Chapter 11
Secretion of Digestive Juices

During a meal, a large volume of digestive juices include the salivary secretions, the gastric juice, the pancreatic and bile secretions. Daily, the total volume of exocrine gland secretions into the gastrointestinal lumen (7 plus liters) is easily three times larger than the water intake. Most of the water of the digestive juices are reabsorbed by the small and large intestines.

This implies that a large increase in blood flow occurs concurrently to the various exocrine glands during stimulated secretions. The aqueous portion of the secretions are derived from the plasma of the blood capillaries that perfuse the glands. Parasympathetic nerve activity increases the salivary and splanchnic blood flow.

Except for salivation which is basically neurally regulated, the gastric, pancreatic and bile secretions are under neuro-endocrine controls The various secretions are timed and sequentially released in concert with the presence of masticated food in the mouth and arrival of the food bolus or chyme at different segments of the GI tract.

Besides digestive enzymes, the digestive juices also has protective roles. The salivary bicarbonate and the pancreatic bicarbonate neutralize acidity and prevents acidophilic bacteria growth orally and duodenal erosion respectively. Gastric low acidity is also bactericidal. An adjacent gastric mucosal secreted layer of bicarbonate and mucus also contribute to the gastric barrier to prevent acidic tissue injury and autodigestion.

Hepatic bile, secreted and stored in the gall bladder is released during digestion to enable the digestion and absorption of fats in the aqueous milieu of the GI lumen. Amphipathic or amphiphilic bile salts are responsi**BILE** for successful fat processing during a meal.

1 Saliva

Elaborate and respond to the following concerning saliva.

a. Amylase is active between pH 4 and 11.

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b. The largest salivary gland secretes little mucins.
c. Maximal blood flow to salivary glands is greater than an equal mass of active skeletal muscle. Comment.
d. What is the tonicity of saliva?
e. The potassium concentration is always much greater than in plasma.

Salivary amylase has the same enzymatic specificity as pancreatic amylase. In the stomach, amylase continues to operate until antral mixing lowers the pH to below 4.0. If chewing is substantial, more than half of starch can be broken down to oligosaccharides.

The parotid glands, the largest salivary glands, are entirely serous. The submandibular and sublingual are mixed mucous and serous glands. Serous acinar cells secrete amylase found in zymogen granules at the apical side of the cell. Maximal rate of saliva production in human is about one ml/min/g. This is equivalent to the gland's weight/min. Blood flow is proportional to the high rate of salivary secretion. Maximal perfusion to salivary glands is about tenfold than in the same weight of contracting skeletal muscle. The parasympathetic nerve innervations release acetylcholine and VIP, both of which produce the vasodilation.

Saliva is always hypotonic to plasma, about 70 % that of plasma. The primary secretion is isotonic. The salivary ducts remove more Na^+ and Cl^- than they add K^+ and HCO_3^-. The faster the salivary flow rate, the nearer to isotonicity it will be. Resting saliva is slightly acidic. With increasing salivary flow, the saliva becomes basic, up to pH 8.0. This is partly due to the greater bicarbonate concentration with higher flow rate.

The salivary K^+ concentration with higher flow rate is very low. The ducts only modify the composition of the primary salivary secretion. The volume of saliva is not affected.

2 Salivary Secretion

a. What is the primary physiological control of salivary glands?
b. How does cyclic AMP affect secretion?
c. What is the role of calcium in serous acinar cell secretion?
d. What is the effect of noradrenaline?
e. How is chloride absorbed by the salivary ducts?

Most of the gastrointestinal secretions are controlled hormonally. In contrast, the major regulator of salivary secretion is the parasympathetic fibers in the facial and glossopharyngeal nerves (cranial nerves VII and IX respectively). Parasympathetic stimulation increases the synthesis and secretion of amylase, mucins. The neural activity also increases ductal transport processes, elevates blood flow as well as enhancing glandular metabolism and growth. Sympathetic activity also increases, salivary flows but the parasympathetic effects are greater and more prolonged.

Noradrenaline acts on alpha and beta receptors to increase cytosolic calcium and cAMP respectively.

Effectors that elevate cAMP result in a primary secretion that is richer in amylase. This includes the action of VIP. Agonists that increase intracellular calcium lead to a greater volume of acinar cell secretion but with a lower concentration of amylase. Substance P and acetylcholine produce this response in the serous acinar cell.

