Digestive Secretion from Pancreas and Liver

Regulation of Secretion Occurs through Secretagogues

The processes involved in the secretion of enzymes and electrolytes are regulated and coordinated. Elaboration of electrolytes and fluids simultaneously with that of enzymes is required to flush any discharged digestive enzymes out of the gland into the gastrointestinal lumen. The physiological regulation of secretion occurs through secretagogues that interact with receptors on the surface of the exocrine cells.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Secretion</th>
<th>secretagogue</th>
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</thead>
<tbody>
<tr>
<td>Salivary gland</td>
<td>amylase</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Stomach</td>
<td>HCl, pepsinogen</td>
<td>Acetylcholine, histamine, gastrin</td>
</tr>
<tr>
<td>Pancreas acini</td>
<td>digestive enzymes</td>
<td>Acetylcholine, cholecystokinin (secretin)</td>
</tr>
<tr>
<td>Pancreas duct</td>
<td>NaHCO$_3$, NaCl</td>
<td>Secretin</td>
</tr>
</tbody>
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Neurotransmitters, hormones, pharmacological agents, and certain bacterial toxins can be secretagogues. Different exocrine cells, for example, in different glands, usually possess different sets of receptors. Binding of the secretagogues to receptors sets off a chain of signaling events that ends with fusion of zymogen granules with the plasma membrane.

Two major signaling pathways have been identified:

1. activation of phosphatidylinositol-specific phospholipase C with liberation of inositol 1,4,5-triphosphate and diacylglycerol; in turn, triggering Ca$^{2+}$ release into the cytosol and activation of protein kinase C, respectively; and
2. activation of adenylate or guanylate cyclase, resulting in elevated cAMP or cGMP levels, respectively. Secretion can be stimulated through either pathway.

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The Pancreas

The pancreas, not the stomach, is the major organ that synthesizes and secretes the large amounts of enzymes needed for digestion. Thus the pancreas plays a vital role in accomplishing the followings:

- Acid must be quickly and efficiently neutralized to prevent damage to the duodenal mucosa
- Macromolecular nutrients - proteins, fats and starch - must be broken down much further before their constituents can be absorbed through the mucosa into blood.

The pancreatic enzymes together with bile are poured into the lumen of the second (descending) part of the duodenum, so that the bulk of the intraluminal digestion occurs distal to this site in the small intestine. However, pancreatic enzymes cannot completely digest all nutrients to forms that can be absorbed. Even after exhaustive contact with pancreatic enzymes, a substantial portion of carbohydrates and amino acids are present as dimers and oligomers that depend for final digestion on enzymes present on the luminal surface or within the chief epithelial cells that line the lumen of the small intestine (enterocytes).

Exocrine Secretions of the Pancreas

Pancreatic juice is composed of two secretory products critical to proper digestion: digestive enzymes and bicarbonate. The enzymes are synthesized and secreted from the exocrine acinar cells, whereas bicarbonate is secreted from the epithelial cells lining small pancreatic ducts.
1. Digestive Enzymes:

   a. Proteases

Digestion of proteins is initiated by pepsin in the stomach, but the bulk of protein digestion is due to the pancreatic proteases. Several proteases are synthesized in the pancreas and secreted into the lumen of the small intestine. The two major pancreatic proteases are trypsin and chymotrypsin both are endopeptidases, which are synthesized and packaged into secretory vesicles as the inactive proenzymes trypsinogen and chymotrypsinogen.

- **Trypsin**: Cleaves peptide bonds on the C-terminal side of arginines and lysines.
- **Chymotrypsin**: Cuts on the C-terminal side of tyrosine, phenylalanine, and tryptophan residues (the same bonds as pepsin, whose action ceases when the NaHCO₃ raises the pH of the intestinal contents).

Once trypsinogen and chymotrypsinogen are released into the lumen of the small intestine, they must be converted into their active forms in order to digest proteins. Trypsinogen is activated by the enzyme enterokinase, which is embedded in the intestinal mucosa.

