

DIGESTIVE SYSTEM -2

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LEARNING OBJECTIVES

1. Explain the regulation of acid production in the stomach.
2. Explain the pathology of ulcer formation due to a loss of the mucus barrier.
3. Explain the target sites and relative effectiveness of drugs used for ulcers.

ACTIVATION OF GASTRIC ACID SECRETION

Gastric acid secretion by the parietal cell of the stomach is not constant. In the fed state, gastric acid secretion increases rapidly reaching a maximal output by 90 minutes (Fig 1). Subsequently as food empties into the small intestine, acid secretion again decreases and remains low when the stomach is empty.

The pH of the stomach content also changes with feeding. In the presence of food, the pH of the luminal content rises from 2.0 to 5.0 despite the increased production of acid. This rise in pH is due to buffering by the food. As the food content decreases, the pH falls to pH 2.0 and remains low during the fasting state.

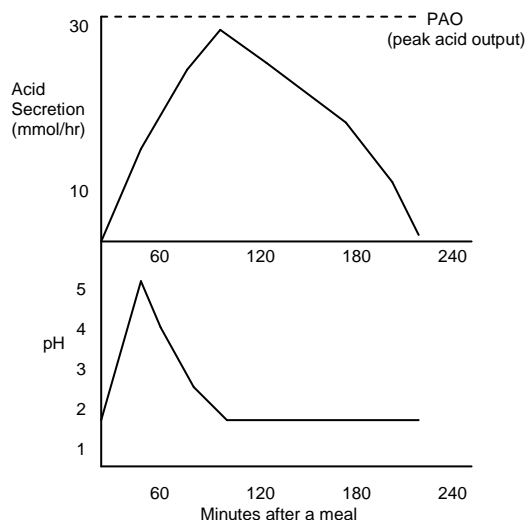


Figure 1. Secretion of HCl during fed and fasting states.

The production of acid is regulated by 3 reflex paths including: the parasympathetic nervous system (acetylcholine, Ach), the hormone, gastrin, and the paracrine, histamine. Each of these factors stimulates the activity of the H^+-K^+ ATPase to increase acid secretion. Their combined effect is known as **potentiation** (Fig 2).

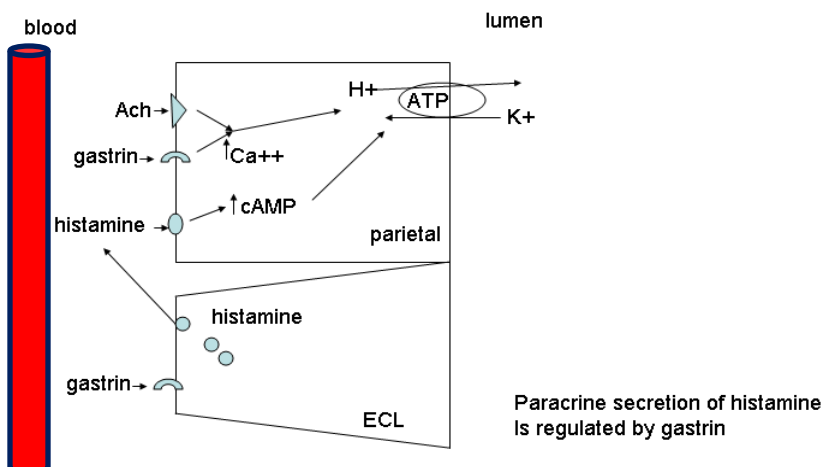


Figure 2. Stimulation by histamine (paracrine), gastrin (hormone), and parasympathetic nervous system (ACh) increases HCl secretion in the stomach.

CEPHALIC PHASE OF ACID SECRETION

The **cephalic phase of gastric acid production** is a **feed forward control** mediated by the parasympathetic nervous system (Fig 2). In the cephalic phase, the smell of food, the thought of food, and the chewing food leads to an increase in the secretion of hydrochloric acid. The cephalic phase accounts for about 40% of the total acid production.

Increased parasympathetic nervous activity regulates two regions of the stomach:

In the **fundic** region, parasympathetic stimulation of the parietal cells increases activity of the $H^+ - K^+$ ATPase (proton pump) and thereby increases acid secretion (Fig 2).

In the **antrum**, parasympathetic stimulation leads to an increase in secretion of the hormone, gastrin. Gastrin, in turn, stimulates the parietal cells directly leading to an increase in $H^+ - K^+$ ATPase (proton pump) activity. Gastrin also acts on the enterochromaffin cells (ECL cells) located adjacent to the parietal cells to increase the secretion of histamine from these cells (Fig 2). Histamine in turn, acts as a paracrine to increase the activity of the $H^+ - K^+$ ATPase in the parietal cells.

