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4

The physiology of nutrient digestion and absorption

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OBJECTIVES

By the end of this chapter you should:

- be able to understand the most important functions of the various parts of the gastrointestinal tract
- be aware of the main actions of digestive enzymes and the neural and hormonal regulators of digestion
- know the main features of absorption and secretion of specific nutrients, water and electrolytes
- appreciate that luminal factors play a role in the regulation of food intake.

4.1 Introduction

The major components of the diet are starches, sugars, fats, and proteins. These must be hydrolysed to their constituent smaller molecules for absorption and metabolism to occur. Starches and sugars are absorbed as monosaccharides; fats are absorbed as free fatty acids and glycerol (plus a small amount of intact triacylglycerol); proteins are absorbed as their constituent amino acids and small peptides. The processes of digestion and absorption occur in the gastrointestinal tract.

The gastrointestinal tract is a digestive and absorptive tube, the largest endocrine organ in the body; it is home to a large part of the immune system and contains more neurons than the spinal cord. It is 'zoned' not only by anatomy, but also in terms of substrate digestion and absorption, electrolyte absorption and secretion, metabolism, and neural control. Anatomically, nutrient absorption can be described by reference to its linear distribution along the intestine; specialized compartments with different digestive and absorptive functions follow each other. Digestive and absorptive processes are very efficient because many are duplicated. This means that impairment of one process by disease does not

necessarily lead to complete malabsorption of a particular nutrient. The digestive and absorptive capacity of the human intestine closely matches the metabolic mass of each individual, just as it matches the metabolic mass of species, small and large, such as the shrew and the whale, respectively. Clearly, an excessively large intestine would be inefficient because, at the extreme, its maintenance cost may exceed the energy value of food ingested. Inefficient digestion also carries penalties. The most rapid period of intestinal growth occurs after birth, and if part of the intestine of a neonate is removed by surgery because of gastrointestinal disease, some adaptation of remaining digestive and absorptive capacity can occur but is not great. As a result, intravenous nutrition may become necessary. Figure 4.1 shows a scheme of the intestinal tract.

The gastrointestinal tract has a very active maintenance metabolism and meets its energy requirements from substrates in arterial blood and the products of digestion in the lumen. The effort of chewing food uses about 1–2% of the energy content of the food itself. About half of dietary protein is utilized to meet the amino acid requirements of the gut, but only 10% of dietary glucose is metabolized by enterocytes before passage into the portal circulation. Ingestion of food leads to increased blood flow around the intestine and to increased transmembrane transport of substrates, water, and ions, all of which are energy-consuming processes.

Intestinal function is modulated by more than 100 gastrointestinal peptide hormones and an enteric nervous system (ENS) that has as many neurons as the spinal cord. Individual neurons are independent of the central nervous system (CNS), but the ENS communicates with the CNS via sympathetic and parasympathetic pathways. This autonomic system controls functions such as contraction, secretion, motility, and mucosal immune defences, and is influenced by central mechanisms which may set the threshold of autonomic phenomena such as appetite and satiety. In addition, the gut itself signals sensations of hunger and will initiate the chain of events

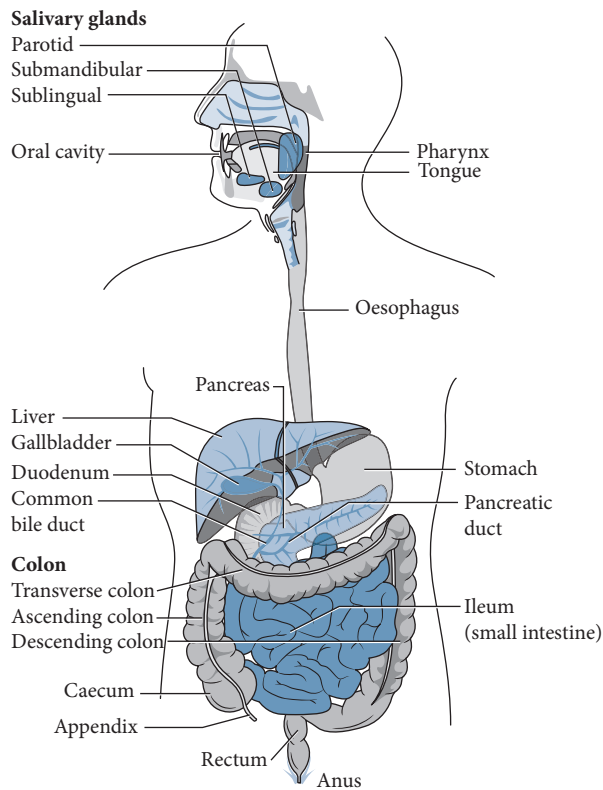


FIGURE 4.1 The gastrointestinal tract

which not only lead to the start of food-seeking and eating behaviours but also to satiety and cessation of eating. These processes are all modified by disease and obesity. See also Chapters 23 and 27 and Figure 4.2.

4.2 The structure and function of the gastrointestinal tract

The gastrointestinal tract is 7–10 metres long and stretches from the mouth to the anus. Together with the liver, it comprises about 3% of adult body weight but consumes 10–20% of resting energy expenditure. It is divided into zones that accomplish different digestive and absorptive tasks. The first zone, the mouth and pharynx, leads to the oesophagus, a pipe that enters the stomach via the oesophageal sphincter. Exit from the stomach is governed by the pyloric sphincter which allows food to pass into the small intestine (duodenum, jejunum, and ileum) which is 2.8–8.5 metres long and is shorter in women, who have lower average metabolic mass than men. The duodenum (20–30 cm long and 5 cm in diameter) leads to the jejunum and ileum which comprise the upper two-fifths and lower three-fifths of the small bowel, respectively. There is no strict anatomical

differentiation between these zones, but the lumen narrows towards the terminal ileum and this reduction in volume per segment length reflects the decreasing luminal fluid loads along the small bowel. Similarly, the jejunal wall is thicker and the villi are longer, and this correlates with the amount of substrate absorbed in each region. Some of these regional differences are summarized in Table 4.1. The small bowel enters the large bowel via the ileocaecal valve which, like the oesophageal sphincter, prevents back-flow or reflux of luminal contents. Zones within the colon are defined as the caecum, the transverse and distal colon which terminate in the rectum, and the anus (Figure 4.3)

Chewing reduces the particle size of food and increases the surface area available for digestive enzyme action. In addition, it will release the intracellular contents of meat and plants. Some enzymes are secreted with saliva. The stomach is a muscular sac which not only physically reduces the particle size of food, but also forms a barrier to ingress of bacteria into the gastrointestinal tract. There is considerable release of enzymes that break down (hydrolyse) lipid and protein. Stomach emptying occurs when the particle size has been reduced sufficiently by grinding in the antrum. Therefore the stomach is a mill, a fermenter, and a pump with built-in particle-size sensing. The thin emulsion of food which enters the small bowel from the stomach is neutralized by duodenal bicarbonate secretions and further digested by enzymes secreted by the pancreas. This process is aided by detergent bile salts released by the gall bladder. During passage along the jejunum, a large amount of water (9 litres) is secreted and then reabsorbed with the products of luminal and brush-border digestion. Efficient reabsorption means that only 60–120 ml of fluid pass the ileocaecal valve each hour, carrying undigested material into the caecum to be metabolized by the numerous bacteria that have established a stable environment there. Colonic fermentation generates short-chain fatty acids (SCFAs) that stimulate absorption of salts and water to produce a formed stool which is passed per rectum.

Table 4.1 summarizes the anatomy of the gastrointestinal tract. The intestinal wall also has a zoned anatomy (Figure 4.3), the absorptive surface of which is amplified by three structures.

1. Folds or ridges (rugae) in the intestinal wall increase the absorptive area.
2. Villi, finger-like projections 0.5–1.0 mm long covered with mucosal absorptive cells (enterocytes) further increase the absorptive capacity of mammals with higher continuous metabolic rates.
3. Enterocytes have further finger-like projections on their luminal surface, known as microvilli, and these define the brush-border membrane.

70 Chapter 4 Physiology of nutrient digestion and absorption

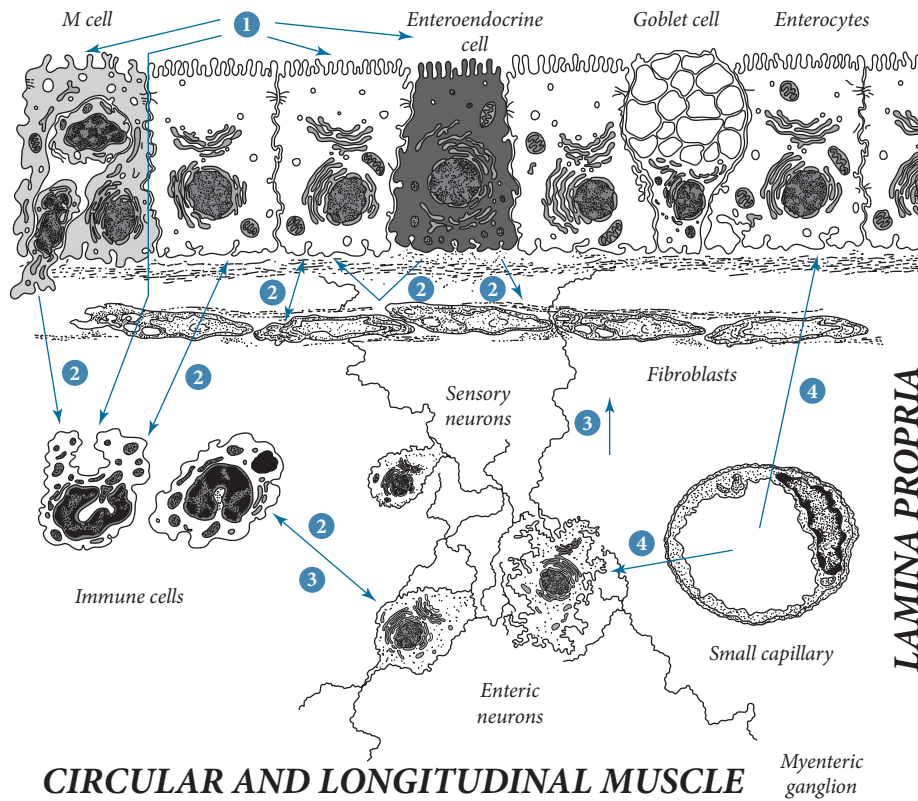


FIGURE 4.2 The regulation of intestinal absorption and secretion by communication between intestinal cells

(1) Luminal stimuli (e.g. glucose, amino acids, fat) interact with enterocytes and with enteroendocrine, immune, or M cells and may cause lymphocytes and macrophages to migrate into pockets on the basolateral surface. (2) These may secrete mediators that influence enterocytes, or other cells of the lamina propria, such as immune cells or enteric neurons. (3) Stimuli and signals from sensory neurons and the central nervous system are integrated by the enteric nervous system which modulates gut motility and mucosal function. (4) Hormonal stimuli delivered by the circulation regulate mucosal function and influence the cells of lamina propria.

From: J. Pacha. Development of intestinal transport function in mammals. *Physiological Reviews*, 80(4), 1633–67, 2000, Fig. 3, with permission.

These features increase the absorptive area of the human intestine to 200 m², which is about the same area as a singles tennis court. Each villus is supplied by an arteriole and is drained by a venule and a lacteal. The venules drain into the hepatic portal vein and carry water-soluble nutrients. The lacteals are part of the lymphatic system and carry the water-insoluble products of fat digestion and absorption to the thoracic duct and then the subclavian vein. This means that most dietary lipids avoid ‘first-pass’ metabolism by the liver and instead are metabolized first by peripheral tissues.

Blood is supplied abundantly (500 ml/min) to the intestine by numerous small arteries that branch from the arch of the mesenteric artery. This blood drains, via the portal vein, to the liver which regulates the supply of nutrients to the periphery through the hepatic vein into the vena cava. Only a quarter of this blood supplies the submucosa, muscularis, and serosa; the remainder goes to the mucosal layer, which has very active metabolism

(and needs a good oxygen supply), where absorbed nutrients are quickly diluted out and removed to the portal vein, thus preventing any high osmotic loads developing. In some respects, the intestine behaves like a ‘pre-liver’ because it:

- metabolizes considerable amounts of dietary glucose and amino acids
- transforms and degrades dietary arginine and nucleotides completely
- detoxifies drugs and dietary toxins through the action of mucosal cytochrome P450 enzymes and the UDP glucosyltransferases and sulphotransferases
- extrudes toxins back into the gut lumen through the action of the membrane transporters which can be classed as conferring multi-drug resistance (i.e. P-glycoprotein and ATP binding cassette (ABC) transporters).

