GASTROINTESTINAL PHYSIOLOGY

Gastrointestinal function

The gastrointestinal tract (GIT) is a continuous tube that extends from the mouth to the anus.

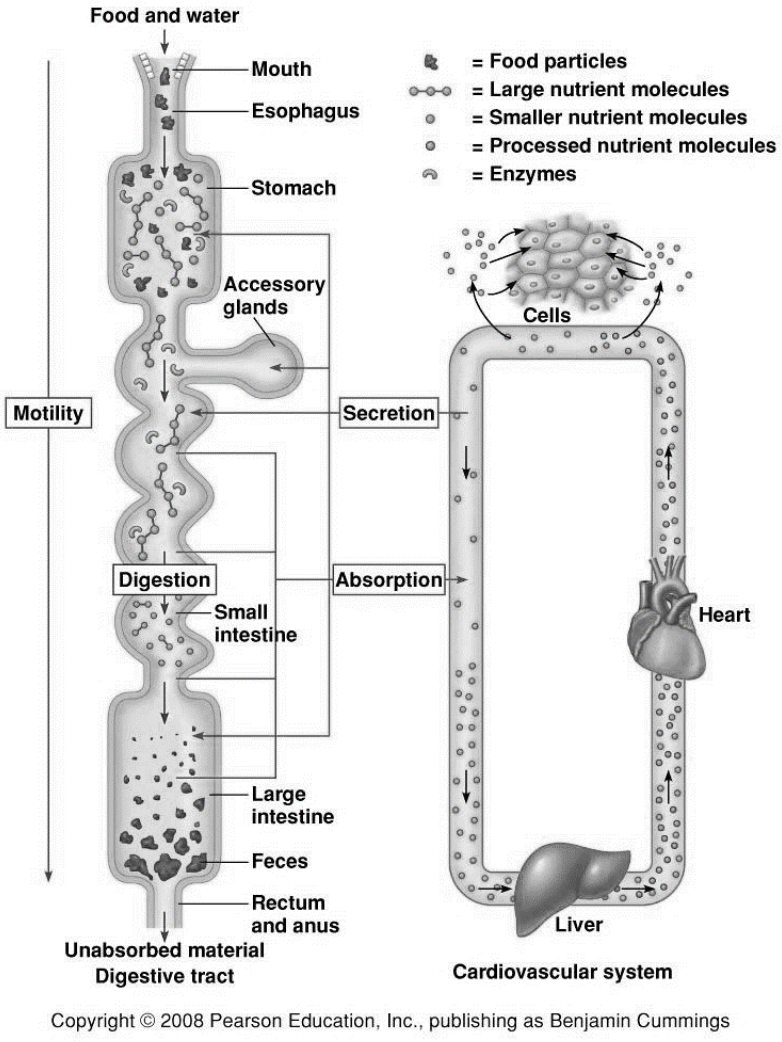
There are four major activities of GI tract

1. **Motility**
   Propel ingested food from mouth toward rectum and mixes and reduces the size of the food.

2. **Secretion**
   Aid in digestion and absorption

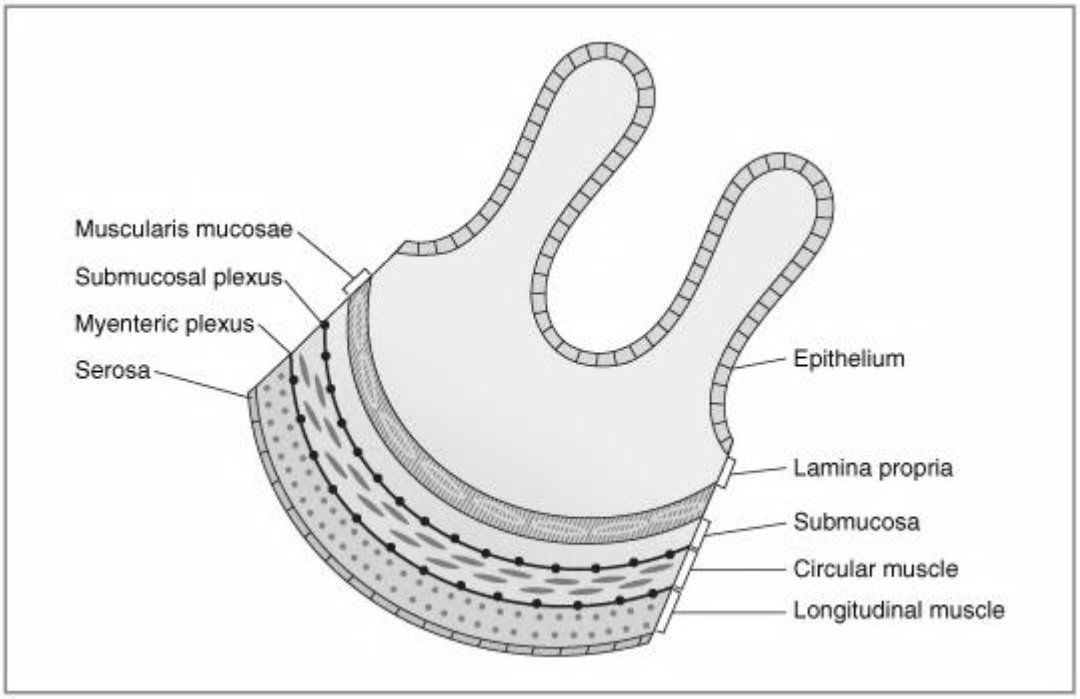
3. **Digestion**
   Breaking down complex foodstuffs into absorbable units by enzymes produced in the digestive system, involves the breakdown of carbohydrates, proteins fats, and other foods.

4. **Absorption**
   Nutrients, electrolytes, and water are absorbed



Structure of the Gastrointestinal Tract

The gastrointestinal tract is arranged **linearly** in the following sequence: **mouth, esophagus, stomach, small intestine (including the duodenum, jejunum, and ileum), large intestine, and anus**. Other structures of the gastrointestinal tract are **the salivary glands, pancreas, liver, and gallbladder*, all of which serve secretory functions*.**



Structure of the wall of the gastrointestinal tract.

The layers of the gastrointestinal wall are as follow, starting from the lumen and moving toward the blood:

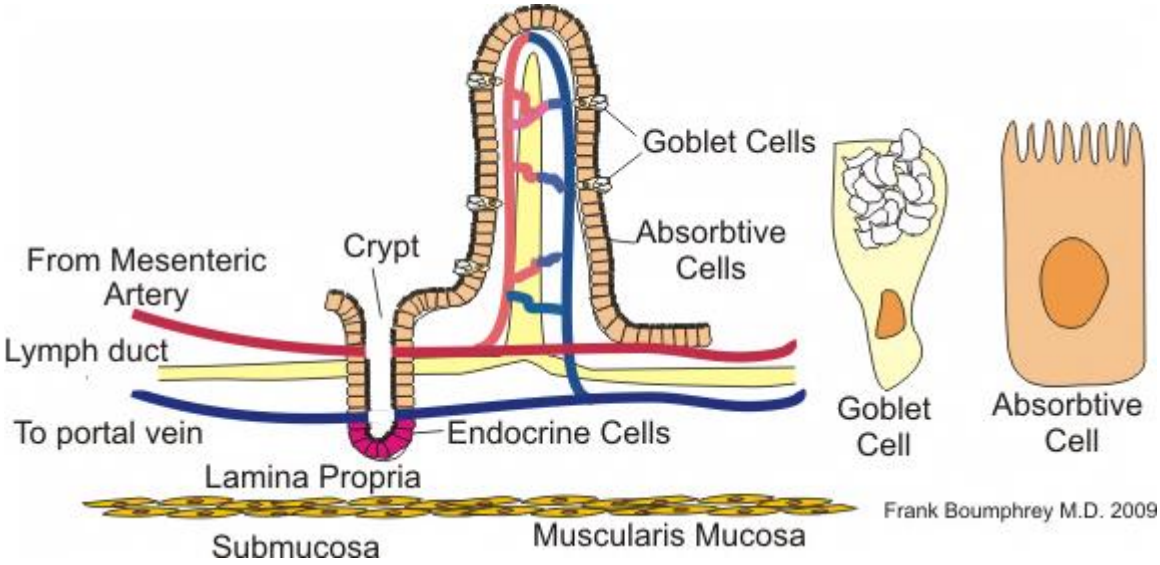
A. **Mucosal layer** consists of a layer of
   1. Epithelial cells, which are are specialized to carry out absorptive and secretory functions.
   2. Lamina propria, consists primarily of connective tissue, but it also includes blood and lymph vessels.
   3. Muscularis mucosae, consists of smooth muscle cells; contraction of the muscularis mucosae changes the shape and surface area of the epithelial cell layer.

B. **Submucosal layer,** which consists of collagen, elastin, glands, and the blood vessels of the gastrointestinal tract.

C. **Muscularis Properia** (**circular muscle** and **longitudinal muscle)** which provided the motility of the gastrointestinal tract.

D. Two plexuses, the **submucosal plexus** and the **myenteric plexus**, contain the nervous system of the gastrointestinal tract.
E. **Serosa;** faces the blood.

The epithelium of the intestine is also further specialized in a way that maximizes the surface area available for nutrient absorption. Throughout the small intestine, it is folded up into fingerlike projections called **villi**. Between the villi are infoldings known as **crypts**.



Innervation of the Gastrointestinal Tract

The gastrointestinal tract is regulated, in part, by the **autonomic nervous system,** which has an extrinsic component and an intrinsic component.

- The **extrinsic** component is the **sympathetic** and **parasympathetic** innervation of the gastrointestinal tract.
- The **intrinsic** component is called **the enteric nervous system**.
  - Contained within wall of GI tract
  - Communicates with Extrinsic component

Parasympathetic Innervation

Parasympathetic innervation is supplied by:

1. The **vagus nerve** innervates the *upper* gastrointestinal tract, including the upper third of the esophagus, the wall of the stomach, the small intestine, and the ascending colon.

2. The **pelvic nerve** innervates the *lower* gastrointestinal tract, including the external anal canal and the walls of the transverse, descending, and sigmoid colons.

The parasympathetic nervous system has long preganglionic fibers that synapse in ganglia ***in or near*** the target organs. In the gastrointestinal tract, these ganglia actually are located in the walls of the organs within the myenteric and submucosal plexuses. Postganglionic neurons of the parasympathetic nervous system are classified as either cholinergic or peptidergic. **Cholinergic neurons** release acetylcholine (ACh) as the neurotransmitter. **Peptidergic neurons** release one of several peptides, including substance P and vasoactive inhibitory peptide (VIP).

The **vagus** nerve is a mixed nerve of afferent and efferent fibers. Afferent fibers deliver sensory information from the periphery (e.g., from mechanoreceptors and chemoreceptors in the wall of the gastrointestinal tract) to the central nervous system (CNS). Efferent fibers deliver information from the CNS to target tissues in the periphery (e.g., smooth muscle, secretory, and endocrine cells)**.**

