CASE 30

A 43-year-old man presents to his gastroenterologist with symptoms of peptic ulcer disease. He states that he has a midepigastric burning pain that is relieved by eating food and worse on an empty stomach. The patient has been on numerous antacid medications without relief. He has had recurrent peptic ulcers for the last 5 years, and has had minimal relief with the usual treatments. A fasting serum gastrin level is drawn and found to be extremely elevated. After further tests are done, the patient is diagnosed with a gastrin-secreting tumor in the pancreas.

- **By what mechanism might elevated gastrin levels cause ulcers?**
- **What cells are stimulated to secrete acid by gastrin?**
- **What cells are responsible for secretion of intrinsic factor?**
ANSWERS TO CASE 30: GASTRIC SECRETION

Summary: A 43-year-old man has recurrent peptic ulcers that are not responsive to normal therapy. He has elevated fasting gastrin levels and is diagnosed with a gastrin-secreting pancreatic tumor (Zollinger-Ellison syndrome).

◆ **Mechanism that might lead to peptic ulcers:** Continuous acid secretion that is not subject to negative feedback and injures the gastric mucosa.

◆ **Cells that secrete acid in response to gastrin:** Parietal cells.

◆ **Cells that are responsible for secretion of intrinsic factor:** Parietal cells.

CLINICAL CORRELATION

Peptic ulcer disease is seen commonly in the primary care physician’s office. Peptic ulcers result when there is a disruption of the mucosal integrity of the stomach and/or the duodenum that leads to inflammation and pain. A patient’s pain usually is described as epigastric in location and burning in nature, with aggravation when fasting and relief with food. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection are the two major causes of peptic ulcer disease. Gastric acid contributes to mucosal injury but does not always play a primary role. Gastric acid production in the stomach is controlled by a variety of mechanisms, including the hormone gastrin, the paracrine histamine, and the neurocrine acetylcholine (ACh). The production of gastrin usually is closely controlled; however, for patients with Zollinger-Ellison syndrome, severe peptic ulcer disease results from hypersecretion of gastric acid from an unregulated gastrin release from a non-β-cell endocrine tumor. Patients with Zollinger-Ellison often present with symptoms of peptic ulcer disease. Suspicion for this disorder should be present when patients have ulcers in unusual locations, ulcers refractory to standard medical therapy, ulcer recurrence after acid-reducing surgery, or ulcers with frank complications. A fasting gastrin level will help confirm the diagnosis, although further studies are needed.

APPROACH TO GASTRIC SECRETION

Objectives

1. Know about salivary secretion, gastric secretion, and pancreatic secretion.
2. Be able to describe bile secretion.
3. Understand the function of the gallbladder.
Definitions

**Amylase**: An enzyme secreted by salivary glands and the pancreas that takes part in starch digestion.

**Pepsinogen**: A pro-enzyme secreted by the stomach that is converted to pepsin that takes part in protein digestion.

**Trypsinogen, chymotrypsinogen, and prophospholipases**: Proenzymes secreted by the pancreas which when activated take part in protein and fat digestion.

**Lipase**: An enzyme secreted by the pancreas that takes part in fat digestion.

**DISCUSSION**

Specialized epithelial cells that line the acini and ducts of the organs that constitute the gastrointestinal system secrete the organic and inorganic components that affect the digestion and absorption of the materials that people ingest and protect the organs from possible deleterious effects of many of the secretions. The chemical makeup of the secretion, as well as the regulation of the secretion, varies remarkably from organ to organ.

In the oral cavity, secretory and absorptive activities of the acinar and ductule cells of the salivary glands result in the production of a large volume, compared with glandular weight, of hypotonic solution that is rich in potassium and bicarbonate compared with plasma. Through a secondary active transport system involving apical membrane chloride channels, acinar cells secrete a solution similar in inorganic composition to that of plasma. As this fluid passes through the ducts, sodium and chloride are absorbed in partial exchange for potassium and bicarbonate to result in the final secretion. In addition to the inorganic components, several of the salivary glands contain cells that secrete amylase and lipase, which begin the process of digestion; lysozyme and lactoferrin, which have antimicrobial activity; and mucus. These components are synthesized in the endoplasmic reticulum and stored in secretory granules until they are released. Regulation of salivary secretion is done almost entirely through neurocrine pathways, primarily parasympathetic. However, salivary glands are among the few organs whose secretions are stimulated by both parasympathetic and sympathetic divisions of the autonomic nervous system.