TABLE 4.1 Regional anatomy of the intestine and sites of nutrient absorption

Region	Functions performed	Mucosal surface	Nutrients digested	Nutrients absorbed	Major site of absorption	Electrolytes absorbed
Mouth	Grinding food to smaller particle size Moistening food (saliva) Initial digestion by lipase and alpha-amylase Initiation of satiety mechanisms	Small folds	Small amount of protein Starch	Small amounts of glucose, peptides and amino acids	No	No
Stomach	Intestinal defence (e.g. acid secretion) Homogenizing food to smaller particle size Moistening food (gastric secretions) Further enzyme digestion Gastric emptying meters delivery of nutrients to the small intestine Feedback of satiety messages	Rugae and pits	Protein, lipid	Insignificant amounts	No	No
Small intestine	Completion of digestion by pancreatic enzymes Absorption of digestion products of carbohydrate, protein and fat Absorption of water and electrolytes Absorption of minerals and micronutrients Feedback of satiety messages	Rugae, villi, and microvilli	Protein, lipid, carbohydrate	Amino acids, peptides, fatty acids, glucose, fructose, galactose, glycerol, and vitamins	Carbohydrate, fat, protein, water, electrolytes	Sodium, potassium, calcium, magnesium, chloride, phosphate
Colon	Final salvage of water and electrolytes Mucin breakdown Conversion of bilirubin to urobilinogen Cholesterol catabolism Organic acid production ('acetate buffer')	Rugae and pits	Dietary fibre—digested by bacteria and fermented to short-chain fatty acids	Acetate, propionate, and butyrate, and dicarboxylic acids	SCFAs, water, electrolytes	Magnesium and calcium in form of soaps with fatty acids

72 Chapter 4 Physiology of nutrient digestion and absorption

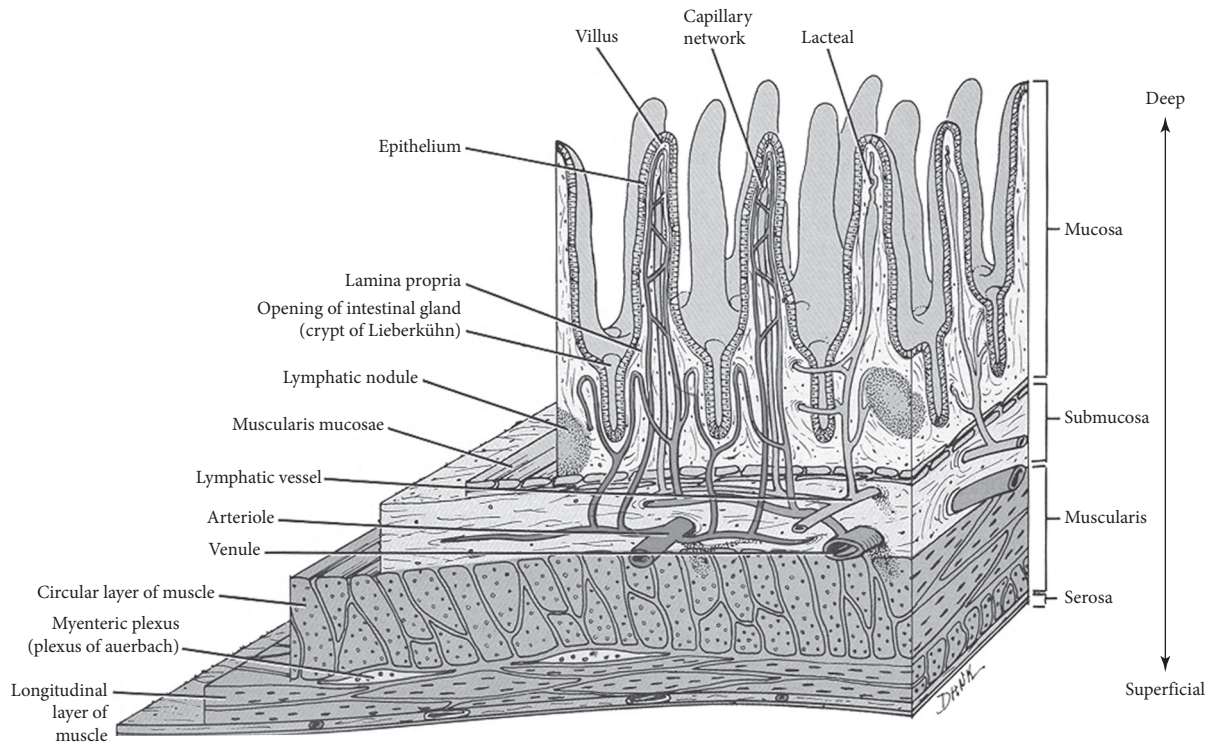


FIGURE 4.3 Intestinal architecture

This is the conventional way to consider the intestine as an organ of digestion and absorption. The villus is covered with absorptive cells called enterocytes. Their outer surface is covered with microvilli, which are rich in digestive enzymes and nutrient and solute transporters. Folds, villi, and microvilli increase the absorptive area of the intestine approximately 1800-fold to about the size of a doubles tennis court. Water-soluble nutrients are carried to the liver through the venules which drain into the portal vein. Lipids and lipid-soluble vitamins are transported via the lacteals into the lymphatic system. Reproduced with permission from G.J. Tortora, N.P. Anagnostukos, *Principles of Anatomy and Physiology*, Harper & Row, New York, 1990.

Therefore the gut is a formidable barrier to dietary carcinogens, and the continual rapid shedding of mature enterocytes from the villus tips may explain why tumours of the small intestine are much rarer than those in the large bowel.

Changes in intestinal motility will alter absorptive efficiency. This is because they might increase the contact time between nutrients and the absorptive mucosal surface. In contrast, motility disorders often cause nutrient malabsorption. The importance of gut motility can be judged from the depth of the muscular zone of the intestine and the size of the enteric nervous system (see Figure 4.2) in which regular nerve plexuses control motility at a local level whilst also responding to signals generated by the presence of luminal nutrients in the lumen and by the vagus nerve.

The intestine also has several lines of defence against ingress of bacteria.

1. The concentration of gastric acid during fasting is about 0.1M HCl (pH 1.0), forming an effective bactericidal barrier.

2. The gastric mucosal surface is very hydrophobic, and damaging agents have limited ability to wet it and thus cause local injury.
3. Goblet cells secrete an adherent sticky film of mucus that has a low viscosity surface layer. Bacteria will therefore be swept off this fragile outer layer by peristaltic waves in the gut. The mucus layer is thickest in the stomach and colon which have highest luminal concentrations of bacteria.
4. About a third of cells in the intestine comprise the gut-associated lymphatic tissue (GALT) which secretes IgA into the gut lumen.

4.3 Processes of digestion

Digestive processes in the mouth

Chewing grinds the food and also mixes it with saliva, which contains enzymes that initiate digestion of dietary starch and protein and hence development of taste during chewing. In addition, these enzymes maintain periodontal health.

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Tooth enamel and gums are covered in a biofilm called the salivary pellicle which is free from bacteria but contains several enzymes from salivary sources (e.g. amylase, proteolytic enzymes) and bacterial sources (e.g. glucosyl-transferase) as well as glycoproteins and mucins. Oral bacteria, which possess specific binding proteins, can attach themselves to α -amylase or to a proteolytic enzyme in this biofilm, as is the case for oral streptococci which maintain the oral ecology of the mouth. *Porphyromonas gingivalis* is a major agent in the development of periodontal disease and binds directly to α -amylase, but this kills the bacterium by an unknown mechanism. Species such as *Leuconostoc mesenteroides* produce lactic and acetic acids and secrete a glucosyl transferase which will synthesize dextran (an α -1,6-linked glucose polysaccharide) from sucrose. Highly branched dextran binds avidly to tooth enamel and is a tight binding site for acid-producing bacteria adjacent to tooth enamel. This is one reason why dietary sucrose is specifically harmful to teeth. The 'furry' feeling on teeth after consuming a sugary drink is actually newly synthesized dextran on the enamel.

Saliva not only lubricates food and aids in formation of the bolus to be swallowed, but also protects the mucosal surface of the pharynx and oesophagus. Bicarbonate in saliva neutralizes acid that refluxes back up the oesophagus (a surprisingly common event) and thus protects the oesophageal mucosa, the growth of which is stimulated by salivary epidermal growth factor (EGF). Impairment of EGF secretion has been associated with the development of Barrett's oesophagus, which predisposes to oesophageal adenocarcinoma. Lipid digestion also begins in the mouth, initiated by lipase secreted by the tongue (lingual lipase).

The efficiency of chewing varies through the life cycle. Infants can efficiently eat only milk and puréed food before they develop teeth, and up to three-quarters of the elderly population in UK have few teeth because of a lifetime of periodontal disease or dental neglect. The link between tooth loss in the elderly and poor nutrition is complex. Fitting dentures does not always improve nutritional status because dentures require a symmetrical bite if they are not to become displaced, and not all people can achieve this because the normal bite is often asymmetrical.

Swallowing transfers a food bolus from the mouth to the oesophagus, and involves contraction and relaxation of at least 14 groups of muscles in about 10 seconds in healthy subjects. A normal swallowing action is present in 80% of young people but in only 16% of those over 70 years old. Whilst an abnormal swallow does not necessarily predispose to swallowing problems (i.e. adaptation has occurred), these nevertheless affect 30–60% of elderly people in care. The swallowing complex is initiated and

distributed by neurons within the dorsal medulla and ventrolateral medulla, respectively, and may be impaired by stroke. Recovery of adequate swallowing after a stroke (and tube-feeding if swallowing is not re-established) remains a major nutritional challenge in the care of elderly people.

Digestive processes in the stomach

Control of gastric secretion

The gastric lumen is an environment hostile to the mucosal surface; gastric juice is chemically very corrosive (typically pH 1.0) and contains aggressive proteolytic enzymes, the action of which is regularly augmented by hot foods, detergent bile reflux, and sometimes alcohol. The first line of defence against this attack is the gastric mucus, which is multilayered. The gastric glands secrete acid through narrow channels in mucus (5–7 μm wide) which guide acid into the gastric lumen and protect the mucosal cells. The total thickness of mucus varies throughout the length of the gastrointestinal tract, but in the stomach it is nearly 0.3 mm thick and is half firmly and half loosely adherent (Atuma et al. 2001). The surface of the mucosa is covered with gastric pits or crypts which are lined with four types of cell.

1. G cells which secrete the hormone gastrin (which stimulates acid secretion).
2. Parietal cells which secrete hydrochloric acid.
3. Chief cells which secrete pepsinogen, the inactive precursor of pepsin
4. Mucous cells which secrete the glycoprotein mucin, whose composition and mechanical properties vary with site. These cells are found at the neck of the pit.

The bulk of the gastric contents typically has pH 3.0, increasing progressively to 5.0 within the strongly adherent mucus layer. At the outlet to the gastric crypt, pH falls to 4.6 and then to 3.0 at the base of the crypt. In contrast, the intracellular pH of cells lining the crypt is neutral, or slightly alkaline in the deepest parietal cells. This pH gradient is maintained by the directional secretion of H^+ into the gastric lumen and formation of HCO_3^- which neutralizes acid and so protects the mucosal cells. The flow of H^+ out of the cells is matched by an influx of K^+ , whilst the outflow of HCO_3^- is balanced by the inflow of Cl^- which will eventually be secreted with H^+ as HCl. This constant pumping of large amounts of ions means that the parietal cells have very high metabolic rates, and helps to explain why the gastrointestinal tract accounts for 10–20% of total energy expenditure even though it is, at most, 5% of body weight if the liver is included. Parietal cells carry receptors for three agents that stimulate acid secretion; acetylcholine, gastrin, and histamine.

Customer	Book Title	Stage	Supplier	Date
OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

74 Chapter 4 Physiology of nutrient digestion and absorption

Following a meal, gastric secretory activity follows three well-defined phases.

1. The 'cephalic phase' of eating (sight, aroma, and anticipation of food) stimulates the parasympathetic intestinal nervous system via the vagus nerve, with acetylcholine release near parietal and G cells leading to acid and gastrin secretion.
2. The 'gastric phase' is defined by increased acid and pepsinogen secretion in response to the stretching of mechanoreceptors by food ingestion. This stimulates gastrin release which increases secretions.
3. The 'intestinal phase' occurs towards the end of liquidization of food in the stomach.

Receptors in other parts of the intestine inhibit gastric emptying through neural and hormonal pathways. This is known as the 'pyloric brake'. Each of these phases has a counterpart that controls appetite and eating behaviour.

Digestive properties of gastric juice

Both dietary lipid (triacylglycerol) and protein are hydrolysed by enzymes secreted in the gastric juice; salivary amylase action continues in the centre of the

food bolus until mixing with gastric acid causes its pH to fall low enough to inactivate amylase. During passage from plate to stomach, food lipid will have been reduced to an emulsion of droplets 10–100 μm in size. Gastric lipase, secreted by the gastric mucosa, has limited activity and its contribution to total lipid hydrolysis is less important quantitatively than qualitatively. This is because this enzyme releases palmitic acid and oleic acids from the sn-3 position of triacylglycerols, and these fatty acids stimulate the activity of pancreatic lipase in the small intestine. It has high activity towards triacylglycerols which form a reverse emulsion of lipid in water micelles. Gastric lipase binds to the surface of the micelle and will hydrolyse triacylglycerol to release free fatty acids which generate osmotic pressure within the micelle and lead to budding of new smaller micelles. Even though only 10–30% of dietary triacylglycerol is hydrolysed by gastric lipase, this is sufficient to emulsify dietary fat very considerably (Figure 4.4). The process is self-limiting as these fatty-acid-rich buds inhibit surface-bound lipase.

Proteins are relatively resistant to enzymic hydrolysis until their structure has been denatured by heat (e.g. in cooking) or extreme pH. Gastric acid achieves considerable denaturation of many dietary proteins,

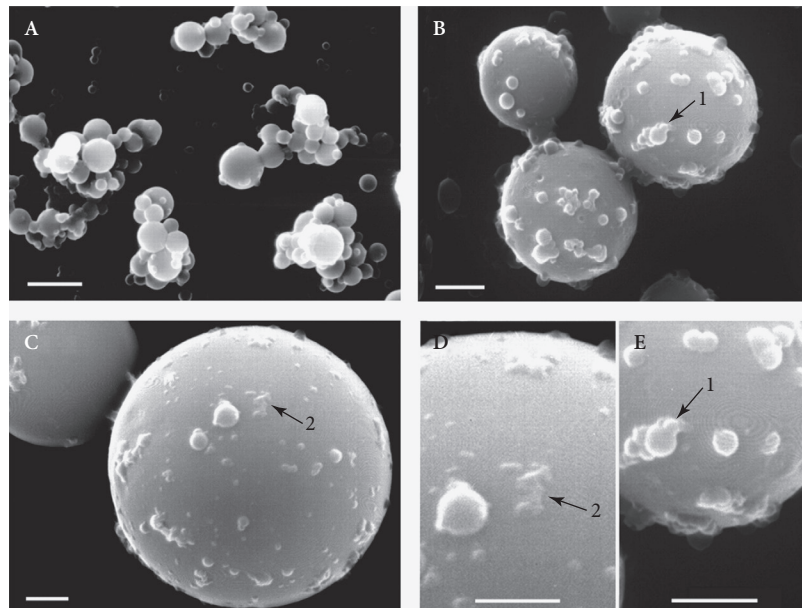


FIGURE 4.4 Hydrolysis of lipid droplets by human gastric lipase

Scanning electron micrographs of lipid droplets during hydrolysis by human gastric lipase (HGL). (A) Before lipolysis the medium-size emulsion comprises smooth spherical lipid droplets (0.5–2 μm diameter). (B) After 5 min incubation with HGL the droplets become swollen (2.6–6.4 μm) and their surfaces become irregularly covered with small spherical 'buds' from the surface (<1 μm) (arrow 1, enlargement in E). (C) After 80 min, the droplet has swollen more (range 5.6–10 μm), and the surface is covered with 'buds' and amorphous lipid clusters (arrow 2, enlargement in D).

