CHAPTER

102

Digestion and Absorption of Dietary Fat, Carbohydrate, and Protein

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CHAPTER OUTLINE

Nutrient digestion and absorption are essential processes for the survival of an organism, making them among the most important tasks of the GI system. Most nutrients are absorbed with remarkable efficiency; less than 5% of ingested carbohydrate, fat, and protein is excreted in the stool of adults who consume a normal diet.[1] Even the 20 to 60 g of carbohydrates that escape digestion and absorption in the small intestine are absorbed from the colon as short-chain fatty acids (SCFAs) that are liberated by bacterial breakdown of fiber.[2,3] The intestinal tract of neonates is less efficient: infants fail to absorb 10% to 15% of their dietary fat, and in prematurity as much as 25% to 35% may be lost in the stool.[4,5] In old age, nutrient absorption remains highly efficient unless the intestine becomes diseased.

Despite considerable variations in types of food ingested and nutritional intake across national, racial, and ethnic groups, absorption remains efficient. Absorptive mechanisms adapt to the nature and amount of various nutrients presented to the GI tract. Such changes occur not only during early development[6] but throughout life, and also at times of specific need (e.g., during pregnancy).[7] In achieving the overall objective of nutrient absorption, the different parts of the GI tract act in a closely integrated and coordinated manner under the control of neural and humoral regulatory mechanisms.

The understanding of intestinal digestion and absorption at a molecular level has improved our knowledge of the integration and coordination of these functions within the GI tract. The pharmacokinetics and pharmacodynamics of several key carbohydrate, fat, peptide, amino acid, vitamin, and nutrient transporters are being increasingly understood. In this chapter, integration of intestinal function with the dietary intake, digestion, and absorption of major nutrients (carbohydrate, protein, fat) is discussed along with evolving genetic and molecular bases of these functions.

AN OVERVIEW OF GASTROINTESTINAL INTEGRATION

The cerebral phase of digestion, whether triggered by the sight, smell, or thought of food, initiates the digestive process.

Salivary and gastric secretory responses to these stimuli are mediated via the autonomic nervous system, and there is modest stimulation of pancreaticobiliary secretion via the vagus nerve.[8] The additional stimulus of nutrients in the mouth and upper GI tract markedly potentiates secretion by both humoral and local neural mechanisms (see Chapter 4).[9]

The rapidity with which food is normally chewed and swallowed affords little time for significant oral digestion of nutrients. Nonetheless, mastication and mixing of food with saliva initiates digestion of starch by salivary amylase. Gastric acid would soon switch off these enzymes were it not for the buffering capacity of food that allows some digestion to continue. The optimal pH for gastric lipases is 4.5 to 6.0, and it has been suggested that a considerable proportion of dietary triglyceride (TG) may be digested by these lipases.[10,11] Protein digestion begins in the stomach when gastric pepsinogens are converted to pepsins by gastric acid. Pepsins become increasingly active as intraluminal pH falls, and therefore the digestive action of pepsins on proteins is restricted to the stomach.

During ingestion of food, intragastric pressure rises little because of neurally mediated receptive relaxation. The mechanisms by which individuals perceive satiety and, therefore, cease eating are complex and explained only partly by the sensation of fullness. Although dozens of enzymes and hormones are secreted by the GI tract in response to intraluminal food, only a few are able to influence food intake directly. Satiety signals are relayed to the hindbrain, either indirectly via neural paths (e.g., vagus nerve) or directly via the blood, and most factors that influence how much food is eaten during individual meals act by changing sensitivity to these satiety signals.[12,13]

CCK, gastrin-releasing peptide, and apolipoprotein (apo) A-IV have all been implicated as messengers that transmit the satiety signal to the CNS[14-18]; they potentiate each other's actions and may act in combination. Additional peptides known as the *anorectic peptides*, including peptide tyrosine tyrosine (peptide YY, PYY), pancreatic polypeptide (PP), glucagon-like peptide 1 (GLP-1), and oxyntomodulin, also have been shown to decrease appetite and promote satiety in both animal and human models.[17,19]

Leptin, a hormone released from adipocytes, is an important peripheral signal from fat stores and acts on receptors in the arcuate nucleus and hypothalamus to diminish food intake.[20] Leptin deficiency and leptin receptor defects produce massive obesity. Only 1 GI signal, ghrelin, has been shown to increase appetite.[12,13]

The major digestive processes are initiated in the duodenum. Delivery of chyme from the stomach is regulated so it enters the duodenum at a controlled rate, thus allowing efficient mixing with pancreaticobiliary secretions. Control of gastric emptying is thus critical to ensure optimal digestion (see Chapter 49) and is determined by the consistency, pH, and osmolality, as well as the lipid and calorie content of the gastric contents.[21] The pylorus is selective in that it allows rapid passage of liquids while retaining solid particles with diameters of 2 mm or more.[22,23] The relatively large particles are progressively reduced in size by the gastric antral "mill," a process referred to as *trituration*. Trituration ensures particles will be small enough to allow them reasonably close apposition to digestive enzymes once the nutrient is allowed to enter the duodenum. Meals of high viscosity empty more slowly than do those of low viscosity.

Duodenal mucosal receptors for pH and osmolality trigger a delay in gastric emptying when the gastric effluent is acidic, hypertonic, or hypotonic.[24,25] When duodenal luminal contents are neutralized by pancreaticobiliary bicarbonate and osmolality is adjusted by water fluxes, gastric emptying is again facilitated. This careful titration in the duodenal lumen ensures that nutrients are presented optimally to the pancreatic enzymes, which function best at neutral pH.

The total calorie content of meals also controls the rate of gastric emptying; on average, the human stomach delivers about 150 kcal/hr to the duodenum.[26] Receptors for FAs, amino acids, and carbohydrates in the duodenal mucosa are involved in this response, which probably is mediated by both neural and humoral feedback mechanisms.[27]

Gastric emptying additionally is controlled by a mechanism involving the ileum and colon. If much nutrient escapes digestion and absorption in the jejunum, its presence in the ileum and colon delays GI transit, thus providing more time for digestion and absorption.[28,29] This "ileal brake" acts to provide more time for digestion and absorption, and perhaps regulates the feeling of hunger.[30-34,74]

A number of secretory events coordinately regulate digestion across the GI tract, and some are triggered by FAs, involving FA receptors (e.g., GPR120, GPR40, CD36) on enteroendocrine cells (EECs).[52,76] GLP-1 and -2 are co-secreted by EECs in the small and large intestine in response to luminal fat and carbohydrate. GLP-1 decreases appetite, slows gastric emptying, and enhances glucose-induced insulin secretion. GLP-2 has effects on gastric acid secretion, gastric emptying, and nutrient absorption. GLP-2 regulates CD36 glycosylation, increasing its apical expression in the proximal intestine, which enhances fat absorption and chylomicron secretion.[77] Circulating levels of GLP-1 and GLP-2, low in the fasted state, increase rapidly after nutrient ingestion.[78]

CCK and secretin stimulate gallbladder contraction and pancreatic secretion and are released by nutrient interaction with receptors on I (CCK) and S (secretin) cells, mostly in the duodenum. CCK stimulates the pancreas by excitation of sensory nerves and by triggering of long vagovagal or enteropancreatic reflexes. Acetylcholine, nitric oxide, and neuropeptides such as gastrin-releasing peptide, generated by neurons of the ENS, regulate the exocrine pancreas. Vagal cholinergic pathways mediate CCK effects on pancreatic secretion. Human pancreatic acini lack functional CCK-A receptors, and a CCK infusion that produces plasma CCK levels similar to those seen postprandially stimulates pancreatic exocrine secretion by an atropine-sensitive pathway.[35]

Serotonin (5-HT) released from enterochromaffin cells in the intestinal mucosa and nerve terminals of the ENS and the intrapancreatic nerves may be involved in both stimulatory and inhibitory mechanisms through its various receptor subtypes; 5-HT also mediates the actions of secretin and CCK. Peptides that affect appetite and originate from the intestine (e.g., leptin and ghrelin) or from the pancreas (e.g., PP and neuropeptide Y [NPY]) appear to modulate the exocrine pancreas via hypothalamic centers.[37,38] Pancreatic juice provides both positive and negative feedback regulation of pancreatic secretion through mediation of both secretin- and CCK-releasing peptides. Pancreatic phospholipase A2 from pancreatic juice and intestinal secretions appears to function as a secretin-releasing peptide.[37,39,40]

The simultaneous release of bile salts, pancreatic enzymes, bicarbonate, and enteropeptidase (enterokinase) from duodenal mucosa provides optimal conditions for further nutrient digestion. Adequate lipid digestion is critically dependent on the presence of bile salts, pancreatic lipase, and co-lipase at nearly neutral pH,[41-43] whereas digestion of carbohydrate and protein depends on the combined sequential actions of intraluminal secreted enzymes and then enzymes situated on the brush border membrane (BBM) and within the intestinal mucosa. At the brush border, the close physical relationship between the sites for terminal digestion of protein and carbohydrate and the active absorption of digestive products

provides a very efficient mechanism for dealing with these nutrients.

Two other simultaneous phenomena encourage efficient digestion and absorption. Ingestion of a meal stimulates salt and water secretion by the jejunal mucosa, thereby maintaining luminal contents in a sufficiently fluid state for proper mixing and digestion (see Chapter 101).[44] The other phenomenon is the motor response of the intestine (see Chapter 99). After feeding, the characteristic repetitive motility pattern that occurs during fasting is disrupted. Instead, a predictable different coordinated pattern is seen that, presumably, ensures nutrients are well mixed and brought into close contact with intestinal mucosa. There is close integration of the neurohumoral control mechanisms involving the motor and secretory responses of the intestine.[45] For rapidly absorbed molecules, intestinal blood flow may be the rate-limiting step.[46,47]

Efficient conservation and recycling mechanisms ensure that GI secretions are not entirely lost. Gastric acid secretion is balanced to a large extent by pancreaticobiliary bicarbonate secretion, so that overall acid-base balance is not disturbed. Although intact digestive enzymes are reabsorbed only in trace amounts, the nitrogen they contain is reabsorbed after their digestion. Finally, an efficient enterohepatic circulation recycles bile salts several times each day so they may be utilized approximately twice for each meal.[48] Although bile salts are passively reabsorbed throughout the small intestine, most reach the terminal ileum, where they are reabsorbed via specific active absorptive mechanisms. Thus, bile salts remain in the lumen where they are needed for lipid digestion, after which they are largely reabsorbed to avoid being lost by the colon (see Chapter 64).

Once intestinal chyme leaves the ileum and enters the colon, most nutrients have been digested and absorbed. Colonic function largely serves to dehydrate luminal contents through absorption of salt and water and to store the residuum. Dietary fiber may be digested by bacteria, with release of SCFAs, which are avidly absorbed. SCFAs are the major source of nutrition for colonocytes.[8] SCFAs have minor nutritional significance, except with high-fiber diets. The type of ingested fat can also influence the absorptive function of the intestinal mucosa for nutrients such as carbohydrate.[82]

DIETARY LIPIDS

The American Heart Association's (AHA) Nutrition Committee recommends that total fat intake not exceed 35% of ingested calories, with intake of saturated fats limited to less than 7% and the remainder consisting of monounsaturated and polyunsaturated fats. Cholesterol intake is recommended not to exceed 300 mg/day. In the United States, fat intake rose from approximately 34% of total energy consumed in the 1930s to around 40% in the late 1960s and 1970s. From 1971 to 2000, the percentage of energy contributed by fat decreased back to 33%, reflecting in part about a 25% increase in total energy intake. During the same period, the percentage of energy derived from carbohydrate increased from 40% to 50%, and these trends have since remained stable (Table 102-1).[49] Excessive intake of fat is linked to obesity because of its high energy content and to its property of increasing food palatability. In the past several decades, emphasis on importance of minimizing dietary fat to protect against obesity and coronary artery disease, combined with the increasing availability of processed carbohydrates and sugars, has led to increased consumption of low-fat, high-carbohydrate foods. The associated decline in fat consumption, however, correlated with an increase rather than a decrease in the prevalence of obesity, especially among children, a phenomenon referred to as the "American paradox." A simple explanation of this paradox is that obesity is caused by a basic excess of energy intake over energy expenditure, and switching the type of dietary nutrient consumed without concern about total caloric intake or energy expenditure is wasted effort.[50] The national trends for an increase in total calorie intake combined with a more sedentary lifestyle are the major contributors to the current obesity epidemic (see Chapter 7). Added to these are the increased consumption of refined sugars and corn sweeteners and the dependence on processed food, which contains high concentrations of added sugar and fat.[49,51] Dietary fats consumed in moderation are an important nutrient essential for human health. They supply the body with essential FAs and fat-soluble vitamins and play an important role in regulating satiety and overall energy homeostasis.[52]

TABLE 102-1 U.S. Trends in the Intake of Macronutrients for Children (≥Age 2 yr) and Adults from 1999-2000 and 2007-2008*

Intake	1999-2000	2007-2008
Total energy (Kcal)	2223	2091
Fat (%)	32.4	32.5
Protein (%)	13.7	14.6
Carbohydrates (%)	54.9	53.8

*Intake for each food group is expressed as percent of total caloric intake.
Data are from Centers for Disease Control and Prevention. Trends in intake of energy and macronutrients. 2004; 53:80-2; and from Alpers D. Digestion and absorption of carbohydrates and proteins. In: Johnson L, editor. Physiology of the gastrointestinal tract. 2nd ed. New York: Raven Press; 1987. p 1469.

Dietary fat consists mainly of TGs (90% to 95%) but also of phospholipids (Fig. 102-1), sterols, and fat-soluble vitamins. The major sterols are cholesterol from animal fat and sitosterol from plants, which is not absorbed by the human intestine. Humans absorb 20% to 80% of cholesterol delivered to the intestine by intake (≈300 mg/day) or via the bile (≈1 g/day). In contrast, TG absorption is very efficient, and 95% of a 500-g fat load can be absorbed per day. Chain length of the FAs in TGs influences absorption, with medium-chain FAs being better absorbed than long-chain (LC)FAs. Position of the FA at the 1, 2, or 3 position on the glycerol backbone determines whether it is absorbed free (1 or 3 position) or as a constituent of 2-monoacylglycerol (2-MG). The major FAs of dietary TG are oleate, palmitate, stearate, and linoleate. Animal TGs contain mostly long-chained (>14 carbon chains) saturated FAs (Table 102-2). Polyunsaturated FAs (linoleic and linolenic acids) are derived from phospholipids of vegetable origin, and because they cannot be synthesized de novo, they are considered essential (see Fig. 102-1). Phospholipid ingestion is 2 to 8 g/day, and the most abundant dietary phospholipid is phosphatidyl choline (lecithin), enriched in linoleate and arachidonate. Phospholipids in the duodenal lumen (10 to 22 g/day) exceed intake as a result of contribution from endogenous sources, particularly bile. Commercial hydrogenation of unsaturated FAs raises their melting points, allowing the production of margarines and spreads of variable consistency. In addition to saturation, hydrogenation results in *cis* to *trans* isomerization of double bonds.[53] Because *trans* FAs were linked to risk of cerebrovascular disease[54] New York City and California passed regulations discouraging their use,[55] and the AHA's Nutrition Committee recommended limiting their intake to less than 2 g/day.

Lipids are efficiently absorbed by the small intestine, and only 5% of ingested lipid is excreted in the stool. By

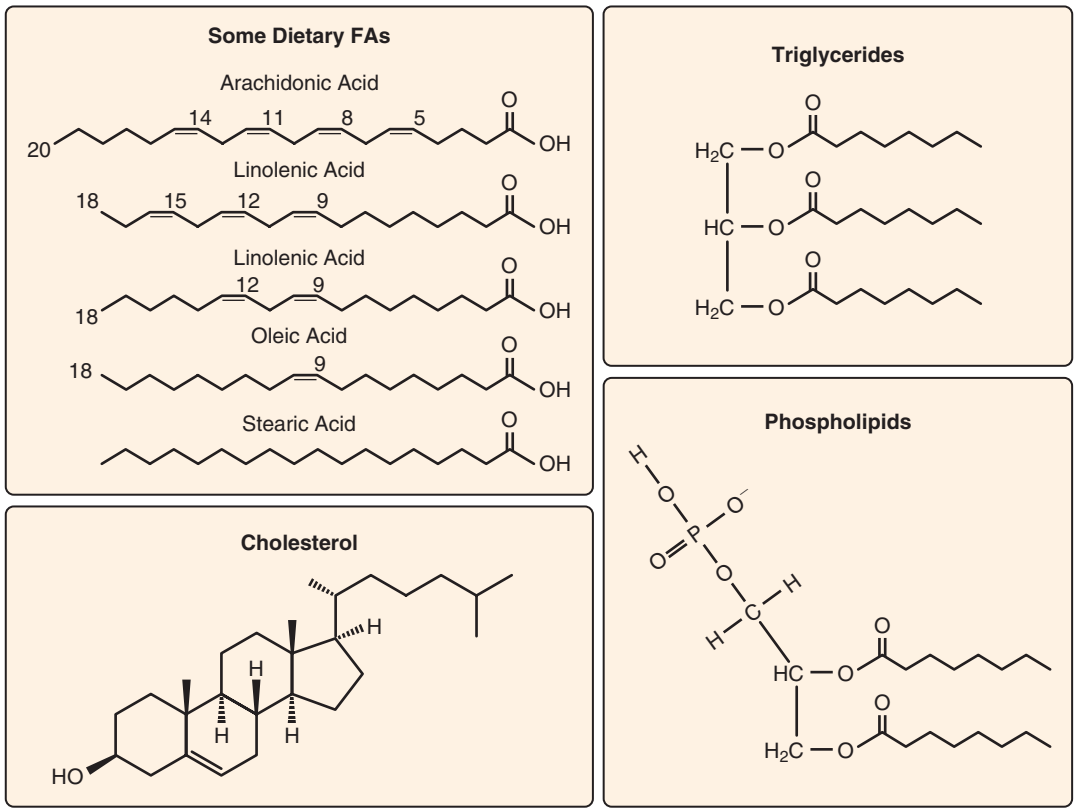

FIGURE 102-1. General molecular structure of fatty acids (FA; representative dietary FAs are shown), TGs, phospholipids, and cholesterol.

