GI Secretion 1: Salivary and Gastric Secretion
Jack Grider, Ph.D.

OBJECTIVES:

1. List the volumes of secretion by various regions.
2. Predict the components of salivary secretion at different flow rates.
3. Describe the neural regulation of salivary secretion.
4. List the secretions and cells of origin for gastric secretions.
5. Explain the cellular steps involved in acid secretion in the stomach.
6. Discuss the interaction between neural, hormonal and paracrine regulatory mechanisms regulating acid secretion at different phases of a meal.

Suggested Reading: Berne & Levy; pp. 566-580

1. GENERAL CHARACTERISTICS

   A. Types of secretion
      1. The table below indicates the volume of secretions and ingested fluids entering the GI tract per day. (About 8.5 liters/day secretion).

<table>
<thead>
<tr>
<th>Source</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Intake</td>
<td>1500ml</td>
</tr>
<tr>
<td>Salivary Glands</td>
<td>1500</td>
</tr>
<tr>
<td>Stomach</td>
<td>2500</td>
</tr>
<tr>
<td>Bile</td>
<td>500</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1500</td>
</tr>
<tr>
<td>Intestine</td>
<td>1000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>8500ml</strong></td>
</tr>
</tbody>
</table>

2. Of this, all but about 200/day ml is reabsorbed (mostly by the intestine).
3. Secretions are of two types: serous and protein. Often these components are derived from different cells within the structure of the gland and its ducts.
4. The **serous component** is composed of water and electrolytes. The nature of the electrolyte varies with the gland and functions to provide the optimal environment for digestion.
5. The **protein component** is composed of enzymes necessary for the digestion of nutrients, and mucus (mucopolysaccharides and glycoproteins) which lubricates the chyme and provides some buffering of pH in food and in chyme leaving stomach.
B. Types of glands

1. **Mucous glands**: These are single cells (goblet cells) interspersed with the epithelial lining cells in the mucosa. These secrete mucus which adheres to and protects the mucosa. (Figure 1a.)

2. **Tubular glands**: These are invaginations of the epithelium which contain secretory cells. Secretions enter the lumen of the tube and flow up and out into the lumen of the gut.
   
   a. Gastric pits and Intestinal crypts are examples. (Figure 1a.)

3. **Compound glands**: These glands are outside of the gut wall. They are composed of two parts (acini and ducts) arranged like a cluster of grapes. The acini are composed of the secretory cells which secrete into the center of the acinus. This secretion is called the **primary secretion**. The primary secretion then flows towards the gut through a system of increasingly larger ducts. The cells lining the ducts often modify the electrolyte and water component of the secretion. The modified secretion or **secondary secretion** is then emptied into the lumen of the gut. The salivary gland and exocrine pancreas are examples of compound glands. (Figure 1b.)
C. Intracellular mediators of secretion

1. Secretory cells have receptors for a variety of hormones and neurotransmitters.
2. Some of these receptors are coupled to activation of adenylyl cyclase. The net effect is to increase intracellular cyclic AMP which leads to secretion. B-adrenergic agents, VIP and members of the secretin family of peptides, and cholera toxin act through this mechanism.
3. Other secretory agents act by causing the hydrolysis of phosphatidylinositol-(4,5) bisphosphate in the membrane to diacyl glycerol (DAG) and inositol-(1,4,5) trisphosphate (IP3). The latter is a water soluble product that enters the cytoplasm and causes a rise in intracellular calcium via release of calcium from intracellular stores in the endoplasmic reticulum. The rise in calcium results in secretion.
Agents acting through this mechanism include: acetylcholine, CCK, tachykinins.

II. SALIVARY SECRETION

A. Three Glands

1. **Parotid gland**: secretion is only serous.
2. **Submaxillary gland**: secretion is serous and mucous.
3. **Sublingual gland**: secretion is serous and mucous, but mostly mucous.

B. Functions of saliva

1. Mucous component lubricates food and also keeps the pH neutral.
2. Enzyme component has ptalin which is an alpha amylase, and a lipase, lingual lipase. These begin the digestion of carbohydrates and lipids in oral cavity.
3. Aids in taste, speech and preventing oral infections.