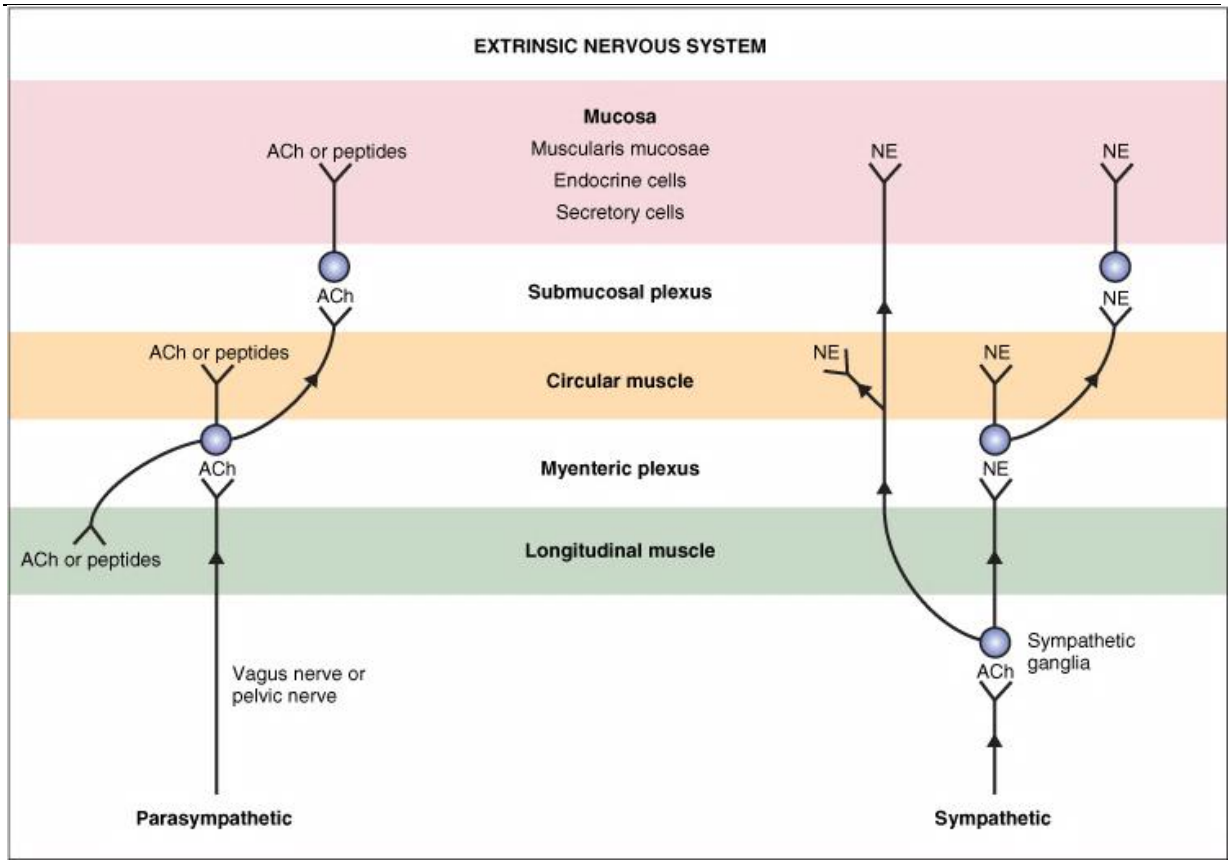
Sympathetic Innervation

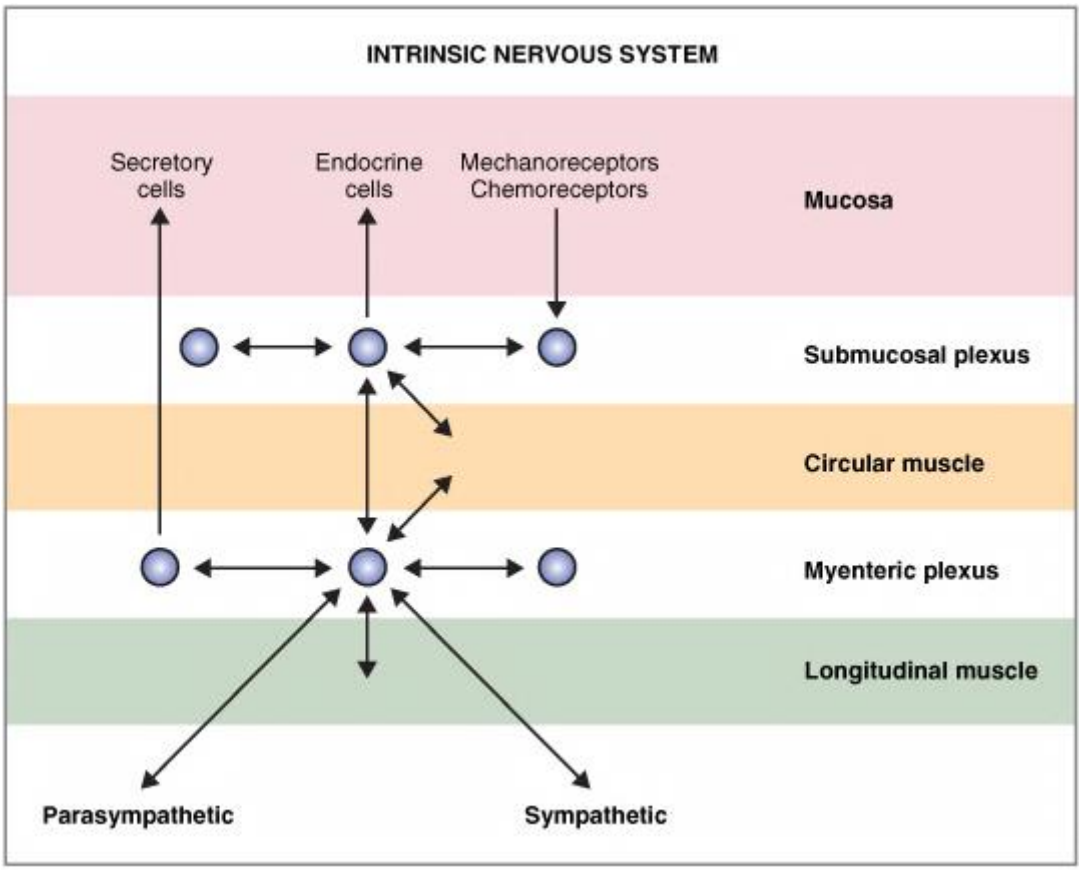
Preganglionic fibers of the sympathetic nervous system are relatively short and synapse in ganglia *outside* the gastrointestinal tract. Four sympathetic ganglia serve the gastrointestinal tract: **celiac**, **superior mesenteric**, **inferior mesenteric**, and **hypogastric**. Postganglionic nerve fibers, which are adrenergic (i.e., release norepinephrine), leave these sympathetic ganglia and synapse on ganglia in the myenteric and submucosal plexuses, or they directly innervate smooth muscle, endocrine, or secretory cells.

The sympathetic nerve fibers are afferent and efferent. Thus, as with the parasympathetic innervation, sensory and motor information is relayed back and forth between the gastrointestinal tract and the CNS.

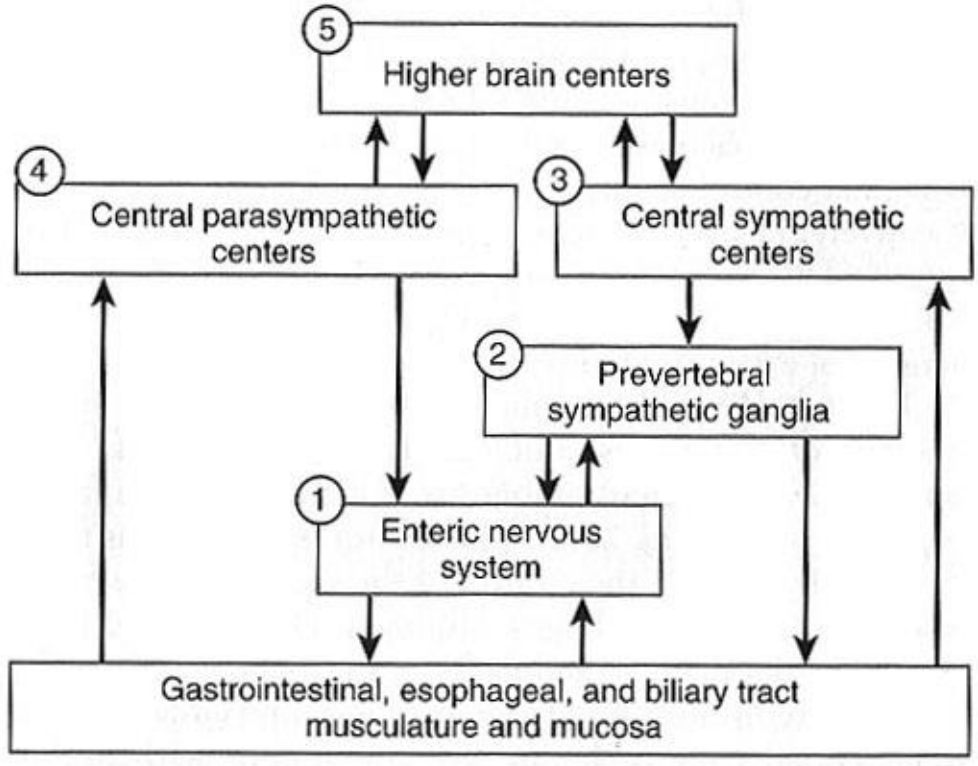
Intrinsic Innervation

- Can direct all functions of GI in the absence of extrinsic innervation
- Controls contractile, secretory, and endocrine functions of GI tract
- Receives input from
    1. Parasympathetic and sympathetic nervous systems
    2. Mechanoreceptors and chemoreceptors in mucosa
- Sends information directly *to* smooth muscle, secretory, and endocrine cells


EXTRINSIC NERVOUS SYSTEM
Mucosa
Muscularis mucosae
Endocrine cells
Secretory cells
Submucosal plexus
Circular muscle
Myenteric plexus
Longitudinal muscle
ACh or peptides
ACh
ACh or peptides
ACh
ACh or peptides
Vagus nerve or pelvic nerve
Parasympathetic
NE
NE
NE
NE
NE
NE
NE
Sympathetic ganglia
ACh
Sympathetic


INTRINSIC NERVOUS SYSTEM
Secretory cells
Endocrine cells
Mechanoreceptors Chemoreceptors
Mucosa
Submucosal plexus
Circular muscle
Myenteric plexus
Longitudinal muscle
Parasympathetic
Sympathetic

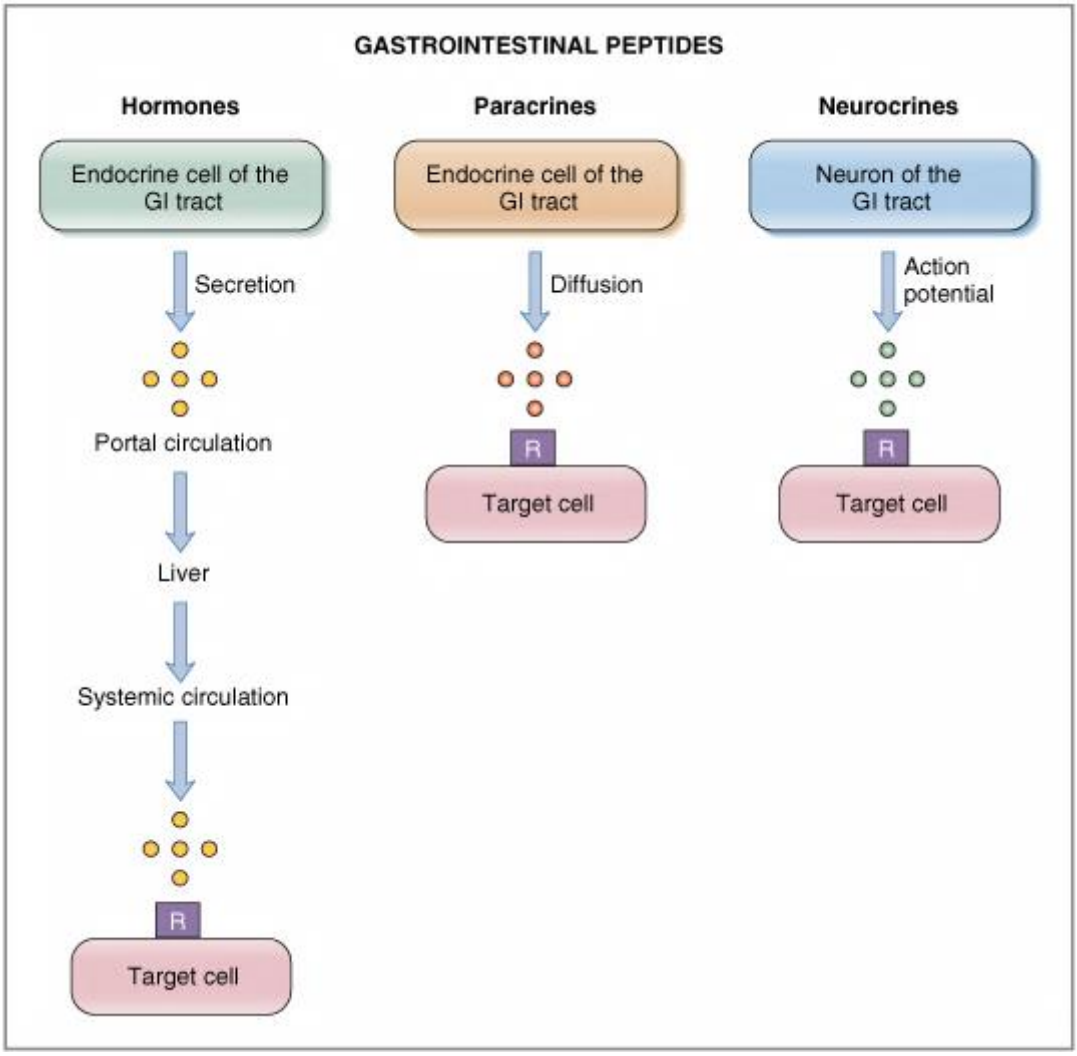
Substance	Source	Actions
Acetylcholine (ACh)	Cholinergic neurons	Contraction of smooth muscle in wall Relaxation of sphincters ↑ Salivary secretion ↑ Gastric secretion ↑ Pancreatic secretion
Norepinephrine (NE)	Adrenergic neurons	Relaxation of smooth muscle in wall Contraction of sphincters ↑ Salivary secretion
Vasoactive Intestinal Peptide (VIP)	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↑ Intestinal secretion ↑ Pancreatic secretion
Gastrin-Releasing Peptide (GRP), or Bombesin	Neurons of gastric mucosa	↑ Gastrin secretion
Enkephalins (opiates)	Neurons of mucosa and smooth muscle	Contraction of smooth muscle ↓ Intestinal secretion
Neuropeptide Y	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↓ Intestinal secretion
Substance P	Cosecreted with ACh	Contraction of smooth muscle ↑ Salivary secretion



Gastrointestinal Peptides

Gastrointestinal peptides, including **hormones, neurocrines, and paracrines**, regulate the functions of the gastrointestinal tract. These functions include:

1. Contraction and relaxation of smooth muscle wall and sphincters
2. Secretion of enzymes for digestion
3. Secretion of fluid and electrolytes
4. Trophic (growth) effects on the tissues of the gastrointestinal tract.
5. Some regulate secretion of *other* gastrointestinal peptides.



- **Hormones**
  - Peptides released from endocrine cells of GI tract
  - Secreted into portal circulation and enter systemic circulation
  - The target cells may be located in the gastrointestinal tract itself (e.g., gastrin acts on the parietal cells of the stomach to cause acid secretion), or the target cells may be located elsewhere in the body

(e.g., gastric inhibitory peptide acts on the beta (β) cells of the pancreas to cause insulin secretion).

- Includes: Gastrin, Cholecystokinin, Secretin, and Gastric Inhibitory Peptide

Gastrin

Gastrin is secreted by **G (gastrin) cells** in the antrum of the stomach. There are two forms of gastrin:

1. ***little gastrin*** which has 17-amino acid and it is secreted in response to a meal.
2. ***Big gastrin***, which has 34 amino acid and it is secreted during the interdigestive period (between meals).

Both types of gastrin are biosynthesized from the precursor **progastrin**.

The physiologic stimuli that initiate gastrin secretion all are related to ingestion of food. These stimuli include the products of protein digestion (e.g., small peptides and amino acids), distention of the stomach by food, and vagal stimulation. Local vagal reflexes also stimulate gastrin secretion. In these local reflexes, the neurocrine released from vagal nerve endings onto the G cells is **gastrin-releasing peptide (GRP),** or bombesin. In addition to these positive stimuli, gastrin secretion is ***inhibited*** by (1) a low pH of the gastric contents and by (2) somatostatin.

Actions of gastrin. Gastrin has two major actions: (1) It stimulates **H^+ secretion** by gastric parietal cells, and (2) it stimulates **growth of the gastric mucosa,** a trophic effect.

Cholecystokinin (CCK)

CCK is structurally related to gastrin. Thus, CCK has *some* gastrin activity. CCK_A receptors are selective for CCK, while CCK_B receptors are equally sensitive to CCK and gastrin.

CCK is secreted by the **I cells** of the duodenal and jejunal mucosa in response to two types of physiologic stimuli: (1) monoglycerides and fatty acids (but not triglycerides), and (2) small peptides and amino acids. These stimuli alert the I cells to the presence of a meal containing fat and protein, which must be digested and absorbed. CCK will then ensure that appropriate pancreatic enzymes and bile salts are secreted to aid in this digestion and absorption.

There are five major **actions of CCK,** and each contributes to the overall process of fat, protein, and carbohydrate digestion and absorption.