Once trypsin is formed, it activates chymotrypsinogen, as well as additional molecules of trypsinogen. The net result is a rather explosive appearance of active protease once the pancreatic secretions reach the small intestine.

Trypsin and chymotrypsin digest proteins into peptides and peptides into smaller peptides, but they cannot digest proteins and peptides to single amino acids. Some of the other proteases from the pancreas, for instance **carboxypeptidase** (exopeptidase) (This enzyme removes, one by one, the amino acids at the C-terminal of peptides). But the final digestion of peptides into amino acids is largely the effect of peptidases in small intestinal epithelial cells.

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**Proteolytic Degradation of Dietary Protein**

<table>
<thead>
<tr>
<th>Substrate (dietary protein)</th>
<th>Trypsinogen</th>
<th>Enterokinase (enteropeptidase, intestine)</th>
<th>Chymotrypsinogen</th>
<th>Elastase</th>
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<td>Carboxy protease</td>
<td>Stomach</td>
<td>Serine proteases</td>
<td>Pancreas</td>
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b. **Pancreatic Lipase**

The major form of dietary fat is triglyceride, or neutral lipid. A triglyceride molecule cannot be directly absorbed across the intestinal mucosa. It must first be digested into a 2-monoglyceride and two free fatty acids. The enzyme that performs this hydrolysis is pancreatic lipase. Sufficient quantities of bile salts must also be present in the lumen of the intestine in order for lipase to efficiently digest dietary triglyceride and for the resulting fatty acids and monoglyceride to be absorbed. This means that normal digestion and absorption of dietary fat is critically dependent on secretions from both the pancreas and liver.

Pancreatic lipase has recently been in the limelight as a target for management of obesity. The drug orlistat (Xenical) is a pancreatic lipase inhibitor that interferes with digestion of triglyceride and thereby reduces absorption of dietary fat. Clinical trials support the contention that inhibiting lipase can lead to significant reductions in body weight in some patients.

c. **Amylase**

The major dietary carbohydrate for many species is starch, a storage form of glucose in plants. Amylase is the enzyme that hydrolyses starch to maltose (a glucose-glucose disaccharide), as well as the trisaccharide maltotriose and small branchpoints fragments called dextrins.

d. **Other Pancreatic Enzymes**

In addition to the proteases, lipase and amylase, the pancreas produces a host of other digestive enzymes, including nucleases, gelatinase and elastase.

- **Nucleases.** These hydrolyze ingested nucleic acids (RNA and DNA) into their component nucleotides.
- **Elastase:** Cuts peptide bonds next to small, uncharged side chains such as those of alanine and serine.

2. **Bicarbonate and Water**

Epithelial cells in pancreatic ducts are the source of the bicarbonate and water secreted by the pancreas. The mechanism of bicarbonate secretion is essentially the same as for acid secretion parietal cells and is dependent on the enzyme carbonic anhydrase. In pancreatic duct cells, the bicarbonate is secreted into the lumen of the duct and hence into pancreatic juice.
Control of Pancreatic Exocrine Secretion

Secretion from the exocrine pancreas is regulated by both neural and endocrine controls. During interdigestive periods, very little secretion takes place, but as food enters the stomach and, a little later, chyme flows into the small intestine, pancreatic secretion is strongly stimulated.

- **Cholecystokinin**: This hormone is synthesized and secreted by enteric endocrine cells located in the duodenum. Its secretion is strongly stimulated by the presence of partially digested proteins and fats in the small intestine. As chyme floods into the small intestine, cholecystokinin is released into blood and binds to receptors on pancreatic acinar cells, ordering them to secrete large quantities of digestive enzymes. It also stimulates the gallbladder to release bile and the pancreas to produce pancreatic enzymes.