TABLE 102-2 Representative Dietary Fatty Acids (FAs), Showing Length of Carbon Chain and Number of Double Bonds

Fatty Acid	Carbon Double Bonds
Saturated FAs	
Butyric	4:0
Caproic	6:0
Lauric	12:0
Myristic	14:0
Palmitic	16:0
Stearic	18:0
Mono-Unsaturated FAs	
Oleic	18:1
Palmitoleic	16:1
Polyunsaturated FAs	
Arachidonic*	20:4
Linoleic*	18:2
Linolenic*	18:3

*Essential fatty acid.

comparison, 10% to 15% and 25% to 35% of dietary fat is excreted by the intestines of neonates and premature infants, respectively. In neonates, this reflect limited capacity for digestion and absorption of FA released from intestinal hydrolysis of TGs.[56] Lipid absorption is regulated by neural and humoral factors that closely coordinate digestion across the different parts of the GI tract. Events that precede food intake, such as seeing, smelling, or thinking of food, induce salivary and gastric secretions via the autonomic nervous system and stimulate pancreatic and biliary secretions via the vagus nerve. These modest secretions are potentiated via humoral and local neural mechanisms when the nutrients are in the mouth and when they reach the upper GI tract.[52,57]

ORAL PERCEPTION OF DIETARY FAT

The orosensory properties of foods are usually perceived through a combination of taste, texture, and olfaction, which are then influenced by cognitive input to modulate the perceived reward value of the ingested food.[58] Individuals differ in their ability to experience the taste of various foods. According to the National Institutes of Health, approximately 25% of Americans are non-tasters, 50% are medium tasters, and 25% are supertasters. Great progress has been recently accomplished in the identification of taste receptors for various sensations such as sweet, salty, and bitter, enhancing our understanding of the interaction between heredity and the environment in determining food preferences and intake patterns. Humans display large variations in the orosensory detection thresholds for dietary fat.[59] Although gustatory detection of carbohydrates and proteins is well documented to involve taste receptors specific for these nutrients, this was not thought to apply to perception of dietary fat. Evidence in rodents and humans, however, now strongly supports involvement of fat taste receptors and of gustatory cues in fat perception[59-61] (Fig. 102-2). Dietary fat is composed mainly of TGs, but the nutrient sensed is LCFA, which has signal transduction capabilities and is generated from TG digestion by

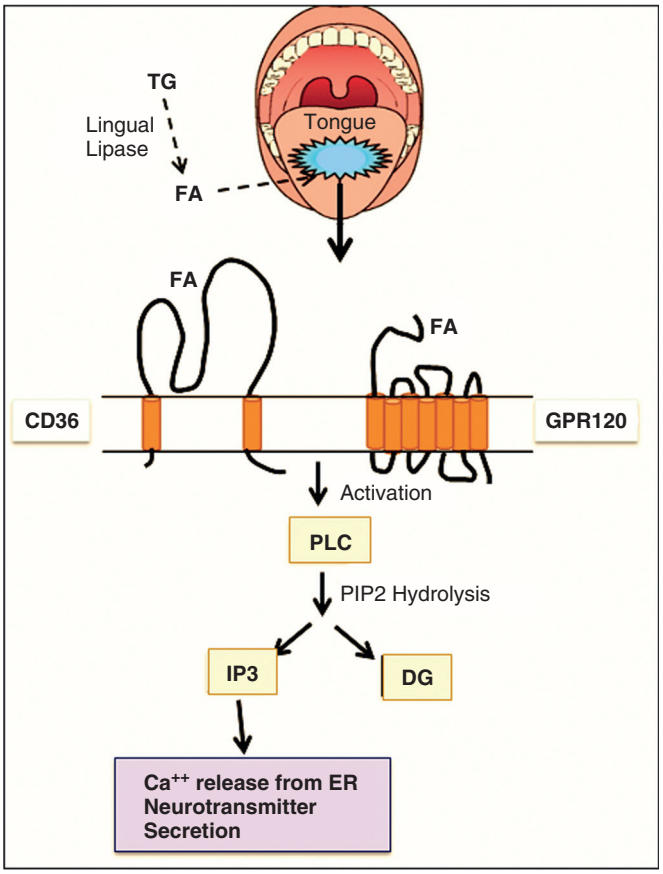

FIGURE 102-2. Oral perception of fat. Accumulating evidence supports gustatory cues in fat perception similar to those for the 5 basic tastes (salty, sour, umami, sweet, bitter). In the case of dietary fat, which is composed mainly of TGs, the nutrient sensed upon exposure of the tongue to fat is long-chain fatty acid (LCFA), which has signal transduction capabilities and is generated from TG digestion by lingual lipase in the mouth. The FA interacts with specific receptors (CD36 and GPR120) expressed on taste bud cells in the circumvalate and fungiform papillae (back and sides of the tongue, respectively) to induce intracellular calcium release from the endoplasmic reticulum. This in turn triggers calcium flux from membrane store-operated calcium channels, leading to neurotransmitter release. The 2 FA receptors identified on taste bud cells in rodents and humans are CD36 and GPR120 (see Table 102-4), and both were shown to impact sensitivity to oral perception of dietary fat. CD36, cluster of differentiation 36; DG, diacylglycerol; GPR120, G protein-coupled receptor 120; IP3, inositol trisphosphate or inositol 1,4,5-trisphosphate; PIP2, phosphatidyl inositol-bisphosphate; PLC, phospholipase C.

lingual lipase. Rodents have robust lingual lipase activity, and its inhibition reduces the spontaneous preference for TG.[62] Humans have low amounts of lingual lipase, but its activity is sufficient to mediate FA generation from TG in the mouth, because its inhibition by orlistat reduces sensitivity to oral perception of triolein but not to oleic acid.[60]

The FAs released by lingual lipase interact on taste bud cells with receptors (see Fig. 102-2) that include CD36[63] and the G protein-coupled receptors (GPRs).[64] CD36 is a heavily glycosylated membrane-spanning protein with high affinity for LCFAs[52]; it is expressed on taste bud cells of rodents, pigs, and humans and was shown to influence fat taste perception and preference in mice[63] and humans.[60,65] CD36 gene deletion in mice abolishes spontaneous preference for FAs in the 2-bottle preference test and the cephalic phase of biliary and pancreatic secretions triggered by the tongue's exposure to FA. The GPRs that function in FA recognition are members of the large family of G-coupled receptors, usually with 7 transmembrane segments.[66] LCFAs are recognized by GPR120 and GPR40, which were shown, using the 2-bottle test, to influence spontaneous preference for fat in rodents.[64] Interaction of the FA with its taste bud cell receptor was shown in the case of CD36 to result in formation of tri-inositol phosphate (IP3), which interacts with its receptor on the endoplasmic reticulum (ER) to release calcium. This in turn induces store-operated membrane calcium flux, which further increases cytosolic calcium and leads to the release of neurotransmitters[63] (see Fig. 102-2). The pathways triggered by FA interaction with the GPR usually involve heterotrimeric G (G_s, G_i, G_q) proteins, resulting in production of cyclic adenosine monophosphate (cAMP) and IP3, as well as activation of MAP kinases and various cellular responses. GPR120[67] and GPR40[68] enhance the response of intracellular calcium to LCFA addition in enteroendocrine cells, resulting in release of intestinal peptides (see later sections). Their effects in taste bud cells might also involve the IP3 pathway for calcium release that is activated by CD36. The increase in intracellular calcium that mediates neurotransmitter release and fat perception also induces the cephalic phase of digestion, characterized by the release of small amounts of bile acids and by an increase in serum TG. Fat-induced cephalic-phase responses also include transient increases of intestinal CCK, PP, PYY, and insulin.[57] GPR120 and CD36 expression was examined in mouse taste buds during the day/night cycle and with dietary manipulations.[69] CD36 expression was down-regulated in the dark period during food intake and associated with a reduction in fat preference.[69] Thus CD36 sensing of dietary lipid might gradually decrease appetite for fat during a meal while GPR120 appears unresponsive to the ingested fat.[69]

The influence of oral fat perception on fat intake remains unclear. In humans, excessive dietary fat intake attenuates the nutrient-sensing response in the oral cavity, which could associate with changes in diet and weight.[70] In humans, common variants in the CD36 gene that influence CD36 protein levels[71] influence sensitivity to fat perception on the tongue[60] and the preference for added fat,[65] but the relationship to fat intake remains unexplored. CD36 variants' association to the BMI was reported in some but not all studies,[72] possibly reflecting interactions with dietary factors. The role of the GPR FA receptors in human fat taste perception remains unknown. GPR120, mRNA, and protein was detected in human taste buds as well as in surrounding epithelial cells, while GPR40 expression was not.[64] A rare non-synonymous variant in the GPR120 gene is associated with obesity.[73] The implications of oral fat taste perception with respect to fat intake, and possibly the etiology of obesity in humans, is an important area for future study.

FAT DIGESTION IN THE STOMACH AND SMALL INTESTINE[74-76]

Oral fat perception prepares the intestine and organism for food arrival and might result in mobilization of an intestinal pool of TG that contributes to early postprandial lipemia.[57] Fat digestion itself, however, begins in the stomach with the action of gastric lipases and continues through nutrient passage in the intestine. These processes are described in the preceding section on An Overview of Gastrointestinal Integration.

Emulsification

The insolubility of fat in water underlies the mechanisms that have evolved to accomplish its digestion and absorption.[83] The digestion products have to be transported across the bulk water phase in the lumen and then across the epithelial cell membrane. Within the cell, the fat is reconstituted into larger molecules, predominantly TG, which requires specialized processing for export from the cell. Despite these complex processes, most ingested fat is absorbed. Dietary fat is mostly TG, and liberation of FA from the glycerol backbone of TG (lipolysis) is achieved by lipases acting at the surface of emulsified droplets (Fig. 102-3). Human gastric lipase, a 379–amino acid protein that does not share homology with pancreatic lipase, contributes 20% to 30% of intraluminal lipid digestion and does not hydrolyze phospholipids or cholesteryl esters.

The gastric milling of food produces an unstable emulsion, but formation of a stable emulsion in the duodenum is important for the close apposition of lipase and TG needed for efficient lipolysis (see Fig. 102-3). To stabilize the emulsion, the fat droplets are coated with dietary phospholipid. The ratio of ingested phospholipid to TG is about 1:30, and more is added in the duodenum from bile. Emulsification is enhanced

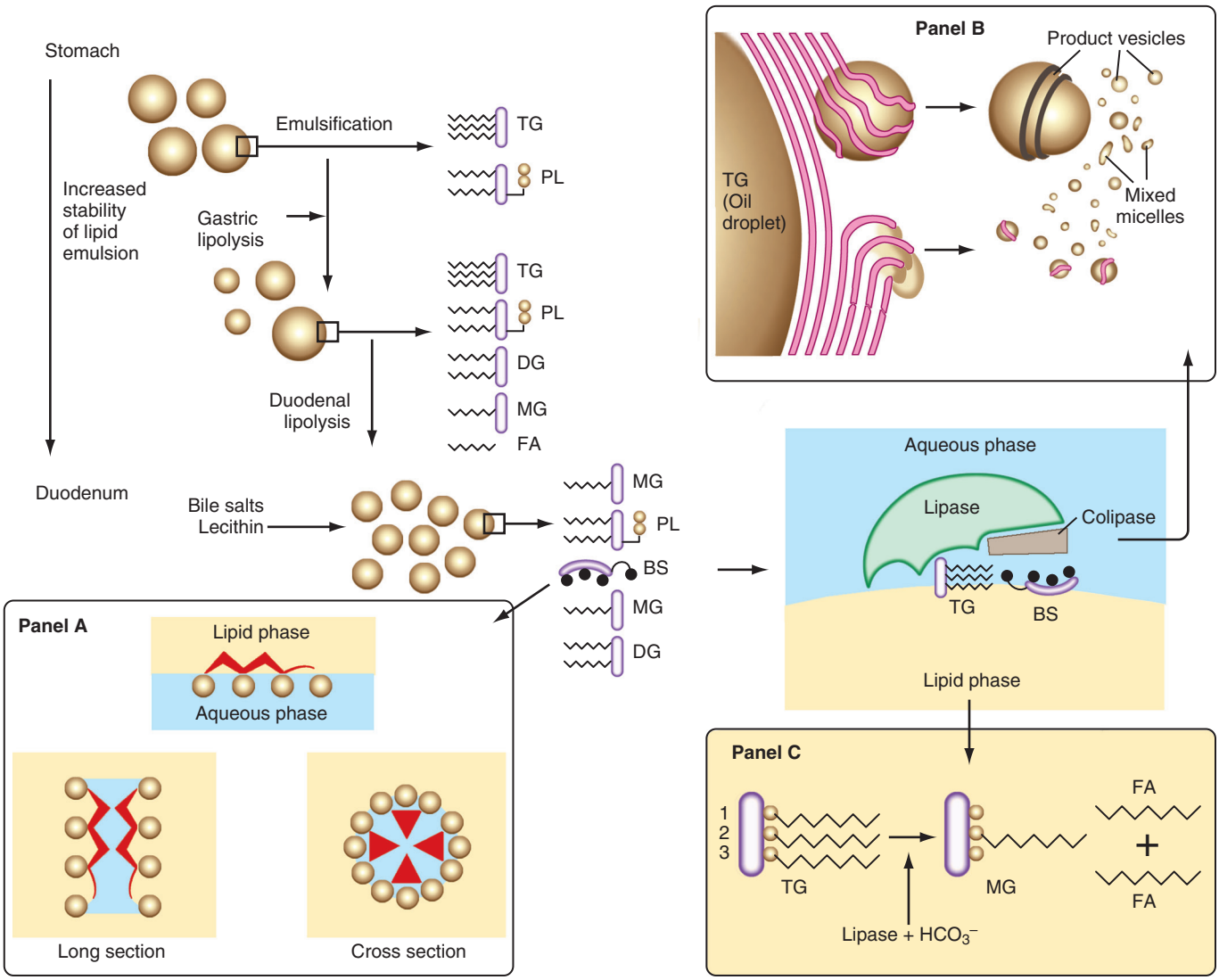

FIGURE 102-3. Steps in lipolysis of dietary fat. The initial step in lipolysis is to increase stability of the fatty emulsion. Gastric lipase acts on TGs to yield fatty acids (FAs) and diglyceride (diglyceride enhances emulsification). This step is enhanced in the duodenum by bile salts and phospholipid (lecithin), which enable lipase, in the presence of co-lipase, to act at the surface of the emulsion droplet to bring it close to the TG molecule, whereupon monoglyceride and FAs are released. Lipolysis in the duodenum yields FAs (from the 1 and 3 positions) and 2-monoglyceride and occurs in a rapid and efficient manner at nearly neutral pH. *Panel A,* Diagrammatic representations of bile salt molecules *(top)* oriented at an oil-water interface with its hydrophobic sterolic backbone in the oil phase, and its hydrophilic hydroxyl and either taurine or glycine conjugates in the aqueous phase. At above their critical micellar concentration, bile salts aggregate as simple micelles in water, with their hydrophilic groups facing into the aqueous phase *(bottom 2 diagrams)*. *Panel B,* Dispersion of lipolytic products into lamellae at the surface of the oil phase, and from there into vesicles and micelles, is shown. *Panel C,* FAs and monoglycerides released from TGs by pancreatic lipase, assisted by co-lipase, transfer to bile salt to form mixed micelles. BS, bile salt; DG, diglyceride; MG, monoglyceride; PL, phospholipid.

by the FA liberated by intragastric lipolysis and by bile salts. The mixed emulsion formed in the duodenum consists predominantly of TGs together with cholesteryl esters and some diglycerides and is coated by phospholipids, partially ionized FAs, monoglycerides, and bile salts (see Fig. 102-3).

Lipases

Pancreatic TG lipase efficiently digests the stabilized lipid emulsion (see Fig. 102-3).[81] The lipolytic domain of the enzyme is hydrophobic, buried within the protein,[84] and is revealed upon close apposition to the lipid surface, a process that requires assistance of colipase, which is secreted by the pancreas in a 1:1 molar ratio with the lipase. Colipase attaches to the TG ester bond and binds the lipase (see Fig. 102-3). Colipase is secreted by the pancreas as pro-colipase that is activated in the small intestinal lumen by trypsin cleavage of an N-terminus pentapeptide (enterostatin), which is a fat ingestion-specific satiety signal.[85] The importance of colipase is illustrated by the finding that an arginine-to-cysteine polymorphism at position 92, which results in protein misfolding, associates with an increased risk of type 2 diabetes.[86] Phospholipase A2 digestion of the emulsion phospholipid coat, which requires calcium for activation, exposes the TG core and enhances colipase-dependent lipase anchoring. Bile salts further assist TG lipolysis by facilitating removal of lipolytic products (see Fig. 102-3). In the absence of colipase, bile salts on the surface of the emulsion inhibit lipase activity.

Pancreatic lipase is most active at neutral pH (Table 102-3), and secretion of bicarbonate by the pancreas and biliary tree is critical to neutralize gastric acid. In the jejunum, luminal pH is around 6; bile salts lower the optimal pH for lipase activity, which efficiently digests TG and cholesteryl esters.[81] Glycine-conjugated bile salts precipitate below pH 5, and FAs are in their protonated form below pH 6, with limited solubility in bile salt micelles. Thus, under conditions where intraluminal pH becomes more acidic, as in the Zollinger-Ellison syndrome, pancreatic lipase is inactive, bile acids precipitate, and FA partitioning in micelles is reduced, resulting in steatorrhea.

In addition to lipase and colipase, pancreatic acini synthesize the homologous pancreatic lipase-related proteins (PLRP-1 and PLRP-2). PLRP-1 has no known activity. PLRP-2 hydrolyzes TG and also phospholipids and galactolipids, 2 fats not hydrolyzed by pancreatic lipase. PLRP-2 mRNA appears before birth, whereas pancreatic lipase mRNA appears at the suckling-weaning transition, suggesting the importance of PLRP-2 for digesting breast-milk fat.[87]

TABLE 102-3 Characteristics of Lipase Activity

Source of Lipase	Optimal pH	Site of Lipase Activity	Other
Milk	7.0	α-1, -2, and -3 ester bonds	Stimulated by bile salts
Stomach	4.0-6.0	α-1 ester bond	Inhibited by pancreatic proteolysis
Pancreas	7.0	α-1 and -3 ester bonds	—

Modified from Farrell J. Digestion and absorption of nutrients and vitamins. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia: Saunders; 2010. p 1699.

Micelles

The transport of lipolytic products depends in part on formation of bile salt micelles (see Fig. 102-3). The concentration of bile salts in bile is approximately 35 mM and is diluted in the duodenum to 10 to 20 mM, which is above the critical micellar concentration (CMC). Mixed micelle formation depends on pH, presence or absence of lipids, and the types of bile salts present (see Chapter 64).[88] Bile salts are amphipathic, with water- and lipid-soluble portions, and act as emulsifying agents at an oil-water interface. Micelles are formed when bile salt levels exceed CMC and aggregate in disk-like particles, with their hydrophobic sterol backbones oriented toward each other and their hydrophilic groups facing the aqueous phase. Bile salt micelles can dissolve FA, monoglycerides, and cholesterol, but not TG.[89] The lipid is surrounded in the micelle by bile salts oriented with their hydrophilic groups facing outward. Mixed micelles are about 50 to 80 nm in diameter and, unlike emulsion droplets, are too small to scatter light; hence, micellar solutions are clear. The phospholipid secreted in bile enlarges the mixed micelles, enhancing capacity for fat dissolution.

Lipid-containing particles other than bile salt micelles might participate in mucosal transfer of lipid. As the emulsion shrinks during lipolysis, multilamellar or unilamellar vesicular structures form at its surface and can be seen under the electron microscope budding off occasionally close to the BBM[90] to possibly provide a physical phase of lipid transfer that is independent of bile salt micelles. This could explain how almost 50% of dietary TG can be absorbed in the absence of bile salts. These vesicles usually rapidly release their lipid to the micelles when adequate concentrations of bile salts are present, and micelles, normally much more common than lipid vesicles, are the major route for lipid traffic.

Unstirred Water Layer

An unstirred water layer (≈40 μm deep in humans) is present on the surface of the intestinal epithelium and rate-limits uptake of long-chain but not short- or medium-chain FAs. The microclimate next to the epithelium is slightly acidic (pH between 5 and 6), owing to activity of a BBM sodium-hydrogen (Na^+/H^+) exchanger. This acidic microclimate decreases micellar FA solubility to promote FA release close to the mucosa and increases the undissociated, protonated FA that can diffuse across the cell bilayer. The FA partitioning model proposes that these conditions yield the high FA concentration necessary for diffusion across the mucosal membrane.[91] Strong evidence, however, now supports a protein-facilitated component of FA uptake in enterocytes (see next section).

A surfactant-like material present close to the BBM is secreted by enterocytes and contains phosphatidylcholine and alkaline phosphatase. Alkaline phosphatase influences dietary fat absorption but its role in this process is unclear. Deletion of alkaline phosphatase in mice increases lipid absorption and accelerates weight gain.[92] It has been reported that CD36 (see next section) is dephosphorylated by alkaline phosphatase, which reduces fat absorption.[93]

Phosphatidylcholine, the major dietary phospholipid (see Fig. 102-1), is hydrolyzed by pancreatic phospholipase A_2 (PLA_2) to yield FA from the 2-position and lysophosphatidylcholine. Pancreatic PLA_2 is activated in the small intestine by tryptic cleavage of an N-terminal heptapeptide and requires a 2:1 bile salt–to-phosphatidylcholine molar ratio for optimal activity. The bulk of intestinal PLA_2 is derived from the pancreas, but there is some contribution from the intestinal mucosa, where PLA_2 is concentrated in the brush border.[94]

The products of phospholipid and cholesterol hydrolysis follow the same route to the BBM as the FAs and monoglycerides from dietary TG. FAs and monoglycerides increase micelle cholesterol solubility, enhancing its absorption. Unabsorbed LCFAs that enter the colon undergo bacterial modification, principally hydroxylation. Normally, no undigested TG is found in the stool, and the fecal fat estimate of 7 g/day reflects the total excretion of saponification products (i.e., FA, mainly arising from bacteria and membrane phospholipid).