1. **Contraction of the gallbladder** with simultaneous relaxation of the sphincter of Oddi ejects bile from the gallbladder into the lumen of the small intestine. Bile is needed for emulsification and solubilization of dietary lipids.
2. **Secretion of pancreatic enzymes.** Pancreatic **lipases** digest ingested lipids to fatty acids, monoglycerides, and cholesterol, all of which can be absorbed. Pancreatic **amylase** digests carbohydrates, and **pancreatic** proteases digest protein.
3. **Secretion of bicarbonate (HCO_3^-) from the pancreas.** This is not a major effect of CCK, but it potentiates the effects of **secretin** on HCO_3^- secretion.
4. **Growth of the exocrine pancreas and gallbladder.** Since the major target organs for CCK are the exocrine pancreas and the gallbladder, it is logical that CCK also has trophic effects on these organs.
5. **Inhibition of gastric emptying.** CCK inhibits or slows gastric emptying and *increases gastric emptying time.* This action is critical for the processes of fat digestion and absorption, which require a considerable amount of time. CCK slows the delivery of chyme (partially digested food) from the stomach to the small intestine, ensuring adequate time for the subsequent digestive and absorptive steps.

Secretin

Secretin is secreted by the **S cells** (secretin cells) of the duodenum in response to H^+ and fatty acids in the lumen of the small intestine. Thus, secretion of secretin is initiated when the acidic gastric contents (pH < 4.5) arrive in the small intestine.

The function of secretin is to promote the **secretion of pancreatic and biliary HCO_3^-,** which then neutralizes H^+ in the lumen of the small intestine. Neutralization of H^+ is essential for fat digestion; pancreatic lipases have pH optimums between 6 and 8, and they are inactivated when the pH is less than 3. Secretin also inhibits the effects of gastrin on the parietal cells (H^+ secretion and growth).

Glucose-Dependent Insulinotropic Peptide (GIP)

Glucose-dependent insulinotropic peptide (GIP) is secreted by **K cells** of the duodenal and jejunal mucosa. It is the only gastrointestinal hormone that is secreted in response to all three types of nutrients: glucose, amino acids, and fatty acids.

The major physiologic action of GIP is **stimulation of insulin secretion** by the pancreatic β cells. This action explains the observation that an oral glucose load is utilized by cells more rapidly than an equivalent intravenous glucose load. Oral glucose stimulates GIP secretion, which stimulates insulin secretion (in addition to the direct stimulatory action of absorbed glucose on the β cells). Glucose given

intravenously stimulates insulin secretion only by the direct action on the β cells. The other action of GIP is **inhibition of gastric H^+ secretion.**

Summary of Gastrointestinal Hormones

Hormone	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	G cells of the stomach	Small peptides and amino acids Distention of the stomach Vagal stimulation (GRP)	↑ Gastric H^+ secretion Stimulates growth of gastric mucosa
Cholecystokinin (CCK)	I cells of the duodenum and jejunum	Small peptides and amino acids Fatty acids	↑ Pancreatic enzyme secretion ↑ Pancreatic HCO_3^- secretion Stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi Stimulates growth of the exocrine pancreas and gallbladder Inhibits gastric emptying
Secretin	S cells of the duodenum	H^+ in the duodenum Fatty acids in the duodenum	↑ Pancreatic HCO_3^- secretion ↑ Biliary HCO_3^- secretion ↓ Gastric H^+ secretion Inhibits trophic effect of gastrin on gastric mucosa
Glucose-Dependent Insulinotropic Peptide (GIP)	Duodenum and jejunum	Fatty acids Amino acids Oral glucose	↑ Insulin secretion from pancreatic β cells ↓ Gastric H^+ secretion

- **Paracrines**
    - Secreted by endocrine cells of GI tract
    - Act *locally* within same tissue that secretes them

Somatostatin is secreted by D cells of the gastrointestinal mucosa in response to decreased luminal pH.

- *Inhibits* secretion of other GI hormones
- *Inhibits* gastric H^+ secretion
- somatostatin is also secreted by the hypothalamus and by the delta (δ) cells of the endocrine pancreas.

Histamine is secreted by enterochromaffin-like cells (ECL cells) of the stomach. Histamine along with gastrin and ACh, stimulates H^+ secretion by the gastric parietal cells.

- **Neurocrines**
    - Released by neurons of GI tract following an action potential
    - Includes: ACh, norepinephrine, Vasoactive Intestinal Peptide (VIP), Gastrin-Releasing Peptide (GRP), Neuropeptide Y, and Substance P

Motility

Motility refers to contraction and relaxation of the walls and sphincters of the gastrointestinal tract. Motility grinds and mixes ingested food to prepare it for digestion and absorption, and then it propels the food along the gastrointestinal tract.

Contractile tissue of GI tract is **Smooth Muscle** *except* in pharynx, upper 1/3 esophagus, and external anal sphincter are **striated muscle**, Smooth muscle cells coupled via **gap junctions** that permit rapid spread of action potentials for coordinated smooth muscle contractions.

- Spontaneous cycles of slow wave potentials in specialised SM cells (***Interstitial cell of Cajal***) stimulate an AP
- Slow wave potentials must reach a threshold in order to stimulate an AP. Frequency can be modified by neurotransmitters, hormones and paracrine signalling.
- The longer the cycle, the more AP generated
- The more APs, the greater the contraction
- This process is Ca^{2+} dependent

When **circular muscle** contracts, it results in shortening of a ring of smooth muscle, which decreases the diameter of that segment. When **longitudinal muscle**

contracts, it results in shortening in the longitudinal direction, which decreases the length of that segment.

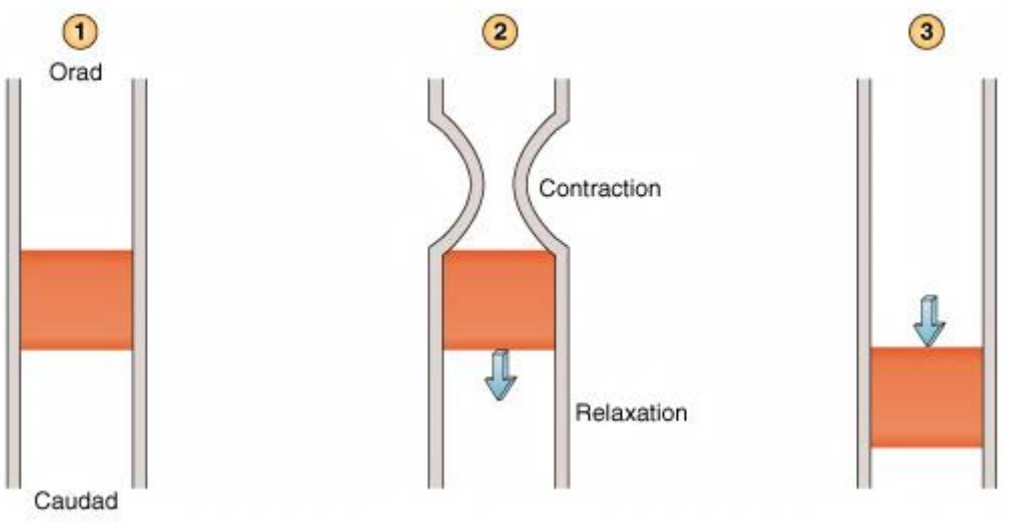
General Patterns of Motility

Peristalsis

Peristalsis is a reflex response that is initiated when the gut wall is stretched by the contents of the lumen, and it occurs in all parts of the gastrointestinal tract from the esophagus to the rectum. The stretch initiates a circular contraction behind the stimulus and an area of relaxation in front of it. The wave of contraction then moves in an oral-to-caudal direction, propelling the contents of the lumen forward.

That result in:

- Longitudinal muscle contracts orad to bolus, propeling chyme along small intestine
- Portion of intestine caudad to bolus, relaxes

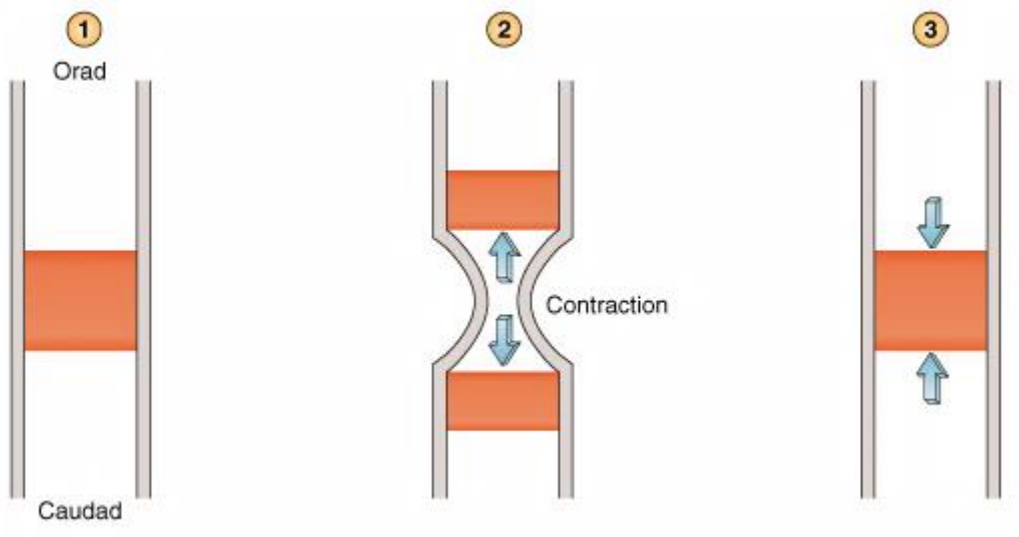


Peristaltic Contraction

Segmentation & Mixing

The enteric nervous system promotes a motility pattern that is designed to retard the movement of the intestinal contents along the length of the intestinal tract to provide time for digestion and absorption, and it provides mixing of the intestinal contents with the digestive juices. A segment of bowel contracts at both ends, and then a second contraction occurs in the center of the segment to force the chyme both backward and forward. This mixing pattern persists for as long as nutrients remain in the lumen to be absorbed. In summary:

- Circular muscle contracts sending chyme in both orad and caudad directions
- Intestine then relaxes allowing chyme to merge back together



Segmentation Contraction

MOUTH AND ESOPHAGUS

Salivary Secretion

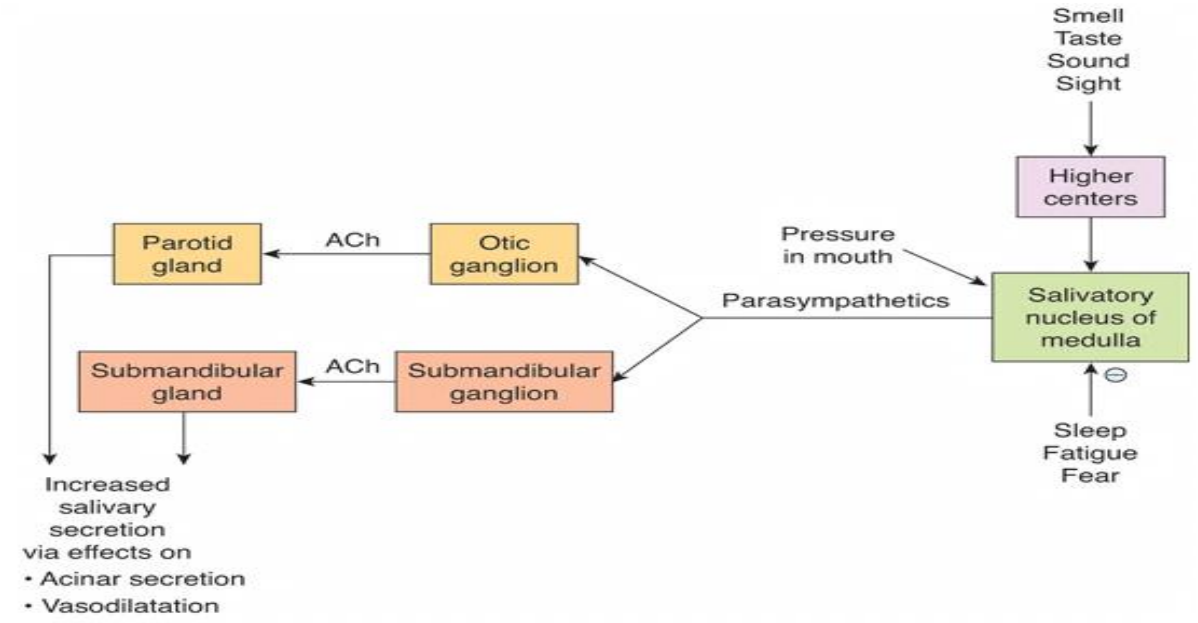
The first secretion encountered when food is ingested is saliva. Saliva is produced by three pairs of salivary glands that drain into the oral cavity. Salivary glands supply 1000 to 1500 mL of saliva per day.

Salivary secretion is almost entirely controlled by neural influences, with the parasympathetic branch of the autonomic nervous system playing the most prominent role. Sympathetic input slightly modifies the composition of saliva (particularly by increasing proteinaceous content), but has little influence on volume. Secretion is triggered by reflexes that are stimulated by the physical act of chewing, but is actually initiated even before the meal is taken into the mouth as a result of central triggers that are prompted by thinking about, seeing, or smelling food, but inhibited by fear or during sleep.

Saliva performs a number of important functions:

1. Initiate digestion (particularly of starch, mediated by amylase)
2. Facilitates swallowing.

3. Keeps the mouth moist
4. Serves as a solvent for the molecules that stimulate the taste buds.
5. Aids speech by facilitating movements of the lips and tongue.
6. Protect the oral cavity from bacteria (has some antibacterial action)
7. Keeps the mouth and teeth clean.
8. The buffers in saliva neutralize gastric acid and relieve heartburn when gastric juice is regurgitated into the esophagus.



Chewing (Mastication)

Chewing has three functions: (1) It mixes food with saliva, lubricating it to facilitate swallowing; (2) it reduces the size of food particles, which facilitates digestion (3) it mixes ingested carbohydrates with salivary amylase to begin carbohydrate digestion.

