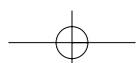
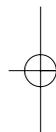
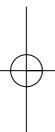
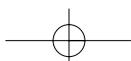
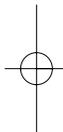
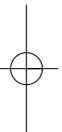


1

Basic mechanisms of normal and abnormal gastrointestinal function





1

A COMPONENTS

Integrative responses of the gastrointestinal tract and liver to a meal

Stephen J. Pandol, Helen E. Raybould, Hal F. Yee Jr

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This chapter provides an overview of the mechanisms involved in the regulation of food intake and the various responses in the gastrointestinal (GI) tract, the liver, and the pancreas to the ingestion of a meal. The coordination of these processes is essential for the regulation of food intake; the digestion and absorption of nutrients in the food; the distribution, storage, and release of nutrients to meet demand; and the elimination of wastes. Each of the processes described in this introductory chapter is explored in greater depth and with extensive references to the literature elsewhere in the textbook.

The GI tract consists of the alimentary canal from the mouth to the anus and the associated glandular organs (i.e., salivary glands, liver, and pancreas) that empty their contents into the canal. In a general sense, the GI tract adds water, ions, and enzymes to a meal to convert it into an aqueous solution of molecules that can be transported within the body. Importantly, most of the added substances are absorbed for reuse. The assimilation of a meal involves major physiological processes that occur in the GI tract: motility, secretion, digestion, absorption, and elimination. Food is taken into the mouth as large particles containing macromolecules that are not absorbable. The breaking down of food into absorbable material occurs by grinding and mixing the food (motility) with various secretions containing enzymes, ions, and water that enter the GI tract. The enzymes convert the macromolecules into absorbable molecules in a

process termed digestion. The products of digestion, as well as the secretions from the upper parts of the GI tract, are then transported across the epithelium to enter the blood or lymph by a process termed absorption. Secretions and luminal contents are moved from the mouth to the anus and eliminated by GI motility. The coordination of GI function is regulated in a synchronized way to maximize digestion and absorption by means of multiple control mechanisms.

The liver and pancreas are anatomically coupled to the GI tract through the biliary and pancreatic ductal systems, respectively. Further, the liver receives blood circulation directly from the GI tract and the pancreas through the portal circulation. The liver has numerous vital functions, including bile formation and secretion; uptake, storage, and release of nutrients; generation of plasma proteins; detoxification; and immune surveillance. The exocrine pancreas provides the major digestive enzymes, whereas the endocrine pancreas plays a central role in the uptake, storage, and release of nutrients in the liver, as well as in other tissues such as skeletal muscle and adipose tissue.

Control systems

Because the macronutrient content of a meal can vary considerably, the GI tract is endowed with mechanisms that can detect the presence of food and mount appropriate physiological responses. In addition, the GI tract communicates with associated organs (e.g., pancreas) such that when events occur in the more proximal GI tract, signals are sent to the more distal parts, and vice versa. Three principal control mechanisms regulate GI function: endocrine, paracrine, and neural (Fig. 1.1).

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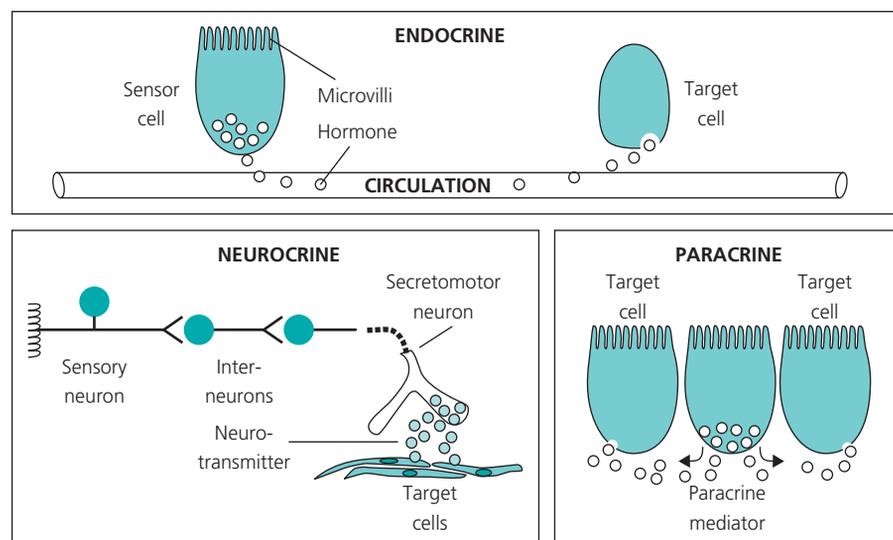


Figure 1.1 Three principal types of control mechanism regulate the function of the gastrointestinal tract: paracrine, endocrine, and neurocrine (neural). Examples of paracrine mechanisms are numerous. In this figure, the target cell is shown as being adjacent to the sensor cell. However, paracrine mechanisms may be mediated over tens or hundreds of micrometers and may involve many different cell types, including epithelial cells, endocrine cells, nerve terminals, and smooth muscle. From Undergraduate Teaching Program of the American Gastroenterological Association, 1996.

Endocrine regulation

Endocrine regulation describes the process whereby the sensing cells in the GI tract, the enteroendocrine cells, respond to a stimulus and secrete regulatory peptides or hormones that travel by way of the bloodstream to target cells. Effector cells respond to the hormones and express specific receptors. Hormones released from the GI tract have effects on cells located in other regions of the GI tract and also on the glandular structures associated with the GI tract, such as the pancreas and the liver.

The secretory products of the enteroendocrine cells are released in response to chemical (nutrients, acid, osmolarity) and mechanical (distention, stretch) stimuli to the wall of the GI tract, although the exact mechanisms by which this occurs are not well understood. Most enteroendocrine cells in the gut wall are of the “open” type; these cells have an apical membrane that is in contact with the lumen of the GI tract (generally regarded as where the sensing occurs) and a basolateral membrane over which secretion occurs.

Examples of hormones secreted by the GI tract abound. Gastrin, one of the better characterized GI hormones, plays a central role in the regulation of gastric acid secretion. Gastrin is released from endocrine cells located in the antral mucosa in response to activation of the parasympathetic outflow to the GI tract. Other hormones include glucoinsulinotropic peptide, which is released by glucose in the intestine and augments insulin secretion from the pancreatic β -cell; cholecystokinin (CCK), which plays a role in the intestinal feedback regulation of proximal GI function, food intake, and the secretion of pancreatic and biliary constituents into the intestine; secretin, which plays a role in neutralizing gastric acid emptied into the intestine; and motilin, which regulates gastrointestinal motility.

Paracrine regulation

Paracrine regulation describes the process whereby a chemical messenger or regulatory peptide is released from enteroendocrine cells and diffuses through the interstitial space to reach target cells. Paracrine agents exert their actions on several different cell types in the wall of the GI tract, including smooth muscle cells, absorptive enterocytes, secretory cells in glands, and other enteroendocrine cells. Histamine is an important paracrine mediator in the gut wall. In the stomach, histamine is stored and released by enterochromaffin-like cells located in the gastric glands, and acts by diffusing through the interstitial space of the lamina propria to neighboring parietal cells to stimulate the production of acid. Somatostatin also is an important paracrine mediator. Released from the antral mucosa in response to acid, somatostatin inhibits the release of gastrin from neighboring gastrin-containing endocrine cells, which results in the inhibition of meal-stimulated gastric acid secretion.