In the body of the stomach, parietal (oxyntic), chief (peptic), and mucus neck cells secrete hydrochloric acid, pepsin, and soluble mucus, respectively. In addition, surface epithelial cells in all regions secrete a more viscous mucus in an alkaline fluid. All of these products are secreted into the gastric lumen to take part in digestion of ingested foodstuffs, and in protection of the stomach. In addition to these digestive and protective secretions, the parietal cells secrete intrinsic factor which is necessary for the absorption of vitamin B<sub>12</sub>. In the antrum, there are endocrine (G) cells that secrete gastrin in an endocrine fashion to stimulate parietal cells, and endocrine cells that secrete somatostatin in a paracrine fashion to inhibit G cell secretion of gastrin. The secretion of acid by parietal cells is accomplished by a primary active transport
process involving a hydrogen-potassium-ATPase (H\(^+\)-K\(^+\)-ATPase). In resting cells, this enzyme is localized to a system of membranes (tubulovesicles) residing just below the surface of the cells’ apical membrane. In this location, the enzyme is inactive. Upon stimulation of the parietal cell, the tubulovesicles fuse with the apical cell membrane, which contains potassium channels. In the presence of these channels, the H\(^+\)-K\(^+\)-ATPase becomes active, resulting in the secretion of HCl in a concentration of 150 mmol/L. During the secretion of this acid into the gastric lumen, bicarbonate is produced and released into the venous blood, producing an alkaline tide. Secretion of the pepsin precursor pepsinogen by chief cells is via exocytosis of protein that has been synthesized in the endoplasmic reticulum and stored in secretory granules. In the presence of acid in the lumen of the stomach, the secreted pepsinogen is converted to the active protease pepsin.

Stimulation of acid secretion occurs when receptors for acetylcholine (ACh), histamine, and gastrin on the basolateral membranes of the parietal cells are stimulated. Occupation of the muscarinic ACh and the gastrin receptors results in an increase in intracellular free calcium; occupation of the histamine H\(_2\) receptor results in an increase in cyclic adenosine monophosphate (cAMP). Calcium and cAMP act in a synergistic manner to bring about HCl secretion. ACh and gastrin also stimulate HCl secretion by acting on receptors on enterochromaffin-like cells (ECLs). These cells, which are adjacent to parietal cells, release histamine, which in turn acts in a paracrine manner to stimulate acid secretion. Antral G cells synthesize and store gastrin in secretory granules. Upon stimulation, gastrin is released into the bloodstream and circulates back to the stomach to act on parietal cells. Initially, the acid that is secreted is buffered by the ingested food. However, as more acid is secreted and the partially digested food empties into the duodenum, the pH falls. When antral pH falls to about 3 or below, somatostatin is released to inhibit gastrin secretion, thus decreasing further acid secretion. However, as in this case, gastrin also can be produced by tumors in areas that are not subject to this negative feedback. Thus, there is a continuous secretion of large amounts of acid. This can cause pain and damage, especially during times when there is no food in the stomach to buffer the acid.

In the pancreas, acinar cells synthesize and then store in secretory granules a large number of enzymes, such as lipase and amylase, and proenzymes such as trypsinogen, chymotrypsinogen, and the prophospholipases. These enzymes are required for the digestion of complex carbohydrates, proteins, and lipids. Cells that line the pancreatic ducts, in contrast, secrete a fluid rich in bicarbonate through a secondary active transport system that involves apical membrane chloride channels and chloride-bicarbonate exchangers. The bicarbonate neutralizes the acid being emptied from the stomach to bring the pH of the chyme closer to 7 to allow for optimal activity of the pancreatic enzymes. Pancreatic acinar cells possess receptors mainly for ACh and cholecystokinin (CCK). When occupied, both, but especially CCK receptors, result in enzyme secretion. Ductule cells, in contrast, possess receptors for secretin as well as for ACh and CCK. It is primarily occupation of the secretin receptor that results in stimulation of ductile secretion.
In the liver, hepatocytes synthesize and secrete conjugated bile acids (which at physiologic pH exist as bile salts), phospholipids, and cholesterol necessary for digestion and absorption of lipids. To these organic constituents is added an inorganic solution rich in bicarbonate that is secreted mainly by cells lining the biliary ducts. Only a small fraction of the bile acids that are secreted into the canaliculi at any given time are synthesized de novo. Most are resecreted as part of the enterohepatic circulation. This circulation is characterized by the secretion of bile acids into the duodenum. Once in the upper small intestine, the acids aid in the absorption of lipid-soluble materials. Most of the bile acids then are absorbed, mostly in the ileum, by a carrier-mediated process. They return to the liver in the portal blood and are extracted by the hepatocytes by another carrier-mediated process, pass through the cell, and are resecreted, thus completing the circulation. The small percentage lost during the circulation is replenished by hepatic synthesis. There seems to be little direct regulation of hepatocyte bile secretion by neurocrine, endocrine, or paracrine pathways; however, secretin does increase water and bicarbonate secretion by the bile ducts. The rate of hepatocyte bile secretion depends mostly on the rate of return of bile acids through the enterohepatic circulation and in part by the rate of de novo synthesis of bile acids.