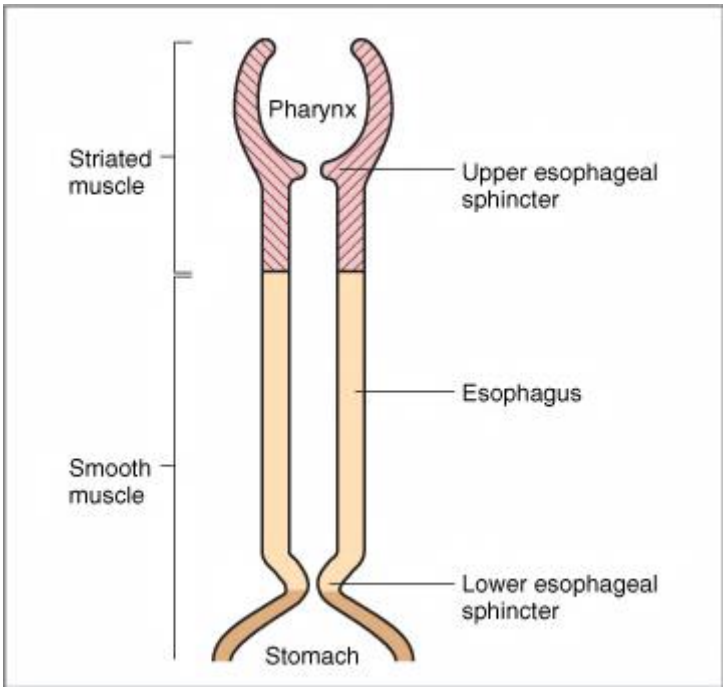
Chewing has both **voluntary** and **involuntary** components. The involuntary component involves reflexes initiated by food in the mouth. Sensory information is relayed from mechanoreceptors in the mouth to the **brain stem,** which orchestrates a reflex oscillatory pattern of activity to the muscles involved in chewing. Voluntary chewing can override involuntary or reflex chewing at any time.

Swallowing

Swallowing is initiated voluntarily in the mouth, but thereafter it is under involuntary or reflex control. The reflex portion is controlled by the **swallowing center,** which is located in the **medulla.** Sensory information (e.g., food in the mouth) is detected by somatosensory receptors located near the pharynx. This sensory, or afferent, information is carried to the medullary swallowing center via the vagus and glossopharyngeal nerves. The medulla coordinates the sensory

information and directs the motor, or efferent, output to the striated muscle of the pharynx and upper esophagus**.**

There are three phases involved in swallowing: oral, pharyngeal, and esophageal. The oral phase is voluntary, and the pharyngeal and esophageal phases are controlled by reflexes.

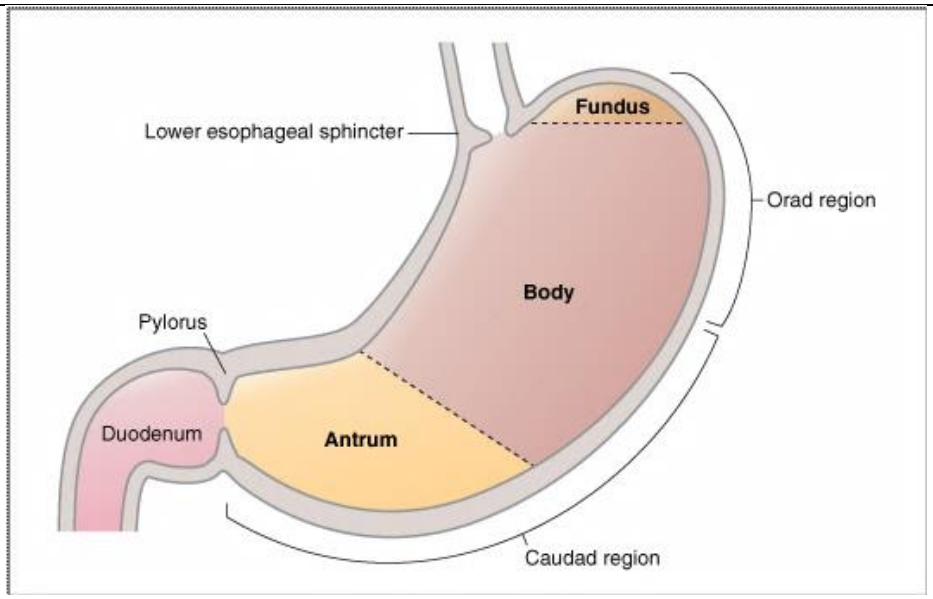


STOMACH

Gastric Motility

There are three components of gastric motility: (1) relaxation of the orad region of the stomach to receive the food bolus from the esophagus, (2) contractions that reduce the size of the bolus and mix it with gastric secretions to initiate digestion, and (3) gastric emptying that propels chyme into the small intestine. The rate of delivery of chyme to the small intestine is **hormonally regulated** to ensure adequate time for digestion and absorption of nutrients in the small intestine.

The stomach has three anatomic divisions: the **fundus,** the **body,** and the **antrum.** Based on differences in motility, the stomach also can be divided into two regions, orad and caudad. The **orad region** is proximal, contains the fundus and the proximal portion of the body, and is thin walled. The **caudad region** is distal, contains the distal portion of the body and the antrum, and is thick walled to generate much stronger contractions than the orad region. Contractions of the caudad region mix the food and propel it into the small intestine.



Receptive relaxation (relaxation of the orad stomach) is a **vagovagal reflex,** mechanoreceptors detect distention of the stomach and relay this information to the CNS via sensory neurons. The CNS then sends efferent information to the smooth muscle wall of the orad stomach, causing it to relax. The neurotransmitter released from these postganglionic peptidergic vagal nerve fibers is **VIP.** Vagotomy eliminates receptive relaxation.

Gastric Emptying

After a meal, the stomach contains about 1.5 L, which is composed of solids, liquids, and gastric secretions. Emptying of the gastric contents to the duodenum takes approximately 3 hours. The rate of gastric emptying must be closely regulated to provide adequate time for neutralization of gastric H^+ in the duodenum and adequate time for digestion and absorption of nutrients.

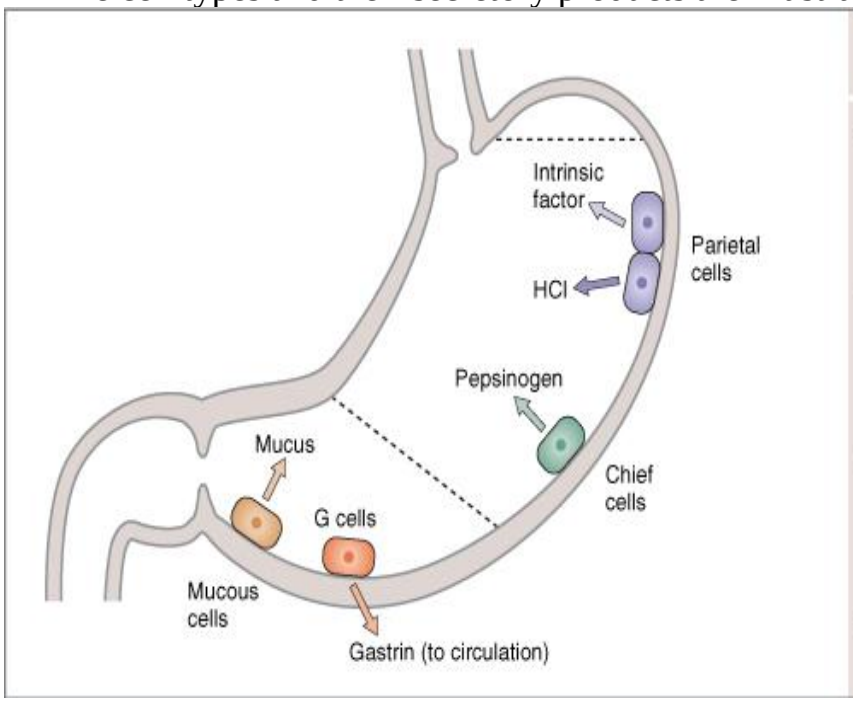
Two major factors slow or inhibit gastric emptying (i.e., *increase gastric emptying time*): the presence of fat and the presence of H^+ ions (low pH) in the duodenum. The effect of **fat** is mediated by **CCK,** which is secreted when fatty acids arrive in the duodenum. The effect of **H^+** is mediated by reflexes in the **enteric nervous system.**

GASTRIC SECRETION

The cells of the gastric mucosa secrete a fluid called **gastric juice.** The four major components of gastric juice are:

1. **Hydrochloric acid (HCl)**: HCl and pepsinogen initiate the process of protein digestion
2. **Pepsinogen**
3. **Intrinsic factor**: required for the absorption of vitamin B_{12} in the ileum
4. **Mucus**: protects the gastric mucosa from the corrosive action of HCl and also lubricates the gastric contents.

The cell types and their secretory products are illustrated below:



Cell Type	Location	Secretion
Parietal cells	Body	HCl Intrinsic factor
Chief cells	Body	Pepsinogen
G cells	Antrum	Gastrin
Mucous cells	Antrum	Mucus Pepsinogen

Secretory products of various gastric cells

A major function of the **parietal cells** is secretion of **HCl,** which acidifies the gastric contents to between pH 1 and 2. The function of this low gastric pH is to convert ***inactive*** **pepsinogen** to its ***active*** form, **pepsin**, a protease that begins the process of protein digestion.

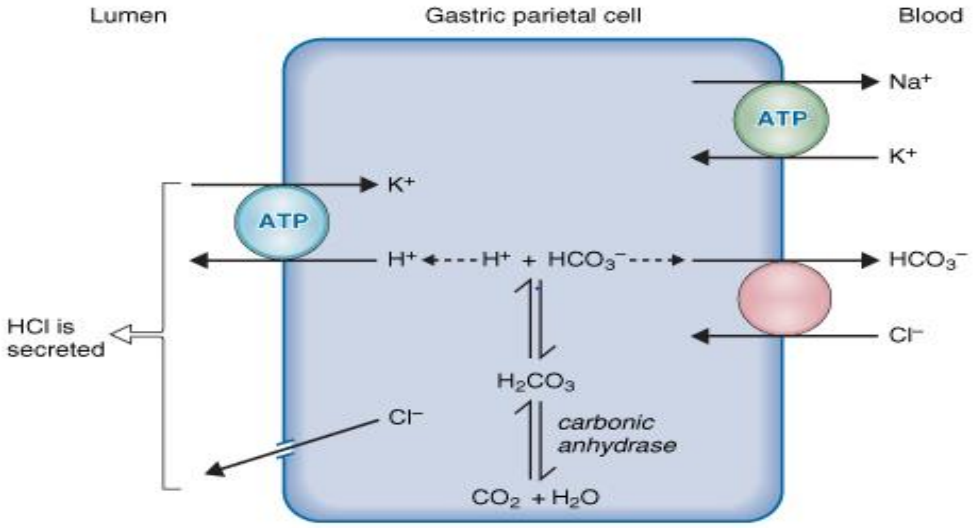
The cellular mechanism of HCl secretion from parietal cells

The cell membranes facing the lumen of the stomach are called the apical or luminal membranes, and the cell membranes facing the bloodstream are called the basolateral membranes. The apical membranes contain **H^+-K^+ ATPase** and **Cl^- channels**, and the basolateral membranes contain **Na^+-K^+ ATPase** and **Cl^--HCO_3^- exchangers**. The cells contain **carbonic anhydrase**.

1. In intracellular fluid, carbon dioxide (CO_2) produced from aerobic metabolism combines with H_2O to form H_2CO_3, catalyzed by **carbonic anhydrase.** H_2CO_3 dissociates into H^+ and HCO_3^-. The H^+ is secreted with Cl^- into the lumen of the stomach, and the HCO_3^- is absorbed into the blood, as described in steps 2 and 3, respectively.
2. At the **apical membrane,** H^+ is secreted into the lumen of the stomach via the **H^+-K^+ ATPase.** The H^+-K^+ ATPase is a primary active process that

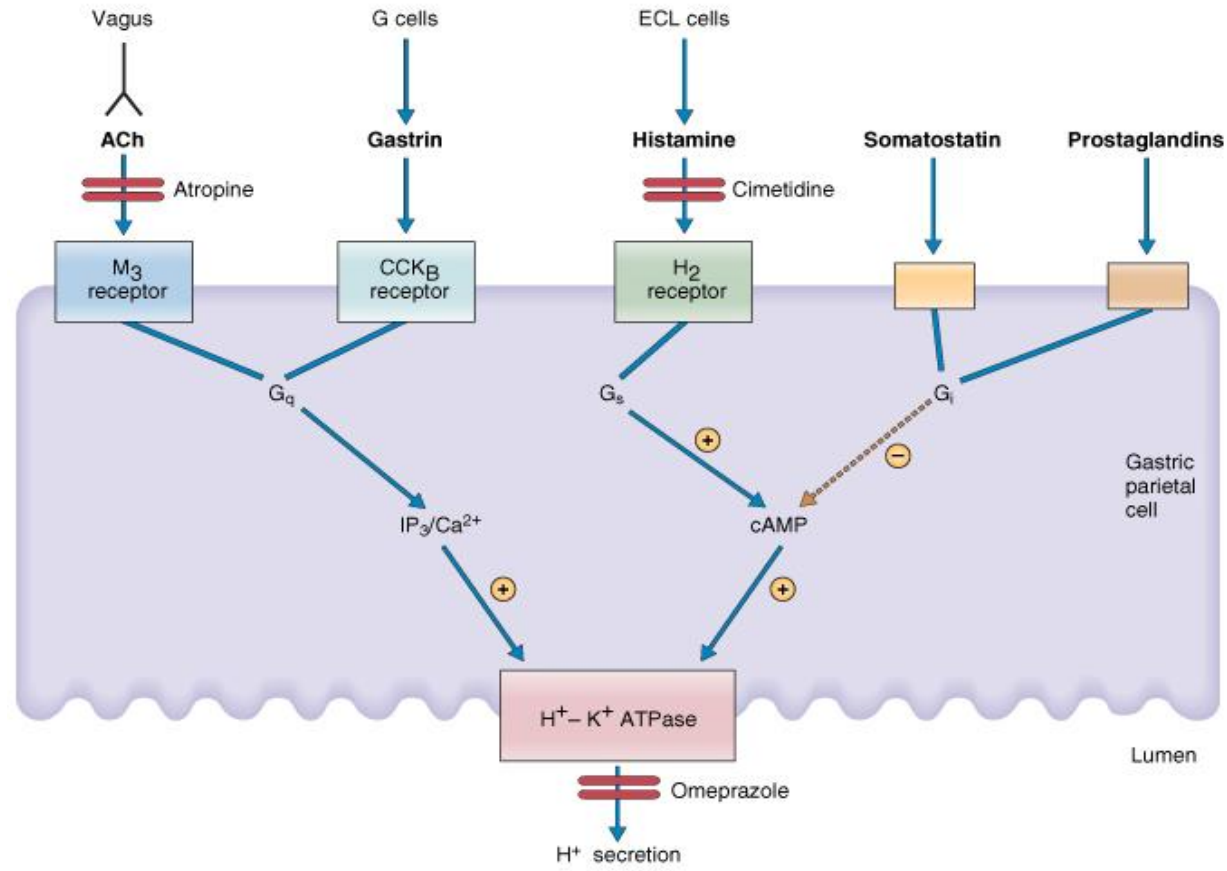
transports H^+ and K^+ against their electrochemical gradients (uphill). H^+-K^+ ATPase is inhibited by the drug **omeprazole,** which is used in the treatment of ulcers to reduce H^+ secretion. Cl^- follows H^+ into the lumen by diffusing through **Cl^- channels** in the apical membrane.