Neural regulation

The functions of the GI tract are controlled by activity in the extrinsic and intrinsic nervous systems. The extrinsic nervous system, defined as those nerves that innervate the gut with cell bodies located outside of the gut wall, is part of the autonomic nervous system. The GI tract is innervated by both the parasympathetic and sympathetic subdivisions of the autonomic nervous system. The parasympathetic innervation to the gut is through the vagus and the pelvic nerves. The vagus nerve (cranial nerve X) innervates the esophagus, stomach, gallbladder, pancreas, small intestine, cecum, and proximal colon. The pelvic nerves innervate the distal colon and anorectal region. The sympathetic innervation is supplied by cell bodies in the spinal cord and by fibers that

terminate in the prevertebral ganglia (i.e., celiac, superior and inferior mesenteric ganglia). The postganglionic neurons innervate all parts of the GI tract.

The intrinsic nervous system, also referred to as the enteric nervous system, has cell bodies that are contained within the wall of the gut in the submucosal plexus and myenteric plexus.

The afferent (sensory) innervation of the GI tract is derived from both parasympathetic and sympathetic innervation. The cell bodies of the vagal afferents are in the nodose ganglion with a central projection terminating in the brainstem and a distal projection to the gut wall. The cell bodies of the afferent neurons that run with the sympathetic pathway are in the dorsal root ganglia. The peripheral terminals of the spinal and vagal afferents are located in all layers of the gut wall, where they detect chemical and mechanical stimuli. The afferent nerves send information to the central nervous system (CNS), which drives reflexes to change secretory and motor function in the GI tract. The afferent innervation is also responsible for transmitting painful stimuli to the CNS.

Enteric nervous system

The enteric nervous system comprises two major plexuses consisting of cell bodies (ganglia) and interconnecting strands that contain nerve fibers. The myenteric plexus lies between the longitudinal and circular muscle layers and the submucosal plexus lies in the submucosa. Neurons in the

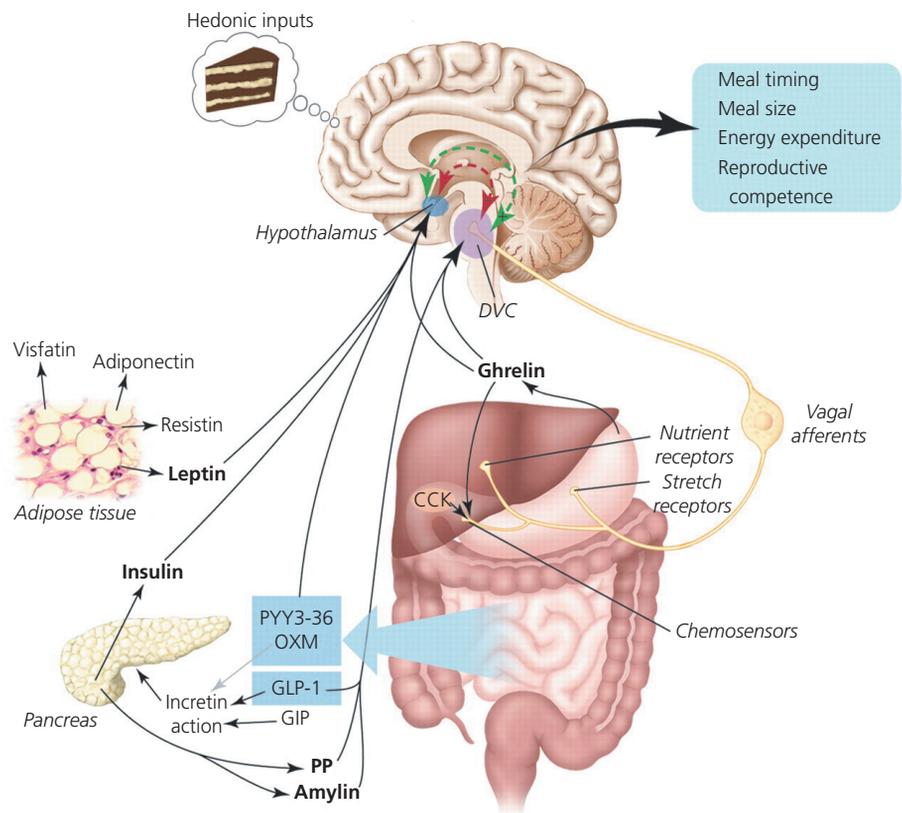
enteric nervous system are characterized by their function and also by the neurotransmitters they contain. The enteric nervous system contains the components of a reflex pathway (afferent neurons, interneurons, efferent neurons) and thus is capable of functioning in the absence of input from the CNS. However, enteric nervous system function is often modulated by the CNS.

Many GI hormones have been identified in the neurons of the enteric nervous system, where they may act as neurotransmitters, and in regions of the brain, where they may be involved in the regulation of autonomic outflow. These mediators and regulatory peptides are thus referred to as brain–gut peptides and the extrinsic and intrinsic components innervating the gut are sometimes referred to as the brain–gut axis.

Regulation of food intake by the gastrointestinal tract

Multiple complex signals from metabolically active tissues and the CNS contribute to the long-term regulation of body weight (Fig. 1.2). In addition, signals derived from the presence of food in the GI tract regulate food intake, particularly in the short term. Perfusion of the intestine with single macronutrients, or mixtures thereof, results in the inhibition

Figure 1.2 Many signaling systems regulate food intake. This graphic presents an overview of inputs from the central nervous system and from peripheral tissues such as adipose tissue (leptin) and metabolic tissue (endocrine pancreas with signals insulin and pancreatic polypeptide [PP]). CCK, cholecystokinin; DVC, dorsal vagal complex; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin. Adapted from Badman MK, Flier JS. The gut and energy balance: visceral allies in the obesity wars. *Science* 2005;307:1909.



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of food intake and intestinal feedback regulation of GI function. These observations have led to the notion of nutrient sensors in the GI tract. Vagal afferents innervating the proximal GI tract are activated by the presence of luminal nutrients, leading to the activation of CNS pathways involved in the regulation of food intake, including the nuclei of solitary tract (the region in the brainstem where vagal afferents terminate) and the arcuate nucleus of hypothalamus.

Humoral factors are also involved in the regulation of food intake. Many GI hormones are termed satiety signals. These signals are characterized by their release from enteroendocrine cells when nutrients are in the GI tract, and by observations that exogenous injection of these hormones, including CCK, glucagon-like peptide (GLP)-1, peptide YY (PYY), and ghrelin, in experimental animals and humans produces a decrease in food intake.

