secretion. *PGL prostaglandins, EGF epidermal growth factor, TGFα transforming growth factor alpha*

epidermal growth factor and the transforming growth factor alpha (EGF/TGFα) that may play an important role in acid secretion by modulating intracellular tyrosine kinase activity [11].

The stomach has a basal acid secretion level of 1–5 mmol/h of HCL and a total of 1–2 L of HCL acid secretion every 24 hours that maintain a luminal concentration of 150–160 mmol/L. The basal acid secretion can be decreased with medical (H2 blockers) or surgical (vagotomy) interventions. Thus, this basal acid secretion is thought to be stimulated by cholinergic as well as histaminergic output [1].

Intracellular Signals for Acid Secretion

Gastrin, histamine, and acetylcholine stimulate the parietal cell through intracellular pathways that involve second messengers (Fig. 3.8) (1). Gastrin binds to the CCK-2 receptors located in the parietal cell membrane. This process activates phospholipase C that activates phosphatidylinositol triphosphate through phosphorylation, which increases cytosolic calcium release, that act on calmodulin kinases that ultimately stimulate the hydrogen potassium ATPase pump (H+/K+ ATPase pump) (2). Histamine binds to the H2 receptors that activates adenylate cyclase, increasing cAMP, which activates protein kinase A that ultimately stimulates the H+/K+ ATPase pump (3). Acetylcholine binds to type 3 muscarinic receptors (M3) that also act through the activation of the phospholipase C pathway mentioned above (4). Somatostatin represents the main inhibitor of acid secretion. Its major role has been the indirect inhibition of histamine release through SSTR2 receptors in the ECL cells. However, this hormone may also bind to SSTR2 receptors located in the parietal cell membrane [12].

Potassium plays a critical and essential role in the activation of the H+/K+ ATPase pump (Fig. 3.9). During the resting state, the parietal cell stores the H+/K+ ATPase pump within tubulovesicular intracellular elements that have a low K+ concentration and an impermeable membrane to K+ ions. After parietal cell stimulation, cellular relocation of the H+/K+ ATPase pump to the apical membrane occurs through cytoskeletal mobilization. This process leads to the exposure of the H+/K+ ATPase pump to K+ ions, which starts exchanging H+ ions. The process is in charge of ion transport to maintain electroneutrality within the membranes. For each H+ ion transported into the canaliculus by the H+/K+ ATPase pump, the basolateral CL-/HC03- exchanger delivers a HCO3- out the parietal cell and a Cl- into the cell. Moreover, in the apical membrane, Cl- is secreted into the canaliculus through Cl- channels (C1C-2 channel). In order to maintain electroneutrality, the Cl- excreted accounts as a counter for the K+ flux across the membrane. The Na+/K+ ATPase