BRUSH BORDER TRANSPORT OF FATTY ACIDS

The hydrolysis products of TGs and cholesteryl esters, FAs, 2-monoglycerides, and free cholesterol, are taken up across the enterocyte BBM, and early studies argued against cellular uptake of whole micelles.[95] Although enterocyte uptake of digestion products was thought to occur by passive diffusion down a concentration gradient, recent work strongly suggests existence of a regulated protein-facilitated component of FA uptake.[52]

Small intestinal cells absorb LCFAs by passive diffusion[96] and protein-facilitated transfer.[52] Passive "flip-flop" of protonated FA across the BBM is favored by the acidic microclimate next to the mucosa. Transfer is proposed to be coordinated with intracellular FA trapping through binding to abundant cytosolic FA binding proteins and/or by conversion to the membrane-impermeable acyl-CoA derivatives.[97] However, a probable scenario for entry of LCFAs across the BBM is endocytosis within vesicles formed from lipid rafts that contain caveolin-1 and *CD36* (Fig. 102-4). Signal transduction mediated by FA interaction with *CD36* might promote formation and endocytosis of the transport vesicles.[52,98]

The protein facilitated component of FA uptake by isolated proximal enterocytes is evident at low nanomolar concentrations of monomeric FA[99] similar to those measured in other cell types. In the intestinal lumen, the FA released from TG digestion is incorporated into bile salt micelles that, like serum albumin, can solubilize millimolar FA concentrations. The FA dissociated from the micelle is the species important for cellular uptake,[95] and its concentration is estimated to be in the low micromolar range[100] compared with the nanomolar range of albumin-dissociated FA in the circulation. Enterocyte FA uptake is a saturable function of the FA monomer, and the cellular entry site (i.e., apical or basolateral) determines metabolic processing of the FA and monoacylglycerol.[101] These observations support a role for apical membrane proteins in FA transfer and metabolic targeting. Three apical membrane proteins, (1) the scavenger receptor *CD36*[102]; (2) FATP4, a member of the very long-chain acyl-CoA synthetases, also known as *fatty acid transport proteins* (FATPs)[103]; and (3) caveolin-1, a protein constituent of membrane caveolae, will be discussed.

CD36

The role of *CD36*, a platelet membrane protein receptor for thrombospondin-1, in lipid uptake was uncovered in 1993 when the protein was identified as important for uptake of LCFAs[104] and oxidized low-density lipoproteins (oxLDL).[105] *CD36* (88-kd, 472 amino acids) is a heavily glycosylated transmembrane protein (Fig. 102-5) with broad ligand specificity[106,107]; it is abundant in tissues such as heart, skeletal muscle, adipose tissue, immune cells, and the intestine.[104] Lipid ligands of *CD36* (LCFAs, oxLDLs, oxidized phospholipids) bind within a hydrophobic loop in the amino terminal half of the extracellular domain. The binding includes hydrophobic interaction that involves the alkyl chain as well as hydrostatic interactions with CD36 lysine 164.[107,108] The protein is subject to post-translational modifications, such as glycosylation, phosphorylation, palmitoylation, ubiquitination (attachment by specific ligases of ubiquitin tags that target the protein to degradation), and acetylation (see Fig. 102-5), and these modifications play a role in CD36 recruitment to the membrane and in its FA uptake and signaling functions. Studies in CD36-deficient mice and humans documented a defect in tissue FA uptake and abnormalities of FA metabolism. Polymorphisms in the *CD36* gene were linked to alterations in plasma FA, cholesterol, and TG levels and to metabolic syndrome susceptibility.[72] For recent reviews on the role of CD36 in FA transport and metabolic phenotypes, refer to references.[52,72,109,110]

CD36 is abundantly expressed in the digestive tract, where it plays a number of roles related to fat perception, regulation of food intake, and fat absorption. In the small intestine, *CD36* is most abundant in the most proximal third of the intestine, where it is detected on the BBMs of duodenal and jejunal villi.[111] *CD36* epithelial cell immunostaining is low in the ileum and colon of humans. This expression pattern is consistent with a function in lipid absorption. The molecular nature of this function is incompletely understood, but it is now established that *CD36* directs FA absorbed in the proximal intestine to chylomicron formation and export via the lymph (see later section). Primary enterocytes isolated from the proximal but not distal intestine of *CD36* null mice show a 50% reduction in FA and cholesterol uptake compared with those from wild-type mice. Intragastric administration of triolein also results in reduced oleic acid enrichment of mucosal lipids in the proximal intestine of *CD36* null mice and in more lipid reaching the distal small intestine. Oleic acid uptake by the mouse duodenum for formation of oleoylethanolamide (OEA), which plays a role in modulating satiety in response to lipid ingestion, is suppressed by CD36 deficiency.[112] Thus *CD36* appears to function in high-affinity (Km in the low nM) FA uptake in proximal enterocytes.[113] CD36 contribution to net intestinal FA absorption, however, appears small. It will be rapidly saturated at luminal FA levels, functioning only in early digestion stages. There is also evidence that FAs down-regulate levels of the CD36 protein by promoting its ubiquitination, and this regulation, which occurs in enterocytes, would tend to minimize CD36 contribution to absorption as digestion progresses. Furthermore, the proximal intestinal defect in FA uptake is compensated for by non-CD36-mediated FA uptake in distal segments.[52]

CD36 deficiency is rare in Caucasians but is relatively common (≈6%) in persons of Asian and African descent and associates with abnormalities of plasma lipids.[72] The abnormal plasma lipids in humans with *CD36* deficiency or with single nucleotide polymorphisms (SNPs) in the *CD36* gene reflect, in part, abnormal peripheral clearance of plasma FAs; impaired tissue FA uptake has been documented in humans with *CD36* deficiency. Contribution of defective lipid processing by the small intestine to the lipid abnormalities, however, is suggested by findings of postprandial lipemia and high *apoB*-48 levels in *CD36*-deficient subjects.[114,115]

Fatty Acid Transport Protein 4 (FATP4)

Among the candidate intestinal FA transporters, FATP4 is especially appealing by virtue of its high expression in mammalian villus enterocytes and because of its endogenous acyl-CoA synthetase (ACS) activity. These properties would provide FATP4 with the capacity to function not only in FA transport but also in the process of metabolic trapping of FA

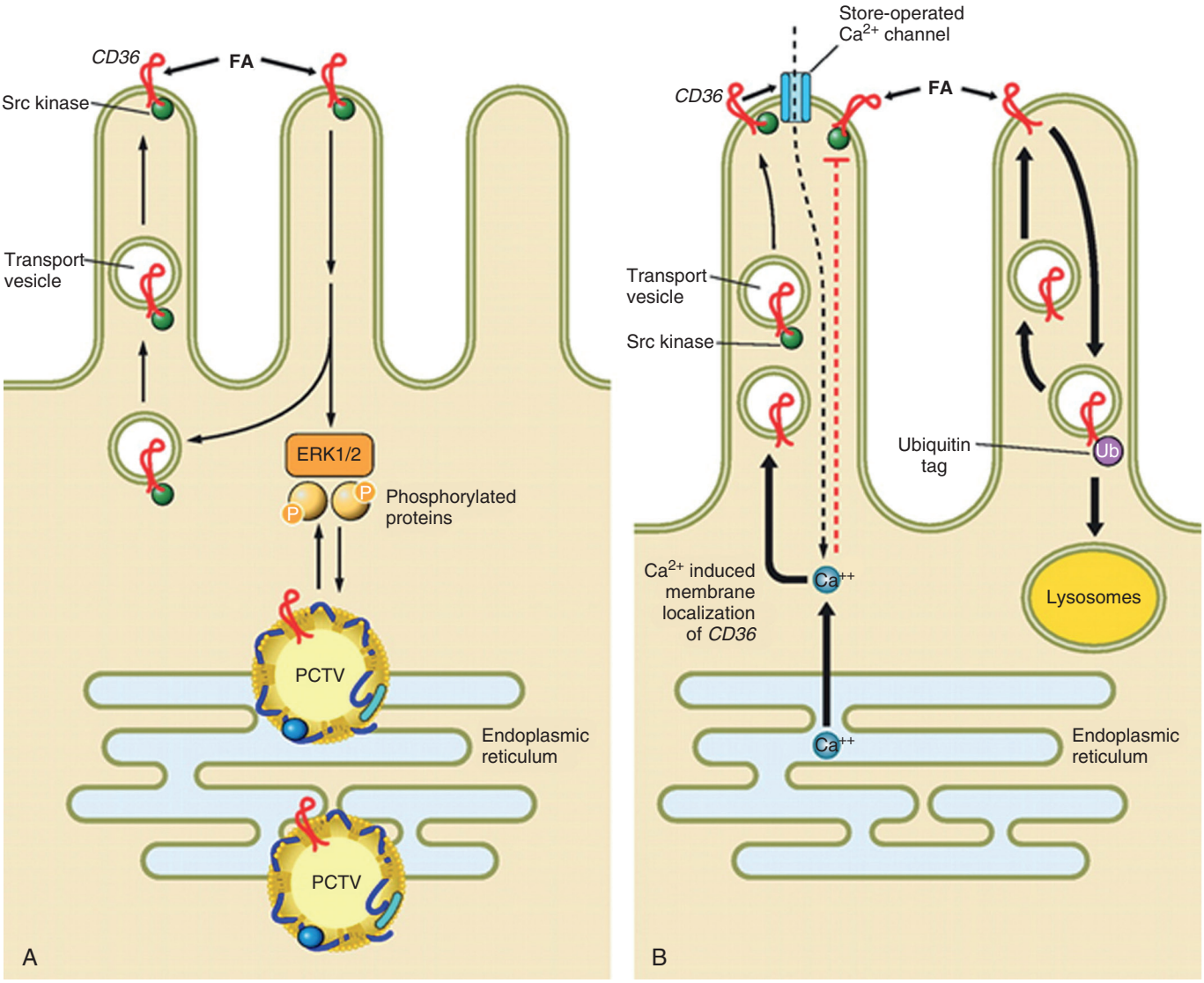

FIGURE 102-4. Working model showing the molecular steps that may be involved in how intestinal *CD36* facilitates fatty acid (FA) uptake and chylomicron formation in the small intestine. *A,* CD36 is highly expressed on the apical side of enterocytes of the proximal intestine, where it interacts with FA released from digestion of dietary TG. CD36 facilitates the uptake of FA, probably by internalizing the FA within vesicles derived from membrane lipid rafts where the protein localizes. CD36-mediated uptake likely occurs during the early phase of digestion when FA concentrations are relatively low and is saturated as digestion proceeds and FA levels increase. CD36-mediated FA uptake, however, associates with intracellular signaling to promote events that facilitate chylomicron assembly. CD36 signaling is initiated in most cases via the sarcoma (Src) kinases that associate with the C-terminus of CD36 *(green circle)* and downstream via extracellular regulated kinase (ERK1/2). This signaling pathway may be important for phosphorylating proteins required to coordinate endoplasmic reticulum (ER) processing of prechylomicron vesicles (PCTV). CD36 has also been identified in the protein complex required for formation of PCTV. *B,* CD36 signaling may be mediated by a rise in intracellular calcium via inositol triphosphate (IP3)-induced release of ER calcium (see Fig. 102-3). ER calcium release promotes membrane CD36 localization and also induces calcium influx via store-operated calcium channels. A sustained increase in intracellular calcium could influence multiple events related to lipid processing or secretion. Panel *B* also illustrates the concept that CD36 is down-regulated by FA that promote its ubiquitination (attachment by specific ligases of ubiquitin tags that target the protein to degradation) on its carboxyl terminus *(circle with Ub)*. This feedback loop may work to reduce CD36 function in the presence of excess FA supply. Inside enterocytes, a FA-induced decrease in CD36 associates with reduced activation of ERK1/2, which may serve to up-regulate an abundance of microsomal TG transfer protein (*MTTP*), initiating chylomicron assembly. *(Reproduced from Abumrad NA, Davidson NO. Role of the gut in in lipid homeostasis. Physiol Rev 2012; 92:1061-85.)*

through conversion to Co-A derivatives.[116] Unlike native LCFAs, which are freely diffusible, fatty acyl-CoA products are hydrophilic and undergo rapid metabolic conversion into various lipids (di- and TGs phospholipids, cholesteryl ester). Careful examination showed FATP4 to localize in the ER and in subapical membranes, so its participation in FA uptake would be primarily mediated by its ACS activity, trapping the FA via acyl-CoA generation.[117] Deletion of FATP4 led either to embryonic lethality or perinatal death, mainly from skin abnormalities that restricted breathing and caused severe

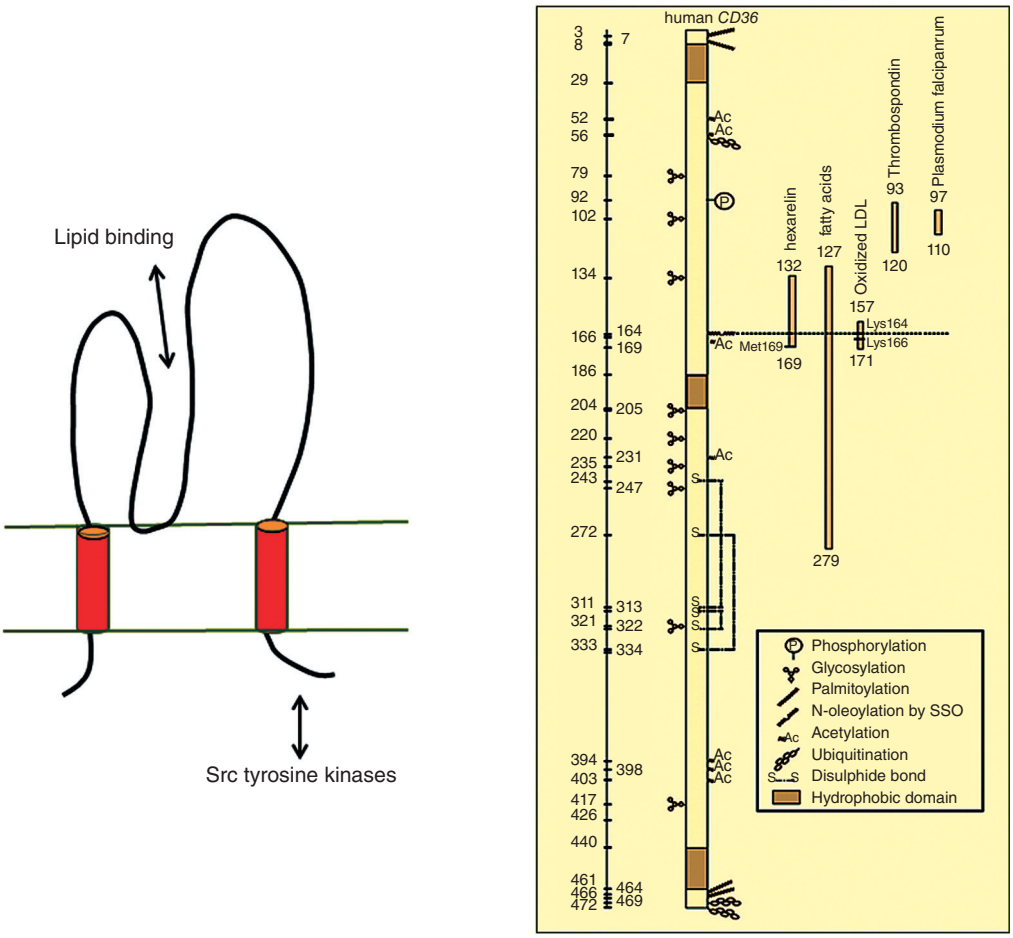

FIGURE 102-5. Schematic representation of CD36 structure, its binding domains, and post-translational modifications. CD36 has 2 short intracellular domains at both termini, 2 transmembrane segments, and a large extracellular domain with a hydrophobic sequence where lipid ligands bind. The C-terminus can associate with Src tyrosine kinases, which usually initiate most of CD36-mediated signal transduction. Post-translational modifications of the protein *(right panel)* include glycosylation, palmitoylation, ubiquitination, phosphorylation, and acetylation. Glycosylation has been shown to be important for CD36 membrane recruitment and is regulated by GLP-2. This regulation was proposed to mediate the effect of GLP-2 to enhance chylomicron production.[77] Dephosphorylation of CD36 accomplished by alkaline phosphatase is thought to reduce the uptake of fatty acids (FAs), and deletion of alkaline phosphatase enhances fat absorption.[93] Both N- and C-termini contain 2 palmitoylation sites that localize CD36 to membrane lipid rafts, which are important for FA uptake.[120] Binding sequences for CD36 ligands are aligned to the backbone of CD36, and the FA-binding site K164 is highlighted with a dotted line (for details, see Ref 107).

dehydration. Rescue of the perinatal lethality was accomplished by transgenic FATP4 expression in keratinocytes in the absence of small intestine FATP4 expression.[118] No detectable effect of intestinal FATP4 deletion on intestinal fat (cholesterol or TG) absorption and no protection from high fat diet–induced weight gain were observed in the transgenic mice. Thus FATP4 appears dispensable for intestinal FA uptake, and its role in mucosal lipid transport remains to be elucidated.

Caveolins and Lipid Rafts

Lipid rafts are membrane domains enriched in cholesterol and sphingomyelin that contribute to the lateral compartmentalization of surface proteins; they function as organizational centers in signal transduction and in the internalization of ligands and receptors. Caveolins 1-3 are proteins that associate with lipid rafts to form smooth invaginations of the plasma membrane or caveolae. Caveolae endocytosis has been implicated in cholesterol transport and is proposed to traffic cholesterol between the plasma membrane and late endosomes and lysosomes.[119] Lipid rafts have been suggested to function in transport of LCFAs by adipocytes.[120] Caveolin-1 was also shown to influence FA uptake into cells.[121] Mice deficient in caveolin-1 are lean and protected from high fat diet-induced adiposity.[122] It has been suggested that caveolins might influence FA uptake by modulating CD36 localization to lipid rafts,[123] but CD36-independent effects of caveolin on FA uptake can be observed.[121] In the intestine, caveolin-1 is expressed on enterocyte BBMs, and the apically absorbed FA appears to be internalized by enterocytes in detergent-resistant and caveolin-1–containing vesicles that also contain alkaline phosphatase and CD36. In cell lysates, alkaline phosphatase, CD36, and caveolin-1 co-immunoprecipitate, consistent with functional interaction. In agreement with the in vitro data, caveolin-1 knockout mice displayed impaired FA absorption; more FA was recovered in the cecal contents of these mice.[98] In addition, these mice display metabolic inflexibility and reduced ability to perform the fuel switching necessary during fasting/feeding transitions,[124] a phenotype shared by CD36

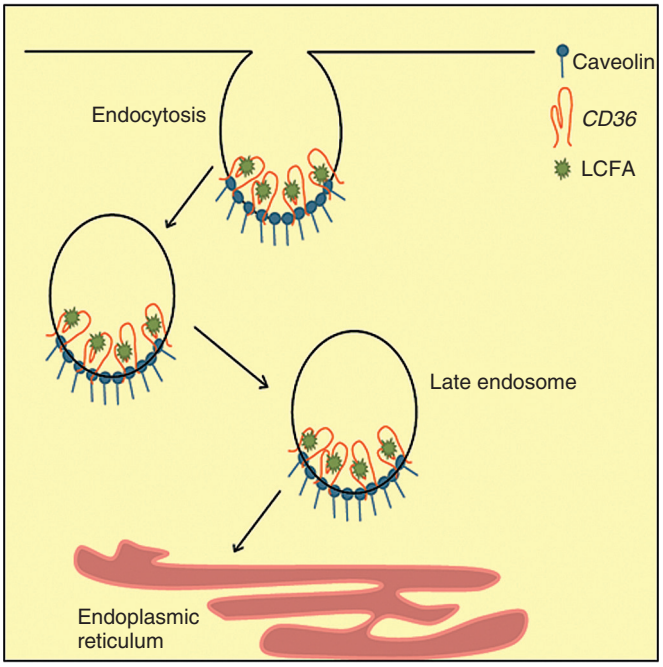

FIGURE 102-6. Role of caveolin-1 in fatty acid (FA) uptake by enterocytes. Lipid rafts are plasma membrane domains that function as organizational centers in internalization of ligands and receptors. Caveolins are proteins that associate with lipid rafts and form smooth invaginations of plasma membrane called *caveolae*. Endocytosis of caveolae has been proposed to traffic nutrients (e.g., cholesterol between the plasma membrane and late endosomes/lysosomes). Lipid rafts have also been suggested to function in transport of long-chain FAs (LCFAs), and caveolin-1 was shown to bind LCFA and influence their uptake into cells. In the intestine, caveolin-1 is expressed on enterocyte brush border membranes, and the apically absorbed FA appears to be internalized by enterocytes in detergent-resistant and caveolin 1–containing vesicles that also contain CD36 (and alkaline phosphatase, not shown). Co-immunoprecipitation of caveolin-1, CD36, and alkaline phosphatase is consistent with potentially functional interactions between the 3 proteins.[98]

null mice.[125] A simplified diagram in Figure 102-6 illustrates the potential role of caveolin-1 and CD36 in FA internalization by enterocytes.

