Gastric Acid and Digestive Physiology

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The primary function of the stomach is to prepare food for digestion and absorption by the intestine. Although various neural and hormonal mediators contribute to gastric function, acid production is the unique and central component of the stomach’s contribution to the digestive process. Liquids pass easily through the stomach and into the small intestine. Solid components remain in the stomach until they are small enough to be slowly released into the small intestine by the coordinated action of the antrum and pylorus. Acid bathes the food bolus while stored in the stomach, facilitating digestion. An intact defense against mucosal damage by the stomach’s acid is essential to avoid ulceration. This article focuses on the physiology of gastric acid production, the stomach’s defense mechanisms against acid injury, and the most common challenges to the gastric defenses. A brief description of the stomach’s nonacid digestive capabilities is included.

THE PROTON PUMP

The mucosa of the gastric body, and to a lesser extent the fundus and antrum, contains the parietal cells. One function of the parietal cell is to produce gastric acid, which activates pepsin from pepsinogen, aids in the digestion of protein, and reduces bacterial colonization of the stomach and duodenum.1 The parietal cell contains the hydrogen (H⁺)/potassium (K⁺)-ATPase, or proton pump, which transports H⁺ out of the cell into the gastric lumen and K⁺ from the gastric lumen into the cell.2 Interestingly, the H⁺ gradient created in the gastric lumen is greater than 10⁶ times that of blood.3 Because of the large amount of energy needed to run the proton pump, the parietal cell has the largest mitochondrial capacity of any cell in the human body.1 In the resting parietal cell, the proton pumps are contained within the membranes of intracellular tubulovesicles.3 There is a constant basal level of acid production, even in the unstimulated parietal cell.1 The basal level of acid secretion is caused by histamine and acetylcholine.4 Basal acid output is approximately 10% of the maximal acid output of the stimulated parietal cell. There is diurnal
variation of basal acid levels, with night levels being higher than day levels.\(^1\) In the stimulated state, the tubulovesicles fuse with the apical cell membrane, thus relocating the proton pumps to the apical surface of the parietal cell.\(^1,3\) The apical cell membrane also contains cotransport channels for \(K^+\) and chloride (\(Cl^-\)), which transport both \(K^+\) and \(Cl^-\) out of the cell into the gastric lumen. Therefore, there is a net transfer of \(H^+\) and \(Cl^-\) into the gastric lumen with stimulation of the proton pump.\(^2\)

**PARIETAL CELL RECEPTORS**

There are three stimulatory receptors on the parietal cell: the muscarinic (\(M_3\)) receptor, the type B cholecystokinin (CCK\(_B\)) receptor, and the histamine (\(H_2\)) receptor (**Fig. 1**).\(^3\) These receptors are located on the basolateral membranes of the parietal cell.\(^4\) The \(M_3\) receptor is stimulated by acetylcholine and activates gastric acid secretion by an intracellular calcium (\(Ca^{2+}\)) pathway that increases intracellular \(Ca^{2+}\) levels.\(^3\) Acetylcholine is released from the stimulation of parasympathetic vagal nerve fibers.\(^1\)

The CCK\(_B\) receptor, or gastrin receptor, is stimulated by gastrin and also activates acid secretion by an intracellular \(Ca^{2+}\) pathway that increases intracellular \(Ca^{2+}\) levels.\(^3\) The gastric antral mucosa, and to a lesser extent the duodenal mucosa, contains G cells, which produce gastrin.\(^1,4\) Protein is the major stimulant for gastrin release.\(^1\) Gastrin is produced in the endoplasmic reticulum and is released through the basal membrane of the G cell.\(^4\) Vagal stimulation also causes the release of gastrin-releasing peptide (GRP), the equivalent to bombesin, from cells in the gastric fundal mucosa.\(^1,2,5\) GRP then stimulates gastrin release from gastric antral G cells.\(^2\) In addition to the stimulation of acid secretion, gastrin also has a trophic effect on both parietal cells and enterochromaffin-like (ECL) cells.\(^1\)