From: Y. Pafumi, D. Lairon, P.L. de la Porte, C. Juhel, J. Storch, M. Hamosh, and M. Armand. Mechanisms of inhibition of triacylglycerol hydrolysis by human gastric lipase. *Journal of Biological Chemistry*, 277(31), 28070–9, 2002, Figure 5, with permission.

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but some resist digestion in the stomach. Up to 75% of ingested lactoferrin, an iron-binding transferrin-like protein in human milk, survives passage through the stomach intact.

Pepsins, which initiate the process of protein digestion, are stored as inactive zymogens in granules of the chief cells of human gastric mucosa (e.g. pepsinogen A) and are secreted as pepsinogens (inactive precursors or zymogens). Pepsinogen is inactive because it contains a peptide sequence that blocks the active site. At low pH, this peptide unwinds and is cleaved off by the active site of the enzyme itself, thus resulting in an active pepsin which may then activate other pepsinogens. They are denatured at pH >7.0.

At least seven pepsins can be assigned to four families (older name): pepsin A (pepsin), pepsin C (gastricsin), cathepsin D (slow moving protease), and cathepsin E (proteinases 1 and 2). They are all aspartate proteinases whose active site is a deep cleft that can accommodate at least seven amino acid residues of the substrate protein. Hydrolysis occurs mainly, but not exclusively, at the carboxyl side of the aromatic amino acids tyrosine, phenylalanine, and tryptophan, resulting in formation of (relatively large) soluble oligopeptides and some free amino acids. Free amino acids in the gastric lumen activate a receptor that leads to further stimulation of gastrin secretion, so dietary protein stimulates gastric secretion.

Pepsins are activated by acid and have an acid pH optimum, but do not necessarily operate at acid pH. Meal-induced acid secretion is rapidly buffered by food, so that the pH of the bulk phase of the stomach lumen rises from pH 1.5 to pH 4.5 within 15 min of the end of a meal. Secreted zymogens are activated at the submucosal layer by gastric acid secretion, whereas hydrolysis of bulk-phase dietary proteins, which have been acid denatured by contact with the mucosal surface, occurs at a relatively high luminal pH.

Control of the rate of gastric emptying

Gastric emptying matches not only the amount of food eaten during a meal, but also nutrients present in the food and the progress made in liquidizing it within the stomach. Simple fluids like water will empty at a rate proportional to gastric volume, whereas nutrients will empty at a rate that depends on their energy density and potency in altering the duodenal brake.

Furthermore, fat that reaches the ileum exerts a profound inhibitory effect on gastric motility, known as the 'ileal brake'. After a meal, the two parts of the stomach show different motility responses.

1. Upper stomach (fundus, upper body)—initially, upon feeding the fundus relaxes to accommodate gastric

contents. That accommodation avoids an increase in intragastric pressure, which itself generates the sensation of satiety. Over time the fundus increases its tone progressively, thus forcing its contents to migrate to the antrum. Therefore the fundus experiences changes in tone rather than phasic contractions. In fact, the ICC-MP or pacemaker cells are absent in the gastric fundus and are only present in the mid-corpus and antrum.

2. Lower stomach (lower body, antrum)—powerful peristaltic contractions towards the pyloric sphincter.

These combined motility patterns, together with hydrolysis of lipids and proteins, lead to liquidization of food that is released into the duodenum in spurts. The upper stomach acts as a 'pressure pump'. In the lower stomach, solid food larger than 1–2 mm is recycled through the 'antral mill' until it is small enough to pass the pyloric sphincter.

Gastric emptying is controlled by neural or hormonal signals arising in response to nutrients which activate chemoreceptors in other parts of the gut. For example, the proximal and distal small bowel detect lipids and inhibit gastric motility, and promote gastric accommodation by relaxation of the fundus; the effect is strongest with free fatty acids with a chain length >10 carbon atoms. There seem to be four types of mechanism by which lipids modulate gastric motility.

1. Luminal lipid stimulates release of the regulatory peptide hormones cholecystokinin (CCK), neurotensin, peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). CCK has local effects on motility.
2. CCK stimulates afferent nerve pathways in the intestine that inhibit gastric activity.
3. The products of lipid absorption, chylomicrons packaged for export to lymph (see the section on digestion and absorption of fat), are also sensed by an as yet unknown mechanism.
4. Short-chain fatty acids (SCFAs) which reflux back into the ileum are sensed and signal the release of PYY that inhibits gastric motility.

In this way, nutrient overload in the intestinal lumen is sensed and motility is inhibited, thus permitting more time before the remainder of the meal is released. Even at rest, the stomach is never quiescent. Rhythmic waves of polarization and depolarization of gastric smooth muscle, starting in the corpus and progressing towards the antrum, occur every 20 sec. These so-called slow waves are controlled by pacemaker cells located in the myenteric plexus, also known as the interstitial cells of Cajal. These cells not only play a role as gut pacemakers, but also facilitate excitatory (cholinergic) and inhibitory (nitric oxide)

Customer	Book Title	Stage	Supplier	Date
OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

76 Chapter 4 Physiology of nutrient digestion and absorption

motor responses, and are distributed throughout the gastric and intestinal smooth muscle layers. Gastric motor dysfunction includes gastroparesis (delayed gastric emptying), impaired gastric relaxation after ingesting a meal (reduced in a proportion of patients with functional dyspepsia and increased gastric compliance in patients with bulimia), and over-rapid gastric emptying (e.g. 'dumping syndrome'). Slow emptying can be treated by prokinetic drugs, whilst dumping can be treated by giving 1–2 g of oleic acid before a meal to stimulate maximum inhibition of gastric motility by both the duodenal and ileal brakes. Currently, there is no licensed drug for improving gastric accommodation, but buspirone and clonidine have been found to promote gastric fundus relaxation.

Gastric emptying is also slowed by increased blood glucose concentration and is accelerated by insulin injection that reduces blood glucose concentration. The mechanism is similar to that for lipid, and involves CCK, PYY, GLP-1, and amylin (co-secreted with insulin). This is an example of a feedback mechanism that matches the amount of nutrient presented for absorption by the small intestine with the amount already absorbed. Unsurprisingly, delayed gastric emptying is a consequence of poorly controlled diabetes and can be treated with appropriate insulin therapy (e.g. continuous subcutaneous insulin infusion in patients with poor glycaemic control). Gastric emptying is also controlled through inhibition of eating behaviours, and this is mediated through a complex ballet of gut hormones (e.g. GLP-1, CCK, PYY, oxyntomodulin, and glucagon) which generally increase satiety.

Finally, gastric distension is a very powerful inhibitory signal that increases feelings of fullness and satisfaction (satiety), and hence counters the stimulatory afferent signals produced by eating tasty food. When the former signal predominates, eating is reduced and the stomach will, on balance, empty.

Digestive processes in the small intestine

Intestinal secretions and their control

Gastrin secreted by the stomach stimulates the secretion of enzymes by acinar cells in the pancreas. As the meal is released by the pylorus, acid-sensing cells in the duodenal mucosa release the hormone secretin which stimulates water and bicarbonate secretion by pancreatic duct cells. This in turn flushes the pancreatic enzymes into the duodenum via the pancreatic duct. A second hormone, cholecystokinin, is also released and elicits two responses: (1) the acinar cells of the pancreas release large quantities of pancreatic enzymes as inactive zymogens; (2) the gall bladder contracts powerfully and squirts bile into the duodenum through the common bile duct.

Although digestion will increase luminal osmolality and mucosal water secretion, the absorption of digestion products reduces osmolality and the water will be reabsorbed. This is an impressive process; it is estimated that every day 7.5 litres of water are secreted and absorbed from the small intestine in this way.

Digestive function of intestinal secretions

The pancreas secretes digestive enzymes in the form of inactive precursors (zymogens), and this may amount to up to 30% of the protein passing through the gastrointestinal tract with the meal. If these pancreatic enzymes were completely hydrolysed in the lower intestine and the amino acids were absorbed, a large amount of protein would need to be synthesized each day in order to digest 80–90 g of dietary protein. There is evidence that patients with an ileostomy (surgical fistula that drains ileal contents) do indeed excrete that amount of partially digested protein. Additionally, the increasing number of secretory granules on the pancreas is associated with a decrease in organization of endoplasmic reticulum (ER). This implies that there is a diurnal rhythm in which autophagy removes part of the ER after sufficient zymogen proteins have been synthesized.

However, there is also evidence that pancreatic enzymes are absorbed intact and recycled in an enteropancreatic circulation that is analogous to the enterohepatic circulation of bile salts (Rothman et al. 2002). Compelling arguments for this view are that pancreatic enzymes can be detected in the circulation (usually considered to be of pathological not physiological significance) and that the pancreas does not have the capacity to synthesize such a large amount of secretory enzymes each day. The mechanism of the proposed selective intestinal absorption of pancreatic enzymes is unknown.

Various pancreatic enzymes hydrolyse proteins (proteases), lipids (lipase, phospholipase), starch (amylase), and nucleic acids (ribonuclease, deoxyribonuclease) together with esterases and two specific proteases, gelatinase and elastase. These enzymes carry out luminal digestion of more highly polymerized substrates of >10 units (e.g. larger maltodextrins) whereas brush-border hydrolases favour shorter oligomers (e.g. maltose—maltopentaose).

Proteases

The pancreatic proteases are either endopeptidases (trypsin, chymotrypsin, and elastase) that cleave internal amino acid bonds or carboxypeptidases (A and B) that will sequentially cleave amino acids from the C-terminal of oligopeptides. The endopeptidases have specificities for bonds adjacent to dibasic amino acids (trypsin), hydrophobic amino acids (chymotrypsin), or small neutral

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amino acids (elastase). The combined actions of these enzymes will reduce dietary proteins to a mixture of free amino acids and peptides with chain lengths of 2–8 amino acids.

Like gastric pepsins, pancreatic proteases are secreted as inactive zymogens. Enteropeptidase (sometimes known as enterokinase), a glycoprotein bound to the enterocyte brush border, converts trypsinogen to trypsin by cleavage of a peptide sequence that blocks the active site of trypsin. Active trypsin which is released cannot catalyse further activation of trypsinogen, but does activate the zymogens of the other major proteases to yield chymotrypsin, elastase, carboxypeptidase A, and carboxypeptidase B. The highest concentration of enteropeptidase is found in the duodenum and decreases distally; and its level of expression on the membrane depends on the luminal presence of pancreatic enzymes, amino acids, or glucose. The sequence of events which leads enteropeptidase to activate the trypsinogen cascade is still unknown. One hypothesis is that enteropeptidase can be inactivated by protein C inhibitor (PCI), which is a serine protease inhibitor and a member of the serpin superfamily. In this model, serpins contain an exposed reactive centre loop which is recognized by the protease, an enzyme inhibitor complex is formed, and the protease then clips off the loop which remains bound to the protease, inhibiting it in the process. Since this inhibitory loop binds reversibly, the enteropeptidase will be activated by dissociation of the serpin fragment. Enteropeptidase is triggered pathologically in the case of acute necrotizing pancreatitis, but the cause is unclear.

This explanation does not tell us what triggers trypsinogen activation but merely pushes the ultimate cause back up the chain. Rothman's scheme for reabsorption of pancreatic enzymes invoked a similar scheme of serpin-like inhibitors which inactivated these enzymes during passage through the blood stream.

Amylase

Both salivary and pancreatic α -amylases are most active at neutral pH and act as endoglucosidases that have an absolute specificity for α -1,4 glucose linkages with two adjacent α -1,4 linkages. Therefore, amylase will not cleave other glucose polymers, such as β -glucans (oats), cellulose (plants), or dextran (dental plaque), or lactose or sucrose. The end-products of exhaustive starch digestion are therefore maltose, maltotriose, and the α -1,6 branched limit dextrans.

No free glucose is released. Further digestion of the branched limit dextrans can only occur at the brush border (catalysed by isomaltose or glucoamylase). The chain length of the linear α -1,4-linked dextrans in the lumen after a starch meal depends on the extent to which

α -amylase digestion has gone to completion, but is probably in the range of 5–10 glucose units.

Lipases

In addition to salivary and gastric lipases, there are four pancreatic lipases:

- pancreatic triacylglycerol lipase (PTL)
- carboxyl ester lipase (CEL)
- pancreatic lipase-related proteins 1 and 2 (PLRP-1, -2)
- group 1B phospholipase A2 (sPLA2-1B).

PTL is the most abundant and important in adult life; PLRP-1 and PLRP-2 are expressed pre- and perinatally but not in adulthood. PTL is a true lipase which preferentially hydrolyses triacylglycerols which form oil-in-water emulsions. Its binding to the surface of the oil droplet is aided by colipase (another pancreatic protein) and bile salt. The *N*-terminal of the enzyme has a 'lid' sequence—a highly mobile hydrophobic structure which, upon lipid binding, will swing aside to reveal the active site and thus allow lipid hydrolysis to occur.

CEL, PLRP, and sPLA2-1B have broad specificity and will hydrolyse phospholipids. Their preference is for emulsions made of micelles formed with bile salts. CEL is activated by bile salts and has a broad specificity towards cholesteryl esters, tri-, di-, and mono-acylglycerols, phospholipids, lysophospholipids, and ceramide. In addition, it will also hydrolyse fat-soluble vitamins and triglycerides. Luminal CEL can be transported into the bloodstream after endocytosis by enterocytes. It associates with low density lipoprotein and is excreted via the kidney.

Fat digestion comprises the following steps.

1. Partial digestion and emulsification in the stomach.
2. Mixing of tri-, di-, and mono-acylglycerols and fatty acids with detergent (bile salts), cholesterol, and phospholipid to form mixed micelles that have a hydrophobic core and hydrophilic outer surface. Their small size and high surface area result in efficient hydrolysis.
3. Binding of colipase and lipase to the surface of these micelles leads to release of free fatty acids and retinol.
4. Osmotic pressures generated within the micelle by triacylglycerol hydrolysis causes budding of smaller monoacylglycerol- and fatty-acid-rich micelles from the surface of these structures. These easily penetrate the unstirred water layer adjacent to the absorptive surface of the enterocyte.
5. This presents lipid substrate for transport across the enterocyte membrane at a much higher concentration than would occur if triacylglycerols arrived there by simple diffusion.