Monoacylglycerol Uptake

Digestion of dietary TG within the intestinal lumen yields 2-MG together with unesterified FA. The few studies that examined 2-MG transport into Caco-2 cells as a model of enterocytes showed 2-MG uptake to be a saturable function of 2-MG concentration and to exhibit sensitivity to trypsin digestion, implying facilitation by a membrane protein.[100] 2-MG inhibited cellular uptake of LCFAs, but triolein (glyceryltrioleate), glycerol, diacylglycerol, or mono-octanoate had no effect, suggesting that FA and 2-MG transport may be coordinated to optimize intracellular TG resynthesis. The metabolic fate of 2-MG in enterocytes, like that of FA, depends on the site of cellular entry.[126] The ratio of TG to phospholipid (TG:PL) formed from 2-MG was 10-fold higher for apical compared with basolateral delivery, findings that were qualitatively similar to those with FA. The role of the cytosolic FA binding protein L-FABP in binding and intracellular targeting of 2-MG in enterocytes helps explain some of the above observations (see later under FABP); however, more studies are needed to identify the apical proteins that facilitate 2-MG uptake and how uptake might influence cellular processing.

BRUSH BORDER TRANSPORT OF CHOLESTEROL

Cholesterol is an essential component of mammalian cell membranes and plays a role in the biosynthesis of bile acids, vitamin D, and steroid hormones. Body cholesterol homeostasis is regulated by endogenous synthesis, intestinal absorption, and fecal excretion. In addition to dietary cholesterol, bile and the sloughing of intestinal epithelial cells contribute to luminal cholesterol levels. Absorption of cholesterol (≈50% of intake) varies among individuals and takes place mostly in the duodenum and proximal jejunum. Digestion of dietary cholesteryl esters and solubilization of free cholesterol in bile/phospholipid micelles are followed by enterocyte uptake of free cholesterol via endocytosis into lipid raft vesicles that target the endocytic recycling compartment (ERC) as discussed later. Several apical proteins have been implicated in enterocyte cholesterol transport (Fig. 102-7), the major player being the Niemann-Pick C1-like 1 (NPC1L1) protein. *CD36* might contribute to the process, while the ATP-binding cassette transporter pair ABCG5/8 removes the excess cholesterol and plant sterols that are not processed by the esterifying enzyme acyl-cholesterol acyltransferase ACAT2. On the enterocyte basolateral side, ABCA1 removes unesterified cholesterol by effluxing it to HDL. The scavenger receptor class B type I (SR-B1) is present on both apical and basolateral membranes, but its function in cholesterol homeostasis by the small intestine remains elusive.

Niemann-Pick C1-Like 1 (NPC1L1)

NPC1L1 plays a crucial role in the absorption of dietary cholesterol, as well as in reabsorption of bile acid cholesterol (see Fig. 102-7). NPC1L1 is a homolog of NPC1, which is the defective gene (≈95% of cases) in Niemann-Pick type C1 disease, a lysosomal storage disease characterized by abnormal accumulation of unesterified cholesterol.[127] NPC1 is a large transmembrane protein that binds cholesterol and oxysterols. NPC1 functions together with NPC2, a cytosolic cholesterol-binding protein[128] that extracts cholesterol from inner membranes of late endosomes, transferring it to NPC1 for export out of lysosomes.[128,129]

Like NPC1, the NPC1L1 protein has 13 transmembrane regions (5 of which constitute the sterol-sensing domain), 3 extracellular luminal loops, 6 short cytoplasmic loops, and a C-terminal cytoplasmic tail.[130] In humans, NPC1L1 is found on the apical membrane of enterocytes and also on hepatocytes, ovary, lung, and muscle cells, whereas in rodents, it is primarily expressed on enterocytes. NPC1L1 cycles between the enterocyte plasma membrane and endocytic compartments[131] (Fig. 102-8). In membranes, NPC1L1 forms cholesterol-rich microdomains with the lipid raft proteins flotillin 1 and 2 that facilitate cholesterol internalization to the ERC.[132] Depletion of ERC cholesterol initiates NPC1L1 recruitment to the plasma membrane to stimulate cholesterol uptake.[52] Ezetimibe reduces cholesterol absorption by blocking internalization of the NPC1L1 cholesterol complex.[133] Poor absorption of plant sterols (<5%) primarily reflects NPC1L1 specificity.[110]

ATP-Binding Cassette (ABC) Transporter G5/8

Beta-sitosterolemia is a condition characterized by hypercholesterolemia, xanthomatosis, and premature atherosclerosis.

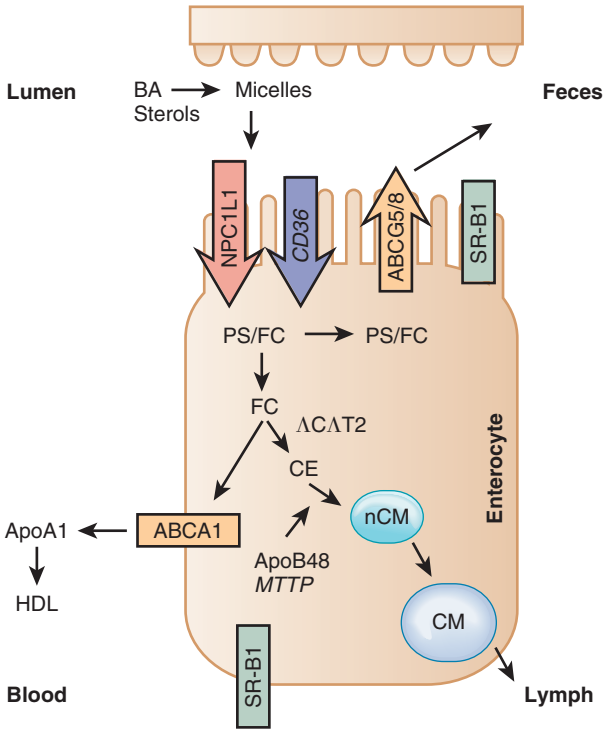

FIGURE 102-7. Intestinal absorption and secretion of cholesterol and plant sterols by enterocytes. Dietary sterols including free cholesterol (FC) and free plant sterols (PS) are mixed with bile acids to form micelles. FC and PS solubilized in mixed micelles are transported across the brush border membrane and into enterocytes mostly via a NPC1L1-dependent mechanism. CD36 also contributes to cholesterol uptake, but its role is unclear. FC is delivered to the endoplasmic reticulum for esterification with fatty acids to cholesteryl esters (CE) by ACAT2. Esterified cholesterol is packaged into nascent chylomicron particles that are further processed in the Golgi apparatus before secretion into lymph. FC that escapes ACAT2 esterification is directly transported to apoA-1 in nascent HDL through ABCA1 located at the basolateral membrane. FC and PS, which are poorly processed by ACAT2, are secreted back to the intestinal lumen by the apical transporter pair ABCG5/G8. ABCA1, ATP-binding cassette transporter A1; ABCG5/8, ATP-binding cassette transporters G5 and G8, which work as heterodimer; ACAT2, acyl cholesterol acyltransferase 2; apoA-1, apoprotein A-1; *apoB*-48, apoprotein B-48; BA, bile acids; CM, chylomicron; HDL, high-density lipoproteins; *MTTP*, microsomal TG transfer protein; nCM, nascent chylomicrons; NPC1L1, Neiman-Pick 1-Like protein 1; SR-B1, scavenger receptor B1.

The condition reflects increased absorption of dietary plant sterols (20% to 30%, compared with 5% in healthy subjects)[134] because of mutations in 2 genes that encode 65-kd protein members of the ABC transporter family: ABCG5 (sterolin-1) and ABCG8 (sterolin-2). ABCG5/G8 proteins (see Fig. 102-7) work together as an obligate heterodimer on the apical membrane of enterocytes, where they function in efflux of cholesterol back into the lumen. In addition, the transporter pair secretes back into the intestinal lumen the sitosterols and sterols other than cholesterol that are poor substrates for esterification by ACAT2. Defects in ABCG5/G8 decreases biliary excretion of cholesterol and plant sterols, leading to 50- to 200-fold increases in plasma sitosterol,[135,136] while intestinal ABCG5/ABCG8 overexpression reduces cholesterol absorption by increasing its fecal excretion.[135]

ATP-Binding Cassette (ABC) Transporter 1

High-density lipoproteins (HDLs) mediate transport of cholesterol from various tissues to the liver for biliary excretion and elimination from the body; this process is referred to as *reverse cholesterol transport* (RCT). The ABC1 transporter transfers cellular cholesterol and phospholipids to apoA-1 in HDL,[137] mediating the rate-limiting step in RCT (see Fig. 102-7). Mutations in ABCA1 result in Tangier disease, characterized by low HDL.[138] ABCA1 promotes cholesterol efflux across the enterocyte basolateral membrane into the blood, so its role in cholesterol absorption is indirect. Absorption in mice lacking intestinal ABCA1 is unchanged.[139]

CD36 and Scavenger Receptor Class B Type I (SR-B1)

The role of CD36 in cholesterol uptake (see Fig. 102-7) was demonstrated using primary enterocytes from the proximal intestine of wild-type (WT) and *CD36* null mice.[52] In addition, in vivo studies demonstrated a 50% reduction in cholesterol output into the lymph of *CD36* null compared with WT mice. Similar to NPC1L1, *CD36* appears to function in cholesterol absorption for chylomicron assembly, but cholesterol absorption measured by 24-hour fecal excretion is unaltered in *CD36* null mice and in mice null for both SR-BI and *CD36*.[140] Thus, *CD36* does not have a primary role in cholesterol absorption but could optimize absorption targeted to chylomicrons along with NPC1L1.

SR-B1 (84 kd), a member of the class B scavenger receptor family, is expressed in the liver, intestine, adrenal gland, testis, and ovary[141] and plays an important role in RCT from peripheral tissues to the liver for input into bile. In the intestine, SR-B1 is found at both apical and basolateral enterocyte membranes[142] (see Fig. 102-7). In vitro BBM treatment with anti-SR-B1 blocking antibodies reduces cholesterol uptake, but studies in mice with SR-B1 deletion or overexpression did not alter intestinal cholesterol absorption.[143] SR-B1 overexpression in the intestine has little impact on cholesterol absorption.[143,144]

In addition to the classic RCT pathway involving SR-B1,[145] an alternate route for cholesterol disposal has been identified in enterocytes, the transintestinal cholesterol efflux (TICE), which involves cholesterol transfer from the basolateral to the apical membrane for its efflux to luminal bile micelles and excretion. SR-B1 was proposed to function in TICE at the apical membrane, but a recent study showed that intestinal overexpression of SR-B1 did not enhance TICE in a mouse model that preferentially uses TICE for cholesterol disposal (NPC1L1-LiverTg mouse).[143]

Additional Proteins That Regulate Cholesterol Absorption

Cholesterol absorption is influenced by transcription factors such as the nuclear hormone receptors that heterodimerize with retinoid X receptors (RXR). These include the oxysterol (LXR) and bile acid receptor (FXR), which regulate intestinal transporters, the cholesterol esterification enzyme ACAT-2, and bile acid biosynthetic enzymes.[146,147] Mice deficient in mucin, which forms the intestinal mucus layer, display 50% reduction in cholesterol absorption.[148] Deletion of ACAT2, which esterifies cholesterol, thereby facilitating its incorporation into chylomicrons by the microsomal TG transfer protein (*MTTP*), reduces cholesterol absorption in mice.[149] Intestinal cholesterol absorption is reduced in *apoB* or *MTTP* knockout mice.[150] Deletion of L-FABP also reduces cholesterol absorption.[151] The proprotein convertase subtilisin/Kexin type 9

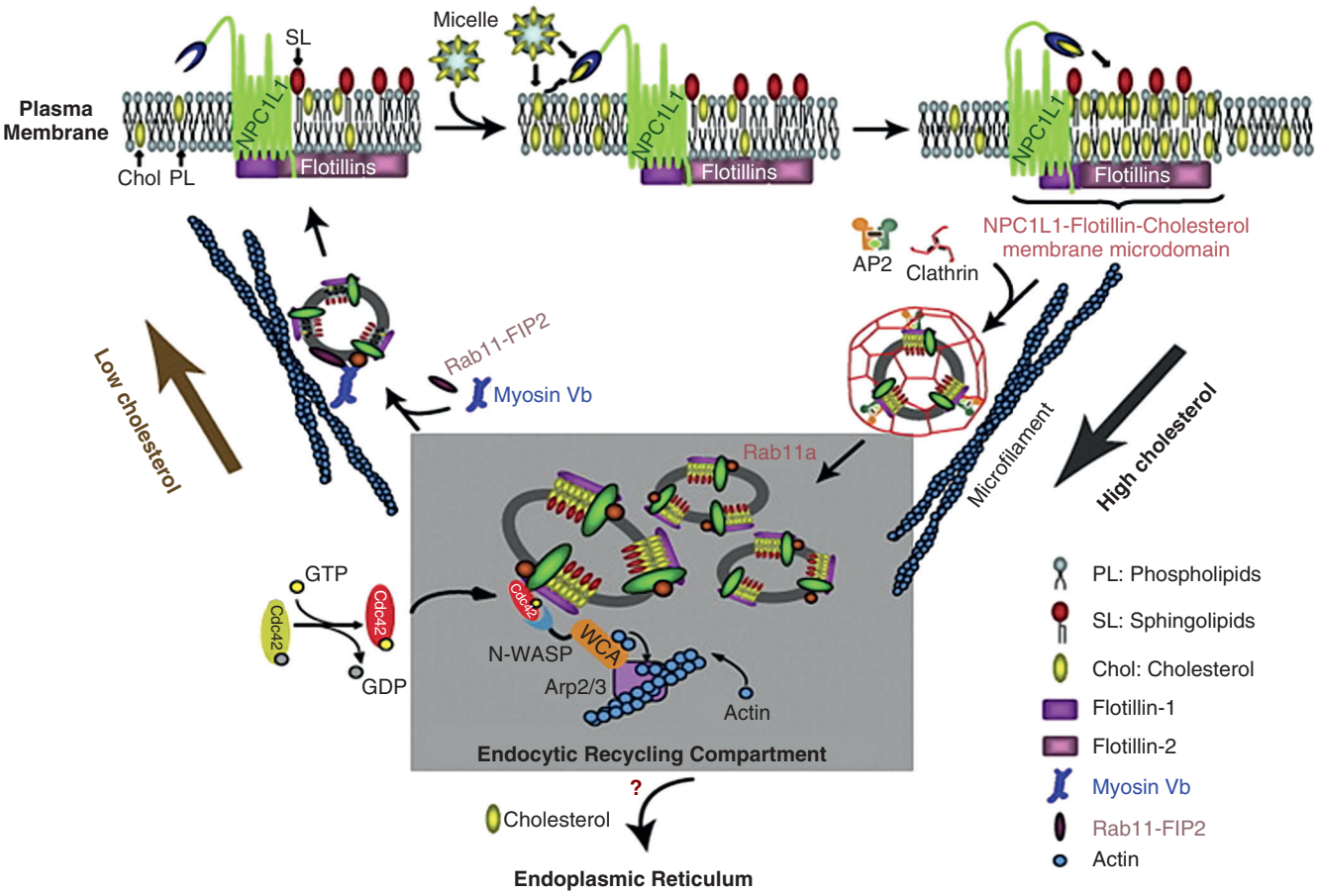

FIGURE 102-8. NPC1L1-mediated cholesterol uptake and intracellular trafficking. NPC1L1 and flotillin proteins associate in cholesterol-rich microdomains that are subsequently coated by clathrin/AP2 complex. These microdomains undergo endocytosis and the internalized vesicles are transported along microfilaments to the endocytotic recycling compartment (ERC). Cholesterol is released from ERC for transport to the endoplasmic reticulum via an unclear mechanism. When intracellular cholesterol level is low, Cdc42 is activated and binds to NPC1L1, promoting recruitment of Myosin Vb and actin. The Cdc42 downstream effectors N-WASP and Arp2/3 are activated and initiate actin polymerization and transport of NPC1L1-flotillin complex to the plasma membrane to enhance cholesterol uptake. Arp2/3, actin-related protein 2/3; Cd42, a member of the Rho family of small GTPases; NPC1L1, Neiman-Pick 1-like protein 1; N-WASP, neural Wiskott-Aldrich syndrome protein. *(Reproduced from Wang LJ, Song BL. Niemann-Pick C1-like 1 and cholesterol uptake. Biochim Biophys Acta 2012; 1821:964-72, with permission.)*

(PCSK9), a proteinase K serine endoprotease family member present in liver and intestine, influences degradation of the low-density lipoprotein receptor (LDLr).[152] It enhances cholesterol uptake in Caco2 cells via up-regulating NPC1L1 and *CD36*. PCSK9 was implicated in chylomicron secretion[152] and in TICE.[153]

CHYLOMICRON ASSEMBLY AND SECRETION

The products of fat digestion, FA, 2-MG, and cholesterol, are re-esterified inside enterocytes, assembled into large TG-rich lipoprotein particles called *chylomicrons*, and secreted into the lymph and then into the circulation (Fig. 102-9). In enterocytes, digestion products must travel to the ER to be resynthesized into complex lipids. Free FAs, which are toxic, are kept at low levels in the cell by binding to cytosolic FA binding proteins (FABPs), a family of abundant small (14 kd) proteins involved in intracellular trafficking of hydrophobic ligands.[154] All FABPs bind 1 FA, except for liver FABP (L-FABP), which binds 2 FAs, and some FABPs bind other hydrophobic molecules such as eicosanoids and bile salts.[154] L-FABP and intestinal (I)-FABP are expressed by enterocytes in the proximal intestine, and ileal (IL)-FABP is expressed in the distal intestine. L-FABP and I-FABP have high affinity for FA, while IL-FABP binds bile acids and is involved in their apical and basolateral transport.[155] L-FABP might target absorbed FA to oxidation versus TG synthesis by I-FABP.[156] L-FABP null mice show reduced recovery of dietary monoolein in intestinal mucosal TG. L-FABP directs 2-MG to TG synthesis,[157] which could explain why L-FABP null mice have reduced secretion of intestinal lipid.[158] L-FABP also contributes to cellular prechylomicron trafficking (see the following section).

