Digestion and Absorption of the Macronutrients 8.5

Learning Objectives

- List three ways the intestine increases its surface area for digestion and absorption of nutrients
- Name the major enzyme involved in the gastric phase of protein digestion
- Describe the activation of pancreatic proteolytic enzymes and their major actions in the luminal phase of protein digestion
- Describe the enzymes involved in the brush border phase of protein digestion
- Describe in general terms how amino acids are transported from lumen to blood
- Explain why humans can digest starch but not cellulose
- List the products of amylase digestion of starch
- List the brush border enzymes involved in the final digestion of carbohydrates
- Describe lactose intolerance and explain the origin of its symptoms
- Name three major monosaccharides and describe how they enter the blood
- Describe what is meant by emulsification of lipids and how this is accomplished in the gut
- List the major lipolytic enzymes
- Define what is meant by "lipoprotein"
- Distinguish among chylomicron, VLDL, LDL, and HDL
- Describe the pathway for lipid digestion and absorption
- Describe the location and mechanism of bile acid absorption

THE INTESTINE INCREASES ITS SURFACE AREA BY FOLDS UPON FOLDS

Digestion involves breaking down the macronutrients (fats, carbohydrates, and proteins) into their constituent parts (fatty acids, glycerol, monosaccharides, and amino acids). This occurs in the intestine, and then the intestine absorbs these nutrients into the blood for use by the rest of the body. To do this, the intestine presents a large surface area to the ingested food because the absorption of nutrients occurs through this surface. The surface area is increased by three levels of folding (see Figure 8.5.1).

The first level of folding is the **folds of Kerckring** that increase the area about threefold. The folds of Kerckring are folds of the entire epithelium along with its vasculature and nerve supply. Lining the walls of the folds are the next level of folding, the **villi**, that increase the area another 10-fold. The villi are finger-like projections of the intestinal epithelium that extend outward from the surface of the folds about 0.5–1.5 mm. The villi in the duodenum are typically longer than those in the distal small intestine. These villi are covered with a layer of columnar epithelial cells, the **enterocytes**. The apical membrane of the enterocyte, facing the lumen, forms a forest of small projections called **microvilli** that increase the surface area another 20-fold. These structures are maintained by cytoskeletal elements that are anchored in the tips of the microvilli and in a web of cytoskeletal elements just below the microvilli, called the **terminal web**. Because of their appearance in the light microscope, the forest of microvilli is also called the **brush border**.

THE INTESTINAL LINING CONTINUOUSLY RENEWS ITSELF

Interspersed among the enterocytes are **goblet cells** that secrete **mucus** to line the luminal surface. Between the villi are pits called the **crypts of Lieberkuhn**. Cells in the crypts are continuous with the villus layer. Some crypt cells secrete water and electrolytes, whereas other cells, **enterochromaffin cells**, secrete 5-hydroxytrypamine upon mechanical stimulation to excite **intrinsic primary afferent neurons**. Still other cells in the crypts, epithelial stem cells, divide to renew the villus lining. The daughter cells migrate up the villus and differentiate to form goblet cells or absorptive cells. As they migrate, the cells express different proteins. At the tips of the villus, the cells are extruded into the lumen. Thus there is a continuous parade of cells from the crypts toward the lumen. The entire epithelium renews itself every 4–5 days.

The villi also surround a central lymph vessel, the **central lacteal**, and arteriolar and venule capillaries. The close approach of these vessels to the absorptive epithelium reduces the diffusion distance from the absorptive cells into the blood and the lymph.

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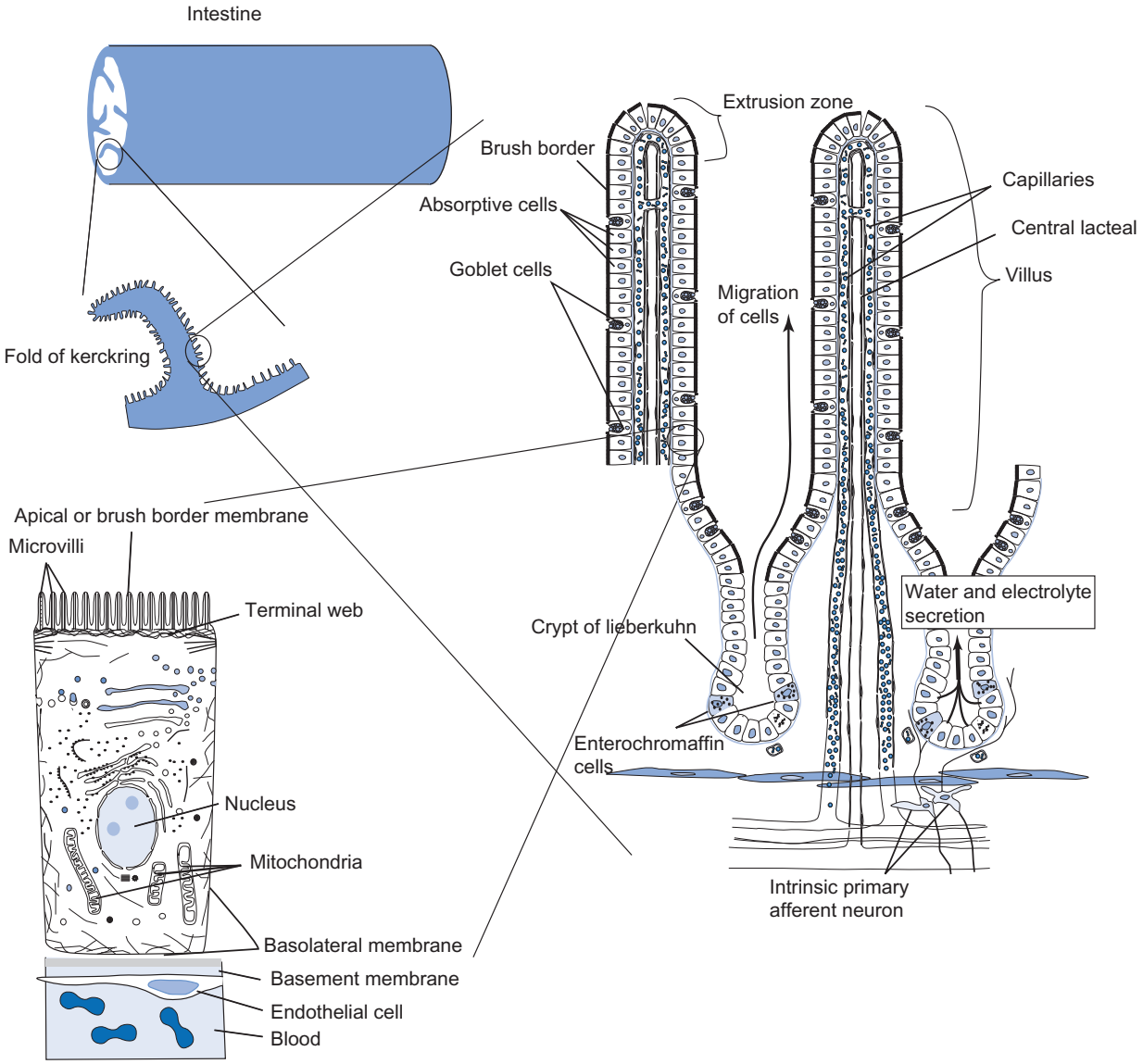

FIGURE 8.5.1 Overall structure of the small intestine with close-up view of the intestinal villus. The overall intestine's dimensions approximate a simple cylinder about 4 cm in diameter and about 2.8 m in length. The folds of Kerckring increase the surface area about threefold. On these folds are the villi, finger-like projections of the intestinal lining, which further increase the surface area about 10-fold. The villi are lined with enterocytes, whose apical membrane is covered by microvilli that increase its absorptive surface an additional 20-fold. The intestinal villi arise from pits called crypts of Lieberkuhn where cells divide and then migrate up the villus, where eventually they are extruded at the tips. As they migrate up the villus the cells differentiate and mature into goblet cells, which secrete mucus, and absorptive cells that take up the digested food and transfer it to the blood. The total area of the intestine is thus increased some 600-fold from about 0.3 m^2 to about 200 m^2.

PROTEIN DIGESTION OCCURS IN A GASTRIC PHASE AND AN INTESTINAL PHASE

PROTEIN DIGESTION BEGINS IN THE STOMACH

The acid in the stomach **denatures** many proteins—it unfolds them and exposes internal peptide bonds for proteolytic attack. The acid also activates pepsinogens to pepsins. The pepsins are a class of **endopeptidases** that cleave peptide bonds in the middle of the polypeptide chain. The pepsinogens are secreted by the chief cells in the gastric glands. Pepsin is active only at pH < 4. Upon mixing with the alkaline duodenal contents (provided by HCO_3^- in the pancreatic and biliary secretions), the pepsins become inactive.