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OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

78 Chapter 4 Physiology of nutrient digestion and absorption

Regulation of small intestinal motility

The intestine has several ways in which it mixes and propels gut contents using different combinations of muscle and nerve systems. This means that there is redundancy in the system because failure of one system (or its deletion in gene knockout animals) does not seem to alter the way the gut moves its contents along.

The methods for measuring intestinal motility have improved beyond all recognition, and the terminology is still in a state of flux. This is because interpretation of electrical and pressure activity along the intestinal lumen (using long multilumen catheters) has been helped by real-time magnetic resonance imaging and improvements in design of fibre-optic manometry catheters with 10 mm spacing between the 72–120 pressure sensors. The use of high resolution mapping of electrical activities using arrays of hundreds of extracellular electrodes on the abdomen is a promising research tool.

Networks of interstitial cells of Cajal (ICC) act as pacemakers and propagate rhythmic slow oscillations of depolarization of membrane potential that increase the likelihood that a voltage-dependent Ca^{2+} -channel opening will cause contraction of smooth muscle in the gut and produce rhythmic peristalsis. This basal contraction is known as the rhythmic propulsive ripple (or rhythmic phasic contraction) and is different from tonic contractions, which are more pronounced. The strongest contractions are defined as rhythmic propulsive motor complexes (or migrating motor complexes or giant migrating complexes). In addition, the expression of the pattern of intestinal motility depends critically on whether the subject is fasted, fed, or post-prandial. Several gut pathologies also disorder motility (e.g. delayed gastric emptying, Chagas disease and megacolon, diabetes, pseudo-obstruction) and are associated with loss of ICC as evidenced by reduced histological localization of their specific marker c-Kit tyrosine-protein kinase Kit (CD117).

The ICC slow waves migrate into adjacent segments of the intestine and force that segment to oscillate at the same frequency. The frequency of gastric oscillations is different to that of the duodenum, and the pylorus acts as an electrical 'break' between the two. However, emptying of gastric contents into the duodenum provides a stimulus for duodenal peristalsis as luminal distension is another mechanism promoting smooth muscle cell contractility.

During the fasting period, a stereotypical pattern of contractility is activated. This pattern, called the migrating motor complex (MMC), starts in the antrum and occurs 4–6 hours after a meal. It is a complex entity, comprising four phases that cycle continuously whilst no further food is ingested:

- Phase I—inactivity (30–40 min)
- Phase II—irregular pressure spike activity (30–40 min)
- Phase III—intense repetitive high amplitude contractions (4–6 min)
- Phase IV—irregular activity.

This cycle moves down the intestine at 4–6 cm/min before slowing in the terminal ileum. The MMC plays an important role in preventing small bowel bacterial overgrowth because it moves bacteria, which have refluxed in from the caecum, distally. Feeding initiates irregular activity throughout the small intestine, which resembles phase II of the MMC. It leads to greatly reduced rates of intestinal contraction and rate of movement, and this lengthens the transit time in the bowel. The absorption of nutrients from the lumen of the small intestine is increased by the way in which the mucosa repeatedly dips into the chyme, minimizing the diffusion barrier to absorption. At the same time, villous contractions help lymph and blood flow to carry away absorbed nutrients. These repetitive segmenting contractions are interspersed with erratic motile patterns which move chyme forwards rapidly by 10–30 cm before segmenting contractions recommence.

These responses are nutrient dependent. Lipid has particularly potent effects because it generates strong clustered contractions that enhance emulsification. In summary, fasting motility sweeps debris, shed cells, and bacteria down the intestine, whereas fed motility enhances digestion and absorption of nutrients. The transition between fasting and fed patterns is modulated by the presence of nutrients in the lumen. During a meal, a small portion of chyme (the head of the meal) will be rapidly swept down to the distal ileum, where the presence of digested fat evokes the ileal brake leading to a marked reduction in transit rate. In addition, the passage of food into the small bowel stimulates colonic segmental movement, known as the 'gastrocolonic reflex'. This reflex is partially controlled by the cephalic phase of eating and leads to increased churning of colonic contents that increases absorption of nutrients, water, and electrolytes from the colon and will eventually lead to defecation. The SCFAs produced by bacterial fermentation in the colon not only stimulate water absorption, but if they reflux back through the ileocaecal valve into the ileum will simultaneously inhibit gastric emptying and stimulate peristalsis in the terminal ileum. The net effect is to sweep colonic bacteria from the distal small bowel.

Colonic motility has been more difficult to describe. Most human studies have used simpler manometric methods and focused on the so-called high amplitude (>100 mmHg) propulsive contraction which is infrequent during each day. Forward-moving (antegrade)

propagating contractions are more frequent after a meal and after waking in the morning. Retrograde (backward) contractions are also frequent and contribute to allowing water absorption. One new idea is the 'neuromechanical loop' hypothesis which proposes that, in general, colonic motility is stimulated by distension by colon contents, but their physical consistency influences the way the colon wall redistributes these contents through a specific pattern of contractions and relaxations of smooth muscle in the gut wall. This is a dynamic system which can adapt to a large range of consistencies of colonic contents. For example, patients with constipation exhibit an increased number of retrograde contractions, whilst both the amplitude and length of propagation of antegrade propagating contractions is significantly reduced.

Nasogastric tube feeding is associated with diarrhoea. One cause is that the slow rate of nutrient infusion (4.2–6.3 kJ/min) is insufficient to trigger a normal post-prandial slowing of intestinal transit. However, it does maintain colonic water secretion and hence provokes diarrhoea.

4.4 The absorption and secretion of nutrients

Absorbed nutrients must cross four barriers to reach the bloodstream (Schultz 1998; Pacha 2000):

- the mucus layer—a diffusion barrier which is rather thin in the small intestine
- the enterocyte apical membrane—a lipid bilayer which requires transport proteins for water-soluble molecules
- the enterocyte—a metabolic barrier which may metabolize the nutrient
- the basolateral membrane—a lipid bilayer which again requires transport proteins for water-soluble molecules.

In addition to transport proteins, absorption is enhanced by metabolic compartmentation or zonation within the enterocyte which prevents excessive metabolism (e.g. only 10% of absorbed glucose).

Most solute absorption occurs across the enterocyte membrane (transcellular) but some occurs via the tight junction between enterocytes (paracellular) (Figure 4.5). The classification of transporters is shown in Figure 4.6, and the main intestinal transporters are given in Table 4.2 which lists the commonly used names of the transport system, their substrates, the name of the transport protein, and finally the name of the gene for that solute carrier (SLC) Family. The process of elaborating

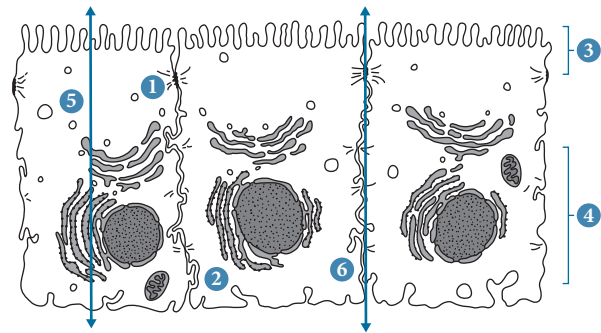


FIGURE 4.5 Intestinal epithelium and routes of solute transport

There are two routes by which nutrients, salts, and water can cross the mucosal barrier. Most transport occurs through the transcellular pathway (5), which is regulated by transporters in the apical (3) and basolateral (4) membranes.

These membranes are defined by the position of the tight junctions (1), which prevent free movement of water and solutes through the space between cells.

From: J Pacha, Development of intestinal transport function in mammals. *Physiological Reviews*, **80**(4), 1633–7, 2000. Figure 2, with permission).

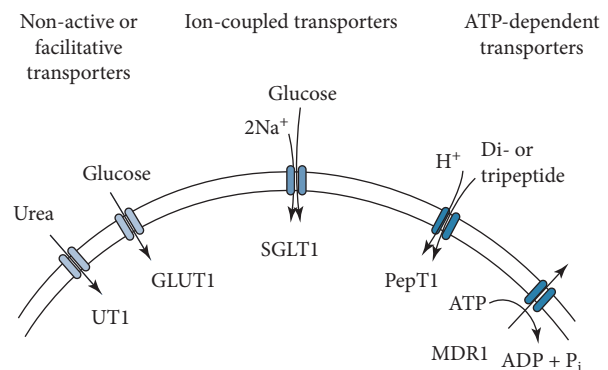


FIGURE 4.6 Transporters and their classification

Three types of transporter are shown, embedded in the plasma membrane of a hypothetical mammalian cell. Non-active or facilitative transporters (monoporters) catalyse the rapid movement of solutes across a membrane in response to a 'downhill' concentration gradient. This may be generated by the active metabolism of the solute within a cell (e.g. glucose oxidation by skeletal muscle). Ion-coupled transporters (symporters) move one solute across a membrane against an 'uphill' concentration gradient, using the drive of a coupled solute which is moving down a concentration gradient (a good example is SGLT1).

ATP-dependent transporters use the energy derived from hydrolysis of ATP. An example is the multidrug resistance protein (MDR1), responsible for transporting toxic compounds out of cells. Over-expression of this transporter is partly responsible for resistance to steroids or chemotherapy drugs. PepT1 lacks ATPase activity, but shares sequence homology with the ATP-dependent transporters.

Adapted with permission from M.A. Hediger, Structure, function and evolution of solute transporters in prokaryotes and eukaryotes. *Journal of Experimental Biology*, **196**, 15–49, 1994, Figure 4.

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80 Chapter 4 Physiology of nutrient digestion and absorption

TABLE 4.2 Substrate transporters present in the human intestine and in other tissues

Transport system	Substrates	Distribution	Transporter protein names	Gene name for solute carrier (SLC) family
Na⁺-dependent				
A	Small aliphatics	Widespread	SNAT2	SLC38
N	Gln, His, Asn	Liver, muscle	SNAT3, SNAT5	SLC38
Bo, ⁺	Ala, Lys, Arg, Orn, Gly	Fibroblasts	BAT1	SLC7
GLY	Gly	Liver, brain, erythrocytes	GLYT, GLYT-1a, -1b, GLYT-2, BGT-1, PRO	SLC6
ASC	Small aliphatics and cysteine	Widespread	ASCT1, ASCT2 SATT	SLC1A4/5
X:AG	Asp, Glu	Widespread	EAAC1, GLAST, GLT1	SLC1A1/2/3/6/7
y ⁺ L	Leu, Met	Intestinal, renal	4F2hc	SLC3
y ⁺	Gln, homoserine, citrulline	Widespread	mCAT-1, -2, -2A, CAT-1, -2A, -2B	SLC7
IMINO	Pro	Intestinal	SIT1?	SLC6A20
Glucose transporter	Glucose	Intestinal	SGLT-1, SGLT-2, SAAT1	SLC5
Na⁺-independent				
L	Leu, Ileu, Val, Phe	Widespread		SLC43
b0, ⁺	Lys, Leu, Trp, Met	As Bo, ⁺	rBAT, D2, NBAT	SLC3SLC7
y ⁺	Basic	Widespread	mCAT-1, -2, -2A, CAT-1, -2A, -2B	
y ⁺ L	Leu, Met	Intestinal, renal	4F2hc	SLC7
x ^c exchange transporter	Glu exchanges Cys Urea	Has wide distribution Wide distribution	UT	SLC7A11 SLC14
Glucose transporter	Glucose and fructose	Widespread	GLUT 1-7	SLC2
Proton-energized				
Peptide transporter	di- and tripeptides, some antibiotics, peptidase inhibitors (eg. bestatin or captopril)	Epithelial membranes	PEPT-1, PEPT-2	SLC15
Organic anion transporter/ATP-binding cassette transporter				
Multidrug resistance protein	Glutathione and glucuronide anionic conjugates	Hepatocytes	MRP1, MRP2 (cMRP/cMOAT) MRP-3	ABCC1
Multidrug resistance protein	Xenobiotics	Hepatocytes, enterocytes	MDR1/MDR2/ p-glycoprotein	ABCB1
Organic anion transporting protein	Glutathione, conjugated bile salts (eg. glycocholate) and other conjugates	Hepatocytes	OATP1	SLC01

TABLE 4.2 *Continued*

Transport system	Substrates	Distribution	Transporter protein names	Gene name for solute carrier (SLC) family
Fatty acid transporter				
Fatty acid transport protein	Long-chain fatty acids	Wide distribution	FATP1/2/3/4/5/6	SLC27
Monocarboxylic acid transporter	Medium-chain fatty acids	Wide distribution	MCT	SLC16
Sodium-coupled monocarboxylate transporter	Short-chain fatty acids	Wide distribution	SMCT1/2	SLC5A12

4F2hc (heavy subunit of LAT1); ASCT1, ASCT2, SATT (alanine/serine/cysteine/threonine transporter, neutral amino acid transporter); BGT-1 (betaine/GABA transporter-1); CAT-1, CAT-2B, CAT-2A, mCAT-1, mCAT-2A, mCAT-2 (cationic amino acid transporter); cMOAT, MRP1, MRP2, MRP3, cMRP, MDR1, MDR2, p-glycoprotein (multidrug resistance protein); EAAC1 (high affinity glutamate transporter); FATP1/2/3/4/5/6 (fatty acid transport protein); GLAST (glial high affinity glutamate transporter); GLT1 (glial high affinity glutamate transporter); GLUT 1-7 (glucose transporter); GLYT-1a, GLYT-1b, GLYT-2 (neurotransmitter transporter, glycine); LAT1 (large neutral amino acid transporter); MCT (monocarboxylate transporter); NBAT, rBAT (cystine, dibasic, and neutral amino acid transporters); OATP1 (organic anion transporter/ATP-binding cassette transporter); PEPT-1, PEPT-2 (peptide transporter); SAAT1 (a glucose transporter, not a sodium-coupled amino acid transporter); SGLT-1, SGLT-2 (sodium glucose-linked cotransporter); SIT1 (sodium/imino acid transporter); SMCT1/2 (sodium/monocarboxylate cotransporter); UT (urea transporter)

the transporters and their genes has been arduous. First, systems were classified according to their ability to transport substrates competitively, with low or high affinity. The next step in the revolution was expression of the transporter in oocytes, which lacked transport functions. Finally, the Human Genome Project has allowed each transporter to be assigned to a gene. The naming might seem haphazard, but it reflects a long process of research. Although different transporters carry very different substrates, they share many common structural features. They have regions of hydrophobic amino acids that can fold into helices which, when grouped together like the staves of a barrel, span the membrane and form a 'pore' through which substrates can be transported. Parts of the protein (often bearing a sugar polymer) are outside the membrane and can act as a signalling receptor to allow other compounds to control the rate of transport of the main substrate. Alternatively, a transport protein may be linked to another regulatory protein that can chaperone the transporter into the membrane and thus modulate transport capacity. Transport may be either passive, allowing the concentration of the transported nutrient to come to equilibrium across the membrane, or active, permitting a higher concentration to be achieved on one side of the membrane than on the other (Figure 4.6).