- **Secretin**: This hormone is secreted in response to acid in the duodenum. The predominant effect of secretin on the pancreas is to stimulate duct cells to secrete water and bicarbonate. As soon as this occurs, the enzymes secreted by the acinar cells are flushed out of the pancreas, through the pancreatic duct into the duodenum. It also stimulates the liver to secrete bile.

- **Gastrin**: This hormone, which is very similar to cholecystokinin, is secreted in large amounts by the stomach in response to gastric distention and irritation, in addition to stimulating acid secretion by the parietal cell; gastrin stimulates pancreatic acinar cells to secrete digestive enzymes.
The Liver

The liver is the largest gland in the body and performs an astonishingly large number of tasks that impact all body systems. One consequence of this complexity is that hepatic disease has widespread effects on virtually all other organ systems.

The three fundamental roles of the liver are:

1. **Vascular functions**: including formation of lymph and hepatic phagocytic system.
2. **Metabolic achievements** in control of synthesis and utilization of carbohydrates, lipids and proteins.
3. **Secretory and excretory functions**, particularly with respect to the synthesis of secretion of bile.

The latter is the only one of the three that directly affects digestion - the liver, through its biliary tract, secretes bile acids into the small intestine where they assume a critical role in the digestion and absorption of dietary lipids.
**Secretion of Bile and the Role of Bile Acids in Digestion**

Bile is a complex fluid containing water, electrolytes and a battery of organic molecules including bile acids, cholesterol, phospholipids and bilirubin that flows through the biliary tract into the small intestine. There are two fundamentally important functions of bile in all species:

- **Bile contains bile acids, which are critical for digestion and absorption of fats and fat-soluble vitamins in the small intestine.**
- **Many waste products are eliminated from the body by secretion into bile and elimination in feces.**

The secretion of bile can be considered to occur in two stages:

- Initially, hepatocytes secrete bile into canaliculi, from which it flows into bile ducts. This hepatic bile contains large quantities of bile acids, cholesterol and other organic molecules.
- As bile flows through the bile ducts it is modified by addition of a watery, bicarbonate-rich secretion from ductal epithelial cells.

In humans: the gall bladder stores and concentrates bile during the fasting state. Typically, bile is concentrated five-fold in the gall bladder by absorption of water and small electrolytes - virtually all of the organic molecules are retained.

Secretion into bile is a major route for eliminating cholesterol. Free cholesterol is virtually insoluble in aqueous solutions, but in bile, it is made soluble by bile acids and lipids like lethicin. **Gallstones (Cholelithiasis)** most of which are composed predominantly of cholesterol, result from processes that allow cholesterol to precipitate from solution in bile.
Role of Bile Acids in Fat Digestion and Absorption

Bile salts are formed in the hepatocytes by a series of enzymatic steps that convert cholesterol to cholic or chenodeoxycholic acids. The rate limiting step is hydroxylation at the 7-alpha position. These reactions include the activity of 8 enzymes belonging to either monooxygenase or dehydrogenase enzyme classes.

The most abundant bile acids (primary bile acids) are:

1. chenodeoxycholic acid (45%) and
2. cholic acid (31%).

Within the intestines the primary bile acids are acted upon by bacteria and converted to the secondary bile acids, identified as

1. deoxycholate (from cholate) and
2. lithocholate (from chenodeoxycholate).

Chenodiol is a natural bile acid that blocks production of cholesterol. Chenodiol (Chenix), is used to dissolve gallstones in patients who cannot tolerate surgery. This action leads to gradual dissolution of cholesterol gallstones.

Synthesis of bile acids is one of the predominant mechanisms for the excretion of excess cholesterol. However, the excretion of cholesterol in the form of bile acids is insufficient to compensate for an excess dietary intake of cholesterol.

Bile acids are conjugated with glycine or taurine and secreted as Na⁺ (or K⁺) salts. Conjugation causes a decrease in their pKa values, making them more water-soluble.