Possibly the best characterized of these satiety signals is CCK. CCK is released from enteroendocrine cells by protein hydrolysates and free fatty acids in the intestinal lumen. Exogenous administration of CCK to humans and experimental animals has determined that CCK inhibits meal size by activating CCK₁ receptors. These receptors are most likely localized to the peripheral terminals of vagal afferent fibers innervating the mucosal wall of the duodenum. However, although it is clear that CCK can inhibit the size of subsequent meals, its role in the long-term regulation of food intake is uncertain. CCK₁-receptor null mice that receive long-term administration of CCK₁ receptor antagonists maintain normal body weight when fed ad libitum, possibly as a result of the effects of longer-term satiety signals.

GLP-1 is a product of the proglucagon gene that is secreted from the distal small intestine in response to glucose and fatty acids and is proposed to be involved in the regulation of appetite and energy intake. Plasma levels of GLP-1 in humans increase after a meal. Exogenous administration of GLP-1 or agonists of the GLP-1 receptor in humans and experimental animals leads to decreased food intake. The site of action is thought to be directly on the arcuate nucleus of the hypothalamus, an area of the brain involved in the integration of short- and long-term (metabolic) satiety signals.

Despite the controversy surrounding the role of PYY, the weight of evidence now suggests that it does play a physiological role in the regulation of food intake and body weight. Plasma levels of PYY increase after a meal, and the hormone is converted rapidly from PYY1–36 to PYY3–36 by the enzyme dipeptidyl peptidase IV. PYY3–36 acts as specific agonist for the PYY Y2 receptor and is the most potent form of the peptide to inhibit food intake. PYY likely acts by way of the vagal afferent pathway but also by exerting a direct effect on the hypothalamus.

Ghrelin is secreted by endocrine cells in the stomach and is an unusual GI regulatory peptide, because, unlike those already discussed, it increases food intake rapidly and transiently after exogenous administration. Circulating levels of

ghrelin decrease with feeding and increase during the fasting period, thus suggesting that it may act as a physiological regulator of appetite. Interestingly, circulating levels of ghrelin are low after gastric bypass surgery, an effect that has been associated with the effectiveness of this procedure in reducing body weight.

The role of water

Water is necessary for the digestion and absorption of nutrients and for the elimination of wastes. Water provides a fluid environment for the movement of luminal contents, a solution for digestive enzyme action, and a medium to deliver solute to absorptive surfaces.

The daily input of water into the GI tract is about 9.0 L per day, which comprises 2 L oral intake, 1.5 L salivary saliva, 2.5 L gastric juice, 0.5 L bile, 1.5 L pancreatic juice, and 1.0 L small intestinal secretion. The daily intestinal content of water entering the colon is 1.5–2.0 L, whereas fecal output consists of only 0.1–0.2 L water. Thus, the distal small intestine and colon reabsorb almost all the water delivered to them.

Electrolytes play a central role in the mechanisms of secretion and absorption of water. For example, electrolytes are secreted or absorbed across the epithelium of the GI tract by ion transport systems. The actively transported electrolytes then cause water to move so that isosmolality is maintained. Another result of the transport of a particular ion across the epithelium is that other ions with the opposite charge flow passively and paracellularly along with water through the paracellular spaces between epithelial cells.

In each organ, specific combinations of ion transport systems mediate the secretion or absorption of ions and water, thus providing the overall effect of that organ on water flow in the GI tract. Although these systems are described in detail in chapters dedicated to specific organs, the illustrations in Fig. 1.3 show prototypes of a secretory epithelium (Fig. 1.3a) and an absorptive epithelium (Fig. 1.3b). In the secretory epithelium, activation of a Cl⁻ channel on the luminal surface along with activation of a K⁺ channel on the basolateral surface of the cell drives Cl⁻ across the epithelium into the lumen. This effect is promoted by the high intracellular K⁺ concentration produced by the basolateral Na⁺,K⁺-ATPase and the increased intracellular Cl⁻ concentration resulting from the effect of the Na⁺,K⁺-ATPase on facilitating the movement of Cl⁻ into the cell using the Na⁺/K⁺/Cl⁻ cotransport system. The end result is that Cl⁻ is transported into the lumen. The electrical and osmotic effect of this transport is the subsequent movement of Na⁺ and water through the paracellular space into the lumen. The net result is water and NaCl secretion.

An example of absorptive transport is provided in Fig. 1.3b. The Na⁺/glucose cotransport on the luminal surface results in absorption of the ion Na⁺ and the nutrient glucose. This

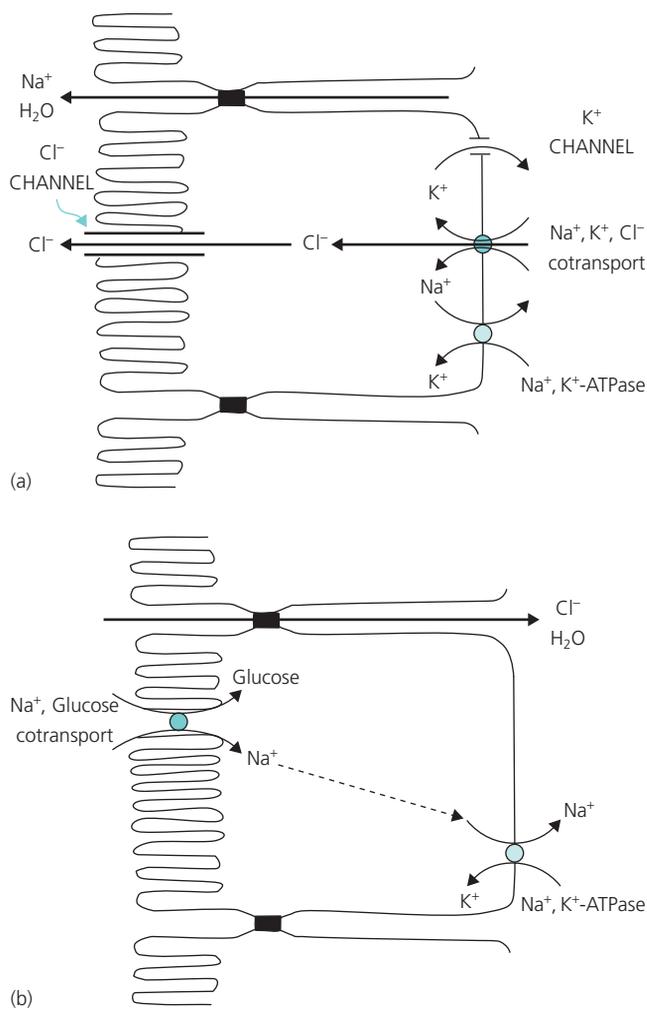


Figure 1.3 Transports of intestinal secretory (a) and absorptive (b) cells.

transport is also facilitated by the Na^+ , K^+ -ATPase. The resulting electrical and osmotic effects of the transport of both Na^+ and glucose cause the additional absorption of Cl^- and water across the epithelium. Of note, much of the water-absorptive process in the small intestine is coupled to nutrient transport. That is, sugars, amino acids, and fatty acids are absorbed using Na^+ -coupled transport systems, accounting for more rapid absorption of liquids containing combinations of nutrients and NaCl .