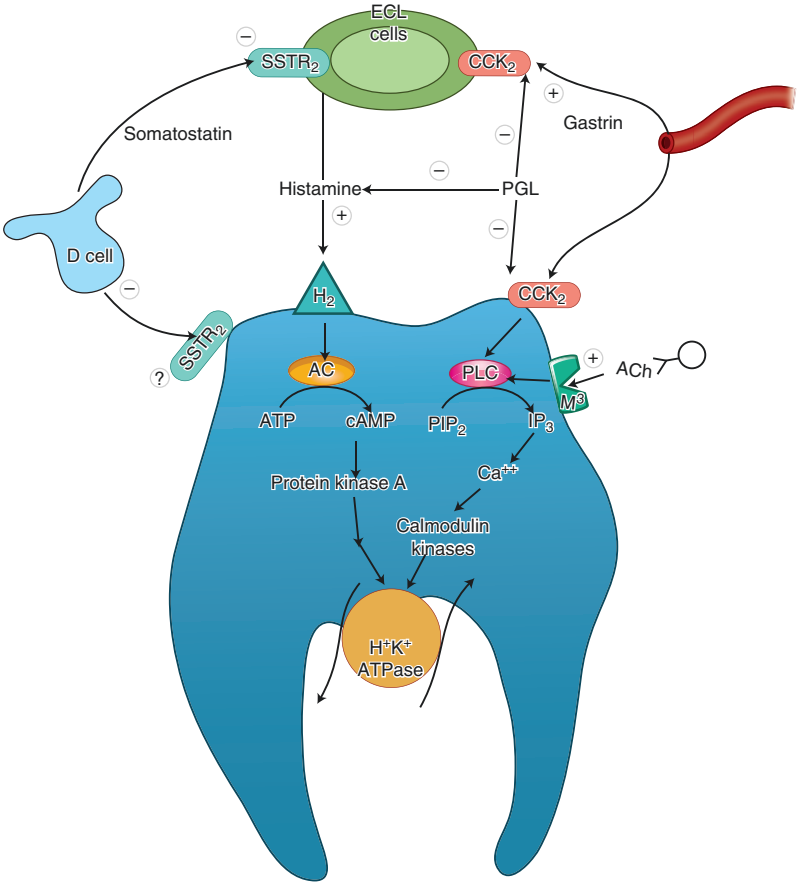

Fig. 3.8 Intracellular control of acid secretion in the parietal cell. *ECL enterochromaffin-like cells, PGL prostaglandins, $SSTR_2$ somatostatin receptor type 2, CCK_2 cholecystokinin type 2 receptor, H_2 histamine type 2 receptor, M^3 muscarinic acetylcholine receptor type 3, Ach acetylcholine, AC adenylate cyclase, ATP adenosine triphosphate, cAMP cyclic adenosine monophosphate, PLC phospholipase C, PIP_2 phosphatidyl 4,5-bisphosphate, IP_3 inositol triphosphate, Ca^{++} calcium ion, K^+ potassium ion, H^+ hydrogen ion, H^+K^+ ATPase hydrogen potassium ATPase*

located in the basolateral membrane also plays a major role in the parietal cell by exchanging intracellular Na + for extracellular K+. Furthermore, also in the basolateral membrane, K+ channels allow the efflux of K+ ion to create a negative cell membrane potential [13].

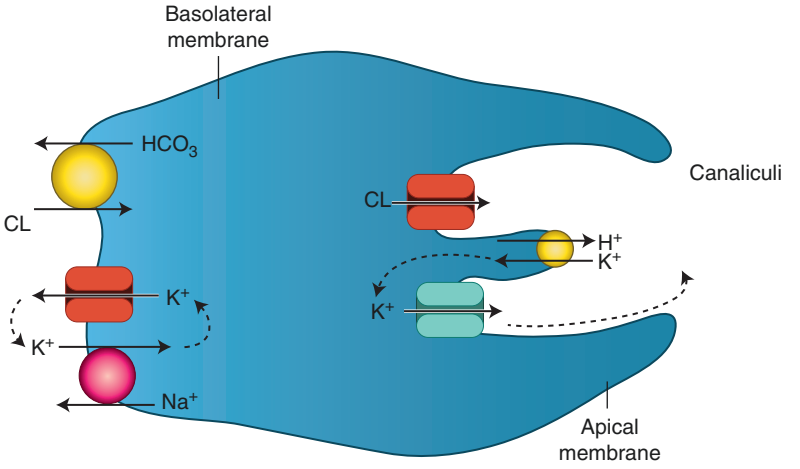

Fig. 3.9 Intracellular ion movement in the parietal cell. *Cl^- chloride ion, HCO_3^- bicarbonate ion, K^+ potassium ion, Na^+ sodium ion, H^+ hydrogen ion*