***** Note that the final effector for acid production in the cephalic phase is the proton pump of the parietal cell.**

GASTRIC PHASE OF ACID SECRETION

The second phase of acid secretion is called the **gastric phase**. It is initiated by **mechanical distension** of the stomach by food and by the arrival of amino acids, alcohol, and caffeine within the antrum region of the stomach. These events stimulate the secretion of the hormone, gastrin, from the G cells of the antrum. Gastrin acts in the fundic region to increase the activity of the parietal cell proton pump as described above. The gastric phase accounts for about 60% of the gastric acid secretion.

INHIBITION OF ACID SECRETION

Tight regulation of acid production is needed because excess acid can be caustic and acid is needed only during feeding. The negative regulation of acid production is mediated by the stomach luminal pH.

During feeding, proteins in the chyme act to buffer the pH to usually above 3.0 (Fig 1). However, in the empty stomach, the pH can fall below pH 3. At this low pH, the **D cells of the antrum** region of the stomach secrete **somatostatin**. Somatostatin acts as a paracrine to inhibit gastrin secretion from the G cells (Fig 3).

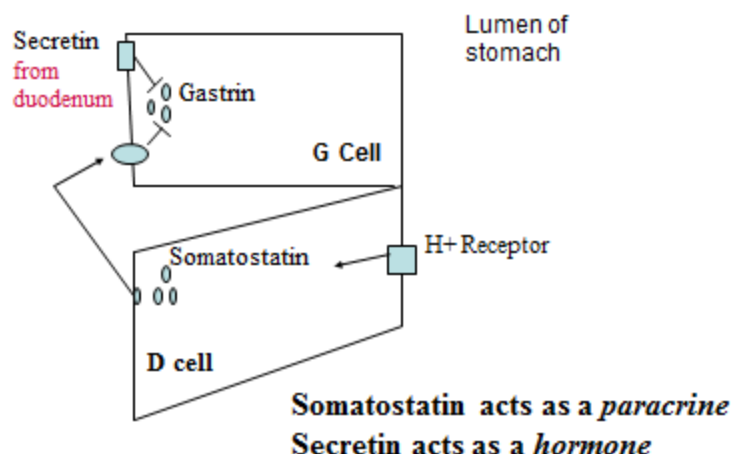


Figure 3. Negative feedback by protons (H^+) inhibits gastrin secretion.

Acid also initiates a negative feedback mediated by the hormone secretin. Secretin is secreted by the first part of the small intestine (called the duodenum) in response to the arrival of acidic chyme. **Secretin acts as a hormone to inhibit gastrin secretion from the G cells of the stomach** (Fig.3).

LOSS OF MUCUS BARRIER & GASTRIC ULCERS

The mucous cells that line the stomach lumen secrete mucus, a carbohydrate rich substance that protects the cells from erosion by acid. Disruption of this mucus barrier can lead to lesions in the epithelium called **ulcers**. This is a painful condition that can lead to severe bleeding if other layers of the stomach wall are also involved.

There are two common causes of ulcers:

1. excess use of non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit the production of mucus by the epithelial cells
2. infection by *heliobacterium pylori*.

Therapy targets include the following:

1. simple buffering of luminal pH
2. inhibition of the parietal cell histamine receptor
3. inhibition of the parietal cell proton pump

The most effective of these treatments is the inhibition of the proton pump but the fastest effect is simple buffering with either bicarbonate or food. Infection by *heliobacterium pylori* is the most common cause of stomach (gastric) ulcers. This infection is treated with antibiotics in addition to the proton pump inhibitor.

GENERAL CONCEPTS

1. In the fed state, gastric acid secretion and pH of the stomach lumen increase in the first 90 minutes after ingestion of food.
2. In the fasting state gastric acid secretion and pH of the stomach lumen decrease and return to basal levels by 4 hours after food ingestion.

3. Secretion of gastric acid is regulated in a positive manner by the parasympathetic nervous system, by the hormone gastrin and by the paracrine histamine. The final effector for each of these factors is the proton pump located in the parietal cell.
4. Secretion of gastric acid is regulated in a negative manner by the hormone secretion and by the paracrine, somatostatin. Secretion of these factors increases in response to low luminal pH. The target for these negative factors is the G cell of the antrum which secretes gastrin.
5. The stomach has a protective mucus barrier to prevent cellular damage by acid. Disruption of this barrier leads to erosion of the epithelium lining the stomach lumen (gastric ulcers).