Passive transporters

These comprise facilitated transporters and ion channels which permit the transfer of a solute across the membrane in either direction. Therefore transport takes place down a concentration gradient (so-called 'downhill transport'). Net accumulation of the transported material in the cell can occur as a result of either onward metabolism to a

compound that does not cross the membrane (e.g. vitamin B₆ is accumulated intracellularly by phosphorylation to pyridoxal phosphate) or by binding to cytosolic proteins (e.g. ferritin, which binds iron).

Active transporters

These transport solutes against a concentration gradient, linked to either direct ATP utilization (P-type transporters) or co-transport of an ion down its concentration gradient (symporters, which transport two solutes in parallel) (Figures 4.6 and 4.7). Direct utilization of ATP involves phosphorylation of the transport protein, which permits it to transport one or more solute molecules in one direction only; solute transport causes dephosphorylation of the protein, so closing the pore.

Symporters commonly utilize a sodium ion gradient across the membrane, although some systems use a hydrogen ion gradient. The ionic gradient is generated by membrane ATPases that pump ions across the membrane. Intestinal absorption of glucose and some amino acids is by sodium-linked symporters.

Digestion and absorption of carbohydrates

The main dietary carbohydrates are starch, lactose, and sucrose, as well as smaller amounts of glucose, sugar alcohols, and fructose. Carbohydrates are only absorbed as monosaccharides, so starch assimilation proceeds in two phases.

Starch is hydrolysed by pancreatic amylase (and to some extent also by salivary amylase) to yield a mixture of glucose oligomers with a chain length in the range

82 Chapter 4 Physiology of nutrient digestion and absorption

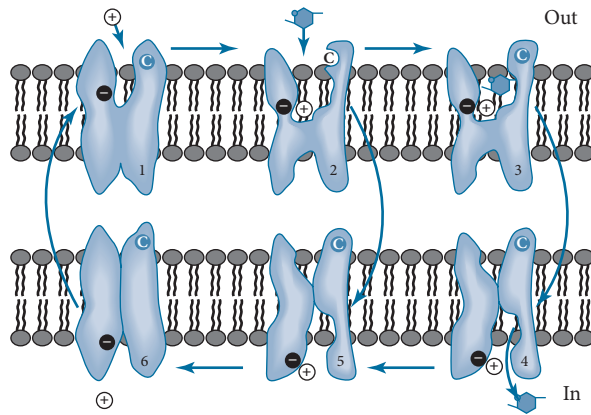


FIGURE 4.7 Glucose transport via the sodium-glucose linked transporter (SGLT1) and GLUT2 are responsible for glucose uptake in the small intestine. For each transport cycle of SGLT1, two Na^+ ions, one glucose molecule, and approximately 220 water molecules move across the membrane. This figure shows a possible mechanism of action in which sodium binding causes a conformational change which allows glucose binding. Thereafter, glucose is transported and released into the cell, followed by sodium. At some point in this cycle, a conformational change temporarily causes the transporter to become a water channel (cf. aquaporins) so that water moves in response to osmotic gradient. The linking of glucose, sodium, and water transport is the basis of oral rehydration therapies for secretory diarrhoea (e.g. cholera). From: E.M. Wright I. Glucose galactose malabsorption. *American Journal of Physiology*, 275(5 Pt 1), G879–82, 1998, Figure 4, with permission.

5–10 glucose 20 units. These are further hydrolysed to glucose by the brush-border glucosidases. In addition, some maltose and isomaltose are formed. Disaccharides are hydrolysed to their constituent monosaccharides by disaccharidases on the brush border of the enterocytes: lactase, trehalase, and the bifunctional enzyme sucrase–isomaltase.

Glucose and galactose are taken up by the same active (sodium-linked) transporter (SGLT1) (Figure 4.7), while fructose, some other monosaccharides, and sugar alcohols are carried by passive transporters. This means that only a proportion of fructose and sugar alcohols can be absorbed, and after a large dose much may remain in the lumen, leading to osmotic diarrhoea.

At present, there is considerable controversy about the major transporter for glucose in the small intestine. Although SGLT1 has a high affinity for glucose, it has a low transport capacity. A second glucose transporter, GLUT2, in the enterocyte is only inserted into the membrane in response to glucose absorption via SGLT1. This process is controlled by insulin and dietary amino acids, mediated by protein kinase C activation. This leads to a great increase in transport capacity in response to dietary load. The controversy is about the relative quantitative

importance of GLUT2 and the role of glucose sensing in the lumen of the intestine to feed-forward and control rates of glucose uptake. Some, but not all, studies suggest that the G protein gustducin from taste is present throughout the small intestine and may be responsible for sensing (or ‘tasting’) luminal glucose concentration.

Starch assimilation provides a good example of the distribution of digestive and absorptive function. It can be inferred that this occurs mainly in the duodenum, upper jejunum, and proximal ileum because (1) they have the highest mucosal expression of sucrase–isomaltase and the sodium glucose-linked transporter (SGLT1), (2) the rapid appearance of blood glucose after a starch meal fits with this site of absorption, and (3) removal of the distal small intestine hardly affects glucose assimilation. By contrast, most fat and fat-soluble vitamin assimilation occurs in the ileum, which has the highest transport capacity, therefore surgical removal of the ileum may leave the patient at risk of essential fatty acid and fat-soluble vitamin deficiency.

Digestion and absorption of protein

The endopeptidases of gastric and pancreatic juice hydrolyse proteins to yield oligopeptides; aminopeptidases secreted by the intestinal mucosa and pancreatic carboxypeptidases then remove terminal amino acids sequentially from these oligopeptides, yielding free amino acids and di- and tripeptides. Early studies indicated the presence of amino acid transport systems with the following characteristics.

1. Stereospecificity—L-amino acids are transported very much faster than D-amino acids.
2. Specificity—only a small number of chemically related amino acids are transported by any one carrier system.
3. Duplication—some amino acids are transported by more than one carrier system.

Some are sodium-linked, while others are not. The main amino acid transport systems are shown in Table 4.2. The naming system is complex because it developed piecemeal.

1. System A (alanine) is a sodium symporter for small neutral aliphatic amino acids.
2. System ASC (i.e. alanine, serine and cysteine) is also a sodium symporter.
3. System L (leucine) is not sodium dependent and carries branched chain and aromatic amino acids.
4. System γ^+ is not sodium dependent and carries dibasic amino acids.
5. System XAG is a sodium symporter and carries dicarboxylic (acidic) amino acids.

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Di- and tripeptides are transported by separate systems from free amino acids. Patients with genetic defects of system ASC (cystinuria), which prevents intestinal absorption of arginine, lysine, and cysteine, or system L (Hartnup disease), which prevents the absorption of aromatic and branched-chain amino acids, still absorb enough of the essential amino acids as small peptides to maintain nitrogen balance.

Di- and tripeptides are taken up into the enterocyte by peptide transporters (PEPT1 and PEPT2), hydrogen ion symporters that take advantage of the acid micro-climate of the submucosal space. Unlike the amino acid transporters, PEPT1 and PEPT2 are:

- stereospecifically promiscuous—they will transport cyclic peptides, D-peptides, and *cis*-peptides
- non-specific—they will transport most, if not all, of the theoretically possible 400 dipeptides and 8000 tripeptides, in addition to β -lactam antibiotics (e.g. penicillin) and valaciclovir, an anti-herpes drug that has no peptide bond.

The absorbed di- and tripeptides are hydrolysed by intracellular peptidases, and the resultant amino acids, together with those absorbed from the lumen as free amino acids, are secreted into the villous microcirculation.

Some relatively large peptides (large enough to elicit antibody formation) enter the bloodstream intact, either by passing between cells or by uptake into mucosal cells. These are normally trapped by the gut-associated lymphoid tissue, but can enter the systemic circulation—this is the basis of food allergy (see Chapter 27).

Digestion and absorption of fat

The process of fat digestion is one of progressive emulsification of dietary lipids and hydrolysis of triacylglycerol to free fatty acids and monoacylglycerols. The final product of fat digestion is the mixed micelle, from which bud smaller micelles (as a result of the osmotic action of the free fatty acids) which are transferred across the enterocyte membrane. Short-chain fatty acids enter the villus microcirculation, but most of the fatty acids are re-esterified to triacylglycerol in the mucosal cell, packaged into chylomicrons and secreted into the lacteals, and then secreted into the lymphatic system (see Chapter 8).

Cholesterol and fat-soluble vitamins are absorbed dissolved in the hydrophobic core of the micelles. Much of the cholesterol destined for chylomicrons is esterified in the enterocyte, and competition between cholesterol and other sterols and stanols for the acyltransferase probably explains why these compounds, taken in dietary spreads, reduce cholesterol absorption and hence have a hypocholesterolaemic action.

There is still debate about how fatty acids can cross the enterocyte apical membrane. The classical view is that, being lipophilic, they can dissolve in the membrane and traverse it, by a 'flipflop' mechanism, as protonated uncharged fatty acids. This process of permeation across a simple lipid bilayer membrane is rapid, about 1000 times greater than for water and more than a million times faster than that of glucose. Protonation of fatty acids in the acidic micro-environment adjacent to the brush-border membrane will promote permeation, whilst ionization of free fatty acids by the higher intracellular pH or incorporation into TAG inside the enterocyte would prevent back-diffusion of fatty acids. Studies in model membrane systems have demonstrated that fatty acid permeation during flipflop is very fast and is only limited by the desorption phase from the inner membrane surface. On balance, it is sufficient to account for known lipid transport rates. The second proposed route of uptake is via membrane-bound transport proteins. Candidates include CD36 (fatty acid translocase) and FATP4 (fatty acid transporter protein 4), and their importance is currently being investigated using knockout mice (Figure 4.8). Most evidence for the significance of the FATP family has come from other organs, such as muscle, heart and adipose tissue. The true situation in the intestine may differ because there may be parallel transport systems of low (FATP) and high (permeation) capacity to cope with feast and famine in the gut lumen. This compares with amino acid and glucose uptake, which are mediated by dual transport systems.

Within the enterocyte, fatty acids are transferred by intracellular fatty acid binding proteins (FABPs) to the nascent lipid droplet where they are re-esterified to triacylglycerol. This lipid droplet enters the endoplasmic reticulum together with cholesterol, phospholipids, fat-soluble vitamins, and apolipoproteins before moving to the Golgi apparatus where the chylomicron matures. Buds from the Golgi apparatus fuse with the enterocyte lateral membrane, leading to exocytosis and the release of chylomicrons into the lymphatic system.

The rate-limiting step in this process is transfer of lipid from the endoplasmic reticulum to the Golgi apparatus, and triacylglycerol from excess dietary lipid may either be oxidized for cellular energy or temporarily stored within the endoplasmic reticulum. Components of chylomicrons (e.g. apoprotein A-IV) that enter the circulation can inhibit gastric emptying. This suggests that the intestinal motility is a key factor in controlling nutrient absorption because it is controlled at every stage of lipid digestion, absorption, and repackaging.

The rate of movement of dietary fat into lymph depends on its fatty acid composition. Olive oil appears to be most rapidly absorbed, and cocoa butter and menhaden oil are most slowly absorbed. In malabsorption syndromes such

84 Chapter 4 Physiology of nutrient digestion and absorption

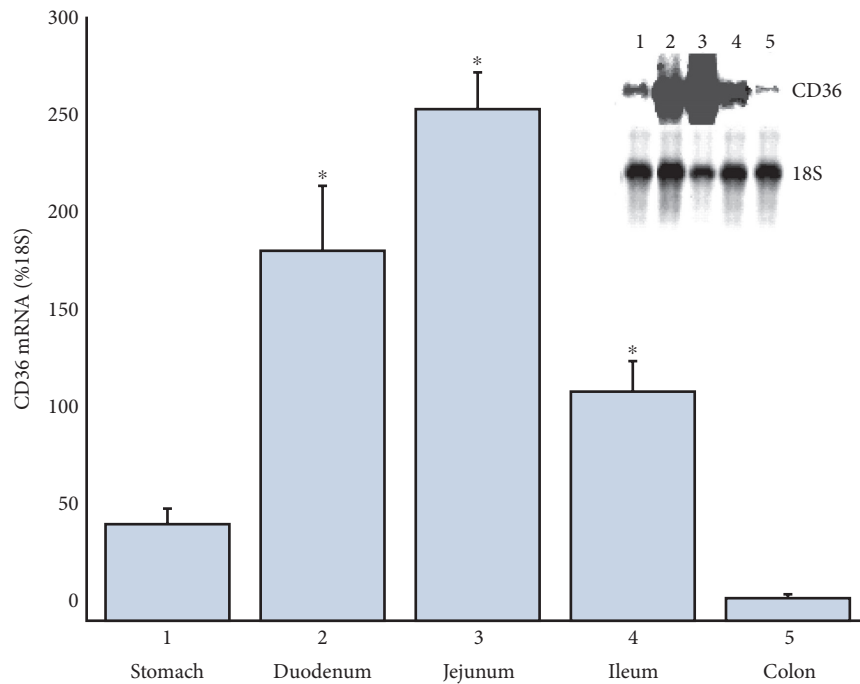


FIGURE 4.8 Distribution of a fatty acid transporter along the intestine

Distribution of the mRNA for fatty acid translocase (FAT) along the longitudinal intestinal axis of the adult rat. This protein is thought to be the transporter for long-chain fatty acids and its distribution is an example of 'zonation' of transporters along the intestine. The highest concentration was found in the jejunum, but the highest amount would be present in jejunum and ileum combined, indicating the site of dietary lipid assimilation.