Chloride enters by a HCO_3^-/Cl^- anion antiporter at the apical membrane. Basolateral K^+ channels that are activated by increased cytosolic Ca^{++} maintain the electronegativity of the cytosol. This helps to drive chloride absorption across the basolateral membrane via a chloride channel. The chloride conductance may be enhanced by increased cytosolic cAMP or Ca^{++}.

The impermeability of the ductal epithelium to water leads to the hypotonicity of the saliva as the ducts modify the salivary composition by a net reabsorption of electrolytes.

3 Gastric Secretion

a. Why does the pH of the gastric contents decrease when chyme moves to the small intestine?
b. What effect has atropine on the vagal stimulation of gastric HCl secretion?
c. Why does cimetidine have a greater HCl inhibitory effect than expected?
d. Why can bet H^+ secretory rate be lower in gastric ulcer?
e. Why is the parietal mass increased in Zollinger-Ellison Syndrome?

Gastric HCl is inhibited when HCl is no longer required to activate pepsinogen to pepsin. This occurs when the gastric chyme has moved to the small intestine. Decreased pH gastric content is the main inhibitory regulator of HCl secretion. The reason is due to the buffering capacity of food. When food is emptied from the stomach, the gastric pH decreases and thus inhibits gastrin release. In addition, somatostatin also inhibits gastrin secretion. Somatostatin is released by acid in the lumen and it probably acts in a paracrine way via gastric juice to suppress gastrin secretion.

Atropine will block the cholinergic stimulation of parietal cells. However, atropine will not inhibit the vagal action on gastrin secretion since the neurotransmitter is not acetylcholine but GRP (gastrin-releasing polypeptide).

The three agonists of parietal cells (acetylcholine, histamine and gastrin) also potentiate each other's effect. The combined response is greater than the sum of the individual responses. Thus, the H_2 receptor blocker, cimetidine produces a bigger HCl inhibitory response than expected. Cimetidine blocks the direct action of histamine as well as the histamine-potentiated effects.

In gastric ulcer, the gastric mucosal barrier is damaged. This then permits the H^+ and pepsin to autodigest the mucosa. Net H^+ secretion can be lower due to the leak

of secreted H^+ into the defective mucosa. Gastrin secretion is elevated due to the reduced inhibition by gastric H^+.

H^+ secretion is greatly elevated in gastrinoma (commonly in the pancreas). Gastrin also has a trophic effect on the parietal cells. Duodenal ulcers develop and acid-inactivation of pancreatic lipases result in steatorrhoea.

4 Gastric Juice Secretion

a. What are the three physiological agonists of HCl secretion by parietal cells?
b. What happens to parietal cell when the basolateral K^+ channels are activated?
c. What happens to the luminal membrane chloride conductance?
d. What stimuli release intrinsic factor?
e. What is the strongest agonist of HCl secretion?

Histamine, gastric and acetylcholine are the three physiological activators of parietal cell HCl secretion. Each of these is an example of paracrine, endocrine and neurocrine control of GI secretions. Acetylcholine and gastrin elevate the cytosolic calcium concentration while histamine increases the intracellular cAMP.

There are two types of potassium channels in the basolateral membranes of the parietal cell. One type of K^+ channel is Ca^{++}-activated and the other type is activated by cAMP. Greater efflux of K^+ through these channels hyperpolarizes the parietal cell. This increases the driving force that promotes chloride anion movement out of the cell through the apical electrogenic Cl^- channels. The chloride conductance during secretion is also markedly increased by the raised cytosolic Ca^{++} and cAMP concentrations. Furthermore, cAMP and Ca^{++} also stimulate the insertion of more Cl^- channels into the luminal membrane. The number of H^+/K^+ ATPase in the canalicular membrane is also increased. This is effected by the secretory canaliculi. During HCl secretion, the parietal cells undergo a morphological change. Extensive membrane fusion occurs to increase the number of HCl-extension sites.

The same stimuli that produce HCl secretion also release intrinsic factor from the parietal cell. Intrinsic factor is the only gastric component that is essential for life.

Histamine has greater potency on parietal cells than acetycholine and gastrin. Much of the response to gastrin is a consequence of gastrin-activated release of histamine from ECL cells. Histamine H_2 receptor blockers can reduce the parietal HCl response that is due to gastrin.