Enzymes for Synthesis of Triglycerides and Cholesteryl Esters

In the enterocyte, FA, 2-MG, and cholesterol are re-esterified to TG and cholesteryl esters. FA is activated by acyl-CoA synthases for LCFA (ACSL) to its CoA derivative before esterification by monoglycerol-acyltransferase (MGAT) and

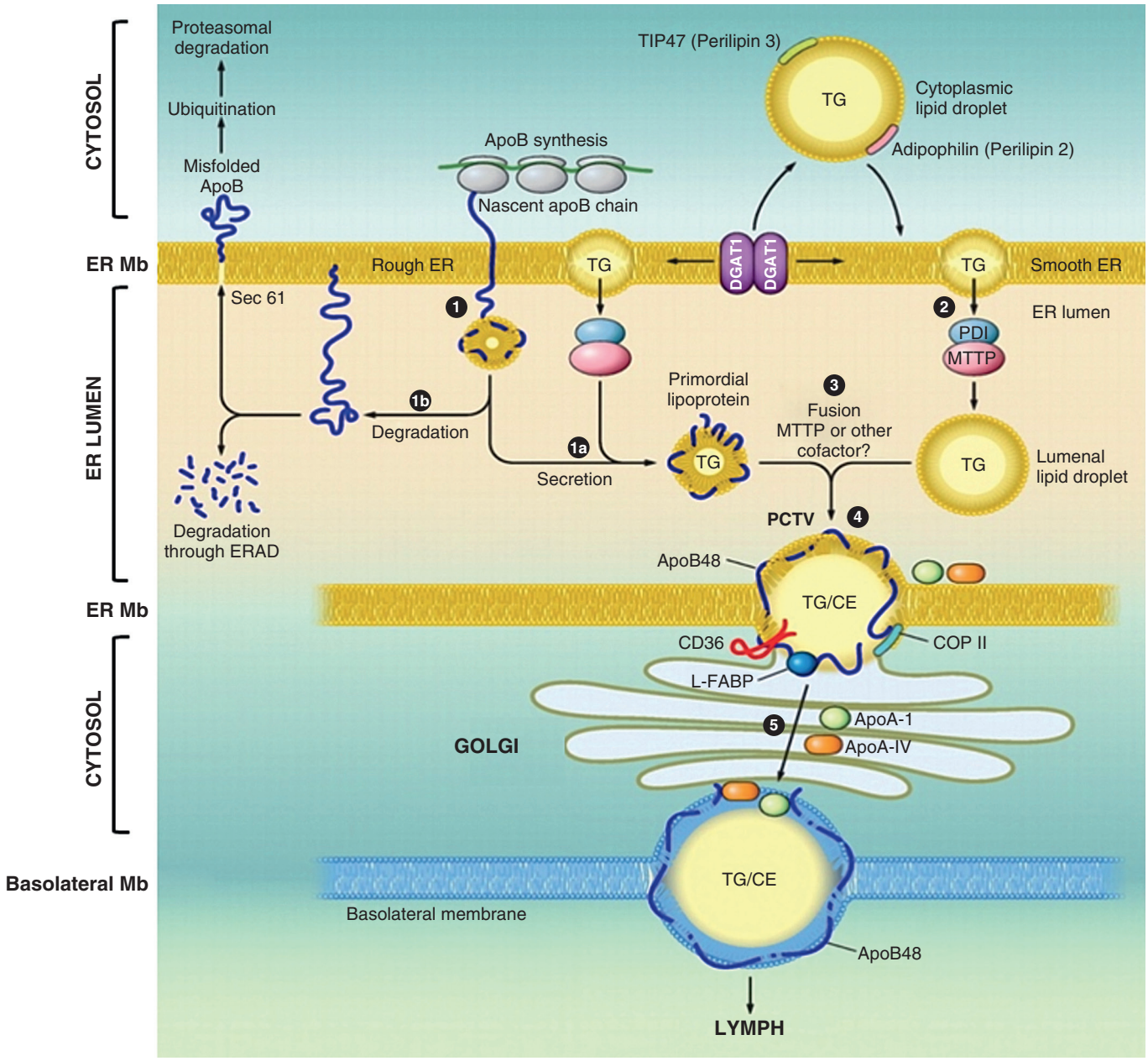

FIGURE 102-9. Assembly of intestinal chylomicrons. Nascent apoB polypeptide *(pictured in blue)* is cotranslationally translocated across rough endoplasmic reticulum (ER). When TG is available, the microsomal TG transfer protein (MTTP) *(pink oval)*, present as a heterodimeric complex with chaperone disulfide isomerase (PDI), interacts with the N-terminal domain of apoB to promote its optimal folding and initiate biogenesis of primordial lipoprotein particle (1a). MTTP can also promote mobilization of TG-rich lipid droplets from the membrane of adjacent smooth ER into ER lumen to generate luminal lipid droplets. Under conditions of low lipid availability or with defective MTTP, nascent apoB is misfolded (1b) and degraded either via ER-associated degradation pathways (ERAD) or proteasomal pathway. During the second step of chylomicron assembly, the primordial lipoprotein particle fuses with lumenal lipid, resulting in prechylomicron. After acquisition of key vesicular transport proteins, including COP II proteins, prechylomicron particles are incorporated into a vesicular complex that buds from the ER. In addition to MTTP and apoB, CD36 and L-FABP participate in PCTV formation and budding. PCTV fuses with Golgi membranes and acquires apoA-1 and apoA-IV apoproteins. Chylomicron particles are then secreted into pericellular spaces where they enter the lymphatic system. *(Reproduced from Abumrad NA, Davidson NO. Role of the gut in lipid homeostasis. Physiol Rev 2012; 92:1061-85.)*

diacylglycerol acyltransferase (DGAT). Cholesterol is converted into cholesteryl ester by acyl cholesterol acyltransferase (ACAT). The synthesized lipid is transferred to *apoB*-48 by *MTTP* to form primordial lipoprotein.

The diacylglycerol (DG) precursor for TG is formed by the monoglycerol (MG) or the glycerol phosphate (Kennedy) pathways. The MG pathway contributes 75% to 80% of TG resynthesis in the intestine and involves acylation of 2-MG.[159] The Kennedy pathway contributes less than 25% and involves acylation of 3-glycerol phosphate twice to generate phosphatidic acid that is dephosphorylated to yield DG, and it becomes the major route for TG formation during fasting.

During lipid absorption, 2-MG is high, and the MG pathway facilitates its esterification with FA to TG while the glycerol phosphate pathway is inhibited.

The acyl CoA synthetases for LCFAs (ACSL) catalyze the first reaction in FA esterification by converting the FA to its CoA ester. Of the 11 ACSL family members for LCFAs,[160] ACSL3 and ACSL5 are the major isoforms present[97] in the intestine, with a small amount of ACSL1. Specificity of intestinal ACSL remains unexplored, but in the liver ACSL3 delivers FA-CoA for phospholipid synthesis,[161] while ACLS5 was shown to increase TG production when expressed in McArdle-RH7777 hepatoma cells.[97]

MGAT forms diacylglycerol from monoacylglycerol and fatty acyl-CoA to generate DG. Of the known MGAT1-3, MGAT1 is expressed in the stomach, MGAT2 is expressed in the proximal intestine,[162] and MGAT3 in the ileum of humans but not rodents.[163] MGAT2 null mice have reduced lipid secretion into the blood[162] and are resistant to high-fat diet–induced obesity. Intestinal rescue of MGAT2 restores the fat absorption rate in MGAT2 null mice.[164]

DGAT is a rate-limiting enzyme for TG synthesis. The intestine expresses DGAT1 and DGAT2. Both localize to the ER, but DGAT2 also co-localizes with mitochondria and lipid droplets.[165] DGAT1 null mice are resistant to high fat diet–induced obesity[166] and have reduced chylomicron secretion[167,168] that is normalized by DGAT1 rescue in the intestine.[169] Pharmacologic inhibition of DGAT1 in mice reduced chylomicron secretion partly by delaying gastric emptying and resulted in lipid accumulation in the distal small intestine.[168,170] DGAT2 null mice die shortly after birth due to skin abnormalities.[171] DGAT1 does not compensate for loss of DGAT2, which is involved in TG synthesis in most tissues except for the intestine.[171] Recent studies implicate DGAT1 in the regulation of intestinal peptide production (GLP-1 and PYY).[172] Thus, DGAT1 is important in TG synthesis for chylomicrons, while DGAT2 contributes to TG synthesis in other tissues.

The free cholesterol in enterocytes is converted by ACAT to cholesteryl ester for chylomicron formation. Two mammalian ACATs have been identified.[173] ACAT-1 is ubiquitously expressed, while ACAT-2 is restricted to mainly liver and intestine.[173] ACAT2 is important for intestinal cholesterol absorption, which drops in ACAT2 null mice to 16% from 46% in wild-type mice and reduces chylomicron cholesteryl ester to about 1% from 12% of chylomicron mass.[174]

During fat absorption, TGs are temporarily stored in enterocytes as cytosolic lipid droplets (LDs), organelles that play a dynamic role in lipid storage and mobilization.[175] The LDs contain a core rich in TG and cholesteryl ester surrounded by a surface layer of phospholipids, cholesterol, and proteins, notably the perilipins (PLN). Intestinal LDs expand or are depleted depending on dietary intake.[176] Two perilipins, PLN2 (adipophilin) and PLN3 (TIP47), coat LDs in the intestine. Perilipin 3 levels are higher after an acute fat challenge, whereas those of PLN2 respond to sustained lipid intake. Thus PLN3 plays a role in the formation of LDs from newly made TG, and PLN2 stabilizes the TG pre-stored in the LDs.[128] Intestinal mucosal LDs harvested after acute intragastric lipid administration differ in size and composition. Analysis of LD content after separation into large (chylomicron-like), intermediate, and small or HDL-like droplets showed the presence of MGAT2 in all LDs. The largest LDs contained *MTTP*, ACAT1/2, and the lipases, hormone-sensitive lipase (HSL) and adipose TG lipase (ATGL). Thus, enterocyte LDs contain enzymes involved in the different steps of FA and cholesterol metabolism and function in the accumulation and possibly metabolic transformation of the absorbed lipids in coordination with the ER.[177]

Enterocytes package TGs, cholesterol, cholesteryl esters, and phospholipids for export in the form of chylomicrons or very-low-density lipoproteins (VLDLs). After a meal, chylomicrons predominate, whereas VLDLs are the major TG-rich lipoprotein during fasting. VLDL and chylomicron TGs have different FA composition that reflects different metabolic sources. The FAs derived from dietary TG are predominantly used for chylomicrons, whereas those from phospholipid are used for VLDL.[178] Chylomicron particles range between 75 and 450 nm[179] in diameter, with a core of TG and cholesteryl esters and a surface coat composed of phospholipids (80%) and apoproteins. Chylomicron assembly (see Fig. 102-9)[180] involves the coordinated functions of *MTTP* and *apoB* to form the primordial particle that is then transferred from the ER to the Golgi apparatus.

Apolipoprotein B (ApoB)

ApoB is a large hydrophobic protein required for the formation of TG-rich lipoproteins. There are 2 forms of *apoB*: *apoB*-100 and *apoB*-48.[181] Transcription of the *apoB* gene generates a 14-kb mRNA that yields a full-length *apoB* (*apoB*-100). ApoB-48 is generated when the mRNA editing complex (apobec-1 and apobec-1 complementation factor [ACF]) introduces a stop codon (cytidine to uridine RNA editing) resulting in translation of the N-terminal 48% of *apoB*-100.[182] ApoB-48 is the intestinally expressed form of *apoB* in rodents and humans. Only *apoB*-100 is expressed in human liver, whereas both *apoB*-48 and *apoB*-100 are expressed in the rodent liver.[182,183] Apobec-1 null mice, which synthesize only *apoB*-100, display slower TG secretion and retain more TG in their intestinal mucosa.[184] Transgenic rescue of apobec-1 in the intestine restored intestinal *apoB*-48 production.[185]

Microsomal Triglyceride Transfer Protein (*MTTP*)

MTTP is a 97-kd heterodimeric protein that transfers lipids to the newly synthesized *apoB*-48 during its translocation to the ER lumen to generate the primordial lipoprotein (see Fig. 102-9). Failure to transfer lipid to *apoB* leads to its misfolding, ubiquitination, and degradation by both proteosomal and non-proteosomal pathways.[186,187] ApoB can also be degraded by ER-associated degradation and autophagy. The primordial particle separates from the ER membrane to form the nascent lipoprotein, which fuses with absorbed lipid to generate the prechylomicron. Supply of *apoB* is not rate-limiting for chylomicron TG output. For example, *apoB* output into the lymph does not change after intraduodenal lipid infusion, even though lymphatic TG output increases 7- to 8-fold. In addition, *apoB*-48 synthetic rates are not increased by acute or chronic fat feeding, but they can be reduced by bile exclusion secondary to a loss of cholesterol.[52]

MTTP is present in the ER lumen of enterocytes (and hepatocytes) in a complex with the chaperone protein disulfide isomerase (PDI). *MTTP* transfers lipid (from membranes and lipid droplets) to nascent *apoB*[188] (see Fig. 102-9). It transfers TG, cholesterol, and phospholipids[189] to form either chylomicrons or VLDL.[190,191] Pharmacologic inhibition of *MTTP* blocks secretion of *apoB* and lipoproteins.[192] Deletion of *MTTP* in mice is embryonic lethal,[193] so its role has been examined using intestine targeted deletion or partial deficiency of *MTTP*. In both mice models, intestinal secretion of *apoB*-containing lipoproteins is reduced.[193-195] In humans, mutations in the *MTTP* gene result in abetalipoproteinemia, a rare disorder with low blood *apoB* lipoproteins and with LD accumulation in the small intestine and liver.[196] Genetic defects associated with abnormal *apoB* are mostly caused by nonsense and frameshift mutations in the *apoB* gene that result in C-terminal

truncations.[197] The population frequency of APOB gene mutations causing truncated *apoB* proteins is about 1:3000. By clinical criteria, heterozygous familial hypobetalipoproteinemia (FHBL) may occur in 1:500 to 1:1000, while homozygous FHBL is rare. Homozygous hypobetalipoproteinemia associates with abnormally low serum lipids and *apoB*. Symptoms can include fat malabsorption, neurologic defects, red cell acanthocytosis, and nonalcoholic fatty liver disease.[198]

Intestinal *MTTP* is highly regulated, exhibiting diurnal regulation in response to visual and nutritional cues and in concert with plasma TG levels. This involves the circadian regulatory clock and nocturnin proteins and the transcriptional repressor SHP (short heterodimeric partner).[199,200] Leptin signaling regulates *MTTP*, involving the melanocortin-4 receptor.[201] ER stress increases intestinal *MTTP*[202] and augments chylomicron secretion.[203]

Transport of Prechylomicrons from the Endoplasmic Reticulum to the Golgi Apparatus

Because of the large size of these particles, transport requires the formation of prechylomicron transport vesicles (PCTV) (≈250 nm in diameter) (see Fig. 102-9). The PCTV consist of *apoB*-48, vesicle-associated membrane protein 7 (VAMP7), *CD36*, and L-FABP.[204] L-FABP is present within a multiprotein complex in the cytosol.[205] Phosphorylation of complex components by protein kinase C (PKCζ) dissociates L-FABP, allowing it to bind to the ER to initiate PCTV formation.[205] Budding of the PCTV from the ER involves L-FABP and *CD36* and is markedly reduced in enterocyte fractions derived from mice deficient in either protein.[204] Fusion of PCTV to the Golgi apparatus involves multiple proteins including SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor), VAMP7, and syntaxin-5.[206] The prechylomicron undergoes maturation in the Golgi apparatus with apoA-I addition, alteration of *apoB*-48 glycosylation, and more TG transfer by *MTTP*. The trans-Golgi–associated ADP-ribosylation factor–related protein 1 (ARFRP1) and its target GRIP domain protein (RAB2) play an essential role in the lipidation and maturation of chylomicrons in the Golgi apparatus, including addition of apoA-I.[207]

Golgi-derived chylomicrons are incorporated into the basolateral membrane and secreted by exocytosis into the lymphatic circulation (see Fig. 102-9). Plasma apoA-IV appears important for chylomicron secretion. ApoA-IV levels rise in response to fat intake, [208] with synthesis of the apolipoprotein increasing by about 5-fold.[209] ApoA-IV is part of the prechylomicron formed within the ER,[210] and its overexpression increases TG output into the lymph by increasing particle size. The C-terminus of apoA-IV (amino acids 344 to 354) is important for chylomicron TG output into the lymph.[211] ApoA-IV interaction with *apoB* in *apoB*-containing particles enhances particle expansion and TG secretion.[212] During absorption, lacteals distend and gaps open between endothelial cells, allowing chylomicron passage.[213]

Disorders of Chylomicron Production

Apolipoproteinemia is a rare genetic disorder in which the liver and intestine fail to make TG-rich lipoproteins.[214] The disorder results from mutations in the *MTTP*[215] that impair its lipid transfer activity leading to *apoB* degradation. Anderson's disease or chylomicron retention disorder is characterized by hypobetalipoproteinemia with selective absence of *apoB*-48 postprandially and the accumulation of lipid droplets in enterocytes.[216] The disease is caused by mutations affecting the Sar1B protein, a small GTPase involved in the vesicular ER to Golgi transport of proteins[217] shown to be required for fusion of PCTV with the Golgi apparatus. *CD36* deficient humans have high levels of plasma TG, and *apoB*-48,[115] which was suggested to increase atherosclerotic risk by enhancing levels of lipoprotein remnants because of increased intestinal secretion of particles smaller than chylomicrons.[115]

FATTY ACID SENSING BY THE GUT AND ITS SIGNALING FUNCTIONS (Fig. 102-10)

The regulation of energy homeostasis involves afferent and efferent signals that connect metabolic organs to the hypothalamus and brainstem. The GI tract plays a role in this regulation through signals transmitted via the blood or vagal afferent fibers. Dietary fat reaching the intestine has pro-satiety effects. It suppresses secretion of ghrelin,[218] a hormone with positive effects on appetite. This suppression requires digestion, but it is unclear whether it is mediated by LCFAs. Dietary fat also stimulates secretion of a number of pro-satiety intestinal peptides (see Fig. 102-10 and following sections). Dysfunction of oral or intestinal fat-sensing or a blunting of the pro-satiety effects of dietary fat by other ingested nutrients might contribute to obesity.[61]

Intestinal Fatty Acid Sensing and Lipid Absorption

LCFAs are recognized on the surface of intestinal cells by membrane receptors that include *CD36* and a number of G protein-coupled receptors (GPRs). FA binding to *CD36* results in signal transduction involving sarcoma (Src) tyrosine kinases, phospholipases A2, and associates with increases in intracellular calcium and cAMP.[111,219] Ligand binding to the GPRs triggers a conformational change that leads to activation of intracellular heterotrimeric G proteins, which activate distinct signal transduction pathways dependent on the type of G-protein coupling.[76] Proteins that are involved downstream of the receptor include adenylyl or guanylyl cyclase, phospholipases A2 and C, phosphodiesterases, and phosphatidylinositol-3 kinases (PI3Ks). GPRs 40, 41, and 43 were identified as FA receptors in 2003.[220,221] The abundant dietary FAs and palmitic, stearic, and oleic acids were reported as GPR40 ligands and SCFA GPR41 and GPR43 ligands. GPR84, GPR119, and *GPR120* are activated, respectively, by medium-chain FAs, the oleic acid derivative OEA, and omega-3 FAs.[76] GPR40 mediates effects of FAs on insulin secretion[222] and *GPR120* that of FAs on intestinal incretin release.[76] The first site of lipid sensing in the GI tract involves FA perception via taste receptors within the oral cavity (See previous section on Oral Perception of Dietary Fat). This interaction also triggers the cephalic phase of digestion, which primes the intestine to optimize absorption. Fat-specific cephalic-phase responses include secretion of lipases, transient increases of intestinal CCK, PP, and PYY, and insulin release.[223]

In addition to the oral cavity, LCFA receptors are distributed throughout the GI tract, where they act to coordinate absorption with nutrient processing through the release of intestinal peptides (Table 102-4). In the duodenum and jejunum, LCFAs released from fat digestion in the lumen influence secretion of peptides that modulate the digestive process. EECs in the intestinal mucosa, which constitute less than 1% of the epithelial cell population, are the sensors and express the LCFA receptors GPR40, *GPR120*,[224,225] and *CD36*.[111] LCFAs stimulate CCK secretion[226] by I cells in the mucosa of the duodenum, jejunum, and proximal ileum. CCK helps optimize fat digestion by regulating gastric emptying, gallbladder contraction, pancreatic secretion, and intestinal motility.[227]