As suggested previously, absorption can be regulated by luminal factors, such as nutrients. Luminal contents can also regulate secretion. An example is salivary secretion stimulated by food in the mouth or even the thought of food before it enters the mouth. In addition, the meal and nutrients in the meal can activate gastric, biliary, and pancreatic water secretion. The mechanisms that regulate each are specific to the organ and involve both neural and humoral pathways as briefly described in the present chapter and in more detail in other chapters in this textbook.

Cephalic and oral phases of a meal

The main feature of this part of the meal is the activation of the GI tract in readiness for the meal. The cephalic phase consists of responses to auditory, cognitive, visual, and olfactory stimuli induced by the meal. The oral phase includes many of the same stimuli, as well as those initiated in the mouth, which are both chemical and mechanical. The effector responses are mediated through various higher brain centers (many involved in cognition) and ultimately converge on the brainstem to increase parasympathetic outflow to the gut. This outflow activates secretory and motor responses including salivary, gastric, and pancreatic secretion; gallbladder contraction and relaxation of the sphincter of Oddi; and relaxation of smooth muscle activity in the proximal stomach. These responses supply the gut with water, ions, digestive enzymes, and bile necessary to initiate digestion.

During the oral phase, contact of the food with the buccal mucosa presents additional chemical and mechanical stimuli. The responses initiated by these stimuli are, in general, the same as those stimulated during the cephalic phase because they share a common efferent pathway of activation through the vagus nerve. Functions of salivary secretions are listed in Table 1.1. Chewing, an important component of the oral phase of the meal, subdivides the food and mixes it with salivary secretions. Digestion starts in the mouth with the action of salivary amylase and lingual lipase. Mucus in the saliva lubricates the food for both chewing and swallowing.

Neural pathways mediate the components of the oral and cephalic phases. For example, salivary secretion is mediated by parasympathetic effector neurons. In the stomach, vagal efferent activity results in the stimulation of chief cells, enterochromaffin-like cells, parietal cells, and G cells. Thus, there is stimulation of function by way of the enteric neurons, which then activate release of paracrine (histamine) and humoral (gastrin) mediators that will further stimulate parietal and chief cell secretion. These mechanisms ensure the rapid initiation of protein digestion as food enters the stomach.

Table 1.1 Functions of chewing and salivary secretion

Disruption of food resulting in smaller particles
Formation of bolus for swallowing
Initiation of starch and lipid digestion
Facilitation of taste
Cleansing of mouth and provision of antibacterial action
Clearance and neutralization of refluxed gastric material in the esophagus
Regulation of gastric and duodenal phases
Regulation of food intake and eating behavior
Assistance in speech

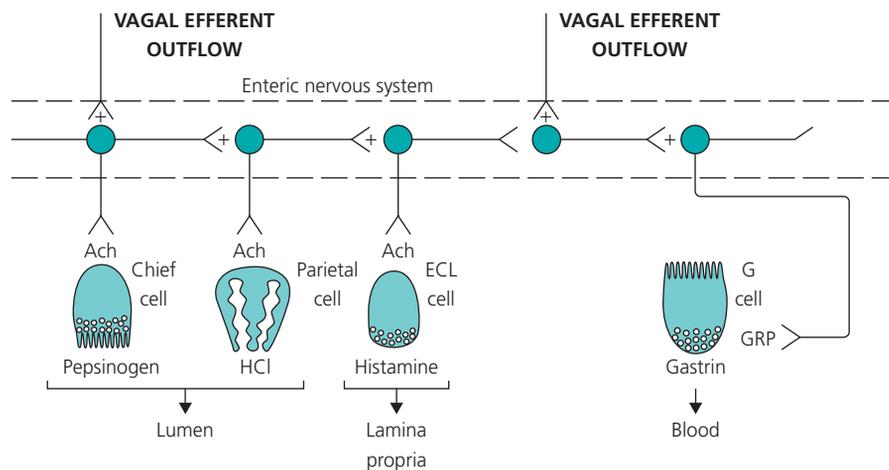
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Figure 1.4 Stimulation of gastric acid secretion by increased parasympathetic outflow is effectively amplified by intrinsic neuronal circuitry in the gastric wall. Vagal efferents synapse with intrinsic cholinergic neurons and with neurons containing gastrin-releasing peptide (GRP). Activation of these intrinsic neurons stimulates a number of cell types in the gastric mucosa. Neurocrine (GRP and acetylcholine [Ach]), paracrine (histamine), and endocrine (gastrin) pathways all contribute to this response. ECL, enterochromaffin-like cell; G cell, gastrin cell; HCl, hydrochloric acid. From Undergraduate Teaching Program of the American Gastroenterological Association, 1996.

Gastric phase of a meal

The presence of food in the stomach initiates several responses within the stomach itself and in other parts of the GI tract. The main functions of the stomach, among many, are to act as a temporary reservoir for the meal and to initiate protein digestion through the secretion of acid and the enzyme precursor pepsinogen. As food enters the stomach from the esophagus it presents two principal stimuli: a mechanical stimulation of the gastric wall caused by distention and stretch of the smooth muscle wall and a chemical stimulation caused by oligopeptides and amino acids in the gastric lumen. The regulation of gastric acid secretion during the gastric phase is dependent on the integrated action of endocrine, paracrine, and neural pathways (Fig. 1.4). Both intrinsic and extrinsic neural reflex pathways are important for the regulation of gastric function. Afferent neurons that pass from the GI tract to the CNS by way of the vagus nerve (and to a lesser extent to the spinal cord) respond to mechanical and chemical stimuli and activate parasympathetic outflow that is both excitatory and inhibitory.

The endocrine pathways include the release of gastrin, which stimulates gastric acid secretion. Important paracrine pathways include the release of histamine from enterochromaffin-like cells, which stimulates gastric acid secretion; and the release of somatostatin from cells in the antral mucosa, which inhibits gastric acid secretion. Activation of these pathways elicits both secretory and motor responses. Secretory responses include acid secretion, pepsinogen secretion, and the production of mucus, intrinsic factor, gastrin, lipase, and bicarbonate (Table 1.2). These secretions initiate protein digestion and protect the gastric mucosa. Motor responses, which are described as changes in the activity of smooth muscle, include inhibition of proximal stomach motility (i.e., receptive relaxation) and stimulation of distal stomach motility causing antral peristalsis. The function of these changes in smooth muscle function is to store the meal, mix

Table 1.2 Major functions of the gastric phase

Gastric responses

- Storage of the meal
- Secretion of pepsinogen and lipase to initiate digestion
- Secretion of H^+ to kill microorganisms and convert pepsinogen to active form
- Secretion of intrinsic factor to bind vitamin B-12 (cobalamin) for absorption
- Secretion of mucus and bicarbonate for gastric mucosal barrier and lubrication
- Secretion of water for aqueous suspension of nutrients and to make hypotonic
- Mixing secretions with food and reduction of particle size (grinding) of the meal
- Regulation of emptying of contents into the duodenum

Distal gastrointestinal tract responses

- Stimulation of pancreatic secretion
- Contraction of the gallbladder
- Increased colonic motor activity
- Relaxation of the sphincter of Oddi

it with secretions, and regulate the flow of contents out of the stomach.