3. At the **basolateral membrane,** HCO_3^- is absorbed from the cell into the blood via a Cl^--HCO_3^- exchanger. The absorbed HCO_3^- is responsible for the "alkaline tide" (high pH) that can be observed in gastric venous blood after a meal. Eventually, this HCO_3^- will be secreted back into the gastrointestinal tract in pancreatic secretions.
4. **net secretion of HCl** and **net absorption of HCO_3^-**

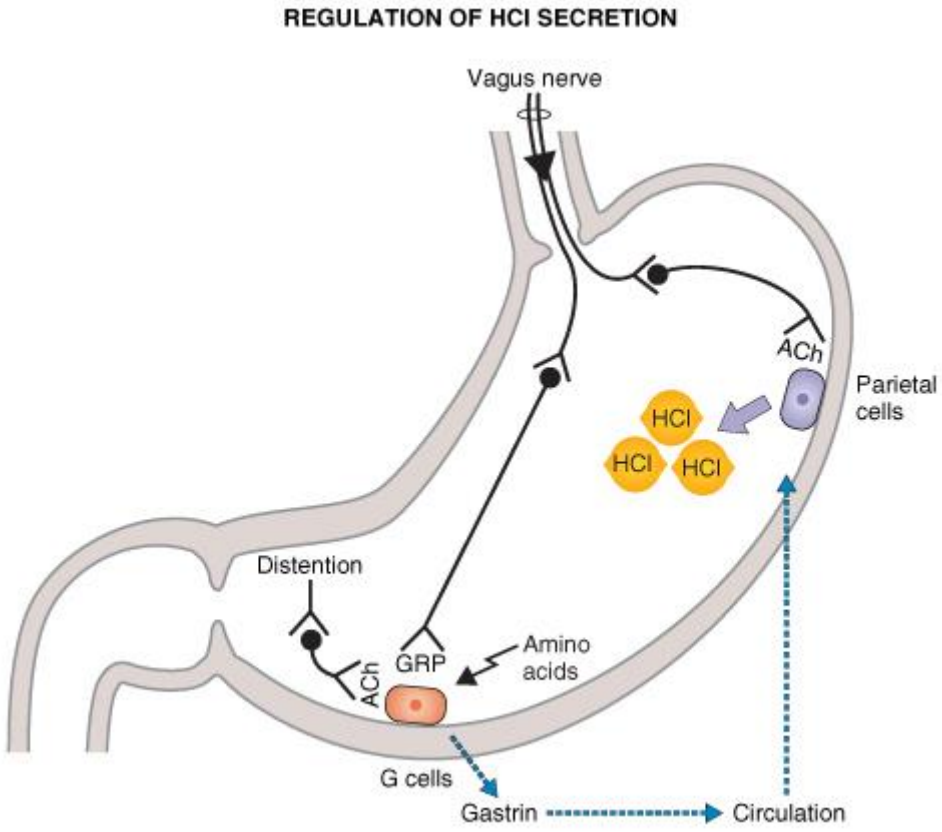


Substances that Alter HCl Secretion

Three substances stimulate H^+ secretion by gastric parietal cells: ACh (a neurocrine), histamine (a paracrine), and gastrin (a hormone). Each substance binds to a different receptor on the parietal cell and has a different cellular mechanism of action



The rate of H^+ secretion is regulated by the independent actions of ACh, histamine, and gastrin, and also by ***interactions*** among the three agents. The interaction is called **potentiation,** which refers to the ability of two stimuli to produce a combined response that is greater than the sum of the individual responses.



Phase	% of HCl Secretion	Stimuli	Mechanisms
Cephalic	30%	Smell, taste, conditioning	Vagus → parietal cell Vagus → gastrin → parietal cell
Gastric	60%	Distention	Vagus → parietal cell Vagus → gastrin → parietal cell
		Distention of antrum	Local reflex → gastrin → parietal cell
		Amino acids, small peptides	Gastrin → parietal cell

Stimulation of H^+ Secretion

Gastric HCl secretion is divided into three phases: **cephalic**, **gastric**, and **intestinal**.

- The **cephalic phase** accounts for approximately **30%** of the total HCl secreted in response to a meal. The stimuli for HCl secretion in the cephalic phase are **smelling** and **tasting,** chewing, swallowing, and **conditioned reflexes** in anticipation of food. Two mechanisms promote HCl secretion in the cephalic phase. The first mechanism is **direct** stimulation of the parietal cell by vagus nerves, which release ACh. The second mechanism is **indirect** stimulation of the parietal cells by gastrin. In the indirect path,

vagus nerves release GRP at the G cells, stimulating gastrin secretion; gastrin enters the circulation and stimulates the parietal cells to secrete HCl.

- The **gastric phase** accounts for approximately **60%** of the total HCl secreted in response to a meal. The stimuli for HCl secretion in the gastric phase are **distention** of the stomach and the presence of breakdown products of protein, **amino acids and small peptides.** Four physiologic mechanisms are involved in the gastric phase. The first two mechanisms, which are initiated by distention of the stomach, are similar to those utilized in the cephalic phase: Distention causes direct vagal stimulation of the parietal cells and indirect stimulation of the parietal cells via gastrin release. The third mechanism is initiated by distention of the stomach antrum and involves local reflexes that stimulate gastrin release. The fourth mechanism is a direct effect of amino acids and small peptides on the G cells to stimulate gastrin release. In addition to these physiologic mechanisms, **alcohol** and **caffeine** also stimulate gastric HCl secretion.
- The **intestinal phase** accounts for only **10%** of HCl secretion and is mediated by products of protein digestion.

Inhibition of HCl Secretion

HCl secretion is inhibited when HCl is no longer needed for the activation of pepsinogen to pepsin.

The major inhibitory mechanism for H^+ secretion by parietal cells involves

1. **Somatostatin.**

   Somatostatin inhibits gastric H^+ secretion through both a direct pathway and indirect pathways.

   A. Direct pathway When somatostatin binds to its receptor on parietal cells, G_i is activated, adenylyl cylase is inhibited, and cAMP levels are reduced; in this way, somatostatin antagonizes the stimulatory effect of histamine on H^+ secretion..

   B. Indirect pathways: somatostatin inhibits both histamine release from ECL cells and gastrin release from G cells.

2. **Prostaglandins** also antagonize histamine's stimulatory action on H^+ secretion by activating a Gi protein and inhibiting adenylyl cyclase.

Pepsinogen Secretion

Pepsinogen, the inactive precursor to pepsin, is secreted by chief cells and by mucous cells. When the pH of gastric contents is lowered by H^+ secretion from parietal cells, pepsinogen is converted to pepsin, beginning the process of protein digestion. In the cephalic and gastric phases of H^+ secretion, **vagal stimulation** is the most important stimulus for pepsinogen secretion. H^+ also triggers local reflexes, which stimulate the chief cells to secrete pepsinogen. These complementary reflexes ensure that pepsinogen is secreted only when the gastric pH is low enough to convert it to pepsin.

Intrinsic Factor Secretion

Intrinsic factor, a mucoprotein, is the "other" secretory product of the parietal cells. Intrinsic factor is required for absorption of vitamin B_{12} in the ileum, and its absence causes **pernicious anemia**. Intrinsic factor is the only ***essential*** secretion of the stomach. Thus, following gastrectomy (removal of the stomach), patients must receive injections of vitamin B_{12} to bypass the absorption defect caused by the loss of gastric intrinsic factor.

PANCREATIC SECRETION

The exocrine pancreas secretes approximately 1 L of fluid per day into the lumen of the duodenum. The secretion consists of an aqueous component that is high in **HCO_3^-** and an **enzymatic** component.

- HCO_3^- neutralizes H^+ delivered to duodenum from stomach
- Enzymatic portion digests carbohydrates, proteins, and lipids into absorbable molecules

Structure of Pancreatic Exocrine Glands

The exocrine pancreas constitutes approximately 90% of the pancreas. The rest of the pancreatic tissue is the endocrine pancreas (2%), blood vessels, and interstitial fluid.

It resembles a bunch of grapes, with each grape corresponding to a single **acinus**, consist of:

- **Acinar Cells**
  - Line blind end of branching duct system
  - Secrete enzymatic portion
- **Ductal Cells**
  - Line the ducts
  - Secrete aqueous HCO_3^- component

The exocrine pancreas is innervated by both parasympathetic and sympathetic nervous systems. **Parasympathetic** activity stimulates pancreatic secretion, and **sympathetic** activity inhibits pancreatic secretion**.**

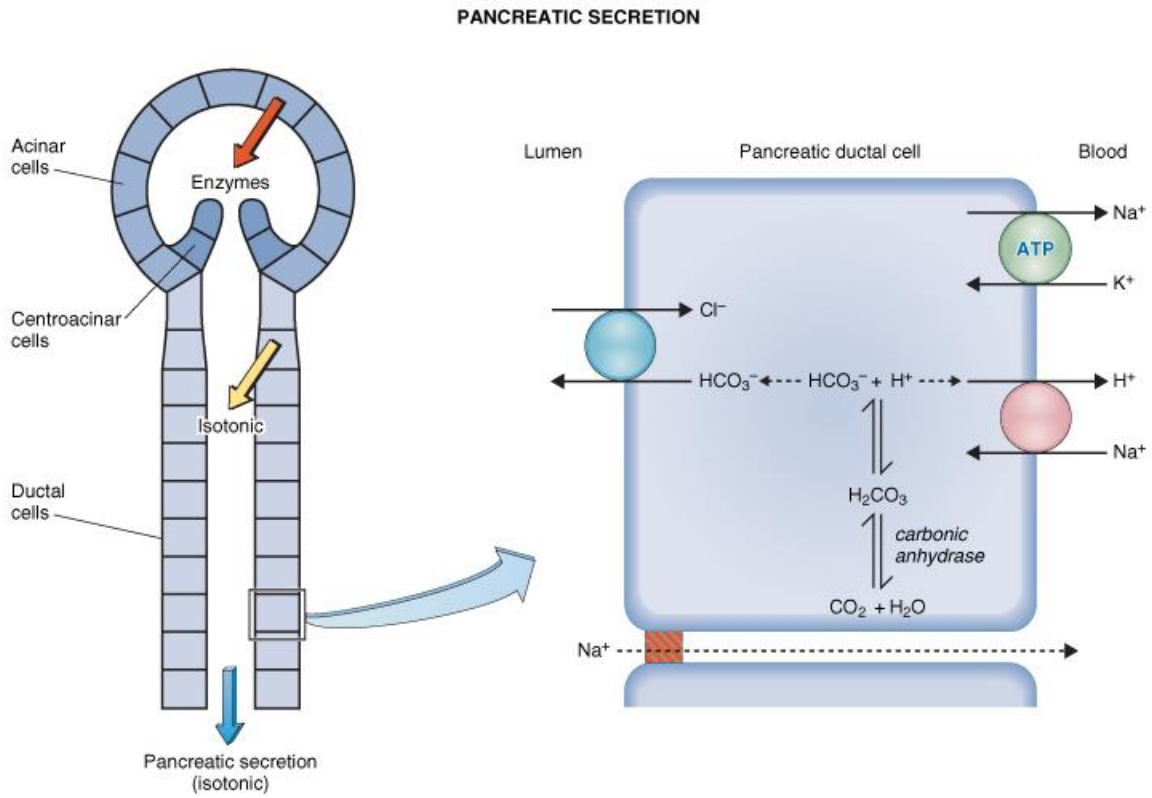
Formation of Pancreatic Secretion

1. **Enzymatic component of pancreatic secretion (acinar cells).** Pancreatic **amylase** and **lipases** are secreted as active enzymes. Pancreatic **proteases** are secreted in inactive forms and converted to their active forms in the lumen of the duodenum.
2. **Aqueous component of pancreatic secretion (centroacinar and ductal cells).**

- Apical membrane of ductal cells contains a Cl^--HCO_3^- exchanger
- Basolateral membrane contains Na^+-K^+ ATPase and a Na^+-H^+ exchanger

1. CO_2 and H_2O combine in cells to form H^+ and HCO_3^-
2. HCO_3^- is secreted into pancreatic juice by Cl^--HCO_3^- exchanger

3. H^+ is transported into blood by Na^+-H^+ exchanger
   - Absorption of H^+ causes acidification of pancreatic venous blood



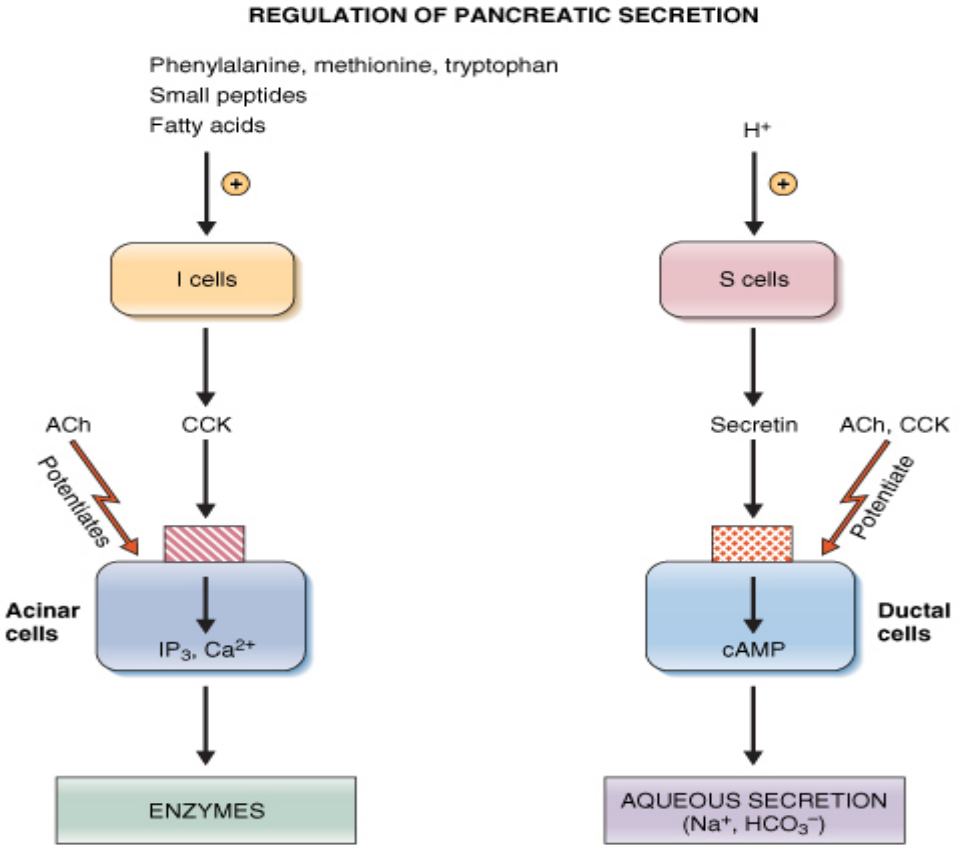
Regulation of Pancreatic Secretion

Like gastric secretion, pancreatic secretion is divided into cephalic, gastric, and intestinal phases.