The \(H_2\) receptor is stimulated by histamine and activates acid secretion by a pathway that increases intracellular cAMP.\(^3\) Histamine is produced by ECL cells, and its release is stimulated by gastrin and acetylcholine.\(^1\) The stimulatory effect of acetylcholine and gastrin is thought to occur through or in combination with histamine.\(^3\) The final outcome from stimulation of the \(M_3\), CCK\(_B\), and \(H_2\) receptors is the activation of the \(H^+/K^+\)-ATPase.\(^2\) Activation of these receptors in any combination results in a greater amount of gastric acid release than with activation of any one of the receptors alone. This effect is known as potentiation.\(^4\) To completely block

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**Fig. 1. The parietal cell.**

- **Acetylcholine** + \(\uparrow Ca^{2+}\) + ATP + cAMP
- **Histamine** + \(\uparrow Ca^{2+}\) + cAMP
- **Gastrin** + cAMP

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\[\text{\(H^+\) and \(Cl^-\) into the gastric lumen with stimulation of the \(H^+/K^+\)-ATPase.}\]

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\[\text{Acetylcholine, Histamine, and Gastrin activate the \(H^+/K^+\)-ATPase.}\]

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\[\text{Somatostatin, Prostaglandin E2 inhibit the \(H^+/K^+\)-ATPase.}\]
stimulation of acid secretion through the activation of these receptors, all 3 receptors must be blocked individually.\textsuperscript{2} However, the use of a proton pump inhibitor alone will block acid secretion by inhibiting the final common pathway, the H\textsuperscript{+}/K\textsuperscript{+}-ATPase itself.\textsuperscript{1,2}

Somatostatin is produced by D cells present in the fundic and antral mucosa and in the small intestine.\textsuperscript{1,4} Somatostatin has an inhibitory effect on gastric acid release. Intraluminal acid has a stimulatory effect, and acetylcholine has an inhibitory effect on somatostatin release. Somatostatin not only inhibits the parietal cell directly, but also indirectly by inhibiting the release of gastrin and histamine.\textsuperscript{1} Direct parietal cell inhibition occurs via the reduction of intracellular cAMP.\textsuperscript{3}

The parietal cell also contains another inhibitory receptor for prostaglandin E\textsubscript{2} (PGE\textsubscript{2}).\textsuperscript{2} PGE\textsubscript{2} also inhibits gastric acid secretion by decreasing intracellular cAMP levels.\textsuperscript{3,4} Additionally, PGE\textsubscript{2} inhibits gastrin secretion and stimulates somatostatin secretion.\textsuperscript{4}

THE CEPHALIC, GASTRIC, AND INTESTINAL PHASES OF GASTRIC ACID SECRETION

Gastric acid secretion can be divided into 3 phases: the cephalic, gastric, and intestinal phases.\textsuperscript{2} The cephalic phase of gastric acid secretion is mediated by vagal excitation stimulated by the thought, sight, smell, or taste of food.\textsuperscript{1,2} This can be elicited by sham feeding. Vagal excitation causes the release of acetylcholine, which stimulates gastric acid and pepsin secretion from mucosal parietal cells and chief cells, respectively.\textsuperscript{2}

The gastric phase of gastric acid secretion is mediated by gastric distention as food enters the gastric lumen.\textsuperscript{1,2} The majority of gastric acid release occurs during this phase.\textsuperscript{1} Gastric antral distention causes the release of gastrin from G cells. Distention of the gastric fundus increases the effects of gastrin and histamine through a local cholinergic pathway. Intraluminal acid inhibits the release of gastrin from G cells.\textsuperscript{2}

The intestinal phase of gastric acid secretion is primarily inhibitory and begins when food enters the small intestine.\textsuperscript{1,2} The least amount of gastric acid is released during this phase.\textsuperscript{1} Intraintestinal acid inhibits gastric acid secretion through an enterogastrone.\textsuperscript{2}