The digestion products of pepsin cause release of gastrin from G-cells in the antrum, thereby stimulating acid secretion (see Chapter 8.2). They are also potent secretagogues for CCK release from the duodenum, thereby indirectly stimulating pancreatic enzyme secretion and gallbladder contraction. Despite these effects, people with total gastrectomies are capable of fully digesting dietary protein. The gastric phase is not essential to protein digestion.

THE INTESTINAL PHASE CONSISTS OF A LUMINAL PHASE, BRUSH BORDER PHASE, AND INTRACELLULAR PHASE

The exocrine pancreas secretes three endopeptidases (**trypsin**, **chymotrypsin**, and **elastase**) and two

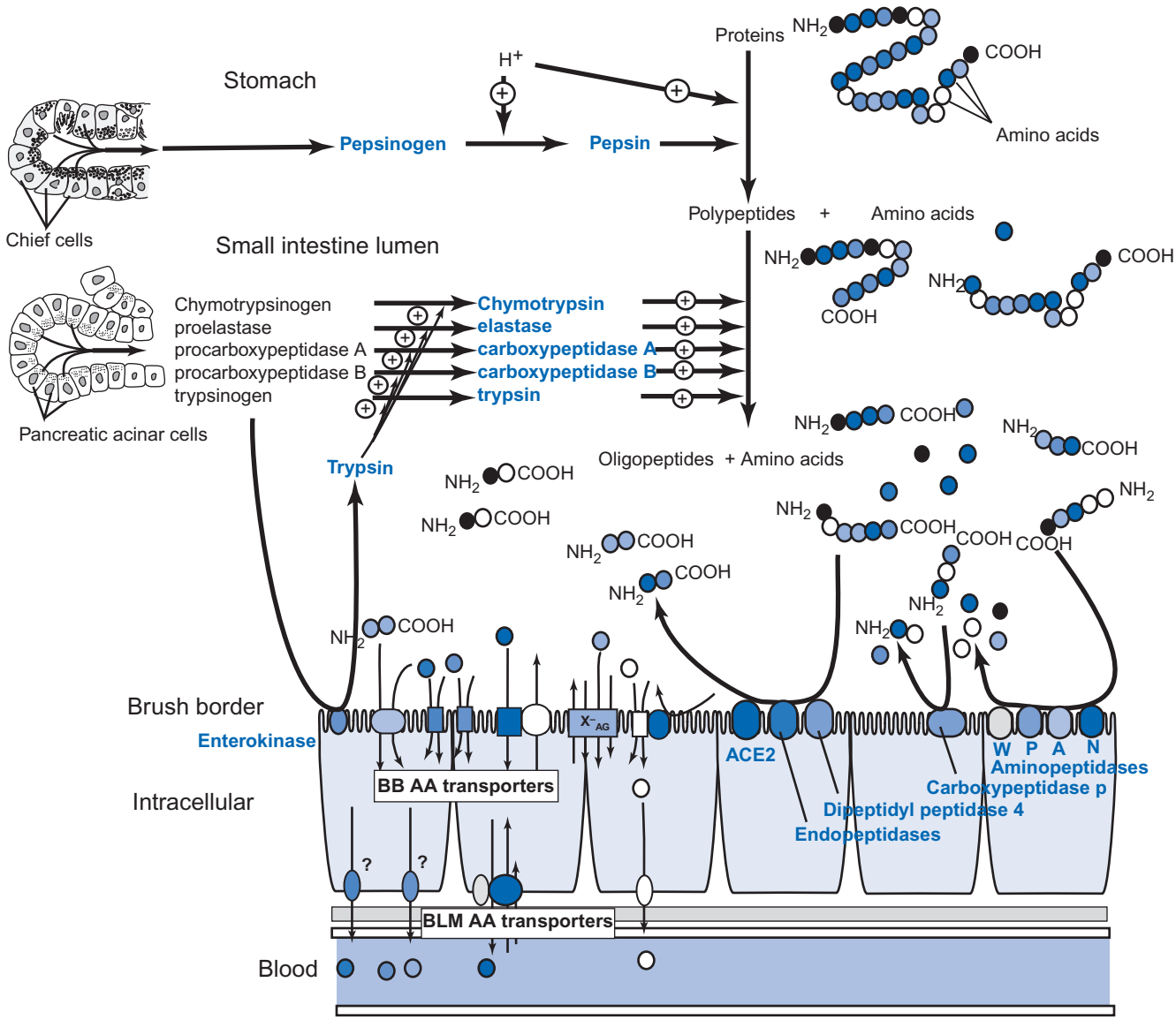

FIGURE 8.5.2 The events in protein digestion and absorption. Individual amino acids are represented by colored circles. In the gastric phase, pepsins break proteins down into polypeptides and some amino acids. In the intestinal phase, pancreatic proteolytic enzymes are activated by enterokinase and further break down proteins to smaller oligopeptides and amino acids. A number of proteases in the brush border complete digestion and feed the released amino acids into transport mechanisms that take the amino acids and some di- and tri-peptides up into the enterocytes. See text for details.

exopeptidases (**carboxypeptidase A** and **carboxypeptidase B**) in inactive forms. **Enterokinase** on the brush border begins a cascade of activation of the pancreatic enzymes by converting trypsinogen into trypsin. The activated trypsin converts more trypsinogen to trypsin and activates all of the remaining pancreatic proteases. The cascade of events is shown in Figure 8.5.2. The endopeptidases cleave proteins in the middle of their chains with specificity. Trypsin, for example, cleaves the peptide bonds in which basic amino acids (lysine and arginine) contribute the carboxyl group. Chymotrypsin cleaves those peptide bonds in which aromatic amino acids (tyrosine, phenylalanine, and tryptophan) contribute the carboxyl group. The carboxypeptidases cleave single amino acids off the free carboxyl ends of proteins. Carboxypeptidase A cleaves off aromatic or branched chain amino acids; carboxypeptidase B cleaves off basic amino acids. The end result of pancreatic proteolysis is some free amino acids and a mixture of oligopeptides.

The brush border contains a variety of peptidases to complete protein digestion. **Aminopeptidase N** cleaves off one neutral amino acid and **aminopeptidase A** cleaves off one anionic amino acid (glutamate, aspartate) from the amino terminus. **Aminopeptidase P** cleaves off one amino acid which is bound to a penultimate proline, P. **Aminopeptidase W** cleaves off one amino acid which is bound to a penultimate tryptophan, W. **Carboxypeptidase P** cleaves a single amino acid preferentially bound to a penultimate proline, P. **Dipeptidylcarboxypeptidases** are like carboxypeptidase except they cleave off dipeptide fragments from the carboxyl end. There are three

types of dipeptidylcarboxypeptidases: dipeptidyl peptidase 4 and **angiotensin-converting enzyme** (ACE) 1 and 2. Two endopeptidases also reside on the brush border.

Inside the enterocytes, intracellular proteases split small peptides into their components. There are several of these. An aminotripeptidase cleaves the amino acids off the NH_2 terminus of tripeptides. The enterocytes contain a variety of dipeptidases that are specific for dipeptides containing specific amino acids. Some peptides are resistant to proteolysis and are not degraded.

SPECIFIC CARRIERS MOVE AMINO ACIDS ACROSS THE BRUSH BORDER AND BASOLATERAL MEMBRANES

Gastric, pancreatic, and brush border proteases reduce ingested protein to a mixture of amino acids and small peptides of from two to six amino acids. Six major transport systems carry these amino acids and small peptides across the brush border membrane, as listed below and shown in Figure 8.5.3.