Medical and Surgical Approaches to Decrease Gastric Acid Secretion

The complex physiological acid secretion control led to the creation of multiple drugs that act through different mechanisms. The most commonly used groups of drugs for patients with increased acid secretion and further symptomatology are proton pump inhibitors (PPIs) (omeprazole, pantoprazole, esomeprazole, dexlansoprazole) and H2 receptor antagonists (famotidine, ranitidine, nizatidine, cimetidine). PPIs act through an irreversible inhibition of the H+/K+ ATPase pump, and H2 receptor antagonists act as competitive antagonists of the H2 receptor. Rebound acid hypersecretion occurs after the cessation of both types of medications. Thus, the abrupt discontinuation of these medications in patients with high risk of recurrence or complications might not be the best approach. It is also important to know that H2 receptor antagonists, but not proton pump inhibitors, have been related to the development of tolerance as soon as 7 days after therapy. Lastly, PPI are among the most commonly prescribed classes of drugs. However, it is important to acknowledge that the chronic use of this class of drugs have been (1) consistently related to the development of fundic gland polyps; (2) have a weak association (Odds ratio <2) with an increased risk of fracture, hypomagnesemia, vitamin B 12 deficiency, cardiovascular risk, *C. difficile* infection, and pneumonia; and (3) have an uncertain and modest association with dementia and renal disease, respectively [14].

H. pylori, a pathogen that is transmitted from human to human, has been implicated in the development of chronic active gastritis, and its eradication cures this disease, altering the progression of its complications. Moreover, *H. pylori* can both increase and decrease acid secretion by different mechanisms. The treatment for *H. pylori* in patients with non-atrophic antral-predominant gastritis and atrophic

gastritis, but not in patients with extensive atrophic changes, leads to a partial correction of the low or high acid state of these patients. However, the treatment for "acid correction" should not be used as an argument to treat this infection as it has not been proven to be of clinical relevance [15].

The surgical approaches to control gastric acid secretion include (1) gastrectomy, (2) antrectomy, and (3) vagotomy. These three approaches act through different mechanisms that each serve to decrease acid secretion. Parietal ECL cells are removed in a gastrectomy. A decrease in both G and ECL cells occurs as part of an antrectomy. Cholinergic stimulation of the parietal cells is interrupted by a vagotomy [2].

Non-Acid Gastric Secretion

Mucus and HC03- are constantly secreted by mucus glands located throughout the entire gastric mucosa, which help to neutralize acid levels and provide a mechanical barrier that protects against mucosal injury. Mucus production is stimulated by cholinergic stimuli and prostaglandins. Thus, nonsteroidal anti-inflammatory drugs and anticholinergics can inhibit mucus secretion, making the gastric mucosa susceptible to injury. *H. pylori* infection has also been related to the secretion of lipases and proteases that cleave mucin, therefore affecting the protective mucosal barrier. Another important role of the gastric mucus that protects the apical cell membrane is its relative impermeability to pepsin and its intrinsic resistance to the diffusion of H+ ions. Lastly, the mucosal blood flow that can be affected by multiple factors is also crucial to maintain a healthy mucosa by delivering the appropriate oxygen and nutrients needed for cytoprotection and cellular function.

Gastric Digestion

The stomach is implicated in the preparation of the ingested food for its digestion and absorption in the small intestine by mixing the ingested food with acid (chyme) and releasing pepsinogen that is consequently activated into pepsin, cleaving peptides into their basic metabolic constituents. The parietal cell also secretes intrinsic factor that helps with the absorption of vitamin B12 in the terminal ileum. Thus, patients with intrinsic factor deficiency secondary to a gastrectomy or pernicious anemia require vitamin B12 supplementation. Gastric acid also promotes the absorption of iron and calcium cations [2, 16]. Therefore, the alteration of gastric pH through medications like proton pump inhibitors can alter the absorption of these types of molecules.