C. **Primary secretion** (Figure 2)

1. Elaborated by acinar cells.
2. Composed of water and electrolytes, mucus and enzyme (ptalin and lingual lipase).
3. Electrolytes: Na⁺, K⁺, Cl⁻, and HCO₃⁻ secreted into acinar lumen at nearly isotonic concentrations.

D. **Secondary secretion** (Figure 2)

1. The secondary secretion is the result of modification of the primary secretion by cells lining duct system.
2. Duct cells absorb Na⁺ and Cl⁻ from the solution and secrete K⁺ and HCO₃⁻. More electrolyte is removed than is added because the cells lining the distal ducts are not fully water permeable so less water follows electrolyte than expected. This results in a secondary secretion that is hypotonic.

E. Effect of flow rate (Figure 3)

1. The rate of flow determines the amount of time the primary secretion is in contact with the cells of the duct. The slower the flow, the longer the contact time and the greater the opportunity for exchange of electrolytes. At rapid flow rates, there is less time for exchange of electrolytes so the final secretion resembles the primary secretion more closely.
2. At **slow flow rates**, the saliva is low in NaCl and HCO$_3^-$ Saliva is very hypotonic.
3. At **rapid flow rates**, the saliva is closer to that described for the primary solution and is nearly isotonic.

Figure 2.
Figure 3.

F. Control of secretion

1. Hormonal
   a. None

2. Neural
   a. **Parasympathetic**: increases secretion. Nerve fibers release both Ach and VIP. Both of these stimulate acinar cells directly (VIP increases cAMP and Ach increases Ca2+). Parasympathetic-stimulated secretion is high in ptyalin and the serous (water & electrolyte) component since the blood vessels around the gland are dilated by VIP increasing blood flow.
   b. **Sympathetic**: increases secretion. Nerve fibers release nor-epinephrine which activates both alpha and beta adrenergic receptors (alpha increases Ca2+ and beta increases cAMP). Sympathetic nerve activation constricts blood vessels limiting blood flow so that the serous component is decreased resulting in a high mucous concentration.
   c. Note: both parasympathetic and sympathetic stimulate secretion but the former is more potent than the latter.

G. Protein component:
1. **Ptyalin or salivary amylase** is active mainly in an alkaline environment (pH optimum: 7.0; pH Range = 4-11). As a swallowed bolus enters the stomach, it encounters an acid environment which begins to inactivate this amylase. However, amylase attached to its substrate is protected from inactivation as is amylase in the core of a bolus where the pH remains alkaline. Thus, a portion of salivary amylase continues to function while the meal is in the stomach. Any salivary amylase surviving passage to the intestine will continue to function in the alkaline environment of the intestine. Thus, this amylase plays an important role in the digestion of carbohydrate.

2. **Lingual lipase**: begins initial digestion of long chain triglycerides. Since its pH optimum is 4.0 (Range of 2 to 8) it continues to digest lipid while the meal is in the stomach. No co-lipase is needed with lingual lipase. This lipase preferentially removes the fatty acid in position 3 of triglyceride.

### III. GASTRIC SECRETION

#### A. Types of secretion

1. **Hydrogen ion**: secreted by parietal (oxyntic) cells located in oxyntic glanda of the fundus and corpus of the stomach. H^+ needed for conversion of pepsinogen to pepsin. H^+ is needed to provide pH optimum for protein digestion by pepsin, and to prevents bacterial growth.

2. **Pepsinogen**: secreted by chief cells of oxyntic gland. Cells secrete an inactive form of the proteolytic enzyme which is then converted to the active form (pepsin) by H^+ in lumen.

3. **Lipase**: A gastric lipase is secreted from the chief cell. It is unlike pancreatic lipase but similar to lingual lipase. Gastric lipase liberates a single free fatty acid and a diglyceride from triglycerides and has an acidic pH optimum.

4. **Intrinsic factor (IF)**: secreted by oxyntic cells. IF is needed for vitamin B12 absorption in ileum.