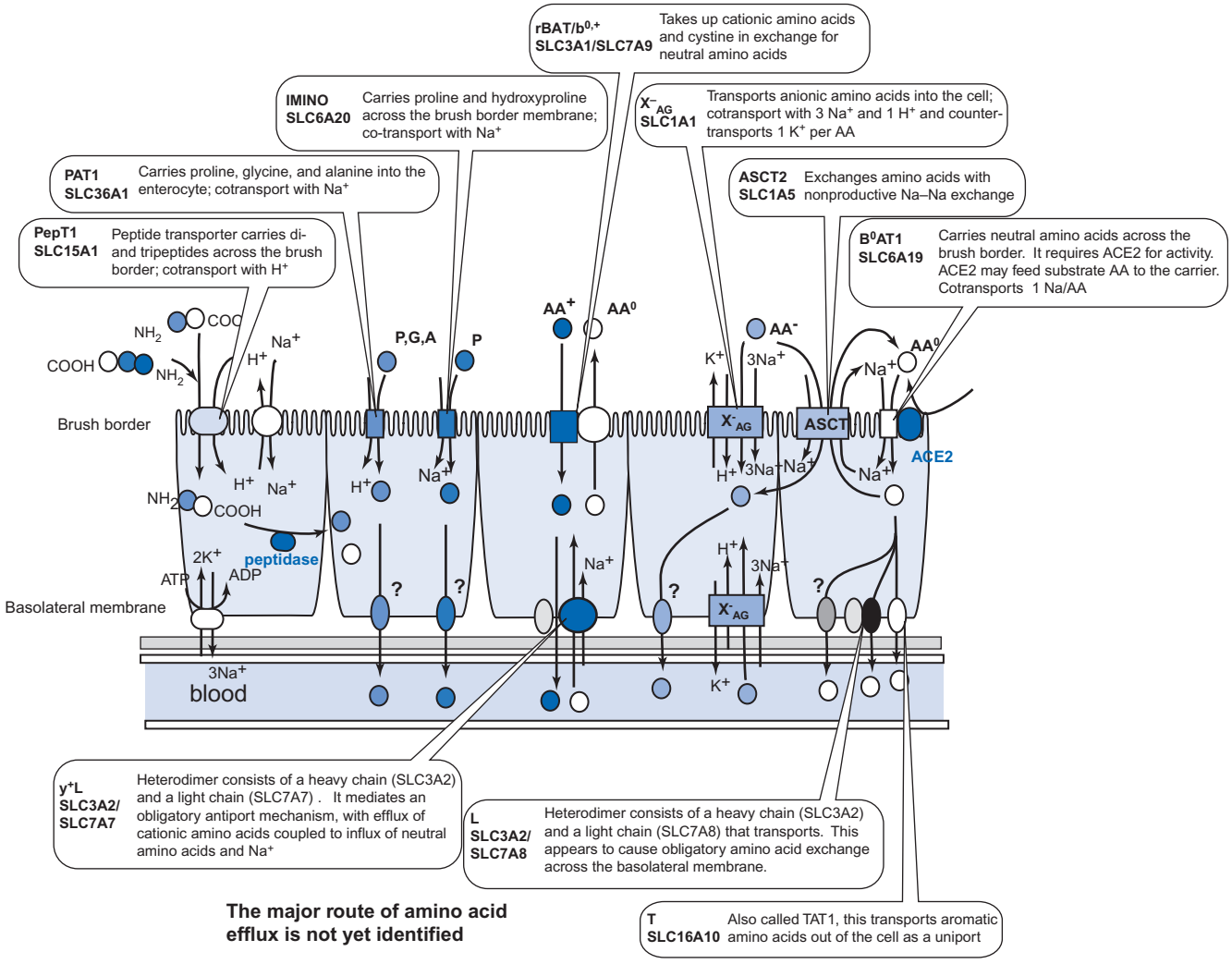

FIGURE 8.5.3 The cellular mechanisms responsible for amino acid absorption from the intestinal lumen into the blood. Proteolytic digestion produces free amino acids and small peptides in the lumen of the intestine. Some of these small peptides are digested on the surface of the enterocytes by aminopeptidase, carboxypeptidases, and dipeptidase that cleave amino acids or dipeptides off small peptides. The free amino acids are taken up into the cell by a set of transporters. Some of these require Na^+ as a cotransported ion and some do not. There are six identified transporters in the brush border that carry neutral amino acids (AA^0), anionic amino acids (AA^-), cationic amino acids (AA^+), imino amino acids, and P (proline), G (glycine), and A (alanine). The anionic amino acid transporter, X^-_{AG}, also cotransports 3 Na^+ and 1 H^+ and countertransports 1 K^+. The ASCT on the brush border produces no net amino acid uptake, but the neutral amino acid carrier, B^0AT1 (=SLC6A19), can supply neutral amino acids so that ASCT can take up a variety of amino acids in exchange for the neutral amino acids. The neutral amino acid carrier requires ACE2 (angiotensin-converting enzyme, a protease) for activity, and evidence suggests it also binds aminopeptidase N. This may form a complex that feeds amino acids directly to the transporter. The cationic amino acid transporter ($rBAT/b^{0,+}$ (=SLC3A1/SLC7A9)) also mediates cationic amino acid influx coupled to neutral amino acid efflux. SLC6A20 carries proline (P) specifically and is a cotransporter. Proline, glycine, and alanine (P,G,A) are carried by PAT1 (=SLC36A1) with energy derived from H^+ influx into the cell. Absorbed amino acids are transported out across the basolateral membrane by a different set of transporters. The major efflux pathway has not yet been identified. Dipeptides are also taken up by the cell, using H^+ as a cotransported ion. The dipeptide carrier exhibits a broad specificity. Some dipeptides and tripeptides are split by proteases within the enterocytes, and the resulting amino acids are transported across the basolateral membrane by the free amino acid transporters. Some dipeptides and tripeptides are absorbed into the blood intact.

Neutral amino acid system: B^0AT1 (=SLC6A19) carries neutral amino acids (M,L,I,V,Q,N,F,C,A,S,G, Y,T,H,P,W,K). This carrier is a symport, using the Na^+ gradient to drive the inward flux of amino acids. The stoichiometry is 1 Na^+:1 amino acid. Its activity requires ACE2, a dipeptidylcarboxypeptidase that apparently releases amino acids that are substrates for B^0AT1. This carrier also associates with aminopeptidase N.
Anionic amino acid system: X^-_{AG} (=SLC1A1) carries anionic amino acids, aspartic acid, and glutamic acid (E,D). This cotransports 3 Na^+ and 1 H^+ for each amino acid, and return of the carrier is facilitated by K^+.
Cationic amino acid system: rBAT/$b^{0,+}$ (=SLC3A1/SLC7A9) is a heterodimer that carries the cationic amino acids (R,K, Cystine). This works through an obligatory exchange mechanism so that there is no net amino acid transport.
Proline transport system: IMINO (=SLC6A20) carries proline and hydroxyproline, and will not carry glycine. Its transport is coupled to the Na^+ electrochemical gradient.
Proline and glycine transport system: PAT1 (=SLC36A1) carries proline or glycine (P,G,A) coupled to H^+ entry.
Di- and tri-peptide transport systems: (PepT1 = SLC15A1) carries di- and tri-peptides across the brush border membrane, coupled to H^+ cotransport. Most di- and tripeptides are hydrolyzed but some di- and tripeptides exit the cell to be absorbed intact into the circulation.

DISTINCT CARRIERS TRANSPORT AMINO ACIDS ACROSS THE BASOLATERAL MEMBRANE

Amino acid absorption is completed by the transport of amino acids across the basolateral membrane (BLM) of the enterocyte where they can enter the blood. The main mechanism for efflux of amino acids at the BLM has not yet been identified. However, several mechanisms that partially explain amino acid efflux are known. These are listed below and illustrated in Figure 8.5.3.

Aromatic amino acids: The T system, also known as TAT1 (=SLC16A10), is thought to mediate the transport of F, Y, and W, across the basolateral membrane.
L system: This system consists of a heterodimer, with SLC3A2 making up a heavy chain that appears to direct the transporter to the BLM. The light chain is SLC7A8. It appears to mediate an obligatory exchange of amino acids.
y^+L system: This system also is a heterodimer, with SLC3A2 and SLC7A7. It also mediates an obligatory exchange of amino acids, with the influx of amino acids linked to Na^+ cotransport.

CARBOHYDRATES ARE MAINLY DIGESTED IN THE SMALL INTESTINE

In Western cultures, 200–300 g of dietary carbohydrates provide 40–50% of the daily caloric intake. Another 30–40% is provided by fats, with the remainder, about 15%, deriving from protein. These carbohydrates are mostly plant products. Lactose (milk sugar) and small amounts of glycogen in meat are the only animal carbohydrates in the diet.

Carbohydrates, or **saccharides**, are organic compounds containing one or more aldehyde or ketone groups and multiple hydroxyl groups. **Monosaccharides** such as **glucose**, **galactose**, and **fructose** have a single aldehyde or ketone group. **Disaccharides** such as **sucrose**, **lactose**, or **maltose** contain just two monosaccharide units. Sucrose consists of glucose and fructose; lactose is made of glucose and galactose; and maltose is composed of two glucose molecules. Oligosaccharides consist of 2–10 monosaccharide units, and polysaccharides are longer yet. About 50% of the calories derived from carbohydrates come from starch. The two main varieties of starch, α-amylose and **amylopectin**, are found in grains such as wheat, barley, and rice and also in many vegetables. Amylose is a linear polymer of glucose units linked by α(1,4)-glycosidic bonds. Amylopectin is a branched chain of glucose units, with α(1,6)-glycosidic linkages occurring at branch points every 15–20 glucose units. These starches form gels upon hydration, which gives certain foods part of their characteristic "mouth feel." The structure is shown in Figure 8.5.4.

Starch digestion has a luminal phase and a membrane phase. The luminal phase is due to α-amylase, an enzyme secreted by the salivary glands and by the pancreas. The α-amylase secreted by the parotid gland originates from the AMY1 gene, whereas the pancreatic product derives from the AMY2 gene, and their products show 94% sequence homology. Salivary amylase is of minor importance because the acid pH in the stomach inactivates the enzyme. Amylase digestion produces a mixture of **maltose** (glucose–glucose linked by α(1,4)-glycosidic bond), **maltotriose** (three glucose molecules linked by α(1,4)-bonds), and structures called **limit dextrins** (see Figure 8.5.4).