The gastric phase also includes the activation of the more distal GI tract, including pancreatic secretion, gallbladder contraction, and relaxation of the sphincter of Oddi. These effects are mediated by the same afferent and efferent pathways that regulate gastric responses and prepare the intestine for the emptying of food from the stomach into the intestine.

Duodenal signals regulating gastric, hepatic, and pancreatic functions

The duodenum and proximal small intestine initiate several regulatory systems that mediate the controlled delivery of

Table 1.3 Duodenal signal-mediated responses

Inhibition of gastric acid secretion
Inhibition of gastric emptying
Stimulation of pancreatic enzyme secretion
Stimulation of pancreatic and biliary ductal ion and water secretion
Stimulation of gallbladder contraction
Relaxation of the sphincter of Oddi
Alteration of intestinal motility from the fasted to the fed pattern

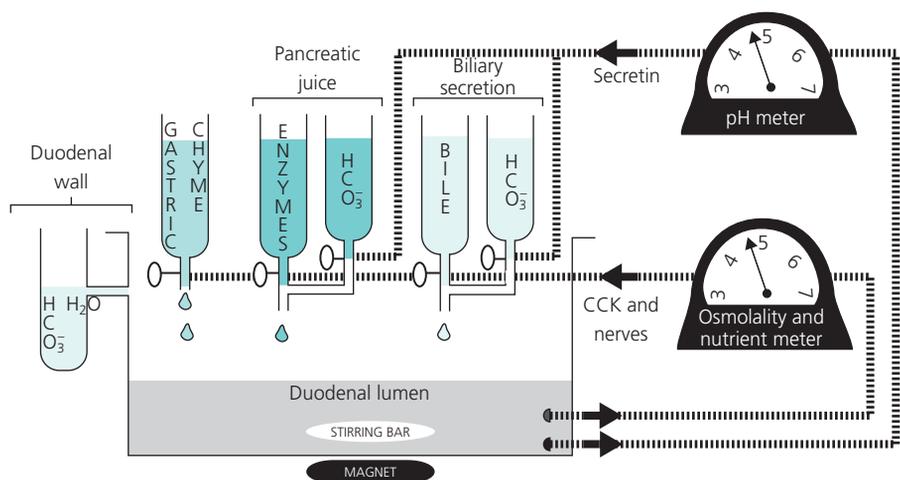
chyme from the stomach and the secretion of pancreatic juice and bile into the duodenum to match the digestive and absorptive capacity of the intestine (Table 1.3). The combination of organs regulated during this phase has been termed the duodenal cluster unit: stomach, duodenum, liver, biliary tract, gallbladder, and pancreas. Luminal and wall stimuli activate neural and endocrine pathways to mediate the responses of these organs. The different organ systems in the duodenal cluster unit have a common embryological origin and are regulated by similar sensory mechanisms and effector pathways. The gastric phase of the response to a meal provides some of the stimuli for the duodenal phase. For example, the products of gastric lipid and protein digestion are potent stimulants of regulation in the duodenum. The important duodenal stimuli are distention, acid, osmotic load, and different nutrients. The sensory pathways consist of spinal and vagal afferents and intrinsic sensory neurons that initiate reflex pathways. Hormonal pathways, especially those medi-

ated by CCK and secretin, are of central importance (Fig. 1.5). Of note, the effector systems regulated include the inhibition of gastric emptying and secretion, the stimulation of pancreatic secretion, gallbladder contraction, relaxation of the sphincter of Oddi, pancreatic and biliary water and bicarbonate secretion, intestinal secretion, and the conversion of small bowel motility from the fasted to the fed pattern.

Gastric emptying depends on the chemical and physical composition of the gastric contents (i.e., chyme) entering the duodenum. Sensory neurons, both vagal and spinal, respond to nutrients, H^+ , distention, and the hyperosmolality of chyme. The effector responses that result in the inhibition or slowing of gastric emptying are not completely understood but involve activation of vagal efferent outflow, which produces a decrease in antral contractions, contraction of the pylorus, and a decrease in proximal gastric tone. In addition to these extrinsic neural pathways, there may also be local pathways, such as an intrinsic neural reflex, mediating the pyloric contraction induced by acid in the duodenum.

The availability of CCK antagonists has contributed to the appreciation that CCK is physiologically important in regulating the function of the duodenal cluster unit. The administration of CCK_1 receptor antagonists reverses the inhibition of gastric emptying, gallbladder contraction, relaxation of the sphincter of Oddi, and stimulation of pancreatic enzyme secretion in response to either a meal or the infusion of nutrients into the duodenum. CCK is released from endocrine cells in the proximal intestine in response to luminal lipid and protein. The action of CCK to inhibit gastric acid secretion and gastric emptying, and to increase pancreatic secretion, is dependent on neural pathways (Fig. 1.6). CCK stimulates

Figure 1.5 Diagrammatic representation of the duodenal cluster unit illustrates the control mechanisms and pathways involved in intestinal feedback regulation during the duodenal phase. The nutrient content and osmolality of the meal are sensed (represented as a meter) and activate predominantly neural pathways involving cholecystokinin (CCK) to open or close various stopcocks to increase pancreatic secretion or delay gastric emptying, for example. The acidity of the meal is sensed and activates the release of secretin and neural pathways to increase bicarbonate secretion from the pancreas, biliary tract, and probably also from the duodenal wall. The contents of the duodenum are mixed with the secretions by the segmenting contractions of the smooth muscle wall, represented as a stirring bar and magnetic stirrer. From Undergraduate Teaching Program of the American Gastroenterological Association, 1996.



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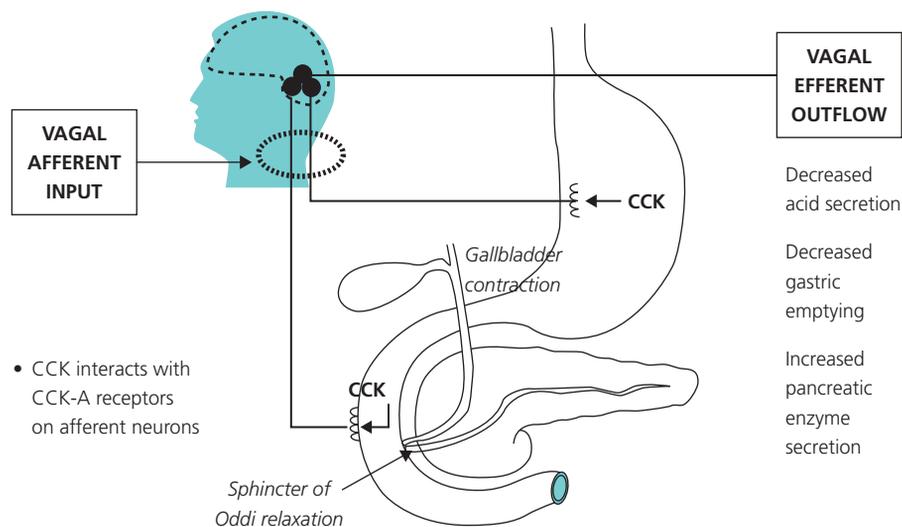


Figure 1.6 Cholecystikinin (CCK) acts predominantly by way of a vagal afferent pathway to integrate intestinal feedback regulation of the duodenal phase of the meal. From Undergraduate Teaching Program of the American Gastroenterological Association, 1996.

specific CCK₁ receptors on vagal afferent nerve terminals in the intestinal mucosa, which results in the activation of vagovagal reflexes to modify gastric, biliary, and pancreatic function. Thus, CCK, long thought of as a classic hormone, actually functions locally as a paracrine effector to stimulate afferent neurons, leading to activation of reflex neural responses.