5. **Mucus**: Secreted by mucous cells in surface epithelium and in neck of oxyntic gland. Mucus adheres to the surface and protects stomach from autodigestion by acid and pepsin (neutralization of acid). (Figure 4.)
B. Functional anatomy

1. Oxyntic gland mucosa (Figure 5)

   a. Epithelial cells of mucosa invaginate into mucosa to form **gastric pits**.
   b. These pits then form epithelial or tubular glands.
   c. In the fundus and corpus, these oxyntic glands contains oxyntic (parietal) cells which secrete HCl and intrinsic factor, Chief cells which secrete pepsinogen, and mucous neck cells which secrete mucus. Parietal cells are more numerous at base of the gland.
   d. Glands are surrounded by an extensive network of blood vessels and capillaries that parallel the gland.
C. Hydrogen ion secretion by parietal cell (Figure 6a)

1. Oxyntic cells have invaginations of the apical surface called **canaliculi** which increase dramatically immediately after cell is stimulated. The cell secretes H+ ion via a **H+/K+ ATPase** that is located on the apical membrane so that the increase in apical membrane generated by the canaliculi results in a greater the amount of active H+/K+ ATPase. This allows the cell to secrete acid rapidly to achieve a final gastric pH of less than 1.
2. $\text{H}^+$ is generated within the cell from $\text{H}_2\text{O}$. The resulting $\text{OH}^-$ is neutralized by reaction with $\text{CO}_2$, derived from the blood and from cellular metabolism, to form $\text{HCO}_3^-$. This reaction is catalyzed by **carbonic anhydrase**.

3. The $\text{HCO}_3^-$ passively diffuses into the blood in exchange for $\text{Cl}^-$.

4. At the canalicular surface (gastric lumen) $\text{H}^+$ is actively pumped out of the cell in exchange for $\text{K}$ by the $\text{H/K}$ ATPase. This is also called the Proton Pump and is the site of action of **Proton Pump Inhibitors (PPIs)** such as Omeprazole used extensively to treat gastric ulcer disease and gastroesophageal reflux disease (GERD).

5. The net reaction is thus: $\text{H}_2\text{O} + \text{CO}_2 + \text{NaCl} \rightarrow \text{NaHCO}_3$ (blood) + $\text{HCl}$ (Lumen).

6. At rest or at low levels of stimulation, NaCl is mainly secreted and at high rates of stimulation, mainly HCl is secreted (Figure 6b).

![Figure 6a.](image-url)
D. Control of Acid Secretion

1. Neural: (Figure 8)

   a. **Enteric:** Nerves of the enteric nervous system can simulate the parietal (and peptic) cell directly. These effects are mainly mediated by ACh (Cholinergic)

   b. **Vagus (Parasympathetic):** Vagal activation during the cephalic and gastric phases (via long arc reflex) leads to increase in activity of local enteric excitatory neurons to release ACh. The vagus can also activate local enteric neurons innervating enterochromaffin-like cells (ECL cell) in the stomach. These secrete histamine, which also stimulates the parietal cell. Finally, vagal stimulation activates an enteric neuron that innervates the antral G cell and causes gastrin secretion. This enteric neuron uses a peptide transmitter called GRP (Gastrin Releasing Peptide).
2. **Hormonal (Figure 8)**

a. **Gastrin**: Gastrin is released into the blood from G-cells located in antral mucosa. Release is stimulated by gastric distension, presence of protein digestion production in the chyme, or vagal stimulation (see above). At the parietal/oxyntic cell, gastrin receptors (Also called - CCK-B receptors) are stimulated, intracellular Calcium is elevated and HCl secretion occurs. CCK can also stimulate this receptors but is of lower potency then gastrin. If CCK concentrations are high, then CCK can act as a **competitive antagonist**.