From: M. Chen, Y. Yang, E. Braunstein, K.E. Georgeson, and C.M. Harmon. Gut expression and regulation of FAT: possible role in fatty acid transport in rat enterocytes. *American Journal of Physiology Endocrinology and Metabolism* **281**(5), E916–23, 2001. Figure 1, with permission)

as cystic fibrosis, medium-chain triglycerides (MCTs), with a chain length 8–10 carbon atoms, are used because their shorter chain length and greater water solubility results in uptake into the portal circulation and hence a faster overall rate of macronutrient uptake.

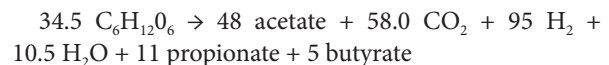
The colon

The colonic microflora of the large intestine should be considered as 'an organ within an organ' because of the diversity of reactions which are performed by about 10^{14} colonic microbes. In addition, there is considerable two-way crosstalk between host and microbe. Their actions take place in an anaerobic environment, which means that those bacteria that salvage and oxidize sugars and amino acids (which have escaped small bowel assimilation) for energy must donate protons to an acceptor such as NAD^+ or NADP^+ . Acetyl CoA is the main two-carbon product of glycolysis and provides feedstock for direct production of acetate (directly), propionate (three carbons, from succinate), or butyrate (four carbons, from acetate via ketogenesis) in the ratio 6:3:1. Butyrate and propionate are both synthesized using energy derived from glycolysis, since the complete tricarboxylic acid

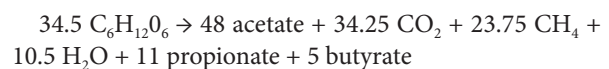
cycle does not operate in an anaerobic environment. Hydrogen is a prominent end-product of this process and represents a 'sink' of reducing equivalents, which can be expelled as gas.

Dietary analyses reveal that the UK population consumes ~18 g/day of dietary fibre (according to the AOAC definition). This is much less than is required to produce normal daily stool weight. Indeed, it is estimated that the amount of fermentable substrate entering the colon each day is ~70 g, in the form of malabsorbed macronutrients (e.g. resistant starch) or mucins and sloughed intestinal cells (Figure 4.9).

If all of this were oxidized, with H_2 as the end-product, the stoichiometry of the overall reaction would be:



In reality, H_2 is consumed by secondary reactions, such as reduction of CO_2 to CH_4 or reduction of sulphate to H_2S .



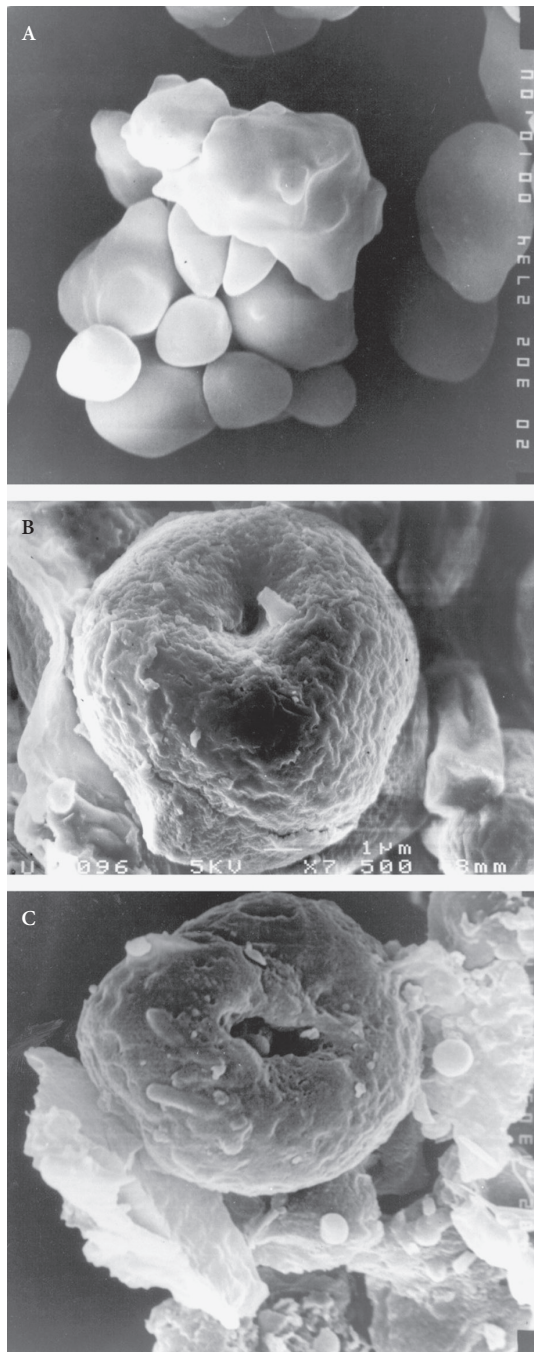


FIGURE 4.9 Resistant starch granules and their digestion in the colon

Scanning electron micrographs of native high amylose starch granules sampled in (A) human ileostomy effluent, (B) the caecum of a pig, (C) the proximal large bowel of a pig. The progressive pitting and etching of the starch granules occurs through the action of intestinal amylase. The glucose oligomers that are released will be fermented in the large intestine.

From: D.L. Topping and P.M. Clifton. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiological Reviews*, 8(3), 1031–64, 2001.

Figure 1, with permission.

In the first reaction, this would equate to 22.4 L/day of flatus, or 6 L/day of CH_4 , but the secondary reduction reactions reduce this to the usual daily flatus production rate of ~1 L.

The presence of SCFA in the colonic lumen is of interest for several reasons.

- The establishment of an ‘acetate buffer’ in the colonic lumen suppresses the growth of some pathogenic bacteria.
- Faecal pancreatic enzyme activity is regulated by trypsin-degrading species such as bacteroides. In patients with inflammatory bowel disease, faecal tryptic activity is high and bacteroides prevalence is low. Gut lesions may be worsened by trypsin activity.
- Conversion of bilirubin (haem breakdown product) to urobilinogen (yellow pigment), which is either reabsorbed and excreted by the kidney or converted to stercobilin (brown pigment) by colonic bacteria.
- Breakdown of mucins shed from the epithelial mucus layer.
- Catabolism and excretion of bile salts, which are synthesized from cholesterol, in faeces represents a drain on cholesterol. It is thought that fermentation of dietary fibre (e.g. β -glucans from porridge) exerts a cholesterol-reducing effect in this way.
- SCFA production.

SCFA absorption can occur by simple diffusion of protonated species across the apical colonocyte membrane or via a sodium-coupled monocarboxylate transporter (SMCT), which is the product of the gene SLC5A8. Water uptake is stimulated by SCFA absorption, and this is likely to be one of the major mechanisms for water and electrolyte salvage in the large intestine.

Butyrate has beneficial effects on the colon and promotes cell differentiation, reduces inflammation in the colonic mucosa, and causes cell-cycle arrest and increased apoptosis in colon cancer cells. Both butyrate and propionate inhibit histone deacetylases, a property they share with all of the SCFA up to a chain length of eight-carbons (including the antipsychotic drug valproate). Acetylation of lysine and arginine residues in histone proteins leads to a looser binding with DNA, which allows chromatin expansion, permitting genetic transcription to take place. Because butyrate maintains the transcription of key genes by preventing deacetylation of the histone, it is in effect a transcription factor. Recent studies in human subjects have shown that after a daily enema of butyrate for two weeks, there was increased transcription of genes which were mainly associated with energy metabolism, increasing fatty acid oxidation, and protecting against oxidative stress. The

86 Chapter 4 Physiology of nutrient digestion and absorption

SLC5A8 gene is a tumour suppressor, which is silenced in colon cancer by DNA methylation. Its product, the SCFA transporter, causes uptake of butyrate and other SCFA into colonic cells where they exert an anti-tumour effect, as described. Two other cell membrane receptors, hydroxycarboxylic acid receptor 2 (HCA2, product of gene GPR109A) and free fatty acid receptor 2 (FFAR2, product of gene GPR43), are activated by butyrate and modulate fatty acid metabolism and provide protection against inflammation, respectively. This provides a satisfying explanation for the cancer-preventing effects of a high fruit and vegetable intake whose colonic fermentation produces butyrate, propionate, and acetate.

Absorption of vitamins

The fat soluble vitamins A, D, E, and K, and the carotenoids (see Chapter 12) are poorly soluble in water and are chaperoned in the circulation by specific transporter proteins or lipoproteins (e.g. chylomicrons or VLDL/HDL) as they shuttle between tissues which comprise the absorptive, storage, or user organs. They are absorbed in the intestine from lipid micelles which are formed by the products of fat digestion. During the process of food digestion and emulsification, these vitamins are released

and selectively partition into the lipid phase of the luminal contents. It was assumed for a long time that, like fatty acids, these vitamins were absorbed by passive diffusion across the brush-border membrane of the enterocyte before repackaging into chylomicrons and being exported in lymph. Current understanding reveals a more complex and controlled process. In the first place, this class of molecules is also absorbed through the action of a group of scavenger receptors which were previously assumed to have other functions. These molecules recognize and take up macromolecules which have negative charge, such as oxidized low density lipoprotein. As the name implies, their function is to clean or scavenge undesirable molecules. They are found in the membranes of many tissues (e.g. macrophages in atherosclerotic lesions) and also in the enterocyte membrane. The most common gut scavenger receptors are scavenger receptor class B type I (SR-BI), CD36 (cluster determinant 36) and Niemann–Pick C1-like 1 (NPC1L1). This dual functionality of control molecules is a common theme in metabolic nutrition. Another example is the activation of vitamin D precursors by enzymes of the cytochrome P450 superfamily, which are also associated with detoxification reactions. The current understanding of the assimilation of the fat-soluble vitamins is summarized in Table 4.3.

TABLE 4.3 Current understanding of the assimilation of the fat- and water-soluble vitamins in the human intestine

Vitamin name	Dietary form	Absorbed from	Brush-border membrane uptake		Cytoplasmic transport	Basolateral membrane efflux transporter	Transport in circulation
			Passive absorption	Transporter			
Vitamin A	Beta-carotene	Mixed micelles	Yes	SR-B1	Cleaved to retinal then retinol OR remains intact as β -carotene	?	Lacteals/chylomicrons
	Retinol	Mixed micelles	Yes	?	CRBP II and some converted to retinyl ester	? But small amount	RBP4
	Retinyl-esters	Mixed micelles	Yes	Hydrolysed before transport	CRBP II and most reconverted to retinyl ester	?	Lacteals/chylomicrons
Vitamin D	Ergocalciferol (D ₂) cholecalciferol (D ₃)	Mixed micelles	Yes	SRBI, NCP1L1, CD36	? None identified yet	ABCA1	Lacteals/chylomicrons
Vitamin E	Tocopherol	Mixed micelles	Yes	SRBI, NCP1L1	? None identified yet	ABCA1	Lacteals/chylomicrons
Vitamin K	Phylloquinone, menaquinone	Mixed micelles and from colon	Yes	?	?	Incorporated into chylomicrons	Lacteals/chylomicrons

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TABLE 4.3 Continued

Vitamin name	Dietary form	Absorbed from	Brush-border membrane uptake	Cytoplasmic transport	Basolateral membrane efflux transporter	Transport in circulation	
Vitamin C	Reduced—ascorbic acid	Aqueous phase	No	SVCT1	None	SVCT2	Portal vein
	Oxidised—dehydro-L-ascorbic acid	Aqueous phase	No	GLUT1, GLUT3, GLUT4	None		Portal vein
Vitamin B ₁	Thiamine	Aqueous phase of small and large bowel	No	THTR1/THTR2	None	THTR1	Portal vein
	Thiamine phosphate			Requires dephosphorylation before absorption			
Vitamin B ₂	Riboflavin	Aqueous phase of small and large bowel	No	RFT1		RFT2	Portal vein
	Flavin mononucleotide			Requires hydrolysis before flavin can be absorbed			
	Flavin adenine nucleotide						
Vitamin B ₃	Niacin	Aqueous phase of small and large bowel	No	OAT10?	None		
Vitamin B ₅	Panθοthenate	Aqueous phase	No	SMVT	None	?	Portal vein
Vitamin B ₆	Pyridoxal, pyridoxine, and pyridoxamine.	Aqueous phase of small and large bowel	No	?	?	?	Portal vein
	Pyridoxal phosphate	Aqueous phase	No	Requires dephosphorylation before absorption			
Vitamin H/B ₇	Biotin	Aqueous phase of small and large bowel	No	SMVT	None	?	Portal vein
	Protein-bound biotin	Requires release from dietary proteins by biotinidase before absorption					
Vitamin B ₉	Folate polyglutamates	Aqueous phase of small bowel	No	Requires removal of polyglutamate before absorption as monoglutamate			
	Reduced folate monoglutamate	Aqueous phase of small and large bowel	No	RFC	?	?	Portal vein
	Oxidized folate monoglutamate	Aqueous phase of small and large bowel	No	PCFT	?	?	Portal vein
Vitamin B ₁₂	Cobalamin	Aqueous phase	Cobalamin binds to haptocorrin or intrinsic factor released from the gastric mucosa. The complex binds to cubilin on the ileal enterocyte brush-border membrane and is taken up by endocytosis	Digestion of intrinsic factor, release of cobalamin	?		Portal vein

ABCA1 (ATP-binding cassette, subfamily A, member 1); CD36 (cluster determinant 36); NCP1L1 (Niemann–Pick C1-like 1); OAT10 (organic anion transporter 10); PCFT (proton-coupled folate transporter); RFC (reduced folate carrier); RFT1 (riboflavin transporter 1); SMVT (sodium-dependent multivitamin transporter); SR-BI (scavenger receptor class B, type I); SVCT1/SVCT2 (sodium vitamin C transporter 1/2); THTR1/THTR2 (thiamin transporter 1/2).