1. **Cephalic phase** is initiated by smell, taste, and conditioning and is mediated by the vagus nerve. The cephalic phase produces mainly an enzymatic secretion.
2. **Gastric phase** is initiated by distention of the stomach and is also mediated by the vagus nerve. The gastric phase produces mainly an enzymatic secretion.
3. **Intestinal phase** is the most important phase and accounts for **80%** of the pancreatic secretion. During this phase, *both* enzymatic and aqueous secretions are stimulated.

- **Acinar cells (enzymatic secretion).** The pancreatic acinar cells have receptors for CCK and muscarinic receptors for ACh. **CCK** is the most important stimulant for the enzymatic secretion. The I cells are stimulated to secrete CCK by the presence of amino acids (phenylalanine, methionine, and tryptophan), small peptides, and fatty acids in the intestinal lumen. In addition, **ACh** stimulates enzyme secretion and potentiates the action of CCK by vagovagal reflexes.
- **Ductal cells (aqueous secretion of Na^+, HCO_3^-, and H_2O).** The pancreatic ductal cells have receptors for CCK, ACh, and secretin. **Secretin** is the

major stimulant of the aqueous HCO_3^--rich secretion. The effects of secretin are potentiated by both CCK and ACh.



BILE SECRETION

- Necessary for **digestion and absorption of lipids** in small intestine
- Mixture of bile salts, cholesterol, phospholipids, bile pigments, ions, and water
- Bile salts emulsify lipids to prepare them for digestion
- Solubilize products of lipid digestion in packets called **micelles**

Secretion and enterohepatic circulation of bile salts

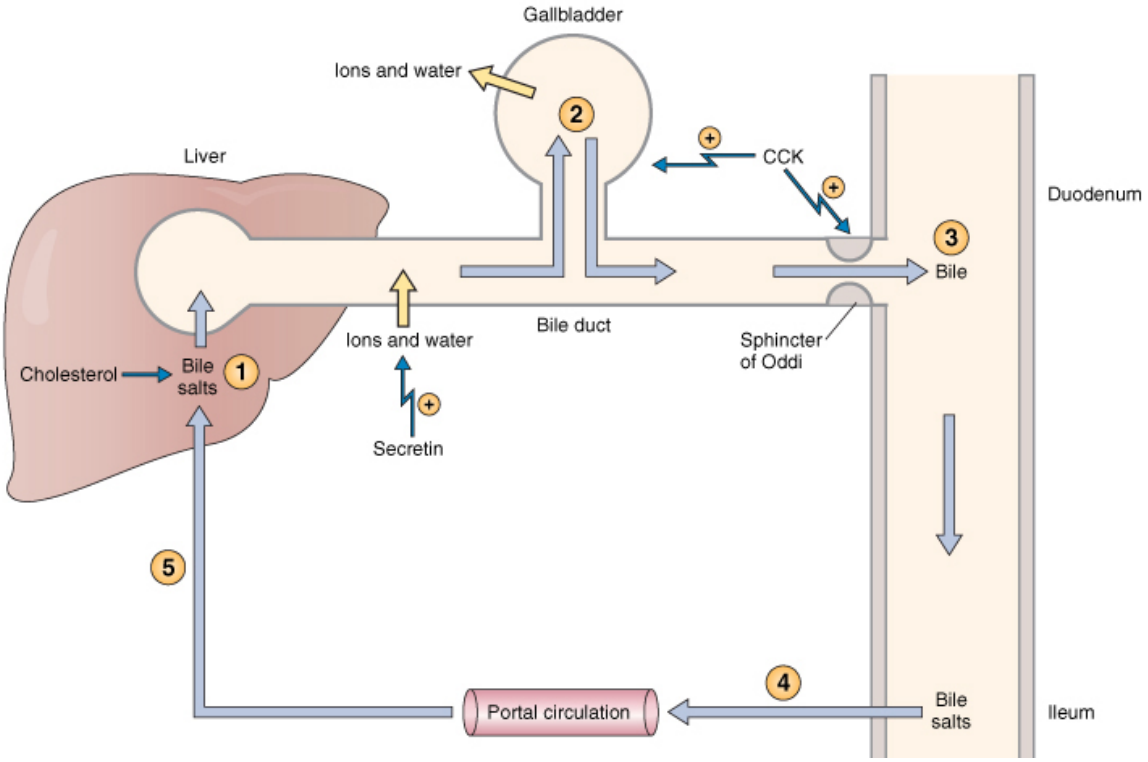
Step 1: The hepatocytes of the liver continuously synthesize and secrete the constituents of bile.

Step 2: The components of bile (the **bile salts,** cholesterol, phospholipids, bile pigments, ions, and water) flows out of the liver through the bile ducts and fills the gallbladder, where it is stored. The gallbladder then concentrates the bile salts by absorption of water and ions.

Step 3: When chyme reaches the small intestine, **CCK** stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi, causing stored bile to flow from the gallbladder into the lumen of the duodenum.

Step 4: When lipid absorption is complete, the bile salts are recirculated to the liver via the **enterohepatic circulation.**

Step 5: extraction of bile salts from the portal blood by the hepatocytes. The recirculation of bile salts to the liver reduces the demand to synthesize *new* bile salt. The liver must replace only the small percentage of the bile salt pool that is excreted in feces.



As noted previously, bile is secreted continuously by the hepatocytes. The organic constituents of bile are bile salts (50%), bile pigments such as bilirubin (2%), cholesterol (4%), and phospholipids (40%). Bile also contains electrolytes and water, which are secreted by hepatocytes lining the bile ducts.

- **Bile salts**: the hepatocytes synthesize two **primary bile acids.** When these primary bile acids are secreted into the lumen of the intestine, a portion of each is dehydroxylated by intestinal bacteria to produce two **secondary bile acids.** The liver conjugates the bile acids with the amino acids glycine or taurine to form **bile salts.** This conjugation step changes the pKs of bile acids and causes them to become *much more water soluble.* The critical property of bile salts is that they are **amphipathic,** meaning the molecules have both hydrophilic (water-soluble) and hydrophobic (lipid-soluble) portions. The function of bile salts, which depends on their amphipathic properties, is to **emulsify** dietary lipids. Without the bile salts, lipids would be insoluble in the aqueous solution in the intestinal lumen and less amenable to digestion and absorption. The second role of bile salts is to form **micelles** with the products of lipid digestion, including monoglycerides, lysolecithin, and fatty acids. The core of the micelle

contains these lipid products, and the surface of the micelle is lined with bile salts.

- **Phospholipids** and **cholesterol** also are secreted into bile by the hepatocytes, and are included in the micelles with the products of lipid digestion. Like the bile salts, phospholipids are amphipathic and aid the bile salts in forming micelles.
- **Bilirubin,** a yellow-colored byproduct of hemoglobin metabolism, is the major bile **pigment.**
- **Ions and water** are secreted into bile by epithelial cells lining the bile ducts. The secretory mechanisms are the same as those in the pancreatic ductal cells. **Secretin** stimulates ion and water secretion by the bile ducts just as it does in the pancreatic ducts.

Function of the Gallbladder

The gallbladder serves the following three functions:

1. Stores bile.
2. Concentrates bile, The epithelial cells of the gallbladder absorb ions and water.
3. When stimulated to contract, it ejects bile into the lumen of the small intestine.

SMALL INTESTIN

- Consist of three parts:
  - Duodenum
  - Jejunum
  - Ileum
- Primary site for digestion and absorption of nutrients
- Bile duct and pancreatic duct empty into duodenum

Small Intestinal Motility

Motility of the small intestine serves to mix the chyme with digestive enzymes and pancreatic secretions, expose the nutrients to the intestinal mucosa for absorption, and propel the unabsorbed chyme along the small intestine into the large intestine.

In the small intestine, slow waves are more frequent in the duodenum (12 waves per minute) than in the stomach. In the ileum, the frequency of slow waves decreases slightly, to 9 waves per minute. As in the stomach, contractions (called **migrating myoelectric complexes**) occur every 90 minutes to clear the small intestine of residual chyme.

Parasympathetic stimulation *increases* contraction of intestinal smooth muscle, and **sympathetic** activity *decreases* contraction. Although many of the parasympathetic nerves are cholinergic (i.e., they release ACh), some of the parasympathetic nerves release other neurocrines (i.e., they are peptidergic).

Neurocrines released from parasympathetic peptidergic neurons of the small intestine include VIP, enkephalins, and motilin.

There are two patterns of contractions in the small intestine: segmentation contractions and peristaltic contractions. Each pattern is coordinated by the **enteric nervous system**.

Vomiting

A **vomiting center** in the medulla coordinates the vomiting reflex. Afferent information comes to the vomiting center from the **vestibular system**, **the back of the throat**, the **gastrointestinal tract**, and the **chemoreceptor trigger zone** in the fourth ventricle.

The **vomiting reflex** includes the following events in this temporal sequence:

1. **reverse peristalsis** that begins in the small intestine
2. relaxation of the stomach and pylorus
3. forced inspiration to increase abdominal pressure
4. relaxation of the lower esophageal sphincter
5. Forceful expulsion of gastric, and sometimes duodenal, contents.

In **retching,** the upper esophageal sphincter remains closed, and because the lower esophageal sphincter is open, the gastric contents return to the stomach when the retch is over.

DIGESTION AND ABSORPTION

Digestion and absorption are the ultimate functions of the gastrointestinal tract.

Digestion is the chemical breakdown of ingested foods into absorbable molecules. The digestive enzymes are secreted in salivary, gastric, and pancreatic juices and also are present on the apical membrane of intestinal epithelial cells.

Absorption is the movement of nutrients, water, and electrolytes from the lumen of the intestine into the blood. There are two paths for absorption:

1. **Cellular** path, the substance must cross the apical (luminal) membrane, enter the intestinal epithelial cell, and then be extruded from the cell across the basolateral membrane into blood.
2. **Paracellular** path, substances move across the tight junctions between intestinal epithelial cells, through the lateral intercellular spaces, and into the blood.

The structure of the intestinal mucosa is ideally suited for absorption of large quantities of nutrients. Structural features called **villi** and **microvilli** increase the surface area of the small intestine, maximizing the exposure of nutrients to digestive enzymes and creating a large absorptive surface. The surface of the small intestine is arranged in longitudinal folds, called folds of **Kerckring**.

The surfaces of the villi are covered with **epithelial cells** (enterocytes), the apical surface of the epithelial cells is further expanded by tiny enfoldings called

microvilli. This microvillar surface is called the **brush border** because of its "brushlike" appearance under light microscopy. Together, the folds of Kerckring, the villi, and the microvilli increase total surface area by 600-fold!

Sources of Digestive Enzymes

Nutrient Group	Saliva	Stomach	Pancreas	Intestinal Mucosa
Carbohydrates	Amylase	-	Amylase	Sucrase
				Maltase
				Lactase
				Trehalase
				α-Dextrinase
Proteins	-	Pepsin	Trypsin	Amino-oligopeptidase
			Chymotrypsin	Dipeptidase
			Carboxypeptidase	Enterokinase
			Elastase	
Lipids	Lingual lipase	-	Lipase-colipase	-
			Phospholipase A_2	
			Cholesterol ester hydrolase	

CARBOHYDRATES

Ingested carbohydrates involves: polysaccharides (like starch), disaccharides (sucrose, lactose, maltose, and trehalose), and small amounts of monosaccharides (glucose and fructose).

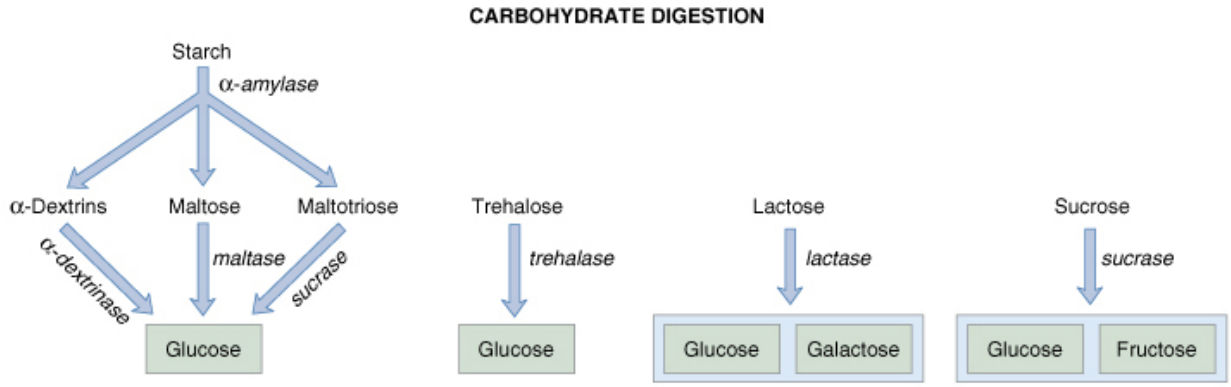
Digestion of Carbohydrates

Only monosaccharides are absorbed by the intestinal epithelial cells. Therefore, all ingested carbohydrates must be digested to monosaccharides: glucose, galactose, or fructose.