INDIGESTIBLE CARBOHYDRATES MAKE UP PART OF DIETARY FIBER

The digestive enzymes in humans can hydrolyze only some carbohydrates bonds. The undigestible carbohydrates make up part of **dietary fiber**. Indigestible fiber can be insoluble (e.g., cellulose) and soluble (e.g., hemicellulose, pectin, and gums). Fibers containing β(1,4) or β(1,3) linkages are indigestible because these bonds are immune to amylase attack.

THE BRUSH BORDER COMPLETES STARCH DIGESTION

The brush border contains several key enzymes that digest the products of luminal digestion to produce monosaccharides. These enzymes are **sucrase-isomaltase**, **lactase**, **maltase-glucoamylase**, and **trehalase**. Sucrase-isomaltase is a single gene product that

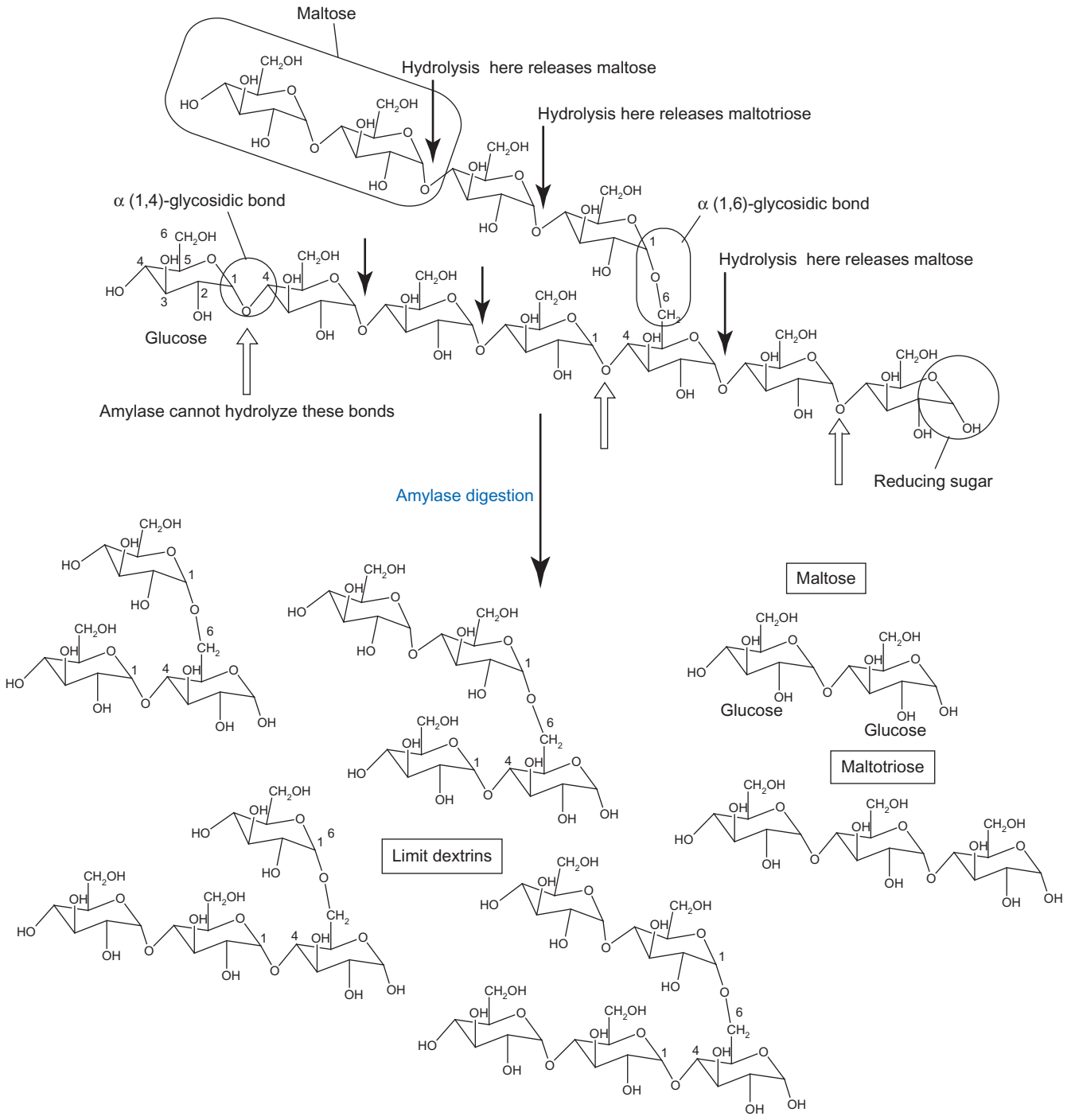

FIGURE 8.5.4 Structure of amylopectin (top) and the action of amylase. Because amylase cannot hydrolyze certain α(1,6) and α(1,4) bonds (all α(1,6) bonds and those α(1,4) bonds at the end of the chains or adjacent to α(1,6) bonds), its digestion of amylopectin is incomplete. Amylase's complete digestion of starch produces maltose (a glucose–glucose disaccharide), maltotriose, and a set of limit dextrins. The set of limit dextrins shown would be produced from the substrate shown.

has two active sites. The **sucrase** site splits sucrose into glucose and fructose. These two monosaccharides can then be absorbed by brush border transporters. The **isomaltase** active site cleaves maltose at its α(1,4) bond and it cleaves limit dextrins at their α(1,6) bond. This enzyme site is also called α-dextrinase. Lactase on the brush border membrane splits dietary lactose, obtained solely from human milk or dairy products, into galactose and glucose, which are both absorbed. Maltase-glucoamylase has two subunits that cleave the α(1,4)-glycosidic bond at the nonreducing end of oligosaccharides, thereby releasing the terminal glucose. Trehalose is an α(1,1)-linked dimer of glucose that is present in some natural foods. Trehalose breaks this bond to form glucose monosaccharides that can be absorbed.

GLUCOSE, FRUCTOSE, AND GALACTOSE ABSORPTION IS CARRIER MEDIATED

Complete digestion of carbohydrates produces three monosaccharides: **glucose**, **galactose**, and **fructose**. These are absorbed into the absorptive cell by two carriers. Galactose and glucose are both carried into the cell by secondary active transport, using Na^+ as the cotransported ion. The carrier is called **SGLT1** (=SLC5A11) for **s**odium **g**lucose-**l**inked **t**ransporter. Fructose is carried into the cell by facilitated diffusion by **GLUT5 (=SLC2A5)**, which, despite its name, appears to be specific for fructose in humans.

The final step in absorption of monosaccharides requires their transfer to the blood. The monosaccharides penetrate the basolateral membranes by carrier mechanisms. Glucose and fructose exit the cell by the **GLUT2 (=SLC2A2)** carrier, which uses a facilitated diffusion mechanism. The process of carbohydrate digestion and absorption is illustrated in Figure 8.5.5.