5 Gastric Acid Secretion

Elaborate on the following regarding gastric parietal cell functions.

a. The gastric glands contain enterochromaffin-like cells.
b. The major anion of gastric juice is chloride.

c. The H^+ concentration gradient across the parietal cell membrane is about one million-fold.
d. Chloride exchanges with bicarbonate across the basolateral membrane.
e. Secretion of H^+ requires an ATPase.

The gastric mucosa can be classified into three distinct regions. In a gastric gland, the mucous neck cells can differentiate into columnar epithelial cells. The parietal and peptic cell (secrete HCl and pepsinogens respectively) are located deeper in the gland. The oxyntic glands also have ECL cells that secrete histamine and D cells that release somatostatin.

Potassium is always higher in gastric juice than in plasma. Thus severe vomiting can precipitate hypokalemia. Chloride is the major anion at all rates of gastric secretion. At higher rates of secretion, gastric juice is like an isotonic solution of HCl. The pH in parietal cell cytosol is 7.0 while the gastric lumen is about 1.0. This corresponds to a million-fold gradient against which the parietal cell must secrete H^+.

The apical membrane of the parietal cell contains a H^+/K^+ ATPase exchanger. Benzimidazole drugs like omeprazole reacts irreversibly with the sulfhydryl groups of H^+/K^+ ATPase at the low pH.

When H^+ is actively pumped out of the parietal cell, there is an excess of gradient across the basolateral membrane. Chloride influx into the cell across the basolateral membrane is driven and energized by the downhill efflux of HCO_3^- via a HCO_3^-/Cl^- countertransporter. The lumen of the stomach is electronegative by 30–80 mV relative to the serosa. Thus chloride enters the gastric lumen against both chemical and electrical potential differences.

6 Gastric Acid Regulation

Respond and elaborate on the following aspects of gastric acid physiology.

a. The most important endogenous antagonist is somatostatin.
b. In the cephalic phase, is the direct vagal input to the parietal cells the only stimulus for acid secretion?
c. How much acid can be secreted during a cephalic phase?
d. The acidity of gastric contents regulates itself? Explain.
e. What effect does intact proteins have on HCl secretion?

Somatostatin directly inhibits HCl secretion by parietal cell. Somatostatin also decreases gastrin secretion from the G cells. The cephalic phase is evoked by the sight, smell and taste of food before the food enters the stomach. The vagal fibers stimulate enteric neurons that are mainly cholinergic. These cholinergic neurons directly produce the cephalic phase gastric HCl secretion. Indirectly, the acetylcholine also increases acid secretion by releasing gastrin from antral G cells and histamine from gastric ECL cells.

In the absence of food, the pH of the antral contents drops rapidly during the cephalic phase. Acid secretion during this period may be up to 40 % of the total secreted during a meal. However inhibitory mechanisms activated by low pH in the antrum limits the amount of acid secreted. When the gastric mucosa is bathed with a solution of pH 2.0 or less, HCl secretion by any agonist mechanism is effectively blocked. The inhibition is brought about by direct action on parietal cells, local inhibitory neural reflexes and reduction of gastrin from G cells.

The gastric phase of gastric secretion is initiated by the presence of food in the stomach. The dominant stimuli are distention of the stomach and presence of protein digestion products (peptides and amino acids). Amino acids, particularly phenylalanine and tryptophan, and peptides cause antral G cells to release gastrin. Distention triggers local and central, vagovagal reflexes via mechanoceptors stimulation. Gastric distention enhances the chemical activation of parietal HCl secretion.

7 Gastric Mucosal Barriers

Elaborate on the following protective parameters of the gastric mucosal barrier.

a. Gastric mucins are about 80 % carbohydrate.
b. The stomach has a very thin layer of viscous, alkaline coat.
c. Gastric secretions can transverse the mucus layer.
d. The pH of the gastric epithelial cell surface is maintained at about 7.0.
e. Non-steroidal inflammatory agents reduce the efficacy of the gastric mucosal barrier.

Mucins are secreted by Mucous neck cells. About 80 % of a gastric mucin is carbohydrate. Mucin consists of four monomers, each 500×10^3 daltons in weight. The protective mucus layer requires continuous production of tetrameric mucins to replace those cleaved by pepsins. The glycosylated part of the mucin is resistant to proteolysis. Mucus production is stimulated by some of the same stimuli that increase acid and pepsinogen secretion. Acetycholine is especially important. Mechanical deformation of the gastric mucosa also elicits neural reflexes that promote mucus secretion.