Digestion of **starch** begins with **α-amylase.** Salivary amylase starts the process of starch digestion in the mouth; **it plays little role overall**, because it is inactivated by the low pH of the gastric contents.

Pancreatic amylase digests starch, yielding three disaccharides, α-limit dextrins, maltose, and maltotriose. These disaccharides are further digested to monosaccharides by the intestinal brush-border enzymes, **α-dextrinase, maltase,** and **sucrase.** The product of each of these final digestive steps is glucose which can be absorbed by the epithelial cells.

The three **disaccharides** in food are trehalose, lactose, and sucrose. They do not require the amylase digestive step since they already are in the disaccharide form. Each molecule of disaccharide is digested to two molecules of monosaccharide by the enzymes **trehalase, lactase,** and **sucrase.** Thus, trehalose is digested by trehalase to two molecules of glucose; lactose is digested by lactase to glucose and galactose; and sucrose is digested by sucrase to glucose and fructose.

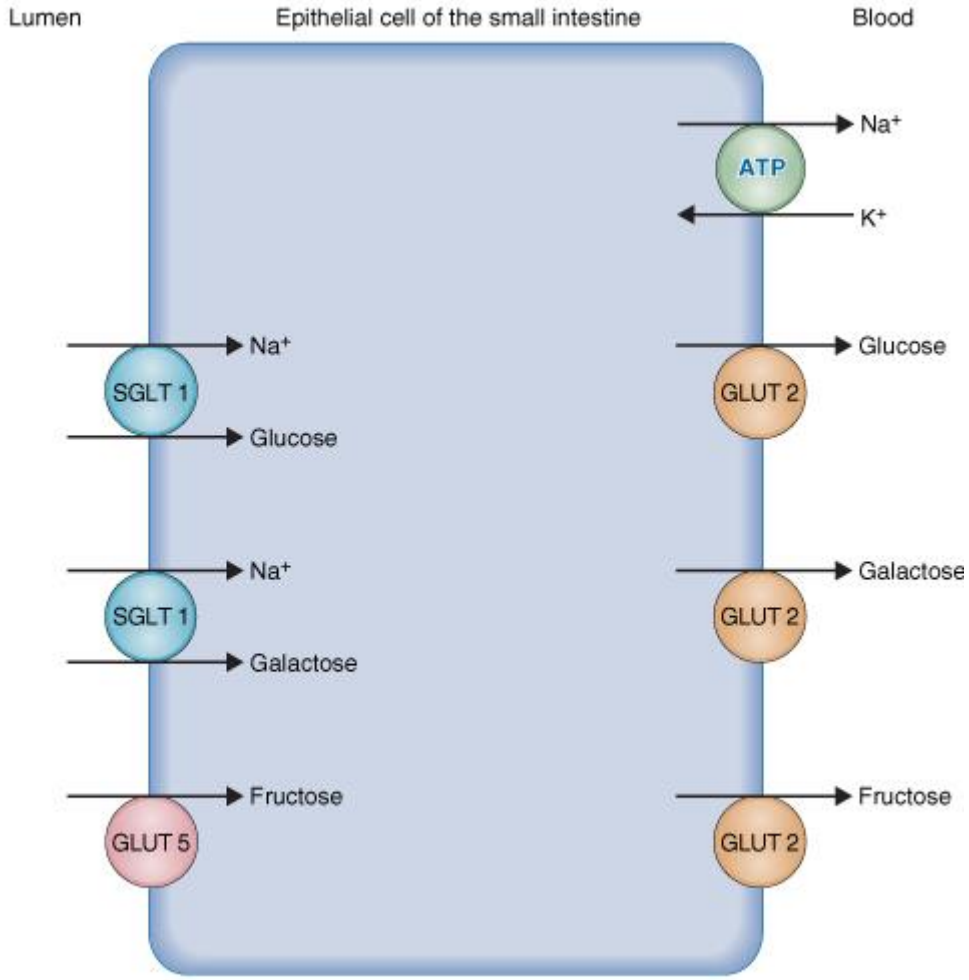


Therefore, there are three end products of carbohydrate digestion: **glucose**, **galactose**, and **fructose**; each is absorbable by intestinal epithelial cells.

Absorption of Carbohydrates

Glucose and galactose are absorbed across the apical membrane by secondary active transport mechanisms similar to those found in the early proximal convoluted tubule. Both glucose and galactose move from the intestinal lumen into the cell on the **Na^+-glucose cotransporter (SGLT 1),** against an electrochemical gradient (high concentration of Na^+ on the mucosal surface of the cells facilitates and a low concentration inhibits sugar influx into the epithelial cells). Glucose and galactose are extruded from the cell into the blood, across the basolateral membrane, by facilitated diffusion **(GLUT 2).**

Fructose absorption does not involve an energy-requiring step or a cotransporter in the apical membrane. Rather, fructose is transported across both the apical and basolateral membranes by **facilitated diffusion**; in the apical membrane, the fructose-specific transporter is called GLUT 5, and in the basolateral membrane, fructose is transported by GLUT 2. Because only facilitated diffusion is involved, fructose cannot be absorbed against an electrochemical gradient (in contrast to glucose and galactose).



PROTEINS

Dietary proteins are digested to absorbable forms (i.e., amino acids, dipeptides, and tripeptides) by **proteases** in the *stomach* and *small intestine* and then absorbed into the blood. The proteins contained in gastrointestinal secretions (e.g., pancreatic enzymes) are similarly digested and absorbed.

Digestion of Proteins

Digestion of protein begins in the **stomach** with the action of *pepsin* and is completed in the **small intestine** with *pancreatic and brush-border proteases*.

There are two classes of proteases:

- **Endopeptidases**: hydrolyze the interior peptide bonds of proteins. Involve: pepsin, trypsin, chymotrypsin, and elastase.
- **Exopeptidases** hydrolyze one amino acid at a time from the C-terminal ends of proteins and peptides. Involve: carboxypeptidases A and B.

The gastric chief cells secrete the inactive precursor of pepsin, pepsinogen. At low gastric pH, pepsinogen is activated to pepsin. There are three isozymes of pepsin,

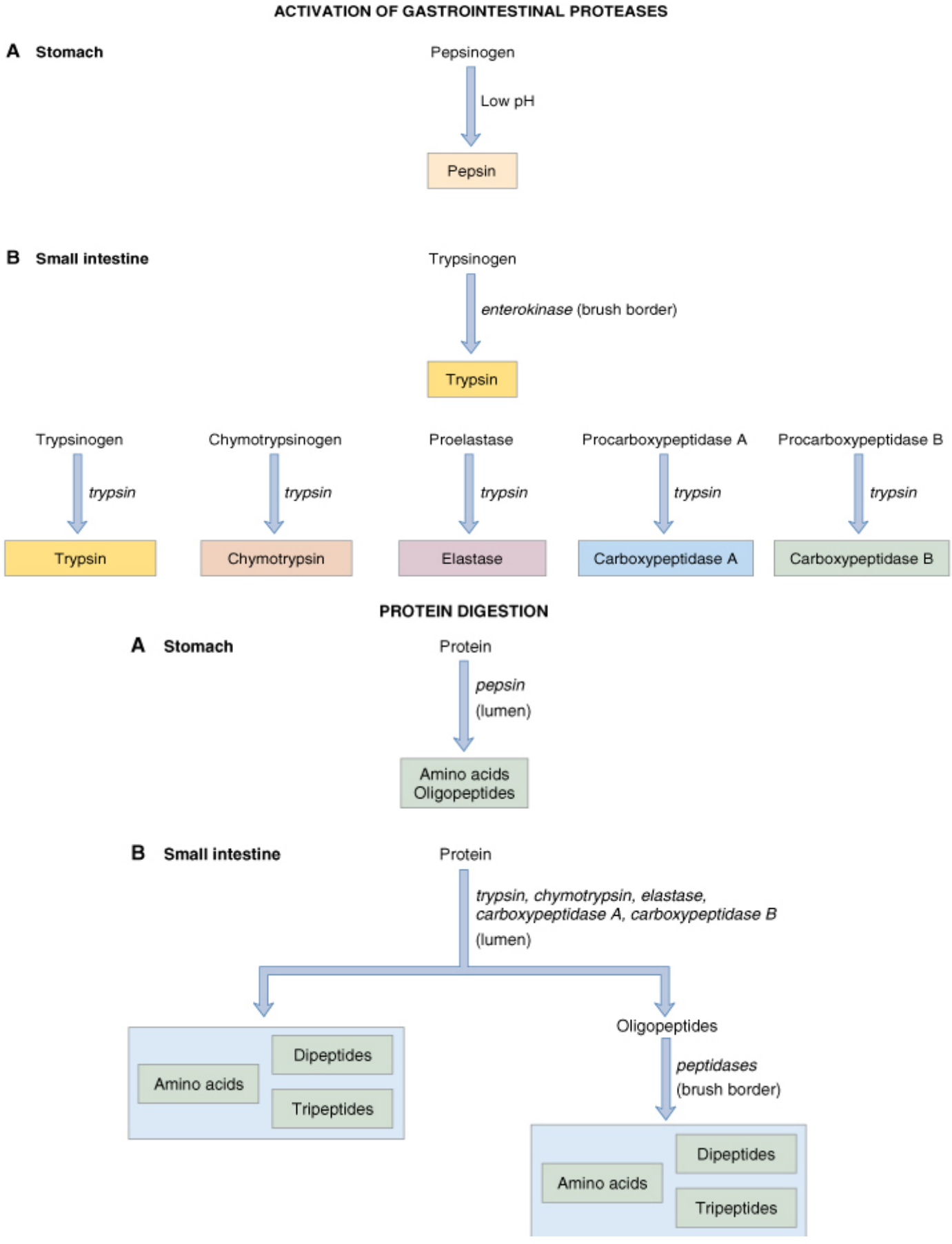
each of which has a pH optimum ranging between pH 1 and 3; above pH 5, pepsin is **denatured** and **inactivated**. Therefore, pepsin is active at the low pH of the stomach, and its actions are terminated in the duodenum, where pancreatic HCO_3^- secretions neutralize gastric H^+ and increase the pH. Interestingly, pepsin is ***not essential*** for normal protein digestion. In persons whose stomach has been removed or persons who do not secrete gastric H^+ (and cannot activate pepsinogen to pepsin), protein digestion and absorption are normal. These examples demonstrate that pancreatic and brush-border proteases *alone* can adequately digest ingested protein.

Protein digestion continues in the **small intestine.** Five major pancreatic proteases are secreted as **inactive precursors**: trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidase A, and procarboxypeptidase B.

The first step in intestinal protein digestion is the activation of trypsinogen to its active form, **trypsin,** by the brush-border enzyme **enterokinase.** Then the initially produced trypsin catalyzes the conversion of all of the other inactive precursors to their active enzymes. Even the remaining trypsinogen is ***autocatalyzed*** by trypsin to form more trypsin. The activation steps yield five active enzymes for protein digestion:

- Trypsin
- Chymotrypsin
- Elastase
- Carboxypeptidase A
- Carboxypeptidase B

These pancreatic proteases then hydrolyze dietary protein to **amino acids, dipeptides, tripeptides, and larger peptides called oligopeptides**. All are absorbable **except oligopeptides** that are further hydrolyzed by brush-border proteases to smaller absorbable molecules
Finally, the pancreatic proteases digest themselves and each other!

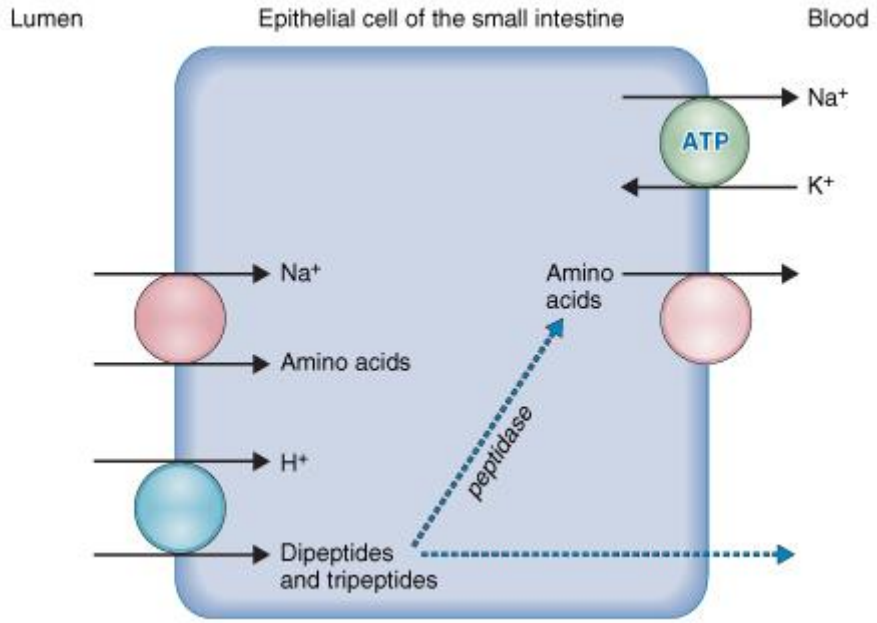

ACTIVATION OF GASTROINTESTINAL PROTEASES
A Stomach
Pepsinogen
Low pH
Pepsin
B Small intestine
Trypsinogen
enterokinase (brush border)
Trypsin
Trypsinogen
trypsin
Trypsin
Chymotrypsinogen
trypsin
Chymotrypsin
Proelastase
trypsin
Elastase
Procarboxypeptidase A
trypsin
Carboxypeptidase A
Procarboxypeptidase B
trypsin
Carboxypeptidase B
PROTEIN DIGESTION
A Stomach
Protein
pepsin
(lumen)
Amino acids
Oligopeptides
B Small intestine
Protein
trypsin, chymotrypsin, elastase,
carboxypeptidase A, carboxypeptidase B
(lumen)
Amino acids
Dipeptides
Tripeptides
Oligopeptides
peptidases
(brush border)
Amino acids
Dipeptides
Tripeptides

Absorption of Proteins

The products of protein digestion are amino acids, dipeptides, and tripeptides. Each form can be absorbed by intestinal epithelial cells by two different absorptive mechanisms:

1. The **amino acids** are transported from the lumen into the cell by **Na^+-amino acid cotransporters** in the apical membrane, energized by the Na^+ gradient. The amino acids then are transported across the basolateral membrane into the blood by facilitated diffusion.
2. **Dipeptides and tripeptides** are absorbed from the intestinal lumen into the cell by **H^+-dependent cotransporters** in the apical membrane, utilizing an H^+ ion gradient created by an Na^+-H^+ exchanger in the apical membrane. Once inside the cell, most of the dipeptides and tripeptides are hydrolyzed to amino acids by cytosolic peptidases, producing amino acids that exit the cell by facilitated diffusion; the remaining dipeptides and tripeptides are absorbed unchanged.