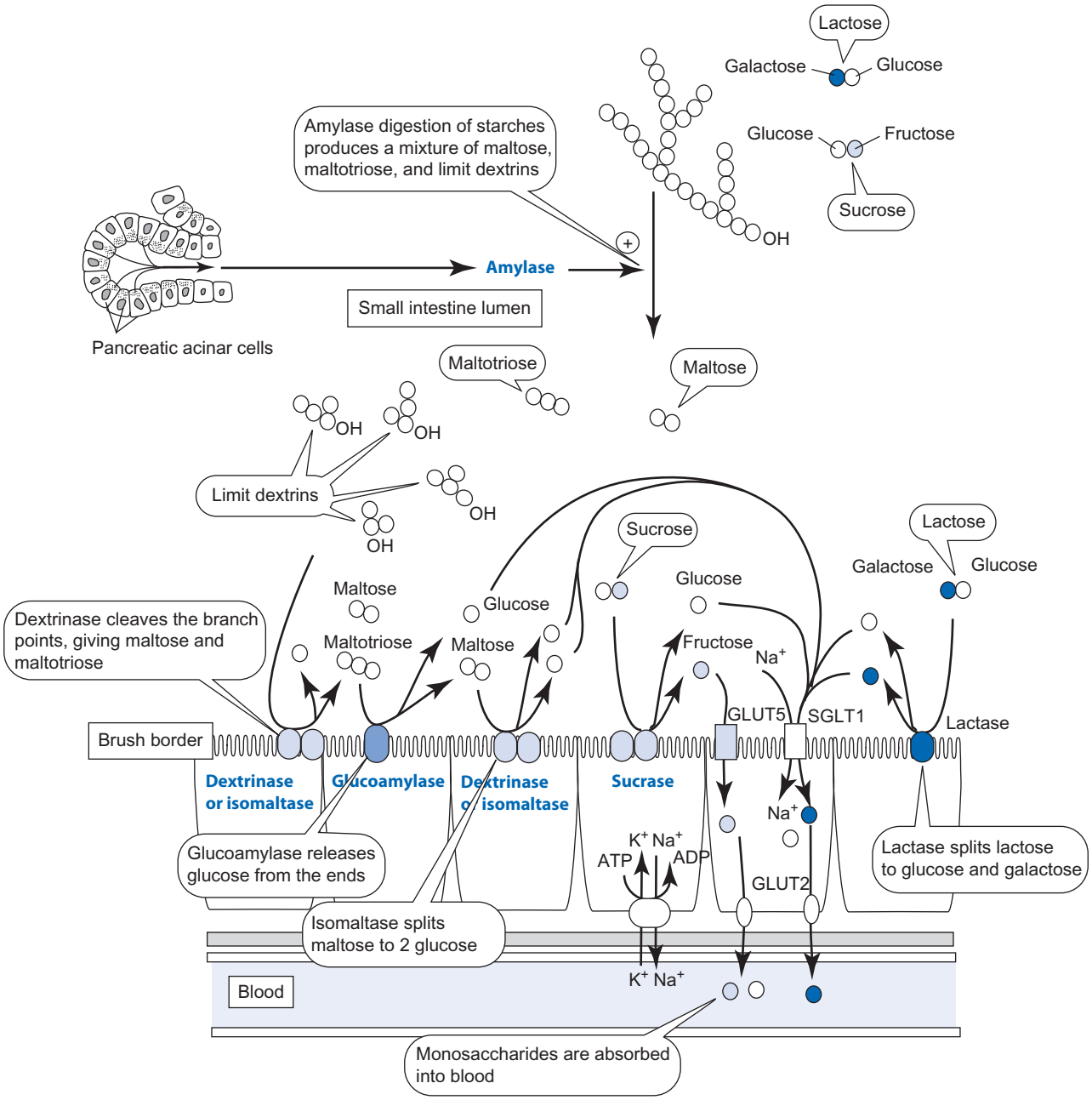

FIGURE 8.5.5 Overall digestion and absorption of carbohydrates. Starch is broken down in the lumen of the gastrointestinal tract to maltose, maltotriose, and limit dextrins. Dextrinase, which is the same enzyme as isomaltase, breaks the limit dextrins into maltotriose and maltose. Glucoamylase breaks maltotriose to glucose and maltose and isomaltase completes the digestion of maltose to two glucose molecules. Lactase cleaves lactose to galactose + glucose. Ordinary table sugar, sucrose, is broken down to glucose and fructose by sucrase, which is the same enzyme as dextrinase and isomaltase. Glucose and galactose are taken up into the cell by SGLT1; fructose is taken up by GLUT5. All of the monosaccharides leave the cell via GLUT2 on the basolateral membrane.

LIPID DIGESTION BEGINS WITH *EMULSIFICATION*

The defining characteristic of lipids is their insolubility in water and their solubility in organic solvents. Digestion of dietary lipids first requires access to the lipids, which is achieved by their dispersion into a stable form with a large surface area. This dispersion of lipid in an aqueous environment is called **emulsification**. Emulsification begins in the stomach with mechanical mixing and absorption of oligopeptides onto the lipid surface. In this crude emulsion, most of the lipid occupies the core of the lipid droplets with little on the surface where digestion occurs. In the small intestine, the bile salts and lipolytic digestion products form finer dispersions of lipid in which the surface area is greatly increased.

MOST LIPOLYTIC ACTIVITY OCCURS IN THE SMALL INTESTINE

Many experimental animals produce a **lingual lipase** and a **gastric lipase**. In humans, lingual lipase makes little or no contribution to the preduodenal lipase activity. Cells in the fundus of the stomach in humans secrete a 43-kDa lipase. This enzyme has a low pH optimum and preferentially cleaves the fatty acyl ester bond at position 3, producing fatty acid and diglyceride. The bulk of lipase activity comes from the pancreas.

The high $[H^+]$ in the stomach binds to the $-COO^-$ group at the ends of fatty acids, keeping them in the uncharged $-COOH$ form. This uncharged form stays dissolved in the hydrophobic core of lipid droplets. In the duodenum, the HCO_3^- neutralizes the acid from the stomach, and the fatty acids are ionized between pH 6 and 7.5. These charged fatty acids line the surface of the droplets and aid in their dispersion. The pancreas secretes a 50-kDa lipase and a 10-kDa colipase. The **pancreatic colipase** binds to the triglyceride surface with the help of the **bile acids** and anchors **pancreatic lipase**. In the absence of colipase, bile acids remove pancreatic lipase from the lipid surface and thereby inhibit lipolysis. The pancreatic enzymes **phospholipase A2** (MW 13.6 kDa) and **cholesterol esterase** also absorb to this surface. Pancreatic lipase hydrolyzes the positions 1 and 3 of triglycerides, releasing fatty acids and 2-monoglyceride. This reaction is shown schematically in Figure 8.5.6. The surface

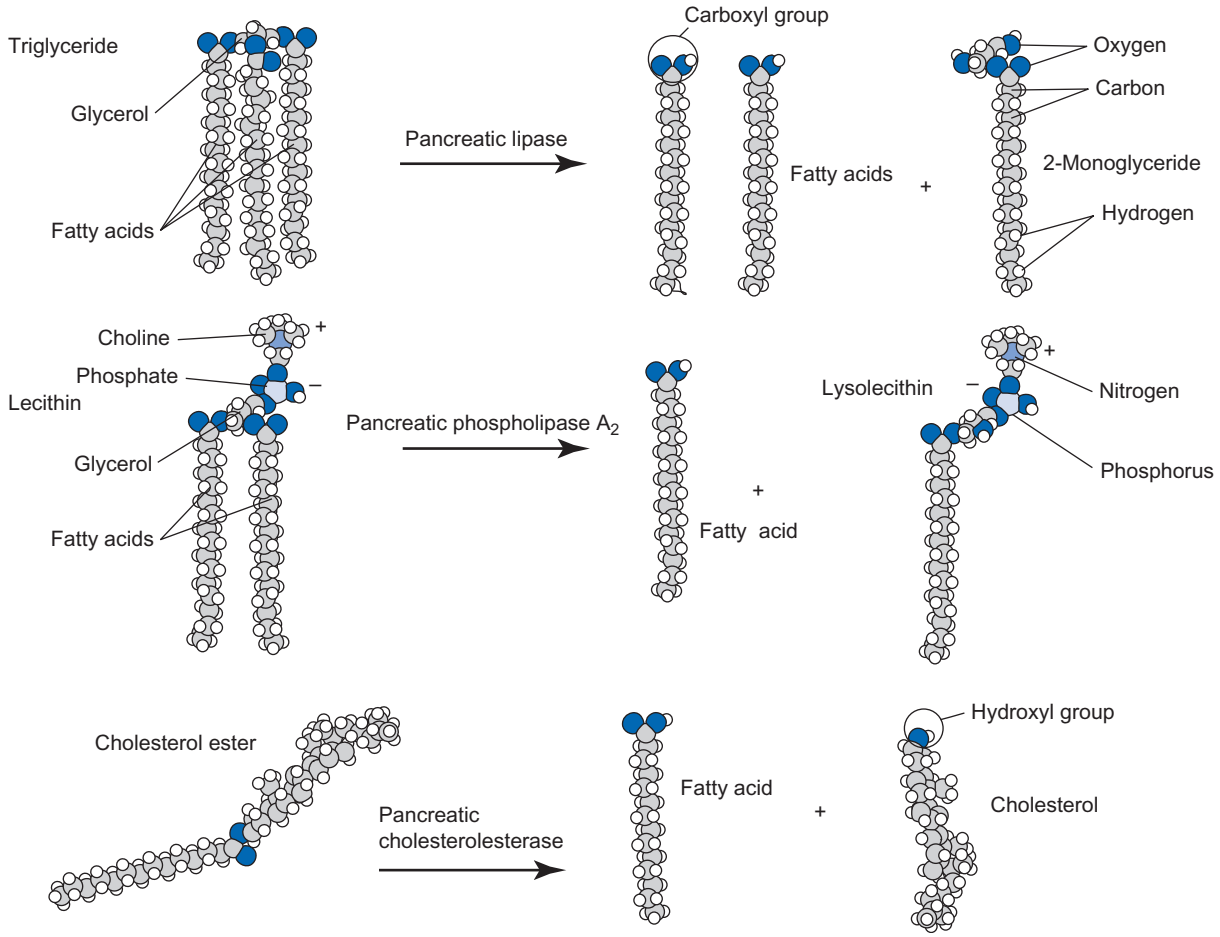

FIGURE 8.5.6 Lipolytic digestion by pancreatic enzymes in the lumen of the small intestine. Pancreatic lipase, anchored and activated by pancreatic colipase, breaks triglycerides down into fatty acids and monoglycerides. Pancreatic phospholipase cleaves phospholipids into fatty acids and lysophospholipids. Cholesterol esterase cleaves the fatty acid off cholesterol esters.

activity of these products is higher than that of the starting triglyceride, and they aid in the dispersion of lipids in the lumen. Pancreatic phospholipase A_2 hydrolyzes the fatty acyl ester bond at position 2 in phospholipids, releasing a free fatty acid and lysolecithin, or **lysophosphatidylcholine**. Like free fatty acids, lysolecithin helps disperse the lipid droplets (see Figure 8.5.6). Cholesterol esters are cleaved by pancreatic cholesterol esterase and absorbed into enterocytes as free cholesterol. The pancreatic cholesterol esterase requires bile acids for activity.