Customer	Book Title	Stage	Supplier	Date
OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

88 Chapter 4 Physiology of nutrient digestion and absorption

Vitamin A may be absorbed as β -carotene via SR-B1 and is either exported into lymph in chylomicrons to be stored in the liver or is cleaved to form retinal and then retinol which is chaperoned inside the enterocyte by cellular retinol binding protein type II (CRBP2). It may be exported and bound to retinol binding protein 4 (RBP4) which is stabilized by transthyretin (TTR, formerly known as pre-albumin). Retinyl esters require prior hydrolysis before uptake and are then re-esterified inside the enterocyte before packaging in chylomicrons.

Vitamin D is absorbed by passive diffusion, and via SRB1, NCP1L1, and CD36, and is excreted at the basolateral membrane by ATP-binding cassette, subfamily A (ABCA1) before packaging into chylomicrons.

Vitamin E is absorbed in the same way by passive diffusion or via SR-B1, or NPC1L1, and is excreted as for vitamin D. Synthetic forms of vitamin E are esterified; natural forms not. Therefore the synthetic forms require hydrolysis in the intestinal lumen before absorption.

Vitamin K is assumed to be absorbed in the same way as other fat-soluble vitamins. There is further conversion to other forms of phyloquinones in the gut, whilst the menaquinones are formed by colonic bacteria or are present in some fermented foodstuffs.

The water-soluble vitamins (see Chapter 11) are presented to the gut mucosal surface in several forms, each of which may have its specific transport protein. Vitamin C is present in the intestinal lumen as both reduced ascorbic acid and oxidized dehydro-ascorbic acid. Ascorbic acid is absorbed by a sodium-dependent transporter (SVCT1), while dehydro-ascorbic acid is structurally similar to glucose (from which some mammalian species can synthesize it) and is absorbed by the sodium-independent glucose transporters GLUT1, GLUT3, and GLUT4. Some vitamins require dephosphorylation before they can be absorbed (e.g. B₁ and B₆) and are trapped inside the intestinal cell by re-phosphorylation (see Chapter 11). Vitamin B₁₂ is absorbed bound to intrinsic factor, a glycoprotein that is secreted by the parietal cells of the gastric mucosa (see Chapter 11). Finally, it should be noted that vitamins are provided by two routes. The small intestine is the site of absorption of dietary vitamins. Patients who have undergone surgical removal of the ileum may often develop deficiency of fat-soluble vitamins. In contrast, the colon is the site of absorption of considerable amounts of vitamin K and most of the water-soluble vitamins (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, cyanocobalamin) because they are synthesized there by the colonic microbiota. The species responsible for this are unknown at present, but some lactobacilli possess some, but not all, parts of the vitamin B₁₂ synthetic pathways.

This concept will be of great importance in the future for several reasons. First, diet affects the colonic microbiome and thus human health. Secondly, diseases such as obesity and diabetes alter the microbiome. Finally, the use of specific prebiotic strains of lactobacilli to produce pre-fermented foods, which contain naturally synthesized vitamins, are likely to revolutionize dietary patterns in the future.

Water and electrolytes

The human small intestine absorbs 6.5–7.5 L of water each day (Figure 4.10). How this gets across the membrane is still unclear, because the lipid bilayer that surrounds each cell is impermeable to water and the intestinal mucosal surface is rather hydrophobic. Before describing several hypotheses of water movement across the mucosa, it is worth summarizing the known characteristics of the process. Water absorption is proportional to the amount of substrate and electrolyte that moves across the membrane. For example, the sodium-glucose linked transporter (SGLT1) moves two Na⁺ ions and 260 water molecules across the membrane with each cycle of transport of one glucose molecule. Absorption of 180 g of glucose in the small intestine would result in the uptake of 4.7 L of water and 116 g of NaCl. The direction of water movement is governed by solute movement. The mechanisms for secretion and re-absorption of water and electrolytes by the intestine are very efficient. Under normal circumstances, daily secretion of Na⁺ and K⁺ by the gut is equivalent to a half and two-thirds, respectively, of these electrolytes present in the human body's extracellular space. These movements are achieved by coupled transport systems which

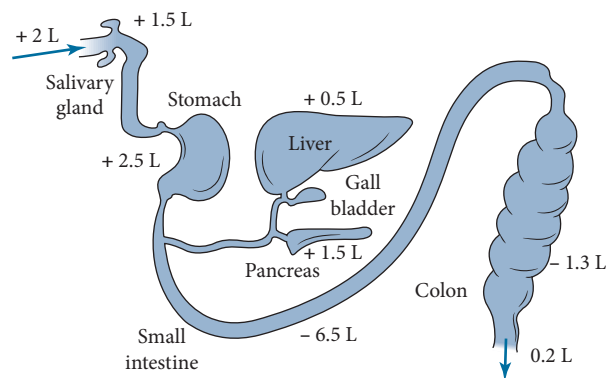


FIGURE 4.10 Water movements in the gut

Dietary intake of water and stool output are modest in comparison with secretion and absorption of water within the human intestine which has large transport capacity. Data from: T. Ma and A.S. Verkman. Aquaporin water channels in gastrointestinal physiology. *Journal of Physiology (Lond.)*, 517 (Pt 2): 317–26, 1999. Reproduced with permission.

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OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

excrete HCO_3^- in response to Cl^- uptake in order to achieve electroneutrality across the mucosal barrier. At more distal sites, Cl^- and HCO_3^- move in the opposite direction to conserve bicarbonate. Similar mechanisms exist for exchange of Na^+ , K^+ , and divalent cations. As a result, despite this huge transfer and counter-transfer of water and ions across the small and large intestinal mucosa, faecal outputs are modest and comprise only 200 g of water, 5 mmol Na^+ , 2 mmol Cl^- , 9 mmol K^+ , and approximately 5 mEq HCO_3^- . In cholera, excessive secretion of chloride into the colon is accompanied by water secretion and diarrhoea, leading to dehydration and eventually death unless treated. Therefore stimulation of water uptake by glucose (and sodium) is the basis of oral rehydration therapy for the treatment of diarrhoea, which is the most important cause of infant death worldwide (Schultz 2007; Li et al. 2013).

The hypotheses for water transport have been reviewed recently by Hill (2008) and Maclaren et al. (2013), and are still the subject of controversy. The intestinal mucosa acts as a semipermeable membrane through which water flows either way in response to differences in osmotic pressure. Luminal nutrient digestion renders the bulk phase hypertonic and water moves from the intestinal fluid into the gut lumen. However, nutrient absorption renders it more hypotonic such that water is absorbed along with these solutes. In this way, the luminal contents are adjusted to near isotonicity throughout the small bowel. There are several models for this process.

1. Simple osmosis across the apical and basolateral membranes may account for some water uptake. The osmolality gradient is small (3–30 mOsmol/kg), and this model would mean that enterocytes replaced their entire fluid volume every few seconds.
2. Water may move between the enterocytes through the so-called ‘tight junctions’ by osmotic flow because enterocytes have absorbed Na^+ (not water) and secreted this into the lateral intercellular space as a hyperosmolar fluid. This is the most popular hypothesis.
3. Specific transporters may move significant amounts of water across the enterocyte membranes. This means that enterocytes will still replace their intracellular water volume every few seconds. These membrane transporters are termed ‘aquaporins’ and are very versatile. Their structure is similar to that of other transporters, except that the hydrophobic inner surface of the transmembrane pore is lined with hydrophilic amino acids which selectively allow passage of water. The aquaporins are versatile and can also transport other small molecules such as urea, CO_2 , NH_3 , and glycerol in addition to water.

4. Water transport occurs simultaneously with transport of ions or substrates (see above for glucose transport) and the transporter itself acts as the channel for uptake when activated by a conformational change caused by the transported substrate.

The colon acts as an organ of water and electrolyte salvage, but its capacity is limited. Rapid infusion of 500 ml or more of water into the colon will provoke diarrhoea through reflex defecation, and this is the basis of rectally administered enemas.

Sugar alcohols used as sweeteners, such as xylitol, lactitol, and sorbitol, are poorly absorbed and will enter the colon with sufficient water to maintain luminal isotonicity before fermentation and the absorption of SCFAs, water, and Na^+ . If the colonic fermentation capacity is exceeded, osmotic diarrhoea ensues because the excess water cannot be absorbed.

Clinically the synthetic disaccharide lactulose (which is not hydrolysed in the small intestine) and the sugar alcohol lactitol are used as laxatives. Other causes of osmotic diarrhoea include dietary fibre such as guar gum, probiotics such as fructose oligosaccharide, and beans that contain large quantities of stachyose, all of which are good substrates for bacterial fermentation. The laxative threshold of unacceptable gastrointestinal symptoms for most readily fermented non-absorbed carbohydrates is about 70 g/day, but most people will notice the effects of 40 g/day. The FODMAPS (fermentable oligo-, di-, and monosaccharides and polyols) diet for treatment of irritable bowel syndrome is an attempt to reduce the amount of fermentable substrate in the diet. It is an alternative to the recommendations of NICE (National Institute for Health and Care Excellence) which include smaller and more frequent meals and a reduction of dietary fibre.

Most minerals are absorbed by carrier-mediated diffusion and are then accumulated by binding to intracellular binding proteins, followed by sodium-dependent transport from the enterocyte into the villous microcirculation. The main system for transport of most divalent metal ions and ferrous iron is the divalent metal ion transporter 1 (DMT1) whose activity responds to systemic signals of adequate nutritional Zn^{2+} , Mg^{2+} , or Fe^{2+} or Fe^{3+} stores. For example, the protein hepcidin inhibits iron transport by binding to the iron export channel (ferroportin) on the enterocyte basolateral membrane. Hepcidin is secreted when iron stores are adequate. Genetic defects of either the intracellular binding proteins or the active transport systems at the basal membrane of the enterocyte can result in mineral deficiency despite an apparently adequate intake. As discussed in Chapter 12, the enterocyte calcium binding protein is induced by vitamin D, and vitamin D deficiency results in much reduced absorption of calcium.

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OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

90 Chapter 4 Physiology of nutrient digestion and absorption

3.5 The role of the gastrointestinal tract in the regulation of feeding

As discussed in Chapter 6, there are both long- and short-term mechanisms for regulating food intake and energy expenditure so as to maintain energy balance

(Figure 4.11). This is a complex topic. Short-term control of appetite is regulated by the gastrointestinal tract as well as by the metabolic response to ingested nutrients. For example, the presence of nutrients such as glucose or SCFA will act directly on taste receptors in the gut (e.g. gustducin) and stimulate $\text{HCO}_3^-/\text{Cl}^-$ secretion by second-messenger activation of enterocyte basolateral membrane ion transport. In the long term, if the intestinal lumen is exposed to chronically increased

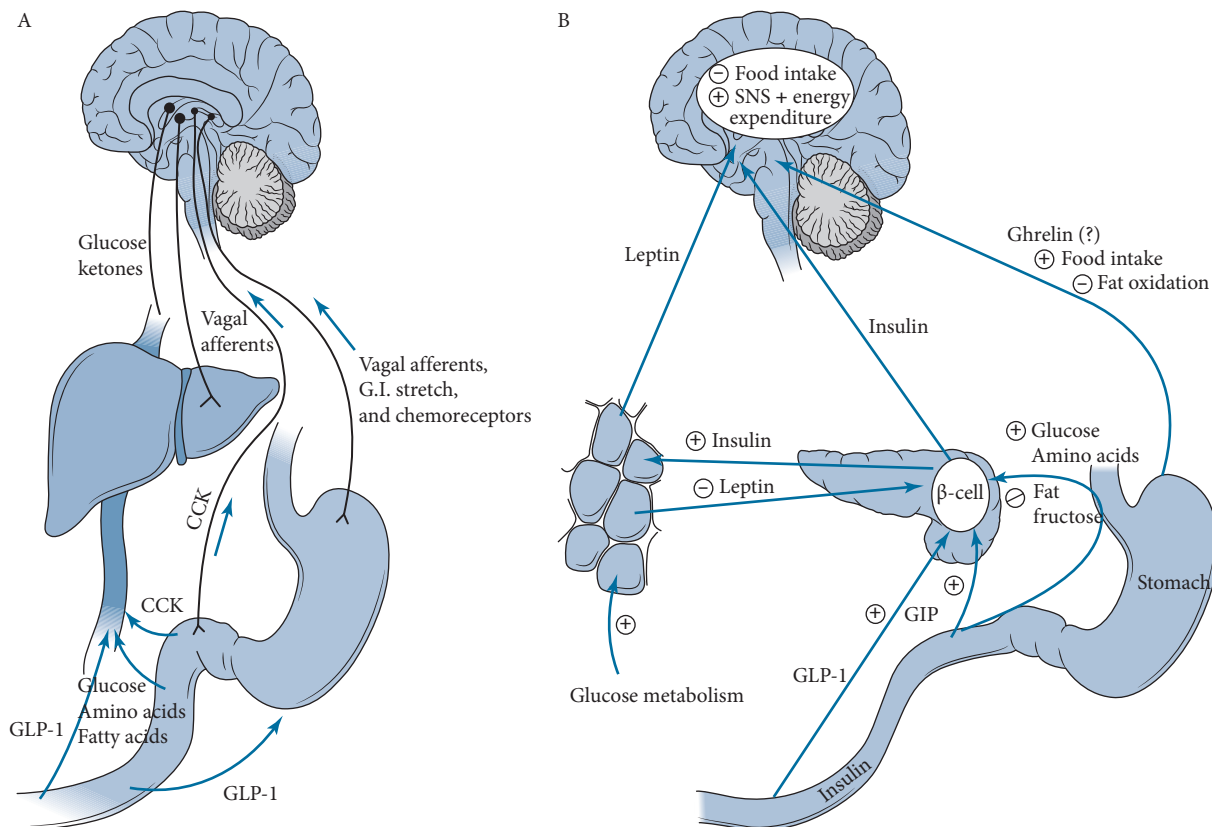


FIGURE 4.11 (A) Short-term signals regulating food intake and control of energy balance. (B) Long term signals regulating food intake and control of energy balance

Short-term regulation of food intake can occur through four pathways. (a) Vagal nerve afferent signals. These act on the CNS and are triggered by (1) gastric stretching, (2) the presence of nutrients in the stomach and small intestine, and (3) nutrients arriving at the liver via the portal vein. (b) Circulating cholecystokinin (CCK). Release of this gut hormone into the circulation stimulates CCK-A receptors in the liver and the central nervous system and inhibits food intake. (c) Direct nutrient effects. Circulating glucose and ketones act on responsive neurons in the CNS. (d) Ileal hormone release. Release of glucagon-like peptide-1 (GLP-1) by L cells in the ileum may act on hepatic sites or inhibit gastric emptying. These signals will not sustain changes in energy intake or body fatness.