3. **Paracrine** (Figures 8&9)

a. **Histamine**: Released from enterochromaffin-like cells in lamina propria in response to vagal stimulation, or local
inflammation. Histamine acts in a **paracrine** manner to diffuse through the extracellular space and activate **H2 receptors** on parietal cells. This results in an increase in intracellular cyclic AMP and increased HCl secretion. **H2 receptor blocking drugs** such as cimetidine are used to treat gastric ulcer disease.

b. **Somatostatin (Sts):** Released from paracrine cells in mucosa. There are cell located in the fundus that release Sts onto parietal cells where it acts on Sts receptors. This results in a decrease in intracellular cAMP and an inhibition of HCl secretion. Similar cells in the antral mucosa act on the G cells to inhibit gastrin secretion. The nNet effect is to decrease HCl secretion. (Figure 9)

![ACID IN THE ANTRUM STIMULATES SOMATOSTATIN RELEASE TO INHIBIT MEAL-STIMULATED GASTRIN SECRETION](image.png)

Figure 9.

**E. Phases of acid secretion**

1. **Cephalic phase:** Sight or smell of food activates neural (vagal) reflex resulting in stimulation of the parietal cell directly as well as inducing the release of gastrin from the G-cell. This phase is in preparation for a meal.
2. **Gastric phase:** presence of a meal in the stomach causes maximal stimulation of acid secretion. Neural (local and vagal) mechanisms directly stimulate the parietal cell. G-cell release of gastrin is stimulated by distension of antrum, protein digestion products in antrum, and neural activity. (Figure 11)

3. **Intestinal phase:** The presence of chyme in the intestine and acid in antrum begin to inhibit acid secretion. A fall in pH of the antrum below 2 inhibits gastrin release via activation of somatostatin release. Presence of food and acid in duodenum initiate neural reflexes which inhibit acid secretion. Also low pH directly inhibits acid secretion.
a. Presence of food and acid in duodenum causes release of hormones (GIP, CCK, secretin, enterogastrone) which inhibit acid secretion.

4. During the course of a meal each phase occurs in sequence to cause a rise then a fall in acid secretion. (Figure 12).

**Figure 12.**

GASTRIC ACID SECRETION OCCURS IN THREE PHASES DURING THE RESPONSE TO A MEAL

F. **Pepsinogen** and **Lipase** secretion

1. Stimulated by vagal and local nervous mechanisms.
2. Usually secreted at same time as acid and flows up gastric gland lumen towards surface with HCl.
3. Acid in lumen converts pepsinogen to activate pepsin by cleavage of short peptide fragment from pepsinogen.

IV. **SUMMARY**

A. As a result of gastric and salivary secretory, motor and digestive activity, the ingested material (now termed “**Chyme**”) had been significantly altered to a state more conductive to further digestion and absorption. Alterations include:

1. Emulsification of fat/lipid material
2. Initial conversion of triglyceride to FFA and diglyceride
3. Initial digestion of protein to oligo/polypeptides and few Amino Acids
4. Initial digestion of large carbohydrates & starches to produce some oligosaccharides
5. Some absorption of water (about 500ml) and ions
6. Acidification of chyme
7. Large increase in osmolarity of chyme

B. Some of these changes are beneficial, some present a challenge to the intestine if uncorrected, and some create intraluminal molecules necessary for release of hormones in the duodenum and for the activation of local and long-arc reflexes in the small intestine.

V. STUDY QUESTIONS

1. The largest total amount of fluid secretion into the gut occurs in the
   A. Oral cavity.
   B. Esophagus.
   C. Stomach.
   D. Small intestine.
   E. Colon.

2. During the intestinal phase of acid secretion
   - Gastrin causes maximal acid secretion.
     A. Pancreatic polypeptide causes gastrin release.
     B. Secretin inhibits acid secretion.
     C. Vagal stimulation is maximal.
     D. Secretion from the Chief cells is stimulated.

3. Salivary gland secretion is stimulated by
   - Secretin.
     A. Gastrin.
     B. Ptyalin.
     C. Parasympathetic nerve stimulation.
     D. Somatostatin.

4. Stimulation of the vagus nerve
   - inhibits the secretion of pepsinogen.
     A. occurs mainly during the intestinal phase of acid secretion.
     B. causes contraction of the gastric fundus.
     C. initiates the secretion of acid and enzymes.
     D. inhibits antral contractions.

Answers 1=D, 2=C, 3=D, 4=D