All of the lipid hydrolysis products are removed from the large lipid droplets to form complexes with bile acids and phospholipids called **mixed micelles**. Bile acids stabilize mixed micelles because of their unique topology (see Figure 8.5.7). The mixed micelles form a tiny disk-shaped aggregate (see Figure 8.5.8).

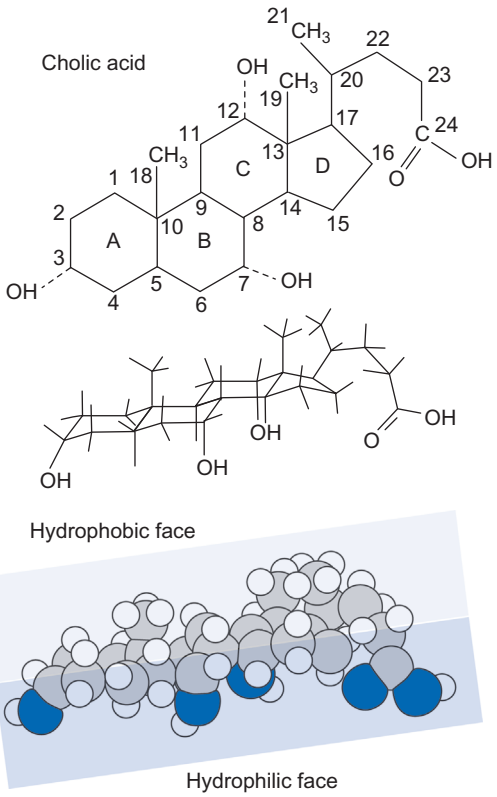

FIGURE 8.5.7 Structure of cholic acid. The diagram at the top shows the structural formula with the numbering system of the A, B, C, and D rings of the steroid nucleus. Below the structural diagram is a framework model showing that the bond angles for the ring carbons occupy equatorial positions (in which the bond points more or less in the plane of the rings) or axial positions, in which the bond points perpendicular to the plane of the rings. The three hydroxyls at carbons 3, 7, and 12 in cholic acid all occupy axial positions that point to the same side of the plane of the rings. The carboxyl group at the end of the cholic acid is at the end of a chain of three C–C bonds that can freely rotate except for the steric hindrance between the CH_3 groups at C-19 and C-21. This forces the carboxyl group to the hydrophilic face of the molecule. Thus the plane of the steroid ring structure divides the molecule into a hydrophilic half and a hydrophobic half. The bottom diagram shows a space-filling model in which the hydrophilic groups (in blue) are clearly separated from the hydrophobic groups.

HYDROLYSIS PRODUCTS OF LIPIDS ARE ABSORBED AND THEN REPACKAGED INTO *LIPOPROTEINS*

The mixed micelles deliver lipolytic products to the microvilli membrane. The mechanism of transport across the brush border membrane is not yet established, but it may involve a number of lipid-binding proteins including FABP pm (fatty acid binding protein, plasma membrane), FATP4 (fatty acid transport protein), CD36 (cluster of differentiation 36), cytosolic FABP (fatty acid binding protein), and other proteins such as Cav-1 (caveolin-1) and clathrin. Similarly, the mechanism for cholesterol absorption is not established, but it involves NPC1-L1 (Nieman = Pick C1-like 1) protein and it is specifically inhibited by some drugs (**ezetimibe**).

The current hypothesis is that at least some fatty acids, such as the short-chain fatty acids, can enter the enterocyte by simple diffusion. Long-chain fatty acids and 2-monoglycerides may enter either by diffusion or by endocytosis mediated through caveolin to form **CEV—caveolae endocytotic vesicles.** These vesicles then fuse with the smooth endoplasmic reticulum and the lipids are reesterified to form triglycerides through the sequential action of monoacylglycerol acyl transferase (MGAT) and diacylglycerol acyl transferase (DGAT). Cholesterol is also esterified by acyl cholesterol acyl transferase (ACAT). The reesterified triglycerides, phospholipid, and cholesterol are packaged into **lipoproteins** in the Golgi apparatus of the enterocytes by **microsomal triglyceride transfer protein (MTP).** Lipoproteins are a class of particles found in the lymph and the blood that contain both lipid and protein coats called **apolipoproteins**. The protein coats help solubilize the lipids and also allow cells to latch onto the lipoproteins. The intestine makes a variety of lipoproteins including **chylomicrons**, very low density lipoprotein (**VLDL**), and high density lipoprotein (**HDL**). These are secreted at the basolateral membrane and reach the lymph and blood vessels that perfuse the intestine. The chylomicrons are transported solely in the lymph. The lymph ducts coalesce to drain into the **thoracic duct** that empties into the subclavian vein and thence into the systemic circulation. After a fatty meal, the lymph vessels appear white because of the light scattering of the many chylomicrons. This white color of the lymphatics gives the **lacteals** their name because they look milky white. The lymph transports about 50% of the absorbed lipids, whereas the portal vein carries the other 50%. The shorter the fatty acyl chain, the larger the percentage of absorbed lipids that is carried in the blood instead of the lymph. Chylomicrons are about 80–500 nm in diameter, are coated with apolipoproteins A-I, A-II, and B48, and are 95% lipid by mass, mostly triglyceride. In the circulation, they pick up apolipoproteins E and C. VLDLs are much smaller than chylomicrons, some 30–80 nm in diameter, are coated with apolipoproteins A-IV and B48, and consist of about 30% triglycerides and 40%

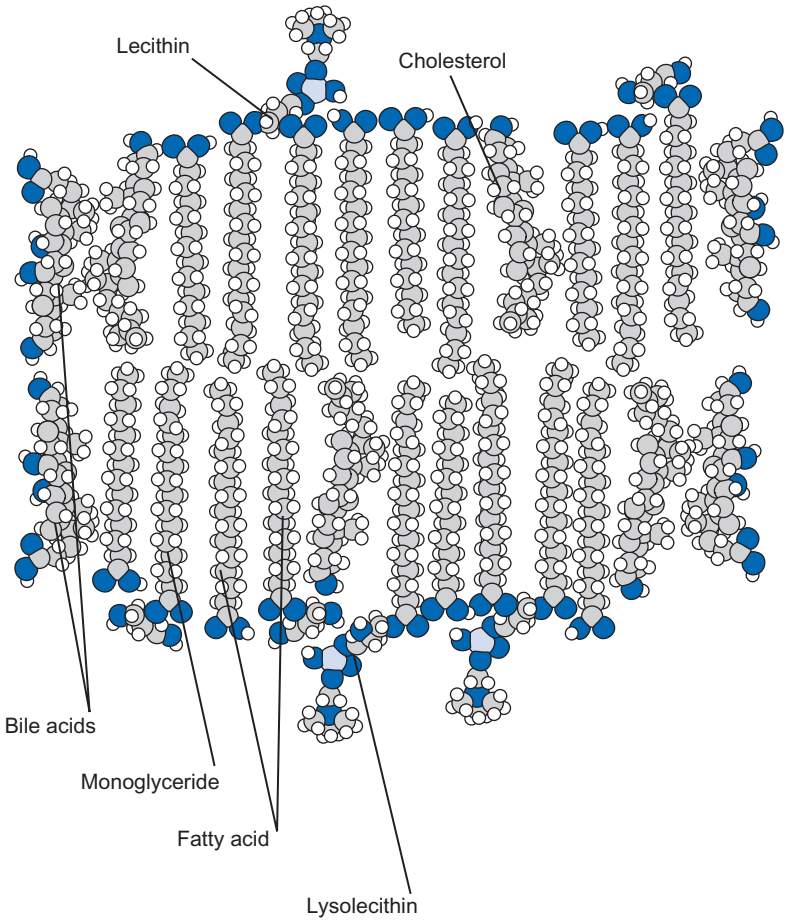

FIGURE 8.5.8 Cross-section through a mixed micelle. The core of the mixed micelles in the intestinal lumen contains lipolytic products such as monoglycerides, free fatty acids, phospholipids, lysophospholipids, and cholesterol. The hydrophobic domains of these lipids face the hydrophobic core of the micelle while their polar ends face the aqueous phase. The sides of the hydrophobic core are coated with bile acids that absorb to it. Their hydrophobic face covers the core of the micelle and their hydrophilic face interacts with water. In this way the bile acids stabilize the structure. The entire structure is actually disk shaped, and the bile acids coat a cylindrical surface.