Bile acids are carried from the liver through ducts to the gallbladder, where they are stored for future use.
The ultimate fate of bile acids is secretion into the intestine, where they aid in the emulsification of dietary lipids. In the gut the glycine and taurine residues are removed and the bile acids are either excreted (only a small percentage) or reabsorbed by the gut and returned to the liver. This process of secretion from the liver to the gallbladder, to the intestines and finally reabsorption is termed the *enterohepatic circulation*.

**Enterohepatic Recirculation**

After the bile acids has been released into the small intestine via the bile duct to play an integral role in the absorption of dietary lipids and lipid soluble vitamins. More than 90% of the bile salts are actively reabsorbed (by a sodium-dependent co-transport process) from the ileum into the hepatic-portal circulation from where they are cleared and resecreted by the liver to once again be stored in the gall bladder. This secretion/reabsorption cycle is called the Enterohepatic Circulation.

*Systemic circulation:* supplies nourishment to all of the tissue located throughout your body, with the exception of the heart and lungs because they have their own systems. Systemic circulation is a major part of the overall circulatory system.

*Portal circulation:* Blood from the gut and spleen flow to and through the liver before returning to the right side of the heart. This is called the portal circulation and the large vein through which blood is brought to the liver is called the portal vein.

The net effect of this enterohepatic recirculation is that each bile salt molecule is reused about 20 times, often two or three times during a single digestive phase.
Note: liver disease can dramatically alter this pattern of recirculation - for instance, sick hepatocytes have decreased ability to extract bile acids from portal blood and damage to the canalicular system can result in escape of bile acids into the systemic circulation. Assay of systemic levels of bile acids is used clinically as a sensitive indicator of hepatic disease.

Bile acids contain both hydrophobic (lipid soluble) and polar (hydrophilic) faces. The amphipathic nature enables bile acids to carry out two important functions:

1. **Emulsification of lipid aggregates**: Bile acids have detergent action on particles of dietary fat, which causes fat globules to break down or be emulsified into minute, microscopic droplets. Emulsification is not digestion per se, but is of importance because it greatly increases the surface area of fat, making it available for digestion by lipases, which cannot access the inside of lipid droplets.

2. **Solubilization and transport of lipids in an aqueous environment**: Bile acids are lipid carriers and are able to solubilize many lipids by forming micelles - aggregates of lipids such as fatty acids, cholesterol and monoglycerides - that remain suspended in water. Bile acids are also critical for transport and absorption of the fat-soluble vitamins.

**Clinical Significance of Bile Acid Synthesis**

Bile acids perform four physiologically significant functions:

1. Their synthesis and subsequent excretion in the feces represent the only significant mechanism for the elimination of excess cholesterol.

2. Bile acids and phospholipids solubilize cholesterol in the bile, thereby preventing the precipitation of cholesterol in the gallbladder.

3. They facilitate the digestion of dietary triacylglycerols by acting as emulsifying agents that render fats accessible to pancreatic lipases.

4. They facilitate the intestinal absorption of fat-soluble vitamins.
Pattern and Control of Bile Secretion

The flow of bile is lowest during fasting, and a majority of that is diverted into the gallbladder for concentration. When chyme from an ingested meal enters the small intestine, acid and partially digested fats and proteins stimulate secretion of cholecystokinin and secretin. These enteric hormones have important effects on pancreatic exocrine secretion. They are both also important for secretion and flow of bile:

1. **Cholecystokinin:** The name of this hormone describes its effect on the biliary system - cholecysto = gallbladder and kinin = movement. The most potent stimulus for release of cholecystokinin is the presence of fat in the duodenum. Once released, it stimulates contractions of the gallbladder and common bile duct, resulting in delivery of bile into the gut.

2. **Secretin:** This hormone is secreted in response to acid in the duodenum. Its effect on the biliary system is very similar to what was seen in the pancreas - it simulates biliary duct cells to secrete bicarbonate and water, which expands the volume of bile and increases its flow out into the intestine.