The physiological release of CCK in response to a meal is modulated by at least two peptides. One is monitor peptide, which is secreted by pancreatic acinar cells. In addition, there is at least one luminal CCK-releasing factor. The proposed mechanism of action for both of these releasing factors is that they are constitutively secreted into the intestinal lumen. In the absence of protein or protein products in the intestinal lumen, both factors are efficiently broken down by digestive enzymes and thus are not available to stimulate CCK release. On ingestion of a meal, however, dietary proteins compete with the releasing factors as substrates for the digestive enzymes. The net effect is that the releasing factors escape digestion and become available to stimulate CCK secretion from endocrine cells in the mucosa.

The most important function of the pancreas in the integrated response to a meal is the production, storage, and secretion of digestive enzymes along with fluid. The major control of pancreatic secretion is exerted by efferent fibers from the parasympathetic nervous system and by the hormones CCK and secretin. As indicated in the previous sections, parasympathetic activation of pancreatic secretion occurs during the cephalic, oral, gastric, and duodenal phases of the meal. Secretion during the duodenal phase accounts for about 70% of the total response to a meal. In this phase, secretion is activated by the presence of chyme in the duodenum by way of extrinsic neural pathways, enteropancreatic neural pathways (i.e., through intrinsic neurons that terminate in both the duodenum and pancreas), and endocrine pathways (i.e., through CCK and secretin). Of note, research indicates that the effect of CCK on pancreatic secretion is

predominantly mediated through neural reflexes similar to those described for the regulation of gastric function.

As the meal enters the intestine, it is acidic and hyperosmotic; however, by the time it leaves the duodenum, it has a neutral pH and is isosmotic. These necessary changes for optimal digestive enzyme activity are achieved by the secretion of large volumes of water and bicarbonate ions by the pancreatic and biliary systems and the intestinal mucosa, as well as by the regulation of gastric motility and secretion as previously described. The alkaline secretions are regulated mainly by the release of secretin from the duodenal mucosa. Acting as an endocrine agent, secretin increases bicarbonate and water secretion from the pancreatic and biliary ductal systems.

Contraction of the gallbladder and relaxation of the sphincter of Oddi result in the addition of biliary secretion to the meal. During the cephalic, oral, and gastric phases, parasympathetic efferent nerves mediate these responses. During the duodenal phase, CCK acting either alone or through a vagal reflex pathway has a pronounced effect on the delivery of bile to the duodenum. Bile is composed of both inorganic and organic constituents. As previously indicated, the inorganic constituents (e.g., water, bicarbonate ions, and other electrolytes) serve to convert gastric chyme into a neutral isosmotic solution. The major organic constituents of bile are conjugated bile acids, phospholipids, cholesterol, and bilirubin; the latter two are excretory products. Both bile acids and phospholipids are essential in maintaining cholesterol in a soluble state and thereby preventing the formation of gallstones. Conjugated bile acids traverse the entire small intestine and are taken up by a receptor-mediated transport system in the terminal ileum. The conjugated bile acids return to the liver by way of the portal circulation and then are secreted back into the biliary system and stored in the gallbladder. This cycling of bile acids is termed the enterohepatic circulation. Bile acids have multiple

important functions in the process of digestion and absorption of lipids and fat-soluble vitamins. They accomplish these functions in part by possessing polar (hydrophilic) and non-polar (hydrophobic) regions that allow them to interface between aqueous and lipid environments. Thus, bile acids are involved in the formation of emulsions and micelles and in the binding of lipolytic digestive products. All these effects enhance the digestion and the absorption of fat in the meal.

The highly regulated duodenal phase is responsible for the addition of water, ions, enzymes, bile acids, and other secretions to the meal in proportions that result in an optimal environment for the digestion of nutrients. The process of digestion in the intestinal lumen is facilitated further by the induction of patterns of motility in the duodenum that promote the mixing of intestinal contents with digestive enzymes.

During the intervals between meals, motility of the GI tract is characterized by periods of intense contractions and periods of quiescence. In humans, these periods cycle at about 1.5 h. The sequential contractions migrate aborally (i.e., toward the anus) and have been termed the migrating motor complex (MMC). This complex of migrating contractions starts in the stomach and moves through the intestine and into the colon, sweeping undigested material and contents through the GI tract in the interdigestive period. Initiation of the MMC is dependent on the integrity of the vagal innervation, which serves to release the hormone motilin, which in turn activates the MMC. Food in the intestine abolishes the MMC and changes intestinal motility from this fasted pattern to a fed pattern of motility.

Nutrient digestion and absorption systems in the small intestine

The small intestine is divided into three functional regions: duodenum, jejunum, and ileum. The jejunum is the major organ for intraluminal and surface digestion and absorption of nutrients. In addition, a significant amount of water and ions are secreted and absorbed in the jejunum to facilitate digestion and absorption. The ileum provides another site for absorption and has two unique absorptive roles. One is the absorption of conjugated bile acids for reuse after they have traversed the length of the small intestine participating in fat digestion and absorption. The other is the absorption of cobalamin (vitamin B-12) bound to intrinsic factor secreted by the stomach. The ileum also releases hormones that have important functions in the gut. For example, PYY inhibits gastric function and satiety regulation. The ileocecal valve prevents the large reservoir of colonic bacteria from entering the small intestine.

Three characteristics of the small intestine make it especially well adapted for its critical role in nutrient assimilation. First, the small intestine has an enormous surface area as a result of folds in the mucosa, villi on the mucosa, and microvilli

on the epithelial cells. Second, the blood flow to the intestine markedly increases with a meal to facilitate the transport of nutrients; it can account for up to 25% of cardiac output during a meal. Third, the enteric nervous system is highly developed in the small intestine, enabling this region of the GI tract to function independently of the extrinsic innervation.

The main responses initiated in the small intestinal phase are alterations in intestinal motility patterns, intestinal secretion, and blood flow, as well as regulation of tight junction permeability. The small intestine exhibits two motor patterns: peristalsis and segmentation. Both of these motility patterns are generated by the enteric nervous system and are independent of the extrinsic nervous system. Peristalsis is characterized by a wave of relaxation followed by a ring of contraction that develops at a point and moves aborally over variable distances. Peristalsis is the primary mechanism by which contents are moved along the intestine in the interdigestive period. Segmentation is characteristic of the fed state and is the process by which rings of contraction develop at uniform intervals, dividing the lumen into segments. Segmentation is the primary mechanism by which the contents of the intestine are mixed with secretions and moved across the mucosa to enhance absorption. Another major effect of segmentation is to slow the transit of the meal in the small intestine to further enhance absorption.