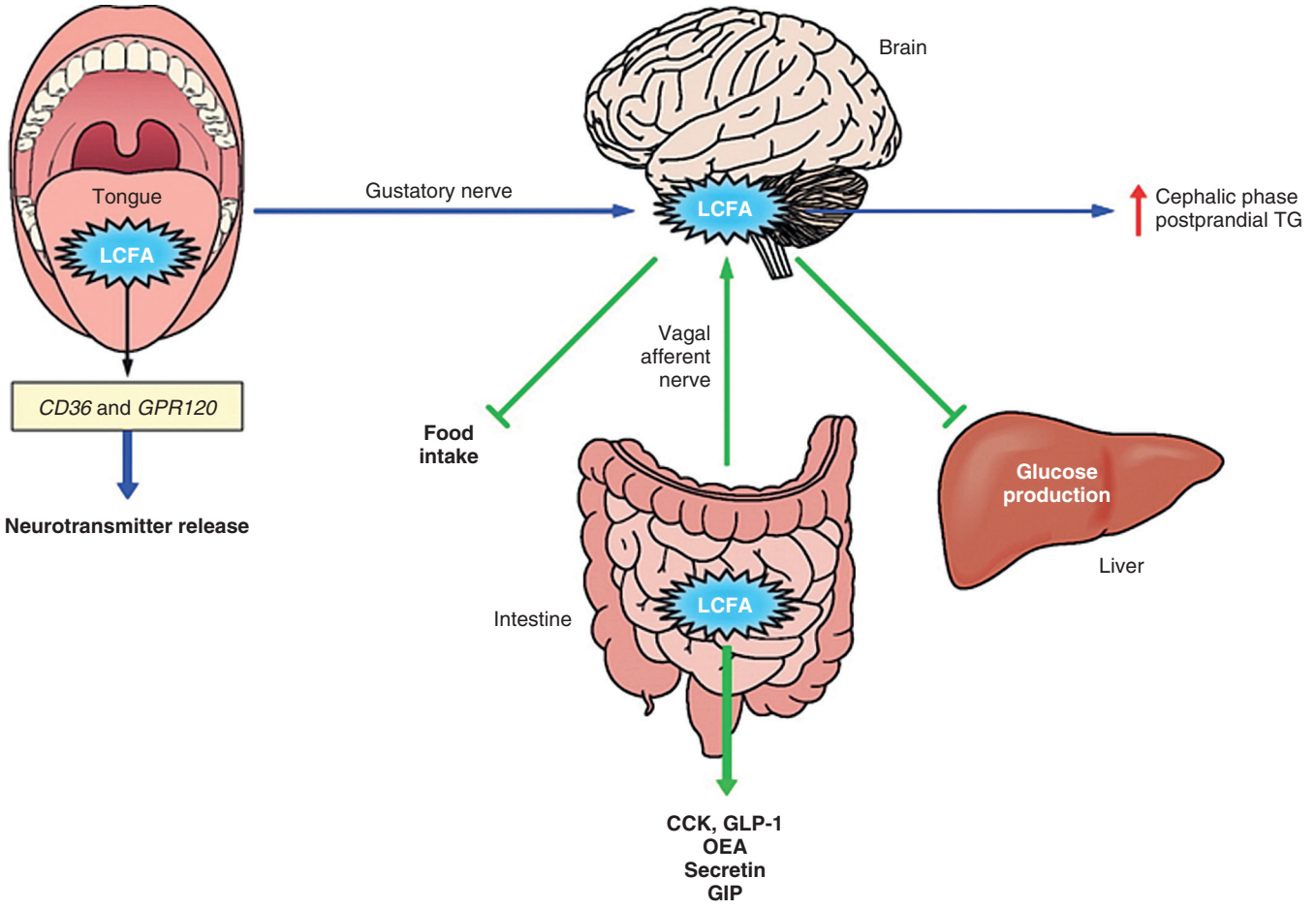

FIGURE 102-10. Signaling functions of intestinal long-chain fatty acids (LCFAs). Dietary TG hydrolysis during digestion releases LCFAs that have important signaling functions at various levels of the digestive tract. In the oral cavity, LCFA receptors (CD36, GPR120) present on apical surface of taste bud cells in the tongue[97,150] contribute to fat taste perception, which associates with secretion of neurotransmitters, signal transmission to brain centers, and induction of the early cephalic phase of digestion[150] *(blue arrows)*. In the intestinal lumen, dietary lipid has satiety effects *(green arrows)* mediated by LCFA signaling to release peptides with inhibitory effects on food intake (GLP-1, CCK, OEA). GLP-1 and CCK also delay gastric emptying and lipid absorption.[71] GLP-1 and GIP enhance insulin release from the pancreas and glucose metabolism.[229] Lipid sensing in the proximal intestine, mediated by accumulation of long-chain fatty acyl-CoA, also activates an intestine-brain-liver axis to inhibit glucose production by the liver.[233] During feeding, TG is resynthesized largely from absorbed FA and monoglyceride. During fasting, TG and phospholipid are synthesized from α-glycerophosphate derived from glucose entering across the basolateral membrane of the enterocyte, and from FA. Unsaturated FAs tend to form phospholipid. CoA, coenzyme A; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; OEA, oleoylethanolamide. *(Reproduced from Abumrad NA, Davidson NO. Role of the gut in lipid homeostasis. Physiol Rev 2012; 92:1061-85.)*

LCFAs induce S and K cells in the duodenum and jejunum to release, respectively, secretin and the glucose insulinotropic peptide (GIP). Secretin inhibits gastric emptying and synergizes with CCK to induce pancreatic secretions.[228] GIP has insulinotropic effects.[229] GPR40[68] and *CD36*[111] have been implicated in mediating the effect of FA on CCK. Isolated I cells that express GPR40 respond to linoleic acid with increases in intracellular calcium and CCK release. CCK secretion induced by oleic acid is reduced in GPR40 null mice.[68] The *CD36* null mouse displays a 50% reduction in release of CCK and secretin in response to gastric administration of oil. Diminished release in response to FA is also observed with CD36-deficient intestinal segments in vitro. In EECs that express CD36, release of CCK and secretin involves FA-induced increases in calcium and the second messenger cAMP.[111] GPR40 is present on EECs expressing GIP, GLP-1, and CCK, and its disruption reduces secretion of these peptides.[224]

GLP-1 is formed in intestinal L-cells in the jejunum, distal ileum, and colon from the post-translational processing of a proglucagon precursor.[230] GLP-1 influences gastric emptying and GI motility.[231] Release of GLP-1 is stimulated in vivo by FA reaching the distal intestine (or administered directly into it) and requires protein kinase C zeta.[232] GLP-1 release from the distal intestine by polyunsaturated FA involves GPR120.[76]

Satiation Effect of Intestinal Lipid

Dietary fat in the intestine inhibits food intake in rats and humans, an effect mediated by LCFA signaling to release several regulatory peptides (see Fig. 102-10). CCK has pro-satiety effects that are mediated by CCK receptors on vagal afferents in the duodenum, which signal to the brain nucleus of the tractus solitarius to reduce the feeling of hunger.[227] LCFAs induce production by the small intestine of OEA, a pro-satiety lipid and agonist of peroxisome proliferator activated receptor alpha (PPAR-alpha). OEA is generated from absorbed oleic acid and acts centrally to prolong

TABLE 102-4 Peptide Secretion Induced by Fatty Acids in The Taste Buds and Enteroendocrine Cells and The Membrane Fatty Acid Receptors Involved in Coordinating Absorption and Nutrient Processing

Taste Bud Cells	Peptide	Primary Site	Fat Type	FA Receptor
	GLP-1	Circumvallate*	LCFA	GPR120
	Serotonin	Circumvallate	LCFA	CD36
EEC				
K cells	GIP	Duodenum/jejunum	LCFA	GPR40,119, 120
S cells	Secretin	Duodenum/jejunum	LCFA	CD36
I cells	CCK	Duodenum/jejunum	LCFA	GPR40, CD36
L cells	PYY	Ileum/colon	SCFA	GPR41, 43
L cells	GLP-1	Ileum/colon	LCFA	GPR40,119, 120

Circumvallate refers to circumvallate papillae of the tongue.
CCK, cholecystokinin; CD36, cluster of differentiation 36; EEC, enteroendocrine cells; FA, fatty acid; GIP, gastric inhibitory polypeptide, also known as the *glucose-dependent insulinotropic peptide*; GLP-1, glucagon-like peptide 1; GPR, G protein–coupled receptor; LCFA, long-chain FA; PYY, peptide tyrosine tyrosine; SCFA; short-chain FA.

inter-meal intervals and reduce feeding frequency.[233] Generation of OEA is CD36 dependent, and disruption of CD36 or PPAR-alpha blunts fat-induced satiety. Effects of OEA on satiety may involve GLP-1 release by EECs after OEA binding to GPR119.[234] Fat intake promotes intestinal secretion of *N*-acylphosphatidylethanolamine (NAPE)[235] and apo A-IV,[236] and SCFAs induce L cells to release PYY,[226] all shown to have central pro-satiety effects (see Table 100-4). The satiety-inducing property of fat, however, can be blunted by factors like simultaneous ingestion of carbohydrates and release of endocannabinoids by a palatable fat-sugar mix (as found in processed food).[237] Also, regulation of fat intake involves a number of factors with positive (e.g., ghrelin, galanin) effects on appetite.[85]

Intestinal Fatty Acid Sensing and Glucose Metabolism

FA sensing by the gut-brain axis regulates glucose metabolism (see Fig. 102-10), mainly via release of GIP and GLP-1, secreted by EECs in response to dietary fat and carbohydrates.[238] GIP and GLP-1 amplify glucose-dependent pancreatic insulin release (incretin effect). GIP has direct effects on adipose tissue to promote glucose uptake and energy storage. GLP-1 has an anti-hyperglycemic action that reflects its reduction of gastric emptying and meal-induced liver glucagon secretion. GLP-1-receptor agonists resistant to hydrolysis by dipeptidyl peptidase-4 are being used for treating type 2 diabetes.[229] Inhibition of gastric emptying by several intestinal peptides released by LCFAs reduces blood glucose.[239] Lipid sensing in the upper intestine also activates an intestine-brain-liver axis to inhibit hepatic glucose output (see Fig. 102-10), a pathway that becomes defective in fat-fed rodents.[240] In the brain, long-chain fatty acyl-coenzyme A accumulation and subsequent activation of PKC directly impact the centers that regulate glucose production and energy homeostasis.[241]

CARBOHYDRATES

Dietary Intake

Glucose plays a central role in energy metabolism. In Western civilization, carbohydrates make up some 40% to 45% of the total caloric intake of human beings. Ingested carbohydrates include simple sugars (e.g., glucose, galactose, fructose), disaccharides (e.g., lactose, sucrose) and complex carbohydrates (e.g., starch, glycogen).[242,243] Simple sugars, disaccharides, and complex carbohydrates account, respectively, for approximately 5% to 10%, 30% to 40%, and 45% to 60% of consumed dietary carbohydrates. In total, the amount of glucose produced by digestion is about 180 g/day (≈1 mol).[244]

Fructose had been increasingly added to our diets (frequently in excess of 50 g/day) through the widespread use of corn syrup as a sweetener.[245-247] All ingested glucose and galactose is absorbed normally, but the capacity to absorb fructose is limited in both young children and adults, as shown by a study of healthy young adults (medical students in the United States and the United Kingdom), 70% of whom developed abdominal pain, bloating, borborygmi, flatus, and a positive hydrogen breath test after ingestion of 50 g of fructose.[248] The increased intake of fructose over the last 4 decades, especially in soft drinks (2 12-oz cans of some popular soft drinks contain about 50 g of fructose in the form of corn syrup), has been associated with a multitude of disorders, including obesity, diabetes, and heart disease.[249-252]

About half of the digestible carbohydrate in an average Western diet is starch (the main storage form of carbohydrates), which is derived from cereals and plants. Starch, as either amylose or amylopectin, is made up of long chains of glucose molecules. Amylose, a linear polymer in which each glucose molecule is coupled to its neighbor by α-1–4 linkage, has a molecular weight of 10^6. Amylopectin, in contrast, is a branched-chain polymer in which α-1–6 links provide angulations between adjacent chains of α-1–4 linked glucose molecules (Fig. 102-11); it has a molecular weight greater than 10^9. Most starches contain more amylopectin than amylose, but the ratio varies widely. Although starches are relatively easily digested, food preparation can influence their biological utilization. Utilization also may be determined by proteins that are associated with the starch, particularly gluten.[1,23]

Other major sources of dietary carbohydrate include milk (lactose), fruits and vegetables (fructose, glucose, sucrose), or purified and cane or beet sources (sucrose). Processed foods form a major source of dietary sugars, particularly fructose and corn syrup; the latter contains not only fructose but also oligosaccharides and polysaccharides. The sugar alcohol sorbitol is used widely in the manufacture of "diabetic" sweets

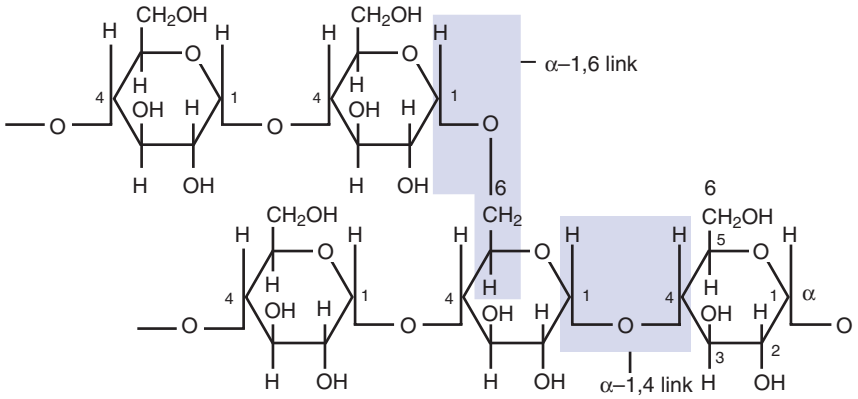

FIGURE 102-11. Part of an amylopectin molecule, indicating disposition of α1–4 and α1–6 linkages between glucose molecules.

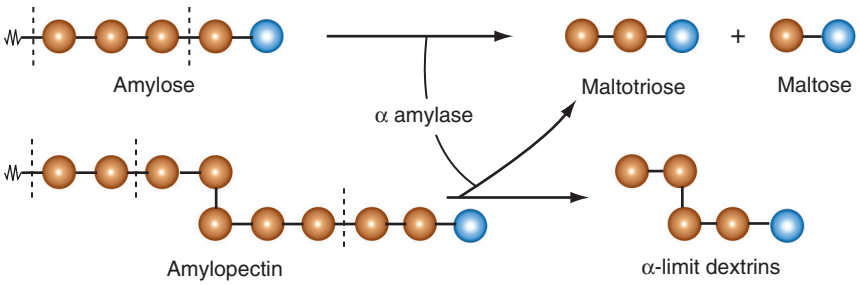

FIGURE 102-12. Action of pancreatic α-amylase on amylose and amylopectin molecules. Because the α1–6 link in the latter is resistant to amylase, the products include α-limit dextrin. *Brown circles*, glucose units; *Blue circles*, reducing glucose units. *(From Gray GM. Carbohydrate absorption and malabsorption. In: Johnson LR, editor. Physiology of the gastrointestinal tract. New York: Raven Press; 1981. p 1064, fig. 42-1.)*

and preserves and is found naturally in apples, pears, peaches, and prunes.[253] Sorbitol is formed when the aldehyde group of glucose is hydrogenated to an alcohol group, slowing its rate of absorption and thus diminishing its effect on blood sugar concentrations.[254]

Glycogen is the major storage form of polysaccharides in animals, but the amounts ingested in a normal diet are small. The structure of glycogen is similar to that of amylose and composed of straight chains of α-1–4–linked glucose monomers.[242]

Non-starch polysaccharides form the majority of unavailable carbohydrates. The dietary fiber component of unavailable carbohydrate is found most abundantly in cereals, peas, beans, carrots, and peanuts. In the United States, 10 to 15 g of dietary fiber, consisting predominantly of celluloses and hemicelluloses, is consumed by each person every day.[255,256] Cellulose is made up of β-1–4-linked glucose molecules in straight chains, and hemicelluloses are pentose and hexose polymers with both straight and branched chains. Both forms are resistant to digestion in the small intestine, because the β-1–4 bond, unlike the α-bond in starch, is resistant to amylases. They are, however, broken down to some extent by colonic bacteria to yield SCFAs that are avidly absorbed by colonic mucosa.[3,257] The quantity of cellulose and hemicelluloses in vegetables and fruit varies markedly and depends on their age and ripeness.[258]

Other unavailable carbohydrates include pectins, gums, and alginates, which are only partially metabolized in the colon. Lignins, elaborated by plants in the process of becoming woody, are completely indigestible.[254,259]

It is well recognized that an increased intake of dietary fiber may ease constipation by increasing fecal bulk, mainly as a result of the increase in the mass of fecal flora. Dietary fiber has other roles, however, and also affects the absorption of other nutrients. For example, fiber delays absorption of sugars and fats and curtails the insulin response to a carbohydrate meal. Some fiber (e.g., lignins) may lower serum cholesterol values by binding bile salts.[260] It may be these effects that have led to the widespread recommendation of a high-fiber diet for management or prevention of diabetes mellitus and atherosclerosis. Satiety is achieved more rapidly from a diet rich in fiber than from a low-fiber diet, and it takes longer to ingest a high-fiber meal. The management of obesity takes advantage of this fact (see Chapter 7).

Intraluminal Digestion

Salivary and Pancreatic Amylase

Salivary and pancreatic α-amylases are endoenzymes—that is, they cleave the α-1–4 links internal to or at the second or third bond from the end of the polysaccharide chain. The products of amylase digestion, therefore, are short, linear oligosaccharides of maltotriose and maltose (Fig. 102-12). Because α-1–6 links and the adjacent α-1–4 bonds in the branched chains of amylopectin are not hydrolyzed by amylase, the products of amylopectin digestion include short, branched oligosaccharides termed *α-limit dextrins*. Amylase proteins are encoded by a clustered gene family located on chromosome 1 of the human genome.[261] In humans, the *AMY1* gene is expressed in the parotid gland, and the *AMY2* gene is expressed in the pancreas.[262] The sequences of the pancreatic and salivary complementary DNAs are 94% similar, encoding for polypeptides with the same number of amino acids.[263]

The initial digestion of complex carbohydrates begins in the mouth with salivary α-amylase, also known as *ptyalin*. This endoenzyme is secreted by the acinar cells of the parotid and submandibular glands and starts the digestion of starch and other complex carbohydrates before ingested food is even swallowed.[244] Salivary amylase depends for its effect on its proximity to the ingested starches and the time they spend within the mouth. Thus, careful, slow chewing affords a good start to digestion, whereas rapid swallowing of poorly chewed foods, often a problem for edentulous persons, may cause suboptimal salivary amylase action.[264] Salivary amylase is rapidly inactivated by gastric acid, but some activity may persist within the food bolus; short-chain oligosaccharides offer further protection for the enzyme against inactivation at acid pH. Approximately 30% to 40% of complex carbohydrate digestion takes place before the food reaches the small intestine, where luminal digestion is completed by pancreatic α-amylase.[242]

Pancreatic amylase is the major enzyme of starch digestion and, as with salivary amylase, produces short oligosaccharides, maltotriose, maltose, and α-limit dextrins; glucose monomer is not produced. Most of this hydrolysis occurs within the intestinal lumen, but because amylase also attaches itself to the BBM of enterocytes, some digestion may occur at this site as well. Amylase concentration becomes limiting for starch hydrolysis only in severe cases of pancreatic insufficiency when luminal enzyme activity levels are reduced to less than 10% of normal.[265] Human milk contains amylase activity, which may be important for carbohydrate digestion in infants.[266]

Brush Border Membrane Hydrolases

The terminal products of luminal starch digestion, together with the major disaccharides in the diet (sucrose and lactose), cannot be absorbed intact and are hydrolyzed by specific BBM hydrolases that are maximally expressed in the villi of the duodenum and jejunum. Several types have been identified.[244,267]

Lactase hydrolyzes lactose (the primary sugar in milk) to produce 1 molecule of glucose and 1 of galactose.

Sucrase-isomaltase (*SI*, sucrase-α-dextrinase) comprises 2 subunits of the same enzyme, each with distinct enzymatic activity. Both sucrase and isomaltase remove glucose molecules from the non-reducing end of α-limit dextrins. Sucrase hydrolyzes sucrose to yield 1 molecule each of glucose and fructose, whereas isomaltase ("debrancher" enzyme) hydrolyzes the 1-6 glycosidic linkages in α-limit dextrins. The concerted action of sucrase and isomaltase is to yield monomeric glucose molecules from sucrose and α-limit dextrins (Fig. 102-13).

In addition, 2 other carbohydrases participate in terminal hydrolysis of starch products: maltase-glucoamylase and α-limit dextrinase. Maltase-glucoamylase acts on 1-4–linked oligosaccharides containing as many as 9 glucose residues, to liberate glucose monomers. The human maltase-glucoamylase gene (*MGAM*) is located on chromosome 7 and has structural homology similar to the *SI* gene.[268] The maltase-glucoamylase enzyme does not undergo intracellular or extracellular proteolytic cleavage and is expressed in the BBM as a monomeric protein. Maltase-glucoamylase is expressed prenatally, with similar levels after birth and into adulthood.[269] It has been suggested that while isomaltase hydrolyzes the smallest α-limit dextrin, another enzyme, α-limit dextrinase, is responsible for rapid hydrolysis of penta- and hexa-α-limit dextrins.[270]

The combination of *SI*, maltase, and α-limit dextrinase serves to liberate glucose monomers very rapidly and close to

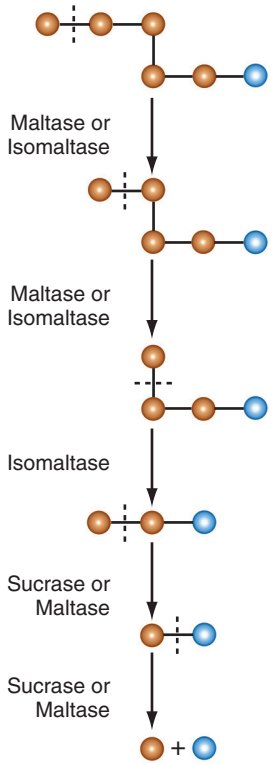

FIGURE 102-13. Actions of brush border membrane hydrolases. Combined actions of maltase, isomaltase, and sucrase yield glucose molecules from α-limit dextrins. Isomaltase is necessary to split α1–6 link. *Brown circles*, glucose units; *Blue circles*, reducing glucose units.

hexose carriers, thus encouraging efficient absorption. Because free hexoses are found in the intestinal lumen, it is likely that the transport process is the rate-limiting step for uptake of monomers into the epithelium, rather than the actions of the carbohydrases.