During the interdigestive state, the bile that is secreted by the liver enters the gallbladder rather than the small intestine. There, the organic components are concentrated as water and electrolytes are absorbed. As the bile acids, phospholipids, and cholesterol are concentrated, they form mixed micelles that are water soluble and stay in solution. With the ingestion of a meal, contraction of the gallbladder and relaxation of the sphincter of Oddi accomplish the expulsion of bile into the duodenum, thus increasing the enterohepatic circulation. Gallbladder contraction is initiated during the cephalic phase of digestion through the release of ACh via extrinsic nerves, but most contraction occurs during the intestinal phase of digestion through the action of CCK, which appears to activate intrinsic nerves, which in turn cause contraction of gallbladder smooth muscle and relaxation of sphincter of Oddi smooth muscle.

**COMPREHENSION QUESTIONS**

[30.1] A 25-year-old woman with inflammatory bowel disease has a large portion of her ileum removed. Bile acid metabolism in such a patient would be characterized by which of the following?

A. Decreased loss of bile acids in the stool
B. Increased de novo synthesis of bile acids
C. Increased return of bile acids to the liver via the portal blood
D. Increased secretion of bile acids by the liver
[30.2] A patient with duodenal ulcers has elevated serum gastrin levels that do not decrease upon acidification of the gastric antrum. In such a patient, which of the following is likely to be depressed?
A. Gastric acid secretion
B. Gastric pepsinogen secretion
C. Pancreatic bicarbonate secretion
D. Release of gastrin from antral G cells
E. Serum secretin levels

[30.3] A 32 year old alcoholic male with chronic pancreatitis in which more than 90% of pancreatic function is lost. Which of the following is most likely to be observed?
A. Decreased serum secretin levels
B. Depressed blood glucose levels
C. Enhanced bile acid micelle formation
D. Increased duodenal pH levels
E. Steatorrhea

Answers

[30.1] B. Removal of the ileum will interrupt the enterohepatic circulation of bile salts by removing the site of active reabsorption. This will result in a loss of bile acids in the feces and a decrease in the return of bile acids to the liver by the portal blood. The decreased flux of bile acids through hepatocytes will result in an upregulation of bile acid synthesis. Synthesis usually will not keep up with loss, and so the secretion of bile acids by the liver will be decreased.

[30.2] D. This patient probably has a tumor that is secreting gastrin in an unregulated manner. This will result in increased gastric acid secretion and very low gastric pH and duodenal pH. The low duodenal pH will lead to increased serum secretin levels and increased pancreatic bicarbonate secretion. The low gastric pH will lead to an increase in pepsinogen secretion but a decrease in the secretion of gastrin from antral G cells.

[30.3] E. This much destruction of the pancreas will lead to a deficiency in the secretion of bicarbonate, digestive enzymes, and islet cell hormones. Decreased bicarbonate will lead to decreased duodenal pH, which in turn leads to increased serum secretin levels and to a decreased solubility of bile acids in the intestinal lumen. The decreased secretion of lipase along with impaired micelle formation will lead to fat maldigestion and steatorrhea. The loss of adequate insulin secretion will result in elevated blood glucose levels (diabetes mellitus).
PHYSIOLOGY PEARLS

❖ Salivary secretion is hypotonic, rich in potassium, and produced in a large volume.
❖ Salivary secretion is stimulated when either or both of its sympathetic and parasympathetic nerves are stimulated.
❖ Acid secretion by gastric parietal cells is accomplished by primary active transport.
❖ Major stimulants of acid secretion are the neurocrine ACh, the hormone gastrin, and the paracrine histamine.
❖ Gastrin release is inhibited in a paracrine fashion by somatostatin, which is released when antral pH drops below approximately 3.
❖ Pancreatic enzymes are secreted by acinar cells, primarily in response to ACh and CCK. Pancreatic bicarbonate is secreted by duct cells, primarily in response to secretin. However, CCK potentiates the effect of secretin on bicarbonate secretion.
❖ Bile is formed in the liver and concentrated in the gallbladder. Bile is expelled by the gallbladder into the duodenum, primarily in response to CCK released from the small intestine.
❖ Bile salts secreted into the duodenum take part in the digestion and absorption of lipids and then are reabsorbed in the ileum to be returned to the liver in the portal blood.

REFERENCES

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