Clinical Applications: Lactose Intolerance

The defining characteristic of mammals is that new born animals are fed milk by their mothers. Milk contains lactose as its major carbohydrate, and so it is crucial that the young animal be able to digest and absorb this disaccharide of galactose and glucose. **Lactase** is the only enzyme that can digest lactose. After weaning, many persons lose much of their ability to digest lactose. They therefore become **lactose intolerant**. Ingestion of too much lactose produces a variety of symptoms including nausea, cramps, bloating, and diarrhea. The lactose passes undigested into the colon where bacteria have a feast on the free sugar. They produce hydrogen gas which can be detected in the exhaled air as part of the diagnosis of lactose intolerance. (More than 20 ppm H_2 in exhaled air after ingestion of 1 g lactose per kg body weight.) The undigested lactose also exerts an osmotic pressure that retains water in the intestine. These two consequences, osmotic diarrhea and excess gas production, can produce an "explosive" diarrhea. The degree of diarrhea and gas depends on the amount of lactose ingested. Even "lactose intolerant" people generally can tolerate small amounts of lactose. Conversely, persons who normally have no problems digesting and absorbing lactose can be overwhelmed by excessive intake.

Lactose increases calcium absorption from the intestine, but how it accomplishes this feat is unknown. Milk has a lot of calcium, and its consumption aids the young animal in its early rapid growth. Lactose aids this growth. Calcium absorption from the intestine requires the hormone 1,25$(OH)_2$ cholecalciferol, which is derived from vitamin D (cholecalciferol) by two successive hydroxylation reactions. Hydroxylation at C-25 occurs in the liver and hydroxylation at C-1 occurs in the kidney. The skin makes vitamin D when it is exposed to ultraviolet radiation from the sun, and so it is sometimes called "the sunshine vitamin." People with adequate exposure to the sun have no dietary requirement for vitamin D. This and its mechanism of action, similar to that of the classic steroids, argue that vitamin D is not a vitamin, but a hormone.

In primary lactose malabsorption, lactase activity is high at birth and decreases in childhood to remain low in the adult. This is the "normal" condition for humans. Typically 70–100% of adults

worldwide are lactose intolerant, with the exception of the population of Northern and Central Europe and their descendants in America and Australia. In North America, about 15% of the white population has lactose malabsorption, whereas about 80% of the black population and 53% of the Hispanic population have lactase insufficiency. The cause of this ethnic distribution is unknown, but one interesting hypothesis is that it arose from the adaptive response to diminished exposure to sunlight in northern climates, both as a result of the tilt of the earth and from covering the skin with insulating clothes. Reduced ultraviolet illumination of the skin reduces synthesis of vitamin D in the skin, which is the only hormone that regulates intestinal absorption of dietary calcium. Over time, these indigenous people shed dark skin pigmentation to favor vitamin D synthesis, but many retained the tanning reaction to protect the skin from the harmful effects of UV radiation. They also retained intestinal lactase into adulthood to enable them to consume dairy foods throughout life. Dairy foods contain the most calcium in a favorable ratio to phosphorus. Thus light skin pigmentation, lactose tolerance, domestication of cattle, and dietary consumption of dairy products were physical and cultural adaptations that coevolved to improve nutrition of neolithic humans who migrated north from Africa. There is no proof for this hypothesis, but it is supported by the observation that even in Europe the indigenous people show a gradation of skin color and lactose tolerance, with the whitest and most tolerant people at the northernmost reaches.

Persons with lactose intolerance can find relief by eating **yogurt**. Yogurt contains live cultures of the bacterium *Lactobacillus acidophilus* that contain β-galactosidase activity that splits lactose into glucose and galactose. The lactase activity survives passage through the acid stomach if it is associated with bacterial cell walls that protect it. Yeast lactase (**lactaid**) can be ingested simultaneously with dairy products to improve lactose tolerance.

Clinical Applications: The Benefits of Dietary Fiber

The modern diet in Western cultures consists of high caloric density foods that have been highly enriched. Much of the nonnutritive components of food have been stripped away by milling and refining. In the last 30 years, we have come to realize that these indigestible components of food are an indispensible part of a healthy diet and that they are needed for normal gastrointestinal function.

Chemical definition of dietary fiber is difficult because of its diversity. Fiber includes cellulose, hemicellulose, pectins, gums, β-glucans, and lignins. Lignin is a mixture of phenolic compounds and is not a polysaccharide.

Much of the current interest in dietary fiber stems from the work of Denis Burkitt and Hugh Trowell, physicians who practiced medicine in Africa after World War II. They postulated that the "roughage" in the African diet afforded them some protection from a variety of ailments that afflicted persons in Western countries. These included cardiovascular disease; colonic dysfunction including diverticulitis, ulcerative colitis, constipation, and colonic cancer; cholelithiasis; appendicitis; hemorrhoids; diabetes; and obesity. The role of dietary fiber in many of these conditions remains to be established, but the effects appear to be consistent with what we know of fiber and gastrointestinal function.

Dietary fiber affects gastrointestinal motility. Depending on the fiber type and particle size, fiber can reduce gastric emptying while enhancing intestinal motility, so that the overall effect on time from mouth to anus can be either an increase or a decrease. Most fiber increases stool bulk, which decreases the intestinal **transit time**. The increased stool bulk dilutes potential colon carcinogens in addition to decreasing the time these carcinogens are in the colon. These effects explain the effect of fiber on colonic cancer and constipation. Dietary fiber, particularly lignin, binds bile acids. Some of these bile acids are believed to be transformed into carcinogens in the gut. Thus formation of bile salts reduces carcinogen formation. In addition, binding the bile acids increases excretion of cholesterol by removing some of the negative feedback on bile acid synthesis in the liver. This may explain part of the beneficial effect of fiber in preventing cardiovascular disease. Dietary fiber expands the bile acid pool and increases the proportion of chenodeoxycholic acid over deoxycholic acid. This lowers the **lithogenic index** of bile and therefore reduces the chances of having gallstones.

Diverticula are little pouches or blind sacs that develop in the lining of the large intestine. They are potentially painful and can become inflamed, causing **diverticulitis**. The condition of having diverticuli is **diverticulosis**. Increasing the stool volume decreases the intraluminal pressure by the Law of Laplace, $P = T/r$. Thus increasing r decreases P at the same wall tension. Lastly, fiber may reduce hemorrhoids by reducing straining during defecation.

Although the cause and effect relationships between dietary fiber and chronic diseases are not fully established, there is reason to think that increasing dietary fiber is good for you. The current recommendation is to consume 18 g of nonstarch polysaccharides per day. This can be accomplished by consuming whole-grain foods, cereal products, fruits, and vegetables that contain natural fiber.

phospholipid. In the circulation, the VLDLs are coated with apolipoproteins B100, C, and E. The intestine secretes discoid-shaped HDL particles. These are 6–13 nm across and are 70% protein, 30% lipid. Half of the lipid is phospholipid. The major apolipoprotein in the intestinal HDL is A-I and A-IV. The overall pathway of lipid digestion and absorption is shown diagrammatically in Figure 8.5.9.