The major changes in the chemical and physical characteristics of food, as well as the absorption of nutrients, trace elements, vitamins, water, and ions, occur in the intestinal phase. Hydrolysis of proteins and carbohydrates and the solubilization and hydrolysis of fats are catalyzed by enzymes in the intestinal lumen (from salivary, gastric, and pancreatic secretions) and on the brush border of the surface of the intestinal mucosa. Examples of luminal and surface digestive systems are listed in Table 1.4. Absorption is the process by which molecules produced by luminal surface digestion are transported into epithelial cells and then carried into the blood or lymph. The duodenum and jejunum have the highest absorptive capacities; most absorption occurs in the upper small intestine, although some occurs in the ileum. Molecules

Table 1.4 Digestive enzymes of the lumen and mucosal surface

Intraluminal

Salivary amylase
Gastric pepsin and lipase
Pancreatic amylase, lipase, phospholipase, cholesterol esterase, trypsin, chymotrypsin, elastase, carboxypeptidase A, carboxypeptidase B, DNase, RNase

Mucosal surface

Lactase, sucrase, isomaltase
Amino-oligopeptidase, aminopeptidase A, dipeptidase, dipeptidyl aminopeptidase, carboxypeptidase P, γ -glutamyltransferase, folate conjugase

PART 1 Basic mechanisms of normal and abnormal gastrointestinal function**Table 1.5** Mucosal absorptive transporters

Na ⁺ -glucose/galactose cotransporter (SGLT1), fructose transporter (GLUT5)
Neutral amino acid transporter (NBB system); PHE system for phenylalanine and methionine; IMINO system for imino amino acids, proline and hydroxyproline; basic amino acid transporter, acidic amino acid transporter
Na ⁺ -dependent transporters for folate, thiamine, riboflavin, pantothenic acid, biotin
Na ⁺ -dependent conjugated bile acid transporter in the ileum
Cobalamin–intrinsic factor receptor in the ileum

are absorbed by two principal mechanisms: transcellular (i.e., passing through enterocytes) and paracellular (i.e., passing between enterocytes). Monosaccharides, amino acids, electrolytes, minerals, and water-soluble vitamins enter the portal circulation and pass through the liver into the systemic circulation. Lipids and fat-soluble vitamins and cholesterol esters (together with lipophilic drugs) enter the lymph, which drains into the systemic circulation. Examples of mucosal absorptive systems are listed in Table 1.5.

Colonic phase of a meal

The colonic phase is important for the further reabsorption of water and ions and for the storage and elimination of waste products. The cecum and ascending colon receive about 2 L of ileal effluent daily. Absorptive transport mechanisms reduce the volume to about 200 mL per day. The transverse, descending, and sigmoid portions of the colon store fecal material and transport the material to the rectum. The rectum signals the defecation reflex. In addition, some fermentation of monosaccharides yields free fatty acids that can be taken up by colonic epithelial cells.

The stimuli induced in the colon are both mechanical (e.g., rectal distention) and chemical (e.g., free fatty acids). Extrinsic and intrinsic neural pathways mediate the motility responses of the colon and the defecation response. Hormonal pathways affecting other parts of the GI tract may also be excited in the colon. For example, PYY may be released from the colonic mucosa if the fat content of the meal is high and not all is absorbed by passage through the small intestine. PYY, in turn, slows gastric emptying and transit of the meal through the small intestine, resulting in increased fat digestion and absorption. Further, PYY decreases food intake through its regulatory effect on satiety.

The effectors in the colonic phase are both motor and secretory. The colon exhibits both storage motor patterns (i.e., changes in tone) and propulsive motor patterns (i.e., phasic contractions). Rectal distention initiates the defecation reflex. This response consists of both involuntary and

voluntary components. Propulsive motility in the descending colon and rectum is increased to move the feces to the anus, where relaxation of internal and external anal sphincters facilitates elimination.

Regulation of nutrient storage and release: roles of the liver and endocrine pancreas

An essential function of the liver and endocrine pancreas is to coordinate the distribution of vital metabolic substrates to the tissues of the body. It must perform this task during both the fed (i.e., absorptive) state, when nutrients ingested during a meal enter the circulatory system from the gut, and the fasted (i.e., postabsorptive) state, when the gut contains no nutrients (Table 1.6). During the fed state, the body's energy requirements are met by a portion of the ingested nutrients, and any remaining nutrients must be stored for later use. Conversely, during the fasted state, the energy needs of the tissues must be satisfied by metabolic substrates generated from the body's stores, chiefly the liver, the adipose tissue, and the skeletal muscle. The integrated responses of the liver and endocrine pancreas to a meal direct the crucial metabolic

Table 1.6 Major characteristics of the fed and fasted states**Fed state**

- Nutrients absorbed from the gut
- Energy needs met by using ingested nutrients
- Insulin released by the pancreas
- Net hepatic glucose uptake
- Hepatic glycogen synthesis and storage
- Hepatic protein and triglyceride synthesis
- Muscle glycogen synthesis and storage
- Muscle protein synthesis
- Adipose triglyceride storage
- Glucose is predominant fuel source

Fasted state

- No nutrients in the gut
- Energy needs met by using stored fuel
- Glucagon released by the pancreas
- Net hepatic glucose release
- Hepatic glycogenolysis and gluconeogenesis
- Hepatic protein and fat catabolism
- Muscle glycogenolysis
- Muscle protein catabolism
- Adipocyte fat catabolism
- Enhanced fatty acid utilization by most tissues

Long-term fast

- Hepatic ketogenesis
- Enhanced ketone utilization by the brain and other tissues
- Proportional increase in renal gluconeogenesis

transition from the fed to the fasted state and back. These responses are controlled by a complex network of endocrine, paracrine, and neural signals, as well as by the concentration of metabolic substrates in the portal blood that feeds the liver and pancreas. Insulin and glucagon, hormones produced in the islet cells of the pancreas, are the principal regulators of the metabolic state, such that the transition from the fed to the fasted state can be explained by a reduction in the ratio of insulin to glucagon in the blood.

Fed state

Extrinsic nutrients enter the bloodstream from the gut while a meal is digested and absorbed. During this period, termed the fed state, ingested glucose is the body's principal energy source. A portion of this glucose, absorbed directly from the portal system, enters the liver where some of it is used to meet the liver's energy needs, and the remainder is converted to glycogen, which will replete the hepatic stores, and to fatty acids and glycerol for synthesis of and storage as triacylglycerols in the adipose tissue. Thus, a key feature of the fed state is net glucose uptake by the liver. Glucose that reaches the skeletal muscle is catabolized for energy and converted to glycogen to replete muscle energy stores. Adipocytes catabolize glucose, and also use it to form α -glycerol phosphate and fatty acids, which are triacylglycerol precursors. Ingested amino acids are taken up by all of the body's tissues and organs, including the liver, for use in protein synthesis. However, excess amino acids are not stored as protein but are converted by the liver to α -keto acids, which are catabolized or converted to fatty acids for storage as fat. Thus, the net synthesis of protein during the fed state simply replenishes the protein degraded during the fasted state, except in growing children and vigorously exercising adults. The lipid contents of a meal are transported to the circulation by way of the lymphatics in the form of triacylglycerols. Lipoprotein lipases in the endothelium hydrolyze the ingested triacylglycerols into fatty acids and glycerol, which are a source of energy for tissues, and the adipocytes store the excess as fat.