Bicarbonate secreted is entrapped by the viscous mucus HCO_3^- makes the mucus layer alkaline. Bicarbonate secretion is enhanced by parasympathetic acetylcholine release. The mucus layer is about 0.2 mm thick, and it effectively separates the HCO_3^- at the surface epithelial cells from the acidic contents of the gastric lumen.

There are 5–7 μm diameter channels through the mucus layer. Through these, the gastric secretions can move. The mucus allows the pH of the epithelial surface to be maintained at around 7.0, while the gastric luminal pH is about 2.0. Gastric mucosal barrier requires both the mucus and bicarbonate secretions.

Drugs like aspirin inhibit both the secretion of mucus and HCO_3^- secretion. This may result in the pathogenesis of stress ulcers.

8 What Is the Role of the Following Factors in the Intestinal Phase of Gastric Secretion?

a. Duodenal distension.
b. Peptides and amino acids.
c. Bulbogastrone.
d. Hypertonic chyme.
e. Low pH of chyme.

The entry of chyme in the duodenum activates neural and endocrine responses that initially stimulate and later inhibit acid secretion in the stomach. This depends on the activity of the gastric chyme. When the buffering capacity of the gastric chyme is exceeded and the pH of the emptied chyme falls below 3.0, inhibition predominates.

Duodenal distention increases gastric acid secretion by vagovagal reflexes that then stimulate the antral G and parietal cells. There are also G cells in the duodenum and proximal jejunum. Peptides/amino acids stimulate gastrin release from these cells. In addition, absorbed amino acids and peptides may circulate to the antral G cells to enhance further gastrin secretion.

Intestinal hormones that influence gastric secretions are called enterogastrones. Acid I the duodenal bulb stimulates bulbogastrone which reduces acid secretion by the parietal; cells. Acid in the duodenum also suppresses parietal cell HCl release via enteric and vagovagal reflexes. Additional inhibition is through the release of the hormone secretin.

Fat digestion products in the duodenum and proximal jejunum inhibits HCl secretion via the hormones cholecystokinin and GIP. An unestablished enterogastrone partly mediates the gastric acid reduction produced by hypertonicity in the duodenum.

9 Pancreatic Secretion

Respond to the following regarding the exocrine function of the pancreas

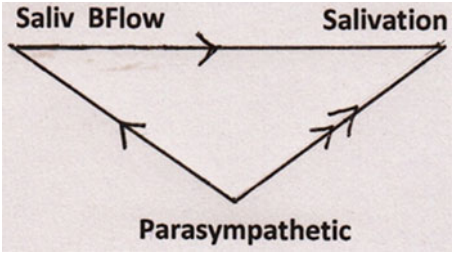
a. What is the principal source of HCO_3^- secreted into the lumen?
b. During which phase does most of the secretion occur?
c. How does CCK potentiate the action of the hormone secretion?
d. The major direct agonist of acinar cell is acetylcholine.
e. What is the nature of the juice secreted during the gastric phase?

Bicarbonate in the perfusing blood of the pancreas is the main source of the secreted bicarbonate. The mechanism is similar to the renal proximal tubular reabsorption of HCO_3^-. It involved secretion of H^+ by the basolateral membrane Na^+/H^+ exchanger and H^+/K^+ ATPase. The CO_2 formed from the reaction between secreted

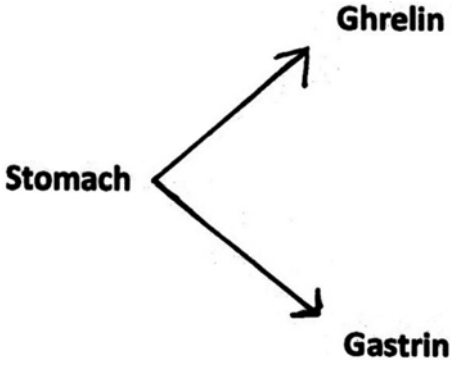
H^+ and HCO_3^- enters the ductal epithelial cells and is hydrated, catalyzed by carbonic anhydrase. Dissociation of the carbonic acid produces HCO_3^- and H^+. The HCO_3^- enters the lumen via the HCO_3^-/Cl^- exchanger.