GASTRIC MUCUS, MUCOSAL DEFENSE, AND REPAIR

Mucus forms a protective layer over the gastric and duodenal mucosa.\textsuperscript{2} Mucus is released by exocytosis from mucus neck cells and surface mucus cells in the stomach and Brunner glands in the duodenum.\textsuperscript{2,5} Mucus contains mostly water and smaller amounts of electrolytes and mucin glycoproteins. Mucin glycoproteins make mucus a viscous gel. The main physiologic stimulus for the release of mucus is acetylcholine. Secretin also stimulates mucus secretion, and prostaglandins increase mucus viscosity and mucin glycoprotein content. Mucus slows the diffusion of acid from the gastric lumen to the gastric mucosa. Mucus also contains bicarbonate (HCO\textsubscript{3}\textsuperscript{-}), which maintains a near-normal pH at the mucosal surface.\textsuperscript{2} This is known as the unstirred layer.\textsuperscript{1} HCO\textsubscript{3}\textsuperscript{-} is secreted by both active and passive processes. Mucus also provides lubrication for the passage of food, thus protecting the mucosa from mechanical stresses. Mucus is not broken down by gastric acid, but it is dissolved by pepsin and N-acetylcysteine. It is easily penetrated by bile salts, ethanol, and nonsteroidal anti-inflammatory drugs (NSAIDs), which lead to mucosal injury.\textsuperscript{2} Mucosal damage is caused by offensive agents or decreased defense.\textsuperscript{1} After injury, a mucus layer is formed containing fibrin and dead cells over the site of injury. Degraded mucus is replaced by continuous mucus secretion.\textsuperscript{2}
The apical membrane of the mucosal cell is impermeable to H\(^+\). However, H\(^+\) can diffuse between cell junctions to reach the basolateral surfaces of the cell. High concentrations of H\(^+\) cause mucosal injury. The mucosa is protected from this by HCO\(_3^-\). The basolateral surfaces of mucosal parietal cells regulate pH through an HCO\(_3^-/\)Cl\(^-\) antiporter. For every H\(^+\) transported out of the cell through the apical membrane during acid secretion, an HCO\(_3^-\) is transported out of the cell through the basolateral membrane.\(^2\) This phenomenon is known as the alkaline tide.\(^5\) This neutralizes any H\(^+\) that reaches the basolateral membranes. The HCO\(_3^-/\)Cl\(^-\) antiporter can also be activated by prostaglandins, even without the stimulation of acid secretion. The parietal cell basolateral membranes also contain an Na\(^+/-\)H\(^+\) antiporter that transports Na\(^+\) into the cell and H\(^+\) out of the cell. This transporter protects against intracellular acidosis. The driving force for this transporter is a basolateral Na\(^+/-\)/K\(^+\)-ATPase.\(^2\)

After mucosal injury, rapid repair, or restitution, occurs within minutes.\(^1,2,5\) Repair occurs through the movement of already established mature mucosal cells over the basal lamina.\(^2\) Therefore, repair does not require the generation of new mucosal cells through cell division.\(^1,2\) This is an important mechanism for repair of the mucosa after normal physiologic stresses. Repair can be impeded by luminal acid, calcium depletion, low HCO\(_3^-\), and altered cell motility. Delayed repair results in the formation of ulcers.\(^2\)

**GASTRIC CIRCULATION**

Vagal stimulation, through the action of acetylcholine, causes vasodilation of the gastric vasculature and increased blood flow. Histamine also causes vasodilation. Therefore, stimulation of acid secretion is associated with increases in gastric blood flow.\(^2\) Endogenous nitric oxide (NO) and PGE\(_2\) also cause vasodilation.\(^4\) Sympathetic stimulation, as well as exogenous epinephrine, norepinephrine, and vasopressin, causes vasoconstriction of the gastric vasculature and decreased blood flow. Hemorrhagic shock leads to decreased blood flow and increased susceptibility of the gastric mucosa to injury by acid and bile salts. Aging is also associated with decreased blood flow. Agents that increase gastric blood flow have a protective effect on the stomach. The relationship between gastric blood flow and mucosal injury is due to the acid–base balance of the tissue. Adequate blood flow prevents tissue acidosis and mucosal injury. Autoregulatory mechanisms maintain a constant gastric blood flow with changes in arterial pressure up to a certain point.\(^2\) Blood flow is an important component in gastric mucosal defense by delivering nutrients and oxygen to mucosal cells. Blood flow of 50% to 75% of normal leads to mucosal injury.\(^1\)

**PEPSIN**

The chief cells synthesize and release the proenzyme pepsinogen, the precursor to pepsin.\(^2\) The chief cells are the most abundant cells in the gastric mucosa. They are found in the body, fundus, and antrum of the stomach, as well as in the duodenum.\(^1\) Pepsinogen is produced in the endoplasmic reticulum, and its release by exocytosis is stimulated by acetylcholine, histamine, and CCK.\(^2,4\) Pepsinogen release is inhibited by somatostatin.\(^4\) Active pepsin is formed in an acidic environment by cleavage of the N-terminal amino acid sequence of pepsinogen.\(^2\) Pepsin, along with gastric acid, facilitates the digestion of protein.\(^5\)