(B) Insulin and leptin, released by the GI tract, are the most important regulators of long-term food intake. They activate the sympathetic nervous system (SNS) by direct action on the CNS. Insulin secretion by pancreatic β -cells is increased if (1) circulating concentrations of glucose and amino acids increase and (2) meal ingestion and absorption lead to secretion of the insulin-stimulating incretin hormones, glucose-dependent insulinotropic polypeptide (GIP), and GLP-1. Leptin will stimulate energy expenditure via the sympathetic nervous system. Insulin stimulates leptin production from adipose tissue when glucose oxidation is high. In contrast, dietary fat and fructose do not stimulate insulin secretion and therefore do not increase leptin production. Conversely, leptin can inhibit insulin secretion from the pancreas. These long-term signals seem to modulate the sensitivity of short-term signals such as CCK release.

From: P J Havel. Peripheral signals conveying metabolic information to the brain: short-term and long-term regulation of food intake and energy homeostasis. *Experimental Biology and Medicine (Maywood)* **226**, 963–77, 2001. Figures 1 and 2, with permission.)

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OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

levels of specific nutrients, the enterocytes respond by upregulating expression of the relevant brush-border digestive enzymes and transporters, and the liver responds by increasing the pathways of metabolism of these substrates. The gastrointestinal tract also provides regulatory feedback signals. These signals arise from direct effects of absorbed nutrients, or their metabolites, in the circulation, from neural signals from the gut and liver, and from hormonal signals (Begg and Woods 2013; Langhans and Geary 2010). The signals which initiate feeding behaviours and control satiety are less obvious. This is because satiety is a short-term action that prevents over-consumption of large meals, which would cause excessive fluctuations in circulating nutrients. In this sense, it can be described as a homeostatic mechanism which controls substrate supply and intermediary metabolism after a meal. However, it is not homeostatic because substrate stores are enormous in relation to daily food intake and the action of counter-regulatory hormones controls release of energy from glycogen and lipid stores. Therefore the link between immediate satiety and nutrient stores is more complex. This is because eating behaviours sit between acute and chronic regulatory systems which balance the immediate needs for substrates (e.g. glucose) and the long-term maintenance (or defence) of body energy stores. Psychological aspects are complex and outside the remit of this chapter. There is enormous plasticity in the system overall, partly because of duplication of actions by different hormones, and partly because hormones modulate the sensitivity of action of other neural and hormonal pathways.

The control of energy balance is impressive. Average lean man and an average obese man contain 170,000 kcal and 413,000 kcal, respectively, in their adipose tissue stores. The process which led to the lean man becoming obese over 30 years involves an imbalance in energy intake over requirements of 20–30 kcal/day, compared with an energy intake of 2,800 kcal/day. The most important question is not ‘Why has this man become obese?’ but ‘Why is he not five times the size?’ In other words, regulatory mechanisms of eating are exquisitely balanced, but are subverted when a plentiful supply of tasty energy-rich food is available in the long term. Starvation or disease-related malnutrition represents a situation that is simpler to understand.

Eating behaviours are modulated by the action of peptide hormones released by the gut and by the hypothalamus. Before initiation of feeding itself, feeding behaviours are stimulated by increasing secretion of the ‘hunger hormone’ ghrelin by the stomach. This occurs in concert with the cephalic phase of feeding which is initiated by signals from anticipation of food and by sight, smell, and taste and mouth sensations of

food. The cephalic phase leads to increased vagus nerve stimulation of oral and gut secretions and anticipatory insulin release. During the gastric phase, several hormones initiate satiety:

1. Cholecystokinin (CCK), secreted by the duodenum (which also stimulates secretion of bile and pancreatic juice, and regulates intestinal motility), acts directly on the vagal afferent nerves and the hypothalamus.
2. Peptide YY (PYY) signals the presence of nutrients in the gut lumen and will lead to decreased voluntary food intake.
3. Leptin is mainly secreted by adipose tissue and its main function is to regulate long-term food intake and energy expenditure in response to the state of fat reserves
4. Glucagon-like peptide 1 (GLP-1) is released by the pancreas in response to intestinal glucose absorption. It slows gastric emptying, initiates the ‘ileal brake’ and has an anorectic effect.

Gastric distention induces satiety, partly through the release of hormones such as gastrin-releasing peptide.

The mouth

The taste of food, as well as its smell before eating, stimulates secretion of gastric juice and intestinal motility. There are five receptor families on the tongue, for sweet, salty, or meaty/savoury (umami) flavours which are generally pleasurable, and for sour or bitter tastes which are generally aversive. In addition, the tongue can sense the fatty acids liberated from triacylglycerols by lingual lipase. Combinations of taste and sensation may have additive effects; for example, sugar mixed with fat is particularly pleasurable, and salt may be useful in masking bitter flavours that are taste-aversive. The importance of taste in controlling sensations of hunger and satiety is seen in patients receiving long-term tube-feeding who experience constant feelings of hunger although nutritionally replete.

The taste of food provides a strong signal to stimulate eating. However, this process operates only when there are sensations of hunger and is suppressed when sensations of satiety become strong. This is known as sensory-specific or conditioned satiety. It is thought that a dominant factor in this process is the action of dopamine on the hypothalamus in response to absorbed fat.

The stomach

During eating, food stretches the stomach and induces a complex series of signals that lead to cessation of eating. The importance of this can be illustrated by taking

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OUP	Human Nutrition	First Proof	Thomson Digital	12 Jan 2017

92 Chapter 4 Physiology of nutrient digestion and absorption

a glass of water with a meal to induce feelings of satiety whilst eating, but not afterwards. Conversely, in rats in which gastric contents are continuously removed during the meal through a fistula ('sham feeding'), the amount of food eaten at each meal is greatly increased. The mechanism is due to stretch, not gastric pressure, and works through direct inhibition of the stimulating effect of pleasurable tastes on eating. Signals from taste receptors in the mouth and gastric stretch receptors are integrated in the parabrachial nucleus of the pons in the brain stem so that one signal will downregulate the other (Figure 4.12).

The small intestine

In addition to stretch receptors, the intestinal mucosa possesses an abundance of receptors for acid and for fatty acids and glucose and amino acids, which will provide information about the contents of the lumen that the brainstem will integrate and use to control eating behaviour. Cholecystokinin, released in response to luminal fat, leads to powerful inhibition of eating.

Absorbed nutrients are also potent signals that modulate eating behaviour. For example, in adequately nourished subjects, the intravenous infusion of lipid stimulates dopamine activity (which acts as a feeding inhibitor) and increases satiety ratings and feelings of fullness, and reduces the desire to select particular foodstuffs. In contrast, studies in the hospital population (40–50% of which experiences malnutrition) have shown that fortification of hospital food with fat actually stimulates energy intake. This mechanism thus depends on sensations of hunger that are related to nutritional status. However, these mechanisms can be overridden centrally. An example of this would be the inability to resist the unexpected offer of a plate of strawberries and cream after a particularly heavy meal.

KEY POINTS

- The gastrointestinal tract provides a linear sequence of events resulting in the hydrolysis of dietary carbohydrates, triacylglycerols, and proteins, and the absorption of the products of digestion.
- Salivary and gastric secretions are stimulated before eating, and then the presence of food in the mouth and stomach stimulates further secretion.

- Gastric emptying is controlled by both the amount of food eaten during a meal, and also nutrients present in the food, and the progress made in liquidising it within the stomach.
- Pancreatic and intestinal secretion is stimulated by hormones secreted in response to the presence of food in the stomach.
- The monosaccharides resulting from carbohydrate digestion, and free amino acids from protein digestion, are absorbed into the hepatic portal vein and the liver regulates the entry of the products of digestion into the peripheral circulation.
- Amylases in saliva and pancreatic juice catalyse hydrolysis of starch to disaccharides and limit dextrans; disaccharides are hydrolysed by intestinal brush-border enzymes, and monosaccharides are absorbed by active transport (glucose and galactose) or passive transport (other monosaccharides and sugar alcohols).
- Lipases secreted by the tongue in gastric juice and pancreatic juice catalyse the progressive hydrolysis of triacylglycerol until dietary lipid is emulsified into micelles small enough to be absorbed across the small intestinal lumen. Most absorbed fatty acids are re-esterified in the mucosal cells and absorbed into the lymphatic system in chylomicrons, but medium-chain fatty acids are absorbed in to the hepatic portal vein.
- Proteolytic enzymes are secreted as inactive zymogens. Pepsinogen in the gastric juice is activated by gastric acid and autocatalysis; trypsinogen in the pancreatic juice is activated by intestinal enteropeptidase. Trypsin then activates the other intestinal zymogens.
- Protein digestion begins with the action of endopeptidases, which hydrolyse proteins at specific sites within the molecule, resulting in the formation of a large number of oligopeptides. Exopeptidases then remove amino- and carboxy-terminal amino acids, resulting in free amino acids and di- and tripeptides.
- Free amino acids are absorbed by a variety of group-specific transporters; di- and tripeptides are absorbed by a specific transporter with wide substrate tolerance, and hydrolysed within the intestinal mucosal cells.

The role of the gastrointestinal tract in the regulation of feeding 93

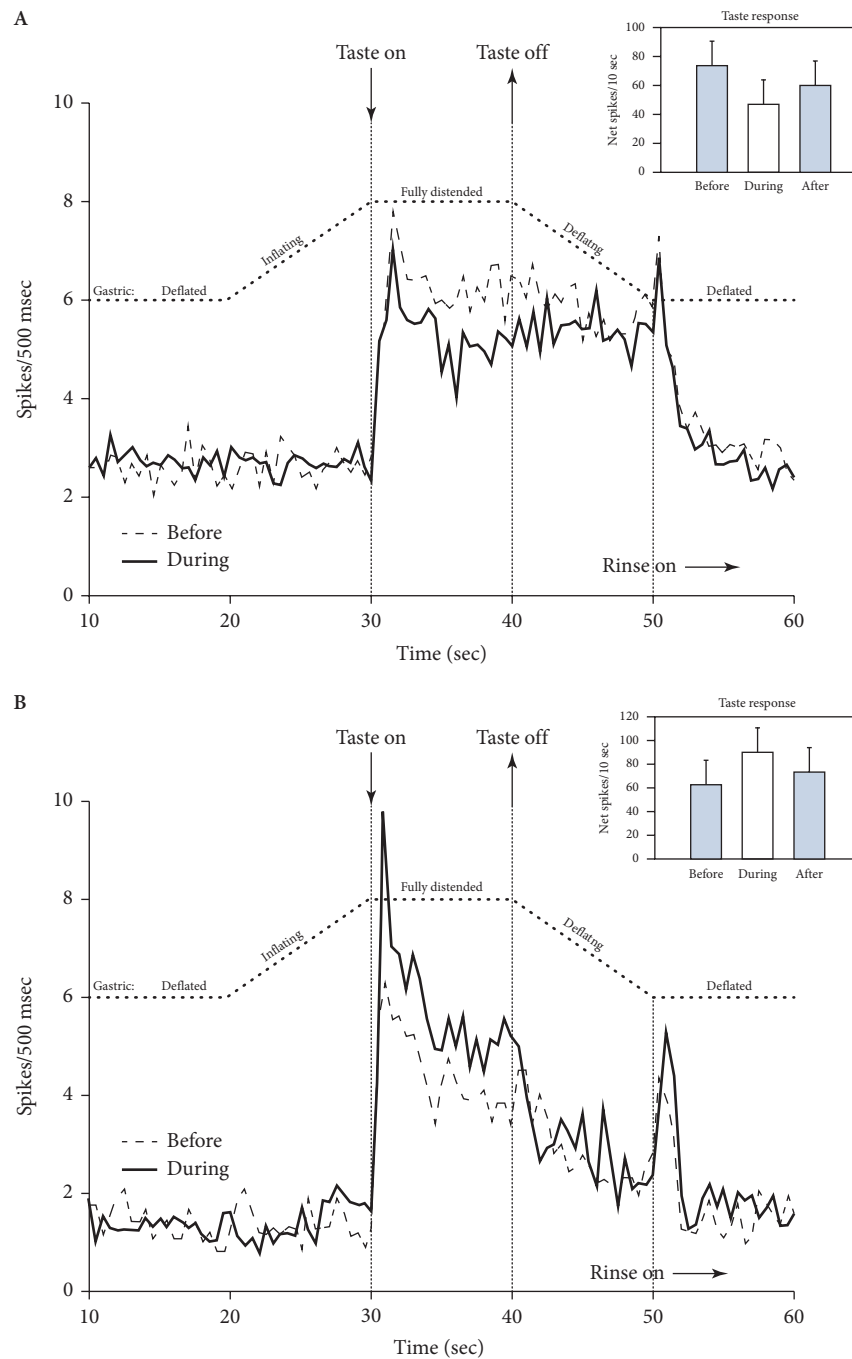


FIGURE 4.12 How the taste of food and gastric distension have opposite effects on appetite

Taste and gastric distension have opposite effects on appetite. This trace shows the electrical activity of the parabrachial nucleus of an anesthetized rat in response to metered application of taste solutions on to the tongue or infused into the stomach. The upper figure shows the time course response of 18 inhibitory cells to taste stimulation before and during gastric distension. (B) The mean time course response of seven excitatory cells to taste stimulation before and during gastric distension. It can be concluded that taste and gastric distension provide dynamic signals that will control food intake during feeding. Gastric distension is an inhibitory feedback signal that enhances satiation and diminishes ingestion.

Feeding behaviour may be an integrated response to excitatory signals that stimulate feeding and satiation. This is like driving a car by pressing the brake and accelerator together!

From: J.P. Baird, S.P. Travers, and J.B. Travers. Integration of gastric distension and gustatory responses in the parabrachial nucleus. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 281(5). R1581-93, 2001. Figure 4, with permission)

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94 Chapter 4 Physiology of nutrient digestion and absorption

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