Gastric Motility

Intrinsic and extrinsic neural mechanisms control and modulate gastric motility. The extrinsic control is carried through sympathetic and parasympathetic pathways, and the intrinsic control is mediated by the enteric nervous system. Gastric motility

differs in the fasting and postprandial state. The *gastric electrical pacemaker* responsible for the motor functions is located in the midportion of the greater curvature. In the fasting state, slow waves travel circumferentially and distally toward the pylorus at three cycles per minute, and a cyclical pattern of slow waves and electrical spikes, also known as the *myoenteric migrating complex*, run through the stomach and help the clearance of gastric content. In anticipation of food intake, the proximal portion of the stomach relaxes, through a process called *receptive relaxation*. This relaxation settles the solid food in the fundus and greater curvature of the stomach, while liquids pass without difficulty through the lesser curvature [16]. In the postprandial state, the proximal and fundus tone relaxes to enable its storage function, and the midportion and antrum create repetitive forceful contractions that help to mix and grind the food into small particles. Even though most gastric motility disorders causing delayed gastric emptying are idiopathic, diseases like diabetes or postsurgical vagotomy and/or iatrogenic vagal injuries are commonly associated with gastric motility disorders.

Gastric Implication in Appetite Control

During the last decades, appetite control has been broadly studied as it has been shown to have an important role after bariatric procedures. However, it has not been completely understood as it involves a complex neurohormonal mechanism. Even though the small and large intestine significantly contribute to appetite control through the release of multiple hormones implicated in this process (GLP-1, PYY, GIP, and oxyntomodulin), the stomach also plays an important role [17]. Ghrelin and gastrin, hormones that are mainly released by the stomach, have also been associated with increased and decreased appetite, respectively. Ghrelin is secreted in a diurnal rhythm that stimulates appetite and food intake. This peptide is released during fasting states to the portal circulation and travels through the systemic circulation to finally stimulate hypothalamic appetite centers. Ghrelin levels decrease dramatically when the stomach begins to fill [18]. Thus, after bariatric procedures (sleeve gastrectomy and Roux-en-Y gastric bypass) that create small pouches that are easily stretched, a dramatic fall of the levels of this hormone is detected. Therefore, decreasing appetite is thought to benefit patients by promoting weight loss and theoretically affecting metabolic status [19].

Gastric Secreted Peptides and Compounds

Gastrin

Gastrin is a peptide produced by G cells located in the antrum of the stomach. Several molecular forms have identified (G-34, G17, and G-14). Most of the antral gastrin is released as G-17. However, G-34 predominates in the circulation due to

the longer metabolic half-life, compared to that of G-17. Gastrin is released by stomach muscle distention and by the presence of food (especially by peptides) in the lumen. Moreover, luminal acid and somatostatin decrease its release. Gastrin functions include (1) an increase production of HCL acid, pepsinogen, intrinsic factor, pancreatic secretions, and bile; (2) the promotion of satiety; and (3) a trophic regulation of the parietal and ECL cells [16, 17, 20].

Ghrelin

Ghrelin is a peptide produced by ghrelin release cells mainly located in the oxyntic area of the stomach. It is secreted during fasting states and its levels decrease after the stomach starts to fill. Ghrelin functions include (1) an increase in appetite, (2) an increase of gastric emptying and motility, (3) the induction of growth hormone release, and (4) inhibition of glucose-stimulated insulin production [17, 18].

Somatostatin

Somatostatin is a peptide produced by D cells located throughout the entire gastric mucosa. It is secreted by the increase in gastric acid, gastrin itself, and vasoactive intestinal peptide and decreases after cholinergic activation. Somatostatin functions include (1) inhibition of histamine release (ECL cells) and may directly inhibit parietal cells, therefore decreasing acid secretion and (2) a decrease of gastrin release [10, 17].

Pepsin

Pepsinogen is released by chief cells located in the oxyntic area of the stomach. Pepsinogen is activated to pepsin (its active protease state) by low gastric pH and inactivated by pH above 4. It is secreted by gastrin, cholecystokinin, and acetylcholine stimuli. Pepsin functions include (1) protease activity and (2) mucolytic activity [21, 22].