At rest, the aqueous component is made primarily by the intercalated and intralobular ducts. When secretin hormone is increased, the additional aqueous component is produced mainly by the extralobular ducts. Secretagogues that elevate cAMP potentiate the effects of those that raise intracellular Ca^{++}. Secretin elevates cytosolic cAMP. Apparently, the more important effect of CCK in stimulating acinar cell enzyme-rich secretion is indirect CCK stimulates the afferent arms of vagovagal reflexes that in turn trigger secretion by acinar cells and ductal cells. In response to a meal, about 65 % of the total pancreatic juice is produced when chyme comes into contact with the duodenum and upper jejunum. In a single day, the pancreas secretes about ten times its mass of pancreatic juice.

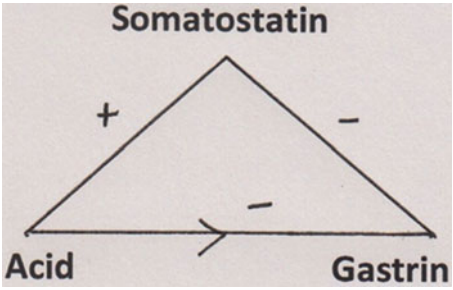
Distension of the stomach evokes vagovagal and enteric gastro pancreatic reflexes that stimulate acinar and duct cells. The juice produced is small in volume with a high enzyme concentration.



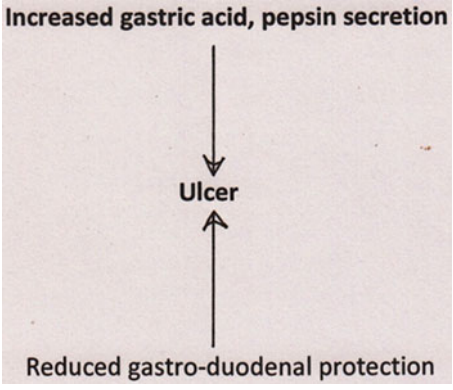
The regulation of salivation, during cepahlic, conditioned reflex or oral phase is mediated predominantly by parasympathetic nerve. The parasympathetics increase simultaneously, the salivary flow and the blood flow to the salivary glands. The aqueous volume in the saliva is derived or secreted from the plasma.



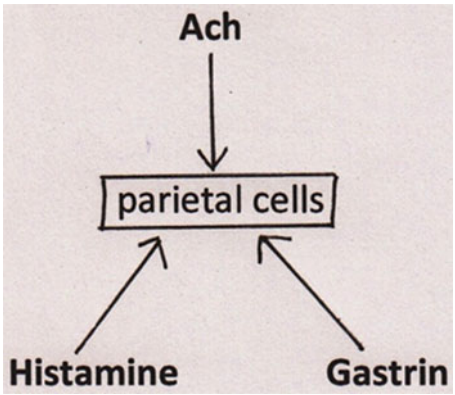
The stomach secretes two major hormones, gastrin during a meal (gastrin) while ghrelin is increased during the inter-digestive period and it stimulates appetite. The name ghrelin is coined from its action in stimulating growth hormone (GH) release. GH is hyperglycemic and ghrelin's effect on GH during fasting does have some physiologic sense. Gastrin increases acid secretion that promotes protein digestion by pepsin and eventually, the amino acid absorbed into the blood stimulates GH secretion, which increases cellular uptake of the amino acids.



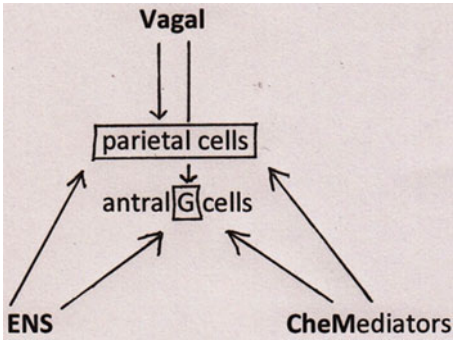
The gastric paracrine somatostatin is the major 'brake' on the secretion of acid. This action of somatostatin is indirect by suppressing gastrin release and this removes a major stimulus on the acid-secreting gastric parietal cells. The low intra-luminal gastric acidity in an empty stomach stimulates somatostatin paracrine secretion.