Fasted state

During the fasted state, the absence of nutrient absorption from the gut forces the liver to maintain the concentration of glucose in the blood. This is imperative because, under ordinary circumstances, glucose is the exclusive energy source for the brain and the erythrocytes. The blood glucose concentration is sustained by hepatic glucose production and by a reduction in glucose use by most tissues and organs. An early event in the fasted state is the hydrolysis of glycogen (i.e., glycogenolysis) in the liver into glucose, which is released into the circulation. However, the hepatic stores of glycogen are limited, so that during prolonged fasts the liver must synthesize glucose from a variety of precursors (i.e., gluconeogenesis), including lactate, pyruvate, amino acids, and glycerol. These glucose precursors result from several extrahepatic

metabolic processes that are stimulated during a prolonged fast. Glycogen is stored in skeletal muscle, as well as the liver. During a prolonged fast or when a muscle is working, skeletal muscle glycogen is hydrolyzed to form lactate and pyruvate. Lipid hydrolysis (i.e., lipolysis) in adipocytes is stimulated in the fasted state, resulting in the formation of glycerol, as well as fatty acids. As the fasted state proceeds, protein mainly located in skeletal muscle is catabolized to amino acids. These precursors are circulated to the liver where they are converted into glucose to help preserve the concentration of glucose in the blood. Consequently, during the fasted state, the liver is a site of net glucose release.

Gluconeogenesis is capable of supplying less than half of the energy necessary for survival. Therefore, the fasted state is also characterized by a substantial reduction in glucose utilization by most tissues and organs of the body. Glucose generated by the liver is thus spared for use by the CNS. Glucose use is reduced by an increase in fat utilization by other tissues. As previously discussed, the enhanced lipolysis associated with the fasted state produces fatty acids in addition to the glucose precursor, glycerol. These fatty acids are released to the systemic circulation where they are used as an energy source by nearly all tissues except, most notably, the CNS.

During long-term fasts (i.e., longer than 24–48 h), further metabolic changes occur that facilitate survival. The kidneys, which also are capable of performing gluconeogenesis, take on an increasingly prominent role in glucose production. In addition, the liver converts acetyl-CoA, a product of fatty acid catabolism, into ketones. These ketones are used as an energy source by many tissues, including the brain. A distinct advantage of shifting the fuel source from glucose to ketones is that muscle is spared as a source of amino acids for gluconeogenesis.

Regulation of the metabolic state

During the fed state, serum glucose in particular, but also amino acids and other sugars in the blood, absorbed from a meal stimulate the secretion of insulin from the β -cells of the pancreatic islets (Table 1.7). In addition to the metabolic substrates absorbed during a meal, gastrointestinal hormones released from duodenal cells facilitate insulin release. These hormones, called incretins, include GLP-1 and glucosulinitropic peptide. In addition, vagal neural pathways and β -adrenergic stimuli regulate insulin release. In contrast, somatostatin and α -adrenergic stimuli inhibit insulin release. Insulin affects mainly the metabolism of the liver, adipose tissue, and muscle, which are the primary sites of fuel storage and release. The hepatic response to insulin is to promote net glucose uptake, glycogen synthesis and storage, and protein and triglyceride synthesis. In adipocytes, insulin stimulates the uptake of glucose, triglyceride synthesis from glucose,

PART 1 Basic mechanisms of normal and abnormal gastrointestinal function**Table 1.7** Regulation and function of key hormonal and paracrine regulators of nutrient storage and release

Peptide	Source	Stimuli and facilitators	Inhibitors	Functions
Insulin	Pancreatic β -cells	Glucose Other sugars (e.g., mannose) Amino acids (e.g., leucine, arginine) GI hormones (e.g., glucagon-like peptides, cholecystokinin, secretin) Vagal input β -Adrenergic signals	α -Adrenergic signals Somatostatin (paracrine)	<p>Liver</p> <ul style="list-style-type: none"> ↑ Glycogen synthesis and storage ↓ Glycogenolysis ↑ Protein and triglyceride synthesis ↑ Very low-density lipoprotein production ↓ Gluconeogenesis ↓ Ketogenesis <p>Muscle</p> <ul style="list-style-type: none"> ↑ Protein synthesis ↑ Glycogen synthesis and storage <p>Adipose tissue</p> <ul style="list-style-type: none"> ↑ Triglyceride storage ↓ Lipolysis
Glucagon	Pancreatic α -cells	↓ Glucose Amino acids (e.g., arginine, alanine)	Glucose Insulin Somatostatin Fatty acids	<p>Hepatic</p> <ul style="list-style-type: none"> ↑ Glycogenolysis ↑ Gluconeogenesis ↑ Ketogenesis
Somatostatin	Pancreatic δ -cells	Glucose Amino acids (e.g., arginine) GI hormones (e.g., glucagon-like peptides, cholecystokinin, secretin)		<p>Pancreatic</p> <ul style="list-style-type: none"> ↓ Glucagon release ↓ Insulin release ↓ Secretion by the exocrine pancreas <p>Gastrointestinal</p> <ul style="list-style-type: none"> ↓ Gastric emptying ↓ Gastric acid and gastrin production ↓ Splanchnic blood flow
Glucagon-like peptide-1	Duodenal L-cells	Glucose Lipids		<p>Pancreatic</p> <ul style="list-style-type: none"> ↑ Insulin release <p>Gastrointestinal</p> <ul style="list-style-type: none"> ↓ Gastric emptying

and net triglyceride storage. The effect of insulin on muscle is to stimulate net glucose and amino acid uptake and use, glycogen synthesis and storage, and protein synthesis.

During the fasted state when there are no nutrients being absorbed from the gut, glucagon secretion is highest. This observation results from the fact that glucagon release is mainly stimulated by hypoglycemia, although certain amino acids, epinephrine (adrenaline), and sympathetic neural activity also stimulate its secretion. Conversely, glucose, insulin, somatostatin, and certain fatty acids inhibit secretion of this peptide. Glucagon, which acts primarily on the liver, counters the effects of insulin by stimulating glycogenolysis, gluconeogenesis, and ketogenesis.

Aside from regulating the secretion of insulin and glucagon, catecholamines and the autonomic nervous system stimulate glycogenolysis by the liver and muscle, gluconeogenesis by

the liver, and lipolysis by adipocytes. Hypoglycemia leads to reflex epinephrine secretion and sympathetic neural activity. Although other hormones, such as cortisol and growth hormone, modulate hepatic metabolism, they do not play an important role in the liver's response to a meal.

In addition to the roles that blood glucose and amino acid concentrations play in the hormonal regulation of the metabolic state, the concentration of glucose in the blood of the sinusoids directly modulates hepatic metabolism. As a result of the activity of certain glucose concentration-dependent enzymes in the liver, elevation of the sinusoidal blood glucose concentration stimulates glycogen synthesis and inhibits glycogenolysis. Together, hormones, the autonomic nervous system, and the concentration of metabolic substrates in blood precisely modulate the hepatic response to a meal.