Histamine

Histamine is nitrogenous compound released by ECL cells and mastocytes located in the oxyntic area of the stomach. It is secreted by gastrin, acetylcholine, adenylate cyclase-activating polypeptide, and vasoactive intestinal peptide, and its secretion decreases by somatostatin, calcitonin, gene-related peptide, PYY, prostaglandins, and galanin. Histamine is the major paracrine stimulator of acid secretion through the stimulation of the parietal cell [16, 23].

Prostaglandins

Prostaglandins are autocrine factors mainly released by macrophages and capillary endothelial cells [24]. Its functions include (1) inhibition of acid secretion, (2) inhibition of histamine-stimulated parietal cell function, (3) inhibition of gastrin-stimulated histamine release, and (4) stimulation of mucus production [25].

Pylorus Anatomy and Physiology

The pyloric sphincter represents a zone of high resting pressure that is easily identified endoscopically (by the underlying muscular ring) and is easily palpated during surgery as a muscular ring on the gastroduodenal junction. The pyloric area is defined by a *proximal pyloric loop* (3 cm lumen) and a *distal pyloric loop* (1 cm lumen) that are not easily identified. However, this entire segment (proximal and distal pyloric loops) contracts as a unit and differs structurally and functionally from the adjacent antrum and duodenum. The proximal loop participates in gastric phasic contractions (every 3 minutes) that lead to a forceful closure of the pyloric lumen, this way, controlling the passage of the chyme from the stomach to the duodenum [26].

The pylorus receives blood supply mainly from the gastroduodenal artery, a branch of the common hepatic artery. The pylorus is innervated by intrinsic (myenteric plexus) and extrinsic (vagal branches and adrenergic fiber) nerves. The myenteric plexus nerve cells contain excitatory (enkephalins and substance P) and inhibitory (vasoactive intestinal peptide and nitric oxide) transmitters. The vagal innervation is mechanosensitive, responding to muscle stretch. However, vagal motor fibers have been also found to mediate excitatory (enkephalins and acetylcholine) and inhibitory responses (vasoactive intestinal peptide and nitric oxide) [26]. Therefore, the stimulation of the pyloric nerves can trigger both phasic contractions and/or relaxation of this segment.

The importance of the pyloric sphincter is not fully appreciated until pathology is encountered, such as in a patient with an intrinsic pyloric disease like infantile hypertrophic pyloric stenosis or patients with destruction or bypass of the pyloric sphincter who present to clinic with dumping syndrome.

Gastric Microbiome

The discovery of *H. pylori* in 1982 by Marshall and Warren led to the consideration of other commensal organisms in the stomach (gastric microbiota), shifting the belief of a "sterile stomach." *H. pylori* is mainly transmitted person to person (fecal/oral or oral/oral), and once it has colonized the stomach, it becomes the predominant gastric microbiota species. The prevalence of *H. pylori* differs between regions, reaching 80% in developing countries [27]. In developed countries, such as the USA, its prevalence has been declining through the years, with a reported prevalence

of 50% in 1991 and 17% in 2010 [28]. *H. pylori*'s urease activity, its ability to penetrate through the gastric mucus layer, and then binding to specific gastric receptors explain its adaptation to the gastric hazardous environment and predilection to the gastric mucosa. Moreover, most of the *H. pylori* positive patients are asymptomatic. However, all carriers will ultimately develop chronic gastritis. The location of the affected part of the stomach has different patterns of gastritis and therefore different changes in gastric acid secretion. Antrum-predominant gastritis, which decreases somatostatin production, is related to gastrin-induced increased acid secretion, and pangastritis or corpus-predominant gastritis, which is associated with extensive gastric atrophy, causes hypo- or achlorhydria and thus a decrease in acid secretion [27].

Other possible commensal organisms of the stomach have also been studied in recent years. Bik et al. characterized bacterial diversity of the gastric mucosa of 23 gastric endoscopy biopsies and found 128 phylotypes, the majority assigned to the *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria* phyla. This finding suggests that the stomach may have a distinct microbiota, and its role in human health still needs to be studied and elucidated [29].

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