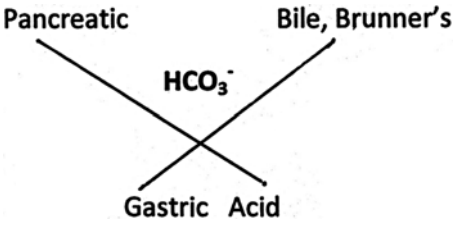
The incidence of GI ulceration is dependent on the balance between gastric proteolytic activities in acidic milieu and the tissue self-protective, structural and functional mechanisms that shelter gastric and duodenal cells from autodigestion and acidic tissue corrosion.



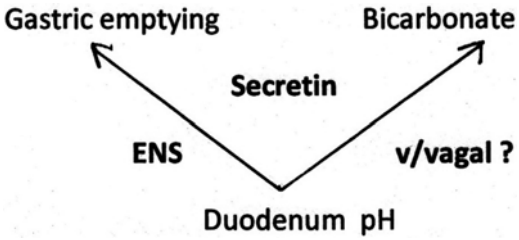
The three major stimuli of proton secretion by gastric parietal cells. Acetylcholine is a neurotransmitter at both ENS neurons and at the post-ganglionic parasympathetic nerve fibers that innervate the stomach.



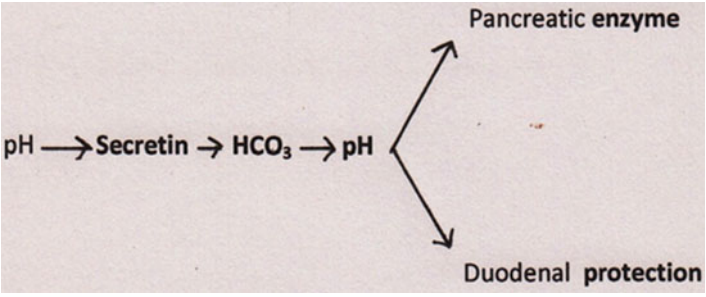
The antral G cells secrete gastrin. In turn, gastrin is released by specific vagal nerve activity, by stretch-activated ENS reflex and by proteolytic products in the stomach. The parietal cells that secrete hydrogen ions are innervated by excitatory enteric and vagal neural inputs. Besides gastrin, local mediator like gastric histamine also increases hydrochloric acid secretion.



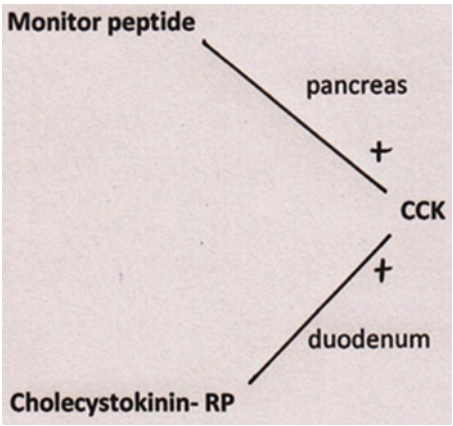
Neutralization of the acidic gastric chyme is needed as the pancreatic enzymes act at a higher pH in the duodenal lumen. The base, bicarbonate is secreted in the pancreatic juice, bile and from intestinal Brunner's glands.



The duodenal hormone secretin (first named 'hormone') is part of two feedback loops, one with the pancreas and the other with the stomach. The trigger for both loops is duodenal pH. Secretin increases the bicarbonate content of pancreatic juice. Secretin also slows down the entry of acidic chyme from the stomach. Besides the mediator role of secretin released in response to pH, there are possibly also local enteric and long loop vagal reflexes, activated by pH that govern gastric emptying and the bicarbonate secretion.



Duodenal pH and secretion of the hormone secretin forms a feedback loop. The release of a bicarbonate rich pancreatic juice by secretin when acidic chyme touches the duodenal wall accomplishes two purposes. The acid neutralization raises the luminal pH for optimal pancreatic enzyme action. Secondly, the duodenum, unlike the stomach, has no definite 'mucosal barrier' and needs to be protected from acidic injury.



Recent studies on cholecystokinin action have revealed two regulatory peptides that regulate CCK release. Monitor peptide is produced by pancreatic acinar cells, while CCK releasing peptide is from the duodenal cells. The two peptides help to match pancreatic secretion of proteolytic enzymes to the requirement for these proteases in the intestinal lumen. When the proteins in the meal are completely digested and absorbed, both these control peptides will themselves be sacrificially degraded by the pancreatic enzymes.