**INTRINSIC FACTOR**

An additional function of the parietal cell is the synthesis and secretion of intrinsic factor (IF).\(^2\) IF is the only essential substance produced by the stomach.\(^5\) It is
necessary for adequate absorption of vitamin B$_{12}$ (cyanocobalamin) in the terminal ileum.$^{1,2}$ IF is produced in the endoplasmic reticulum and is released from the apical surface of the parietal cell.$^4$ The same factors that stimulate the secretion of acid also stimulate the secretion of IF; however, acid secretion and IF secretion may not be linked.$^{2,5}$ The production of IF greatly exceeds that which is necessary for adequate absorption of cobalamin. Most patients manufacture adequate IF after subtotal gastrectomy, making vitamin B$_{12}$ supplementation unnecessary.$^2$

NSAIDs

NSAIDs cause damage to gastric mucosa by direct injury and by affecting prostaglandin production, specifically PGE$_2$. NSAIDS are lipophilic weak acids; therefore they bind to gastric mucosa and induce local injury. Their major mechanism of action is systemic inhibition of cyclooxygenase (COX), an enzyme in the pathway of the production of prostaglandins from arachadonic acid. Two isoforms exist: COX 1 and COX 2. Nonselective NSAIDs block both isoforms, but selective inhibitors block only COX 2. The COX 1 pathway results in production of PGE$_2$. PGE$_2$ protects the gastric mucosa by decreasing gastric acid secretion, increasing mucus production and bicarbonate secretion, and increasing mucosal blood flow.$^2$ The net effect of nonselective NSAIDs is reduction of prostaglandins (including PGE$_2$), which leads to mucosal injury. COX 2 is primarily expressed during inflammatory events, and the prostaglandins produced by this pathway promote the inflammatory response. Selective NSAIDs block COX 2 but have little effect on COX 1, which results in an anti-inflammatory effect without the deleterious effects on gastric mucosa. Synthetic PGE$_2$, or misoprostol, acts by inhibiting gastric acid secretion and enhanced mucosal protection.$^6$ This can be used in patients requiring long-term nonselective NSAIDs to prevent injury to gastrointestinal mucosa.$^6,7$ H2 blockers and proton pump inhibitors can also be used to reduce the risk of complications from nonselective NSAIDs.$^7$

**HELICOBACTER PYLORI**

*Helicobacter pylori* is a gram-negative flagellated rod that possesses the enzyme urease. Urease converts urea into ammonia (NH$_3$) and carbon dioxide (CO$_2$), allowing the organism to survive in the low pH of the stomach. Colonization leads to gastric mucosal inflammation and injury.$^8$ *H pylori* also produces enzymes that break down mucus. In addition, patients with *H pylori* infection have a lower D cell population than those without infection. This leads to lower somatostatin levels, higher gastrin levels, and increased acid secretion. Only gastric mucosa, or gastric-type mucosa, contains receptors specific for *H pylori*.$^7$ Up to 50% of the population is infected with *H pylori*.$^8$ Patients infected with this organism may be asymptomatic or may develop antral gastritis, gastric or duodenal ulcers, or mucosa-associated lymphoid tissue (MALT) lymphoma.$^{1,2}$ Almost all cases of chronic antral gastritis and duodenal ulcers and most gastric ulcers are associated with *H pylori* infection.$^9$ Eradication of *H pylori* restores the D cell population with the resultant decrease in gastric acid secretion.$^1$ Treatment shortens the healing time of ulcers and decreases the chance of relapse.$^2$

**SUMMARY**

Gastric acid physiology is a complex process involving the parasympathetic vagus nerve and a variety of hormones including gastrin, histamine, somatostatin, and prostaglandin. In addition to gastric acid, the stomach produces pepsin and intrinsic
factor. The gastric mucosa is protected by mucus and bicarbonate secretion. Mucosal defense is adversely affected by *H pylori* infection and NSAIDs. Gastric acid production facilitates digestion; however, damage from excess acid or inadequate mucosal defense can result in ulceration.

REFERENCES