Trehalose is a disaccharide found predominantly in mushrooms, insects, algae, and other fungi, so it is an insignificant element of the normal diet; nevertheless, there is a specific brush border enzyme, trehalase, for its hydrolysis (α-1,1 linkage) to its 2 glucose molecules. If consumed by individuals with trehalase deficiency, trehalose may cause GI distress in the form of bloating, flatulence, and diarrhea.[271] Congenital trehalase deficiency is very rare in Caucasian Americans but has been reported in up to 8% of Greenland natives, resulting in severe diarrhea after ingestion of mushrooms.[269]

Disaccharidase Biosynthesis and Regulation

Much has been learned about the gene regulation, biosynthesis, and processing of the disaccharidases.[272-276] The human trehalase gene (*TREH*) is located on chromosome 11 and encodes a 583–amino acid protein with a molecular mass of about 75 kd. *SI* is encoded by a single gene in the human,[277] located on the human chromosome 3 at locus 3q-25-26.[278] The 5′ flanking region of the *SI* gene has a number of DNA regulatory regions that control initiation of gene transcription.[279,280] Using mouse genetics, all 4 epithelial cell types in the small intestinal mucosa have the transcriptional machinery to express the *SI* gene.[281,282] The elements necessary to direct intestinal epithelial cell-specific expression are embodied in a 201-nucleotide, evolutionary conserved, 5′ flanking region of the gene.[283] At least 3 types of transcriptional

proteins are involved in *SI* promoter transcription, including hepatocyte nuclear factor 1 (HNF1),[284,285] GATA family members (GATA 4 and 5),[286] and caudal-related homeodomain proteins (Cdx).[287] The interaction of tissue-specific and tissue-restricted transcription factors facilitates the transcription of genes in a single cell type.[288]

Congenital *SI* deficiency (CSID) is an autosomal recessive intestinal disease that is characterized by the absence of the sucrase and most of the maltase digestive activity within the *SI* enzyme complex; the isomaltase activity varies from absent to normal. Clinically, the disease is manifested as an osmotic-fermentative diarrhea upon ingestion of disaccharides and oligosaccharides. Analysis of this disorder at the molecular and subcellular levels has unraveled a number of phenotypes of CSID, which are characterized by perturbations in the intracellular transport, polarized sorting, aberrant processing, and defective function of *SI*.[289-291]

Changes in diet have a marked effect on the expression of *SI*. Starvation leads to a decline in brush border proteins and *SI* activity; this decline in *SI* activity is restored rapidly after refeeding.[292] The type of carbohydrate ingested is important for regulation of *SI* expression. Starch and sucrose both induce *SI* activity, although sucrose is a more potent inducer.[293] Study of the intestinal cell line Caco-2 has shown that a promoter region of the human sucrase gene (nucleotides −370 to +30) can down-regulate *SI* transcription in the presence of glucose.[294]

The human lactase gene is approximately 55 kb long with 17 exons and is located on the long arm of chromosome 2.[295,296] Studies in intestinal cell lines have identified functional DNA elements in the lactase gene promoter that interact with nuclear transcription factors.[297] Cdx proteins and GATA 5, a member of the GATA-type zinc-finger transcription factor family, and HNF-1 alpha all have been shown to interact with the human lactase gene promoter and to activate transcription.[298]

Lactose intolerance is the most common manifestation of disaccharidase deficiency and results from an absence or drastically reduced level of lactase. In humans, lactase is expressed in fetal small intestine at a time in gestation just after the onset of expression of *SI*. Lactase expression is maintained throughout development and during childhood, although sometime during childhood, lactase activity declines to 5% to 10% of early childhood levels in most of the world's populations. This decline occurs at the same time that intestinal *SI* activity is increasing. Ingestion of milk or milk products by persons with diminished lactase activity leads to flatulence, abdominal cramping, and diarrhea. This pattern of reduction of lactase activity has been termed *late-onset lactase deficiency* or *adult-type hypolactasia*. Although initially it was thought that the regulation of lactase-phlorizin hydrolase (LPH) was post-translational and associated with altered structural features of the enzyme, it is now believed that the major mechanism of regulation of LPH is transcriptional.[299-301] Other forms of lactose intolerance include the rare congenital lactase deficiency and secondary forms, such as those caused by mucosal injury resulting from infectious gastroenteritis, parasitic infection, celiac disease, drug-induced enteritis, and Crohn's disease.[302]

Differential activation of both the lactase and the *SI* promoter is effected by multiple similar transcription factors, including GATA factors, HNF-1 alpha, and Cdx-2, alone and in combination. This synergistic activation may be a method to achieve higher levels of tissue-specific expression.[303]

Disaccharidase synthesis occurs within the ER, and the proenzymes then follow the path for secretory proteins through the Golgi complex before being inserted into the BBM. All are glycoproteins and all undergo extensive intracellular processing, with removal of redundant segments of the molecule. In the case of *SI*, final processing occurs on insertion into the BBM after exposure to luminal pancreatic proteases (Fig. 102-14).[304] At this point, it is cleaved into its 2 active subunits; in contrast, lactase is already completely processed before its insertion.[305,306]

In their final active form, the carbohydrases project into the intestinal lumen, forming part of the glycocalyx, and they are attached to the membrane by a hydrophobic anchor that represents about 10% of the total mass of the molecule. Evidence suggests that MYO1A (brush border myosin I), a group of monomeric actin-based motors that are known to associate with membranes in intestinal villi, are involved in the retention of *SI* within the brush border.[307]

Disaccharidases are synthesized by both crypt and villus cells but are expressed only on the latter. Expression of these genes in the intestine exhibits a complex spatial pattern along the vertical (crypt-to-villus) and horizontal (proximal-to-distal) axes.[308] There is little *SI* activity in the crypts and villus tip cells, with maximal activity in lower- and mid-portions of the villus.[309] The major mechanism for regulating expression of the *SI* protein along the crypt-villus axis is the steady-state level of *SI* mRNA; however, post-transcriptional and post-translational regulation likely play a role in the expression of the functional *SI* protein along the intestinal crypt-villus axis.[310]

A functional difference also exists between the jejunum and distal ileum that reflects differences in the expression of different genes, or gradients of gene expression, along the proximal-distal axis of the intestine. For example, *SI* activity is 4- to 5-fold greater in the jejunum than in the ileum,[311] although *SI* mRNA appears to be similar in the 2 areas. Although there are minor differences in the pattern of glycosylation in the Golgi apparatus, the major difference in regulation between the jejunum and ileum appears to be at the level of mRNA translation.[312]

Pancreatic proteolytic enzymes shorten the half-life ($T_{1/2}$) of the carbohydrases.[313] After meals, *SI* $T_{1/2}$ may drop as low as 4.5 hours, compared with more than 20 hours during fasting. Presumably, proteolysis, as largely determined by meals, is responsible for the diurnal variation in carbohydrase activity.[254]

The levels of *SI* and other saccharidases also may decrease with infection and inflammation. In some cases, a decline in enzyme activity leads to malabsorption of carbohydrates, with resultant diarrhea, flatulence, and weight loss. In most disease processes, however, diminished levels of *SI* are associated with global dysfunction of the small intestinal mucosa.

Transport Across the Mucosa

The 3 major diet-derived monosaccharides—glucose, galactose and fructose—are absorbed by saturable carrier-mediated transport systems located in the BBM of enterocytes in the proximal and middle small intestine.[314] These transport proteins facilitate transport of D-isomers (but not L-isomers) of hexoses.[244]

Active transport of glucose and galactose is achieved by the sodium-coupled secondary active transport symporter, also known as the *sodium-glucose transporter* (primarily *SGLT1* [see Chapter 101])[315]; active glucose transport is driven by the sodium gradient across the apical cell membrane. First, a low intracellular sodium concentration is generated by the sodium pump (sodium-potassium-adenosine triphosphatase [Na^+, K^+-ATPase]) located in the basolateral membrane of the enterocyte, which transports 3 Na^+ out of the cell and 2 K^+ into the cell, resulting in a low intracellular Na^+ concentration. Then 2 Na^+ ions bind to the outer face of the transporter, producing a conformational change that permits subsequent high-affinity

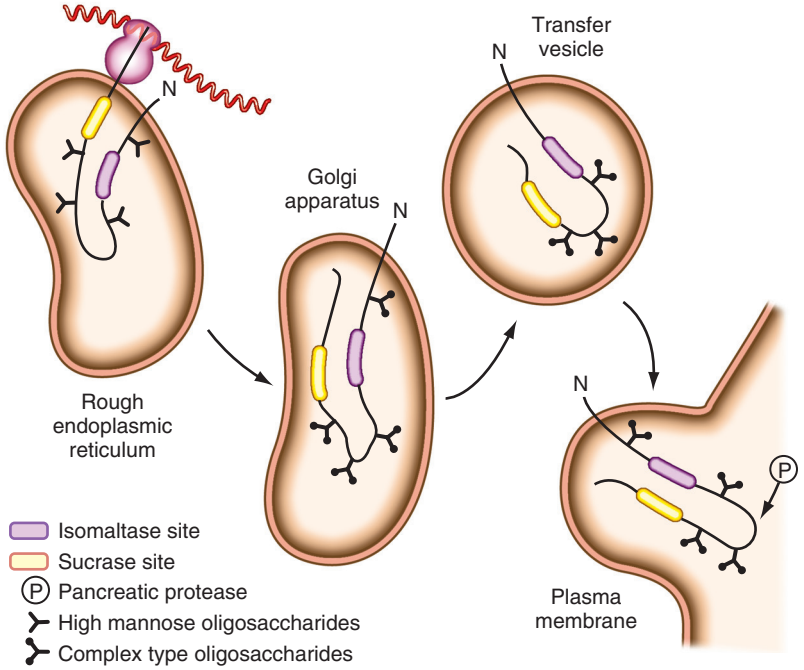

FIGURE 102-14. Biosynthesis of sucrose isomaltase. Nascent polypeptide is translocated across the endoplasmic reticulum membrane after ribosomal mRNA translation. Oligosaccharide side chains join the polypeptide to be transferred to the Golgi apparatus for further processing. After incorporation in the plasma membrane, luminal proteases cleave the molecule into its active subunits. *(From Lloyd ML, Olsen WA. Intestinal carbohydrases. Viewpoints Dig Dis 1991; 3:13-8.)*

sugar binding, after which the 2 Na^+ ions and the glucose molecule are transferred to the cytoplasmic face of the membrane through another conformational change involving a coordinated rotation and/or tilt of transmembrane helices.[316] At the cytoplasmic surface, the 2 Na^+ ions dissociate from their binding sites, causing the transporter affinity for glucose to decrease, with subsequent release of the sugar into the cytosol and production of a ligand-free transporter. The low affinity of the cytosolic sites for glucose and Na^+, and the low intracellular Na^+ concentration relative to the extracellular concentration (10 vs. 140 mEq/L), promote these dissociations. The ligand-free transporter then relaxes to the outward-facing conformation to complete the cycle. The complete enzymatic turnover of the transporter occurs about 1000 times a second at 37°C.[244]

Although some of this glucose fuels cellular metabolism, a sizable fraction passes out of the cell across the basolateral membrane into the blood, either through facilitated glucose transporters/uniporters (GLUT2), exocytosis, or simple diffusion. GLUT 2 also has the capacity to transport fructose (see below), galactose, and mannose across the basolateral membrane.[317,318]

The net result of the above process is that for every glucose molecule transported across the brush border, Na^+ ions (and 2 accompanying anions) also are transported across the epithelium. This in turn draws about 1100 water molecules across the epithelium to maintain iso-osmolarity of the absorbate. Ion and nutrient absorption across the intestine do not increase the osmolarity of the fluid remaining in the intestinal lumen. The coupling between glucose, salt, and water absorption provides the explanation for the finding that water absorption across the upper and mid-intestine is glucose dependent, and is the rationale for the oral rehydration therapy (ORT) used so effectively to treat patients with secretory diarrhea, including cholera (see Chapter 110).[319,320]

The prevailing opinion is that there are 2 types of glucose transporters found across brush borders: 1 is a high-affinity Na^+-dependent, phlorizin-sensitive transporter (*SGLT1*), and the other is a low-affinity transporter that may be Na^+-dependent and phlorizin-sensitive; candidates for the latter role in humans include GLUT2, SGLT4, and SGLT6.[321]

SGLT1 has been characterized extensively.[322-324] Activity of this 73-kd co-transporter in the intestinal BBM rests with the presence of 4 independent, identical subunits arranged in a homotetramer. The sodium glucose co-transporter resides on chromosome 22 and has been cloned and sequenced. The cloned complementary (c)DNA encodes for transport activity with the same relative specificity as the previously characterized native transport system: D-glucose > α-methyl-D-glucose > D-galactose > 3-*O*-methyl-D-glucopyranose ≫> L-glucose.[325] The cDNA encodes a 662–amino acid protein with a predicted molecular weight that correlates well with the biochemically defined size. *SGLT1* is predicted to have 14 membrane-spanning domains, with 1 asparagine-linked carbohydrate group on the third extracytoplasmic loop.[326]

Expression and activity of glucose transport in the intestinal brush border are regulated by both short-term and longer-term processes. In the short term, activity of glucose transport is increased by both protein kinase A- and C-dependent processes.[327] The mechanism of this enhanced activity is an increase in the number of membrane transporters, mediated by changes in exocytosis and endocytosis of membrane vesicles that contain the transport protein. Longer-term regulation of glucose transport is mediated by changes in the expression of *SGLT1*, which is controlled by changes in the nutrient environment.[328]

Glucose-galactose malabsorption is characterized by the neonatal onset of severe diarrhea.[329] Multiple distinct mutations in the *SGLT1* gene have been identified, including missense, nonsense, frameshift, splice-site, and promoter

mutations, most of which are responsible for defective passage of *SGLT1* through the biosynthetic machinery from the ER, or poor trafficking from the Golgi apparatus to the BBM. Rarely do mutant *SGLT1* proteins reach the brush border at a normal rate, in which case, the glucose transport is defective.[321,330]

Fructose absorption occurs by facilitated diffusion (i.e., transport that occurs not against a concentration gradient but with a carrier protein to achieve transport rates greater than one would expect from simple diffusion). This process is completely independent of glucose absorption. Studies in humans have shown that there is a saturable facilitative transport system for fructose in the intestinal epithelium that has a lower activity than that for transport of glucose and galactose. The protein responsible for most apical membrane fructose transport is a member of the facilitative monosaccharide transporter family called GLUT5[331] and encoded by the gene *SLC2A5*. In humans, this 501–amino acid protein has 12 membrane-spanning domains, as do other GLUT molecules, and transports fructose exclusively[332]; GLUT2 may assist in absorption of excess luminal fructose.[331] Little fructose is metabolized in the enterocytes, and fructose is transported across the basolateral membrane (by both GLUT2 and GLUT5), taken up, and metabolized rapidly by the liver, with resultant low postabsorptive blood levels of fructose. There may be more than 1 type of fructose transport system. Malabsorption of fructose in humans can be prevented by the simultaneous administration of glucose, suggesting that there maybe another, glucose-responsive, system present in the enterocytes. No inherited disorders of fructose transport (GLUT5) have been reported, and no mutations in the protein coding region of the *SLC2A5* gene in patients with fructose malabsorption have been detected to date.[333,334] Overall, fructose is not as well absorbed as glucose, and high levels of dietary fructose may cause diarrhea, excessive intestinal gas, and recurrent abdominal pain. Fructose malabsorption has been associated with similar symptoms.[335]

Debate has developed over the mechanism of the passive or "diffusive" component of intestinal glucose absorption and, indeed, whether it exists.[336] Pappenheimer and colleagues proposed that paracellular solvent drag contributes a passive component, which, at high concentrations of sugars similar to those in the jejunal lumen immediately after a meal, is several-fold greater than the active component mediated by the Na^+-glucose cotransporter *SGLT1*.[337] Other investigators have argued that the kinetics of glucose absorption can be explained solely in terms of *SGLT1*, and that a passive or paracellular component play little if any part.[338,339] More recent data suggest that the passive component of glucose absorption exists, but that it is facilitated and mediated by the rapid glucose-dependent activation and recruitment of the facilitative glucose transporter GLUT2 to the BBM. This process is regulated through a protein kinase C-dependent pathway activated by glucose transport through *SGLT1* and also involves mitogen-activated protein kinase (MAP kinase) signaling pathways.[340]

Exit from the Epithelium

Most hexoses are exported from the epithelial cell by way of the basolateral membrane, although small amounts are utilized for intracellular metabolism. Exit across the basolateral membrane depends on facilitated diffusion (not requiring energy) via a specific carrier. The 2 genes that encode these facilitative sugar transporters are *SLC2A2* (which encodes GLUT2), a predominantly basolateral membrane-associated glucose transporter, and *SLC2A5* (encodes GLUT5), an apical membrane fructose transporter.[341-344] GLUT 2 has molecular structural characteristics similar to those of the other members of this family of genes. The protein has approximately 500 amino acids with many hydrophobic residues that predict a total of 12 membrane-spanning domains. There is 1 long extracellular loop between membrane-spanning domains 1 and 2 that contains an asparagine that is *N*-glycosylated, and 1 long cytoplasmic loop between membrane spanning domains 6 and 7.[345,346] Once the hexoses have entered the interstitial space, they diffuse into the portal circulation.

A congenital defect in glucose transport by GLUT2 has been identified and named the *Fanconi-Bickel syndrome*. Because GLUT2 is normally expressed in the liver, pancreas, and kidney as well as in the intestine, defects in this transporter are expected to have a widespread effect on glucose homeostasis. Indeed, patients with the Fanconi-Bickel syndrome exhibit tubular nephropathy, fasting hypoglycemia, rickets, stunted growth, and hepatomegaly secondary to glycogen accumulation.[347,348]

The accepted dogma of intestinal glucose absorption at the basolateral membrane by glucose transporters has been challenged by studies of intestinal glucose absorption in GLUT2 null mice and in patients with GLUT2 deficiency; in both cases, glucose absorption was not impaired.[349,350] Additional work has suggested that there are 2 separate pathways for the exit of sugar from enterocytes: 1 that involves GLUT2 and another that requires glucose phosphorylation, the transfer of glucose-6-phosphate into the ER, and the release of free glucose into the blood. The release mechanism is unclear, but it has been proposed to involve vesicle trafficking. This postulate is supported by oral tolerance tests performed in a patient with congenital deficiency in glucose-6-phosphate translocase 1 in whom glucose absorption was impaired but not eliminated.[348]

Not all potentially digestible carbohydrate is absorbed in the small intestine. As much as 20% of dietary starch may escape into the colon, particularly that derived from cereals and potatoes.[2] Most of this unclaimed carbohydrate, however, is metabolized by colonic bacteria, and the SCFAs thus derived are readily absorbed. Hydrogen and methane also are generated and contribute to flatus production.[3]

PROTEINS

Dietary Intake

Proteins are essential for a vast array of enzymatic, immunologic, mechanical, and structural functions within living organisms. Dietary proteins are the major source of amino acids, and in the average Western diet provide about 10% to 15% of energy intake. Affluent populations ingest more protein than needed to maintain their normal protein balance. An average adult in a Western country consumes 70 to 100 g/day of dietary protein, whereas the poor in Asia and Africa consume 50 or fewer g/day.[242,244,254,351]

Almost half of all protein that enters the intestine is derived from endogenous sources. Of this, 20 to 30 g/day include enzymes, hormones, and immunoglobulins present in salivary, gastric, pancreatic, biliary, and jejunal secretions. Another 30 g/day of protein are provided by epithelial cells desquamated from the villus tips, and 2 g of plasma proteins are delivered into the intestinal lumen each day.[242,244,351]

Recommended dietary requirements vary from 0.75 to 1 g/kg of body weight per day, but deficiency states are rare, even with intakes of 0.5 g/kg/day or less.[351] Recent data from the National Health and Nutrition Examination Survey (NHANES) showed that 7.7% of adolescent females and about 8% of older adult women were not getting the minimum recommended amount of protein in their diets.[352] Little harm

appears to occur in the unusual subgroups of society who consume very large amounts of protein, although renal function can be impaired by this dietary habit. The Masai tribes of Africa and the Gaucho of South America, who consume 250 to 300 g/day (largely of animal origin), suffer no obvious untoward effects.[254,353]

The variety of types of animal and plant proteins is enormous. Generally, plant proteins are less digestible than those derived from animals, but some fibrous animal proteins (e.g., keratin, collagen) are also relatively indigestible. High-proline proteins such as the glutenins are less thoroughly digested than are others. The quality of proteins depends largely on their amino acid composition; those proteins rich in essential amino acids are regarded as being of high quality. Proteins from animal sources have a high content of essential amino acids, unlike proteins from certain specific plant sources, which are said to be incomplete because they lack or contain certain essential amino acids.[354] Such deficiencies in essential amino acids typically are overcome in a mixed diet, although the relative contribution of dietary animal and plant protein varies according to geographic region. In developed countries like North America and Europe, animal protein contributes about 70% of the total protein, compared with developing nations in the Middle East and Africa where the animal protein contribution can be as low as 20%.