Most ingested protein is absorbed by intestinal epithelial cells in the **dipeptide** and **tripeptide** forms rather than as free **amino acids**.



LIPIDS

The dietary lipids include triglycerides, cholesterol, and phospholipids. A factor that greatly complicates lipid digestion and absorption is their insolubility in water (their hydrophobicity). Because the gastrointestinal tract is filled with an aqueous fluid, the lipids must somehow be solubilized to be digested and absorbed. Thus, the mechanisms for processing lipids are more complicated than those for carbohydrates and proteins, which are water soluble.

Digestion of Lipids

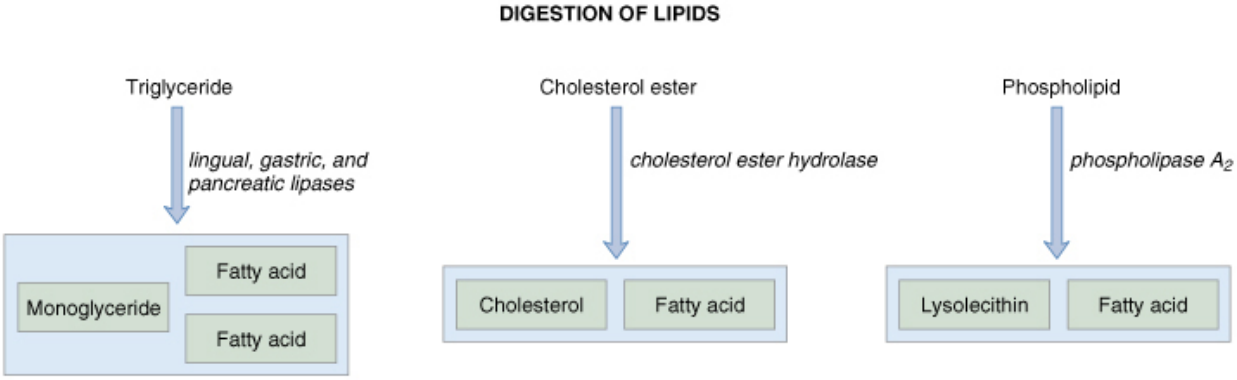
Digestion of dietary lipids begins in the **stomach** and is completed in the **small intestine**:

A. The function of the stomach in lipid digestion is to churn and mix dietary lipids and to initiate enzymatic digestion. The churning action breaks the lipids into small droplets, increasing the surface area for digestive enzymes. In the stomach, the lipid droplets are emulsified (kept apart) by dietary proteins. **Lingual and gastric lipases** initiate lipid digestion by hydrolyzing approximately 10% of ingested triglycerides to glycerol and free fatty acids. The rate of **gastric emptying,** is **slowed by CCK.** CCK is secreted when dietary lipids first appear in the small intestine.

B. Most lipid digestion occurs in the small intestine. **Bile salts** are secreted into the lumen of small intestine. These bile salts, together with lysolecithin and products of lipid digestion, surround and emulsify dietary lipids. **Emulsification** produces small droplets of lipid dispersed in the aqueous solution of the intestinal lumen, creating a large surface area for the action of pancreatic enzymes. The **pancreatic enzymes** (pancreatic lipase, cholesterol ester hydrolase, and phospholipase A_2) and one special protein (colipase) are secreted into the small intestine to accomplish the digestive work.

- **Pancreatic lipase** is secreted as the active enzyme. It hydrolyzes triglyceride molecules to one molecule of monoglyceride and two molecules of fatty acid. A problem in the action of pancreatic lipase is that it is inactivated by bile salts. Bile salts displace pancreatic lipase at the lipid-water interface of the emulsified lipid droplets. This "problem" is solved by colipase. **Colipase** is secreted in pancreatic juices in an inactive form, procolipase, which is activated in the intestinal lumen by trypsin. Colipase then displaces bile salts at the lipid-water interface and binds to pancreatic lipase.
- **Cholesterol ester hydrolase** is secreted as an active enzyme and hydrolyzes cholesterol ester to free cholesterol and fatty acids. It also hydrolyzes ester linkages of triglycerides, yielding glycerol.
- **Phospholipase A_2** is secreted as a proenzyme and, like many other pancreatic enzymes, is activated by trypsin. Phospholipase A_2 hydrolyzes phospholipids to lysolecithin and fatty acids.

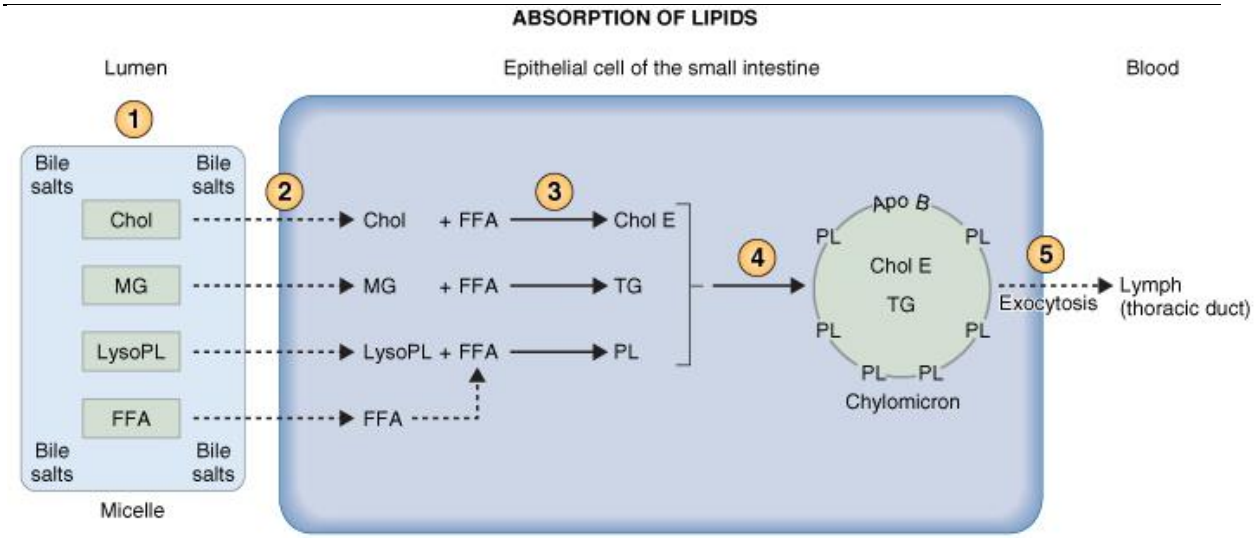
The final products of lipid digestion are **monoglycerides, fatty acids, cholesterol, lysolecithin, and glycerol**. Each end product is hydrophobic (**except glycerol**), and therefore is not soluble in water. Now the hydrophobic digestive products must be solubilized in micelles and transported to the apical membrane of the intestinal cells for absorption.



Absorption of Lipids

Absorption of lipids occurs in the following *steps:*

1. The products of lipid digestion (cholesterol, monoglycerides, lysolecithin, and free fatty acids) are solubilized in the intestinal lumen in mixed **micelles,** except glycerol, which is water soluble.
2. The micelles diffuse to the apical (brush-border) membrane of the intestinal epithelial cells. At the apical membrane, the lipids are released from the micelle and diffuse down their concentration gradients into the cell. The bile salts (the outer shell of the micelles) are left behind in the intestinal lumen to be absorbed downstream in the ileum.
3. Inside the intestinal epithelial cells, the products of lipid digestion are **reesterified** with free fatty acids on the smooth endoplasmic reticulum to form the original ingested lipids, triglycerides, cholesterol ester, and phospholipids.
4. Inside the cells, the reesterified lipids are packaged with apoproteins in lipid-carrying particles called **chylomicrons.** The chylomicrons are composed of triglycerides and cholesterol at the core and phospholipids and apoproteins on the outside. Apoproteins, which are synthesized by the intestinal epithelial cells, are essential for the absorption of chylomicrons.
5. At the basolateral membranes there is **exocytosis** of the chylomicrons. The chylomicrons are too large to enter vascular capillaries, but they can enter the **lymphatic capillaries** (lacteals) by moving between the endothelial cells that line the lacteals. The lymphatic circulation carries the chylomicrons to the **thoracic duct,** which empties into the bloodstream.



Mechanism of absorption of lipids in the small intestine. Apo B, β-Lipoprotein; **Chol**, cholesterol; **Chol E**, cholesterol ester; **FFA**, free fatty acids; **LysoPL**, lysolecithin; **MG**, monoglycerides; **PL**, phospholipids; **TG**, triglycerides.

VITAMINS

Vitamins are required in small amounts to act as coenzymes or cofactors for various metabolic reactions. Because vitamins are not synthesized in the body, they must be acquired from the diet and absorbed by the gastrointestinal tract. The vitamins are categorized as either fat soluble or water soluble.

Fat-Soluble Vitamins

The fat-soluble vitamins are vitamins A, D, E, and K. Fat-soluble vitamins are absorbed in the same manner as dietary lipids. In the intestinal lumen, fat-soluble vitamins are incorporated into **micelles** and transported to the apical membrane of the intestinal cells. They diffuse across the apical membrane into the cells, are incorporated in **chylomicrons,** and then are extruded into lymph, which delivers them to the general circulation.

Water-Soluble Vitamins

The water-soluble vitamins include vitamins B_1, B_2, B_6, B_{12}, C, biotin, folic acid, nicotinic acid, and pantothenic acid. In most cases, absorption of the water-soluble vitamins occurs via an **Na^+-dependent cotransport** mechanism in the small intestine.

The *exception* is the absorption of **vitamin B_{12}** (cobalamin), Absorption of vitamin B_{12} requires **intrinsic factor** and occurs in the following steps: (1) Dietary vitamin B_{12} is released from foods by the digestive action of pepsin in the stomach. (2) Free vitamin B_{12} binds to **R proteins,** which are secreted in salivary juices. (3) In the duodenum, pancreatic proteases degrade the R proteins, causing vitamin B_{12} to be transferred to intrinsic factor. (4) The vitamin B_{12}-intrinsic factor complex is resistant to the degradative actions of pancreatic proteases and travels to the ileum, where there is a specific transport mechanism for its absorption.

CALCIUM

Ca^{2+} is absorbed in the small intestine and depends on the presence of the active form of vitamin D, **1,25-dihydroxycholecalciferol,** which is produced as follows: Dietary vitamin D_3 (cholecalciferol) is inactive. In the liver, cholecalciferol is converted to 25-hydroxycholecalciferol, which also is inactive. In the proximal tubules of the kidney, 25-hydroxycholecalciferol is converted to 1,25-dihydroxycholecalciferol, catalyzed by **1α-hydroxylase.** 1,25-Dihydroxycholecalciferol, the biologically active metabolite of vitamin D, has actions on intestine, kidney, and bone. Its most important action is to promote Ca^{2+} absorption from the small intestine by inducing the synthesis of vitamin D-dependent Ca^{2+}-binding protein (**calbindin D-28K**) in intestinal epithelial cells.
In vitamin D deficiency or when there is failure to convert vitamin D to 1,25-dihydroxycholecalciferol (as occurs in chronic renal failure), there is inadequate Ca^{2+} absorption from the gastrointestinal tract. In children, inadequate Ca^{2+} absorption causes **rickets,** and in adults, it causes **osteomalacia.**

IRON

Iron is absorbed across the apical membrane of intestinal epithelial cells as free iron (Fe^{2+}) or as heme iron (i.e., iron bound to hemoglobin or myoglobin). Inside the intestinal cells, heme iron is digested by lysosomal enzymes, releasing free iron. Free iron then binds to **apoferritin** and is transported across the basolateral membrane into the blood. In the circulation, iron is bound to a β-globulin called **transferrin,** which transports it from the small intestine to storage sites in the liver. From the liver, iron is transported to the bone marrow, where it is released and utilized in the synthesis of hemoglobin.

Intestinal Fluid and Electrolyte Transport

The gastrointestinal tract absorbs vast quantities of fluid and electrolytes. Together, the small and large intestines absorb approximately 9 L of fluid daily, an amount almost equal to the entire extracellular fluid volume! *What is the source of this large volume of fluid that is absorbed?*

Summary of Mechanisms of Digestion and Absorption of Nutrients

Nutrient	Products of Digestion	Site of Absorption	Mechanism
Carbohydrates	Glucose	Small intestine	Na^+-glucose cotransport
	Galactose		Na^+-galactose cotransport
	Fructose		Facilitated diffusion
Proteins	Amino acids	Small intestine	Na^+-amino acid cotransport
	Dipeptides		H^+-dipeptide cotransport
	Tripeptides		H^+-tripeptide cotransport
Lipids	Fatty acids	Small intestine	Bile salts form micelles in the small intestine
	Monoglycerides Cholesterol		Diffusion of fatty acids, monoglycerides, and cholesterol into intestinal cells
			Reesterification in the cell to triglycerides and phospholipids
			Chylomicrons form in the cell (requiring apoprotein) and are transferred to lymph
Fat-soluble vitamins		Small intestine	Micelles form with bile salts and products of lipid digestion
			Diffusion into the intestinal cell
Water-soluble vitamins Vitamin B_{12}		Small intestine Ileum	Na^+-dependent cotransport Intrinsic factor
Bile salts		Ileum	Na^+-bile salt cotransport
Ca^{2+}		Small intestine	Vitamin D-dependent Ca^{2+}-binding protein
Fe^{2+}	Fe^{3+} reduced to Fe^{2+}	Small intestine	Binds to apoferritin in the intestinal cell
			Binds to transferrin in blood

Intestinal Fluid and Electrolyte Transport

The gastrointestinal tract absorbs vast quantities of fluid and electrolytes. Together, the small and large intestines absorb approximately 9 L of fluid daily, an amount almost equal to the entire extracellular fluid volume! *What is the source of this large volume of fluid that is absorbed?*