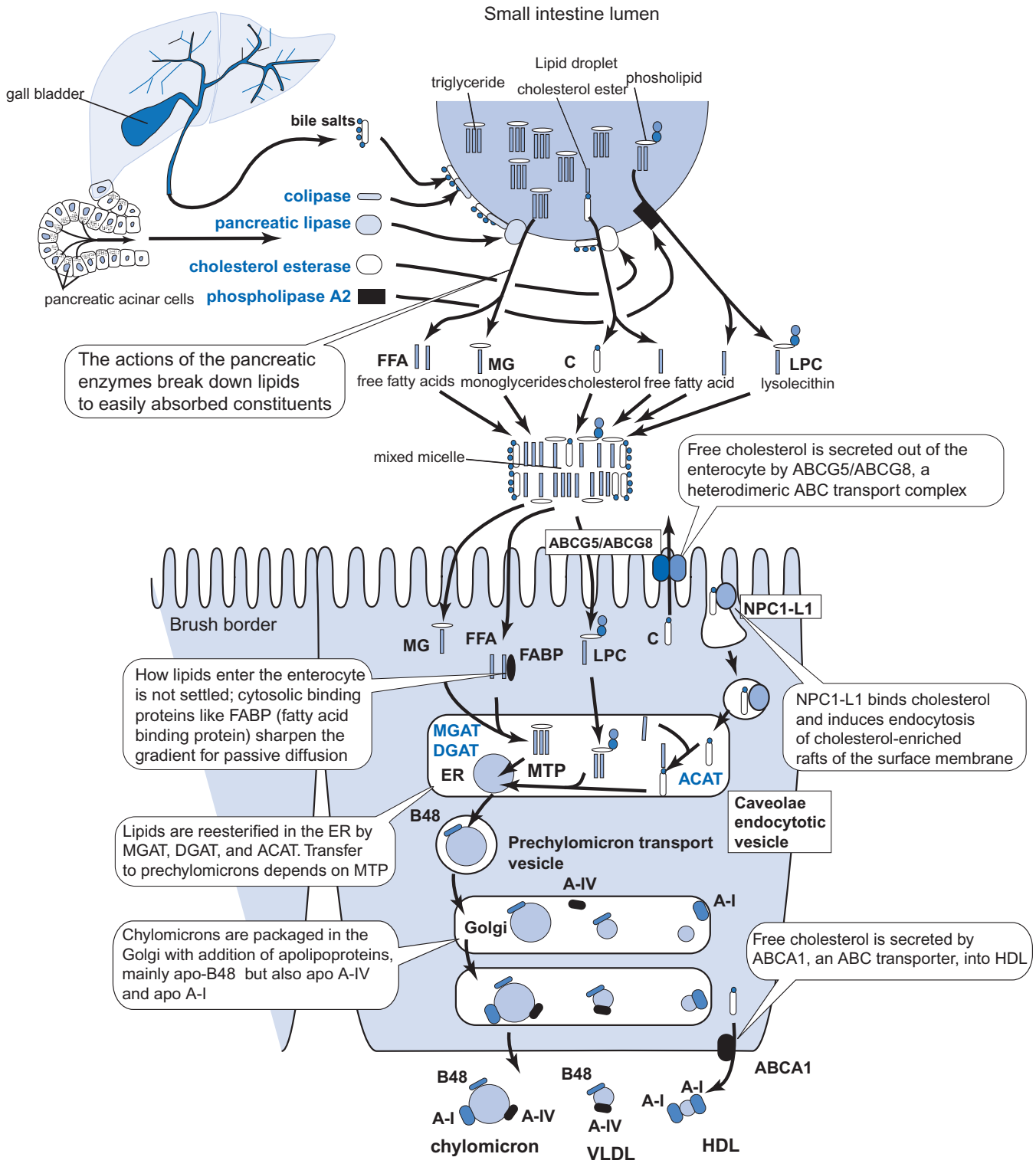

FIGURE 8.5.9 Overall processing of lipids by the intestine. Some lipid digestion occurs in the stomach, but most occurs in the intestine by pancreatic lipase, acting in concert with bile acids and colipase. This breaks down triglycerides into 2-monoglycerides and fatty acids. Pancreatic phospholipase degrades lecithin to fatty acids and lysolecithin, and cholesterol esters are hydrolyzed by pancreatic cholesterol esterase. All of the products are abstracted from lipid droplets to form mixed micelles. These transfer the hydrolysis products to the brush border where they are absorbed and then reesterified in the smooth endoplasmic reticulum of the enterocytes. The lipids are then packaged into lipoproteins that are released to travel in the lymph or in the portal blood. The lipoproteins consist of lipid interiors covered by apolipoproteins (B48, A-I, and A-IV). VLDLs are very low density proteins; HDLs are high-density lipoproteins.
MG, monoacylglycerides; FFA, free fatty acids; C, cholesterol; LPC, lysophosphatidylcholine; FABP, fatty acid binding protein; NPC1-L1, Nieman Pick C1-like-I protein; MGAT, monoacylglycerol acyl transferase; DGAT, diacylglycerol acyl transferase; ACAT, acyl cholesterol acyl transferase; ABCG5 and ABCG8, ATP-binding cassette transport proteins G5 and G8 that form a heterodimer for export of cholesterol from the enterocyte; ABCA1, ATP-binding cassette for cholesterol export along the basolateral membrane.

BILE ACIDS ARE ABSORBED IN THE TERMINAL ILEUM

As described in Chapter 8.4, the bile acids that are secreted by the liver are absorbed by the terminal ileum back into the portal blood and taken back up again by the liver. Passive absorption of bile acids occurs throughout the small intestine, but the active transporters are present only in the ileum. Absorption is mediated by secondary active transport, using Na^+ influx to drive transport of the bile acids into the enterocyte.

SUMMARY

In order to efficiently absorb nutrients, the intestine presents a huge surface area for absorption. The folds of Kerckring multiply the area by 3; the villi add another factor of 10; the microvilli on the enterocytes multiply this by 20. The villus cells continuously parade up the villus from their origins in the crypts of Lieberkuhn to their extrusion at the villus tips. The entire villus surface renews itself every 4–5 days.

Protein digestion begins in the stomach where chief cells secrete pepsinogen that is activated to pepsin by stomach acid. Pepsins are endopeptidases. The intestinal phase begins with proteolytic attack by the pancreatic enzymes trypsin, chymotrypsin, elastase, and carboxypeptidases A and B. These are secreted by the pancreas as inactive precursors. Enterokinase in the duodenum cleaves trypsin from trypsinogen, which then activates all the other proteolytic enzymes. These degrade dietary proteins into amino acids and oligopeptides. The brush border contains aminopeptidases and carboxypeptidases that cleave off single amino acids from the amino or carboxyl end of oligopeptides. Dipeptidylcarboxypeptidase cleaves off two amino acids from the carboxyl end of oligopeptides. Amino acids are transported into the blood using six distinct amino acid transporters and one dipeptide transporter. Some of these use secondary active transport with Na^+ as a cotransporter, but others use countertransport of other amino acids. Basolateral efflux of amino acids is less well known.

Starch digestion begins in the mouth with salivary amylase, but its action is quickly quenched by stomach acid. It resumes with the secretion of pancreatic amylase, which degrades starch into maltose, maltotriose, and limit dextrins. A number of enzymes on the brush border complete the digestion of starch. Dextrinase debranches the limit dextrins. Glucoamylase on the brush border cleaves maltotriose, producing maltose and glucose. Isomaltose breaks maltose down to two glucose molecules. Sucrase, another activity of the dextrinase/isomaltase enzyme, cleaves sucrose to glucose and fructose. Lactase breaks down lactose to galactose and glucose. These monosaccharides are reabsorbed by brush border carriers, either by facilitated diffusion (GLUT5) or by secondary active transport using Na^+ cotransport (SGLT1). The monosaccharides exit the enterocyte into the blood by facilitated diffusion via GLUT2.

Lipids are first broken down in order to gain entry into the enterocyte, and then they are reassembled into lipoproteins. Gastric lipase digests some of the ingested fat, but most of it is digested by pancreatic enzymes. Bile acids secreted by the liver and stored in the gallbladder are released by CCK stimulation of gallbladder contraction and relaxation of the sphincter of Oddi. The bile acids help secure pancreatic colipase on the surface of lipid droplets in the intestine. Pancreatic colipase then anchors pancreatic lipase, which then sets about hydrolyzing dietary triglycerides into fatty acids and 2-monoglyceride. Pancreatic phospholipase A_2 and cholesterol esterase also absorb to the lipid surface and hydrolyze phospholipids and cholesterol esterase. The released fatty acids, monoglycerides, lysolecithin, and cholesterol form mixed micelles with the bile acids. The mixed micelles deliver the lipids to the brush border where the lipids are taken up into the enterocytes. The enterocytes then reesterify the absorbed lipolytic products and reassemble them into lipoproteins. The intestines produce chylomicrons, VLDLs, and HDLs. These are distinguished by their lipid composition and presence of specific apolipoprotein coats. The chylomicrons are absorbed into the lymph. About 50% of dietary lipid travels through the lymph, the rest through the portal circulation.

REVIEW QUESTIONS

1. How much of an increase in area is caused by the folds of Kerckring? By the villi? By the microvilli?
2. How fast do cells in the intestine turn over? Where do new ones come from? Where do the old ones go?
3. What does acid do to proteins in the stomach? What enzyme breaks down proteins in the stomach? What cells secrete it? How is it activated?
4. What proteolytic enzymes does the pancreas make? How are they activated? Why doesn't trypsin inhibitor inhibit trypsin in the lumen of the gut? What products result from luminal proteolysis?
5. What proteolytic enzymes are on the brush border?
6. How are amino acids absorbed into the enterocyte? How do they get into the blood? Are all proteins broken down to single amino acid for absorption?
7. What does pancreatic amylase do? What is a limit dextrin?
8. What enzymes for carbohydrate digestion are on the brush border? What sugars get absorbed? How are they absorbed?
9. What is lactose intolerance?
10. What is emulsification? Why does pancreatic lipase need pancreatic colipase and bile acids? What is a mixed micelle? What happens to fatty acids, glycerol, and other lipolytic products in the enterocyte?
11. Where and how are bile acids absorbed?