Food processing (e.g., by heat or alkaline treatment) may cause inter- and intramolecular bonding in the proteins to produce polymeric forms that are relatively resistant to hydrolysis.[1] Other constituents of the diet may also interfere with protein digestion; for example, starch and reducing sugars have the potential to impair digestion.[254,355] Despite these interferences, digestion and absorption of proteins are remarkably complete, and only about 3% to 5% of ingested nitrogen is lost in the stool, probably because of the resistance of some peptide bonds to hydrolysis.[1] A few selected proteins are resistant to proteolysis in the small intestine, including secretory IgA and intrinsic factor. Among the 20 common amino acids that form animal and plant proteins, 8 cannot be synthesized by animals: leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. These 8 "essential" amino acids have to be ingested, usually in plant-derived foods. Histidine also is required for growth in infants.

Intraluminal Digestion

Pepsins

For many years it was believed that proteins are completely hydrolyzed to free amino acids in the intestinal lumen and that their absorption is mediated by various amino acid transporters. In the 1970s, however, studies revealed that small peptides of 2 and 3 amino acids in length (i.e., di/tripeptides) are the main product of intestinal protein digestion.[356] Luminal digestion of proteins begins with gastric proteases, followed by pancreatic proteases, and unlike the digestive enzymes for carbohydrates and lipids, these proteases are secreted as proenzymes that require conversion to their active form for protein hydrolysis to occur.

Pepsins are a family of endoproteases that hydrolyze internal peptide bonds in proteins. They act preferentially on peptide bonds that are formed by the aromatic amino acids phenylalanine and tyrosine, and by the branched-chain amino acid leucine. There are 2 immunologically distinct groups of pepsins (groups 1 and 2), although 8 fractions are identified electrophoretically. Both of the immunologically separated species are secreted as inactive pepsinogens by chief cells, but group 2 isoforms also are present in the mucus cells in the oxyntic and pyloric areas of the stomach and in Brunner's glands of the duodenum. Their substrate specificities vary little, and their pH optima differ slightly (between 1.8 and 3.5); all are irreversibly inactivated in alkali. At neutral or alkaline pH, the pepsinogen amino-terminal region is folded in such a way as to mask the catalytic site. In the acidic environment of the stomach, the catalytic site is uncovered and then proceeds to remove the amino-terminal region, which consists of 40 amino acids, thereby generating the active form of the molecule, pepsin. Pepsinogen release from chief cells is stimulated by gastrin, histamine, and cholinergic stimulation, and closely mirrors acid secretion.[351,357]

Pepsins remain active at the acid pH of gastric contents to produce a mixture of peptides with a small portion of amino acids. Pepsin activity is therefore confined to the stomach and accounts for the digestion of 10% to 15% of dietary proteins. The completeness of intragastric proteolysis depends in part on the rate of gastric emptying, the pH of intragastric contents, and the types of protein ingested. Moreover, the products of protein digestion by pepsins in the stomach may further influence acid and pepsinogen secretion as well as gastric emptying. Subjects who are achlorhydric or have altered gastric emptying as a result of pyloroplasty or partial gastrectomy do not appear to have a problem with assimilation of protein, suggesting that gastric proteolysis is not an essential component of digestion.[244]

Pancreatic Proteases

Similar to pepsin, and in contradistinction to amylase and lipase, which are secreted in their active forms, each of the pancreatic proteases is secreted as a proenzyme (or zymogen) and, therefore, must be activated within the intestinal lumen. *Enteropeptidase*, also known as *enterokinase*, plays a key role in proteolysis. It is liberated from its superficial position in the BBM by the action of bile acids,[358] its action being to convert trypsinogen to trypsin by removing the hexapeptide of its NH_2 terminus. Trypsin in turn activates the other proteases and continues to split more trypsin from trypsinogen (Fig. 102-15).

Pancreatic proteases are classified as endo- and exopeptidases, according to the sites of the peptide bonds against which they are most active. Endopeptidases include trypsin, chymotrypsin, and elastase, and exopeptidases include carboxypeptidase A and B. Trypsin, chymotrypsin, and elastase split peptide bonds within the protein molecule to produce short-chain oligopeptides, in contrast to exopeptidases, which remove a single amino acid from the carboxyl terminal end of the peptide.[359] Trypsin is the most specific of the endopeptidases and cleaves internal peptide bonds at lysine and arginine residues; chymotrypsin cleaves bonds at aromatic or neutral amino acid residues, and elastase cleaves bonds at aliphatic amino acid residues. The resulting oligopeptides are further hydrolyzed by the exopeptidases carboxypeptidase A and B. Carboxypeptidase A cleaves aromatic amino acids, while carboxypeptidase B cleaves arginine or lysine peptides from the carboxy terminal end of proteins and peptides. The final products of intraluminal digestion thus are produced by cooperative activity of endo- and exopeptidases and consist of a number of neutral and basic amino acids together with peptides of 2 to 8 amino acids in length. About 30% of luminal amino nitrogen is found in amino acids and about 70% in oligopeptides.[360]

In addition to nutrient protein hydrolysis, pancreatic proteases have other functions: They split vitamin B_{12} from R protein, to which it is linked, so it can then bind intrinsic factor[361,362]; they increase the turnover of BBM hydrolytic enzymes and, as discussed above, initiate the final steps in

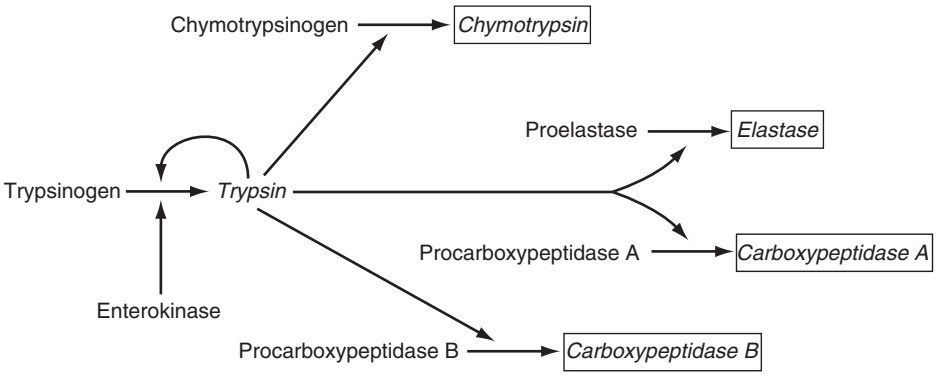

FIGURE 102-15. Activation of pancreatic proteolytic enzymes. Enterokinase (enteropeptidase) plays a critical role in activating trypsinogen to form trypsin. Trypsin in turn activates not only more trypsinogen but also other proteolytic enzyme precursors.

processing of the *SI* complex[304]; and finally, they may have a role in the inactivation of some microorganisms.[1]

Digestion at the Brush Border Membrane and in the Cytoplasm

In contrast to the absorption of carbohydrate, which is largely restricted to uptake of hexose monomers across the BBM, amino acids can be absorbed either as monomers or as di- or tripeptides.[363] Indeed, amino acid absorption is achieved more efficiently in the form of peptides than as single amino acids (Fig. 102-16).[364] The fact that the vast majority of the end-products of protein digestion that reach the portal circulation are amino acids, however, speaks strongly in favor of the presence of peptidases in the epithelium.

Patients with cystinuria and Hartnup disease, who have specific defects in the absorption of basic and neutral amino acids, respectively, do not develop protein-deficiency states, because the absorption of peptides in these patients is normal.[351] The discovery that di- and tripeptides are actively transported by the BBM of enterocytes has been in valuable in explaining this observation, and emphasizes the need for critical evaluation of the supposed nutritional advantage provided by elemental diets that consist only of free amino acids.

A range of peptidases are present on the brush border and in the cytoplasm of villus epithelial cells, in contrast to oligosaccharidases, which are found only at the brush border (Table 102-5). These peptidases account for the hydrolysis of oligopeptides up to about 8 amino acid residues in length.[351,365-367] The peptidases on the BBM differ in several important respects from those within the cytoplasm. About 90% of the dipeptidases are found in the cytoplasm and only about 10% in the brush border, whereas peptidases for pentapeptides and larger molecules are confined almost entirely to the BBM. Tripeptidases are the most variable in their distribution. Cytoplasmic enzymes are much more heat labile than those in the brush border, and there are differences in the electrophoretic mobility patterns for the 2 sets of enzymes.[368]

Most oligopeptidases appear to be aminopeptidases—that is, they act by removing residues from the amino terminus of the peptide. The chain length of the peptides is an important factor that determines not only whether the site at which hydrolysis occurs is at the brush border or within the cell but also its rate. Thus, rates of BBM hydrolysis for tripeptides are most rapid, and for dipeptides least rapid, while tetra- and pentapeptide hydrolysis rates occupy an intermediate position.[363,364,369]

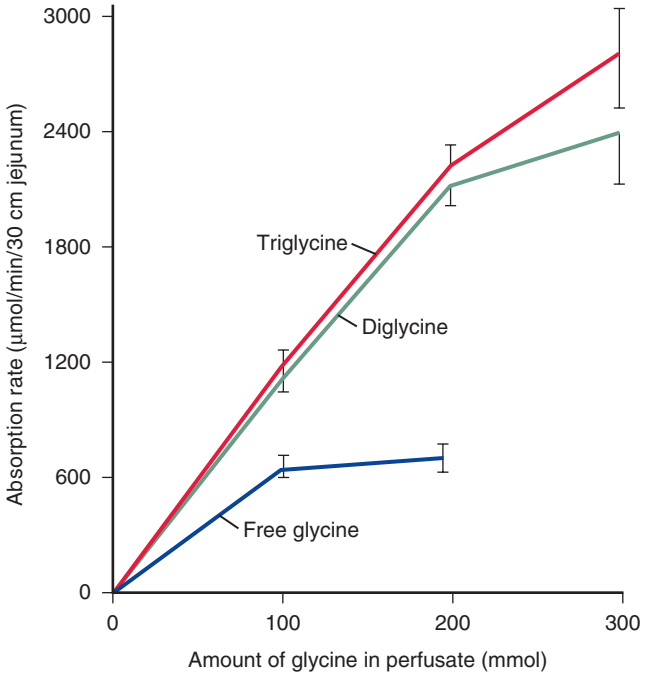

FIGURE 102-16. Rates of glycine absorption (mean ± standard error of mean) from perfusion solutions containing equivalent amounts of glycine in free or peptide form. Results are from studies in the jejunum of 4 normal humans. *(From Adibi SA, Morse EL, Masilamani SS, et al. Evidence for 2 different modes of tripeptide disappearance in human intestine. Uptake by peptide carrier systems and hydrolysis by peptide hydrolases. J Clin Invest 1975; 56:1355-63.)*

Distinct from the amino oligopeptidases are at least 3 other peptidases. Aminopeptidase A has specificity for peptides with acidic amino acids at their amino terminus. Aminopeptidases 1 and 3 (distinguished on electrophoretic mobility) have specificities for different substrates with different amino acid peptide bonds.[1,351,369]

Proline-containing oligopeptides are not readily hydrolyzed by most proteases, despite the fact that many proteins (e.g., collagen, gliadin, casein) are rich in proline. Two proline-specific carboxypeptidases, however, have been demonstrated in the BBM. They have slightly different substrate

TABLE 102-5 Peptidases Found on The Brush Border Membrane and in The Cytoplasm of Villus Epithelial Cells

Peptidase	Action	Products
Brush Border Membrane Peptidases		
Amino-oligopeptidases	Cleave amino acids from carboxy terminus of 3-8 amino acid peptides	Amino acids and dipeptides
Aminopeptidase A	Cleaves dipeptides with acidic amino acids at amino terminus	Amino acids
Dipeptidase I	Cleaves dipeptides containing methionine	Amino acids
Dipeptidase III	Cleaves glycine-containing dipeptides	Amino acids
Dipeptidyl aminopeptidase IV	Cleaves proline-containing peptides with free α-amino groups	Peptides and amino acids
Carboxypeptidase P	Cleaves proline-containing peptides with free carboxy terminus	Peptides and amino acids
GGTP	Cleaves gamma glutamyl bonds and transfers glutamine to amino acid or peptide acceptors	Gamma glutamyl amino acid or peptide
Folate conjugase	Cleaves pteroyl polyglutamates	Monoglutamate
Cytoplasmic Peptidases		
Dipeptidases (several types)	Cleave most dipeptides	Amino acids
Aminotripeptidase	Cleaves tripeptides	Amino acids
Proline dipeptidase	Cleaves proline-containing dipeptides	Proline and amino acids

specificities[370] and, together with a cytoplasmic proline dipeptidase, are likely to be responsible for hydrolysis of proline-rich peptides.

A number of other BBM peptidases merit mention. GGTP hydrolyzes gamma glutamyl peptide bonds, with the transfer of the gamma glutamyl group to another amino acid to form a gamma glutamyl amino acid or peptide derivative.[1] The role of this BBM in the intestine is not yet clear. Folate conjugase, an enzyme concerned with hydrolysis of dietary folate, will be considered later. Angiotensin I-converting enzyme (ACE) has now been demonstrated in intestinal mucosa, suggesting that it too may hydrolyze dietary peptides.[371] Indirect evidence suggests that endopeptidases also may be present on the BBM, because protein digestion occurs even in the complete absence of pancreatic function; these enzymes have yet to be isolated.

As with other proteins, synthesis of each specific peptidase occurs in the rough endoplasmic reticulum; following transfer to the Golgi apparatus, the proteins are transported to the BBM, where they are inserted by exocytic fusion.[372,373] They are attached to this membrane by short anchoring pieces in a manner analogous to the attachment of disaccharidases[374]; however, unlike the latter enzymes, there is little post-translational processing, either within the cytoplasm or by pancreatic enzymes on the brush border. These membrane-bound peptidases produce the most absorbable products of protein hydrolysis, including amino acids, dipeptides, and tripeptides. Although these peptidases are active throughout the small intestine, they appear to be most active in the ileum.[375]

The most abundant of the cytoplasmic dipeptidases appears to be one with broad specificity for neutral amino acid-containing dipeptides.[376] The cytoplasmic tripeptidase that has been isolated has broad specificity for amino-terminal residues and high specificity toward tripeptides containing proline as the amino-terminal residue, which distinguishes it from the BBM amino oligopeptidase. Other characteristics of a tripeptide that are required for rapid hydrolysis include a free alpha amino group, an alpha carboxyl group, and an L-configuration for the 2 amino acid residues.[377]

Absorption

Peptides

The small intestine is the primary site of protein absorption. Although protein digestion starts in the stomach (with pepsin), almost no absorption of protein products occurs at that site.[378] Substrate inhibition studies indicate that tri- and dipeptides inhibit uptake of each other from the lumen, but neither is affected by single amino acids. Such evidence suggests that small peptides use a separate transporter system from those utilized by single amino acids. By contrast, tetrapeptide absorption is inhibited by single amino acids but not by di- and tripeptides, suggesting that tetrapeptides are split before absorption.

The advantage of dipeptide absorption over single amino acid absorption has been largely demonstrated experimentally with single peptides containing a single amino acid, usually glycine.[364] Several studies, however, have demonstrated the kinetic advantage of peptides over amino acids, even in complex mixtures of partial digests of proteins.[379,380] Absorption was greater from tryptic hydrolysates of proteins than from a mixture of amino acids. Furthermore, the wide variation in rates of absorption seen with different individual amino acids was reduced when they were presented as a tryptic hydrolysate.

A number of other factors influence digestion and absorption. The presence of amino acids in the lumen inhibits peptide hydrolysis (product inhibition), whereas luminal glucose and luminal acidification each inhibit amino acid and peptide absorption.[364] There is good evidence to suggest that di- and tripeptides are taken up by a single type of transporter in the small intestine with some stereospecificity, because the length of the amino acid side chains on the di- or tripeptides is important; the longer the side chain on dipeptides, the more preferred the substrate for the absorption site.[381] For dipeptides, L-isomers of the amino acids are much preferred to the D-isomers, whereas the presence of acidic and basic amino acid residues in a dipeptide reduces its affinity for the transport system, compared with neutral amino acid residues. The

tripeptide transporter is more specific for the D-isomer acidic or basic amino acids and for short side chains. Affinity is also greater for dipeptides than for tripeptides, at least in peptides that contain glycine. The transporter for peptides is not dependent on sodium, but co-transport with protons instead.[382]

While there are several specific amino acid transporters, the proton-coupled uptake of the more than 8000 different oligopeptides (specifically di/tri-peptides) is performed by the peptide transporter PEPT1.[383,384] The oligopeptide transport family includes PEPT1 (found primarily in the intestines and kidneys) and PEPT2 (found mainly in the kidneys).[385] PEPT1 is the major intestinal transporter of oligopeptides and also facilitates the absorption of numerous peptidomimetic drugs, including many antibiotics.[386,387] PEPT1 is encoded by the *SLC15A1* gene on chromosome 13 and is a member of a superfamily of H^+-coupled peptide transporters. In humans it is expressed in the duodenum, jejunum, and ileum but not in the esophagus, stomach, or colon. In the small intestine, it is expressed only on absorptive epithelium. The human protein consists of 708 amino acids, with a predicted core molecular size of 79 kd that contains 12 transmembrane domains. It recognizes a variety of neutral, anionic, and cationic dipeptides as substrates, which explains the broad substrate specificity of the intestinal peptide transport system.[390-392]

A most interesting feature of this transport process is that it uses a transmembrane electrochemical H^+ gradient rather than a transmembrane electrochemical Na^+ gradient as its driving force.[393] There is an acid pH microclimate on the luminal surface of the intestinal BBM that creates a H^+ gradient across the BBM in vivo. This acid pH microclimate is generated and maintained by the combined action of the Na^+-H^+ exchanger in the BBM and Na^+, K^+-ATPase in the basolateral membrane of the enterocyte. The mechanism of the transport process is a simultaneous translocation of H^+ and peptide that involves a single H^+ binding site on the protein (Fig. 102-17).[394,395] A multitude of well-established processes are involved in the absorption of peptides and include a Na^+/H^+ exchanger located in the BBM that maintains an intracellular alkaline pH; a Na^+, K^+-ATPase located in the basolateral membrane that maintains an inside negative membrane potential; and several cytoplasmic peptidases that prevent intracellular accumulation of absorbed peptides. These enzymes convert most of the absorbed oligopeptides to amino acids that are either used by the absorbing cells or are released into the portal circulation via the amino acid transporters located on the basolateral membrane of these cells. The oligopeptides that escape hydrolysis by the cytoplasmic peptidases are transported across the basolateral membrane into the portal circulation by a peptide transporter that appears to be different from the PEPT1 transporter. Oligopeptide transport could be regulated by alteration in the activity or abundance of PEPT1, Na^+/H^+ exchanger, Na^+, K^+-ATPase, cytoplasmic peptidases, and basolateral oligopeptide transporter.[244,396,397]

Studies of individual substrates and hormones in cell culture have shown that the membrane population of PEPT1 is increased by dipeptides, certain amino acids, insulin, and leptin, and decreased by EGF and triiodothyronine. In the case of dipeptides, EGF, and thyroid hormone, there are parallel changes in the gene expression brought about by alteration of transcription and/or stability of PEPT1 mRNA. In contrast, treatment with insulin and leptin does not induce any alteration in the expression of PEPT1. The apparent change in protein expression appears to be increased trafficking from a preformed cytoplasmic pool to the apical membrane.[396-399]

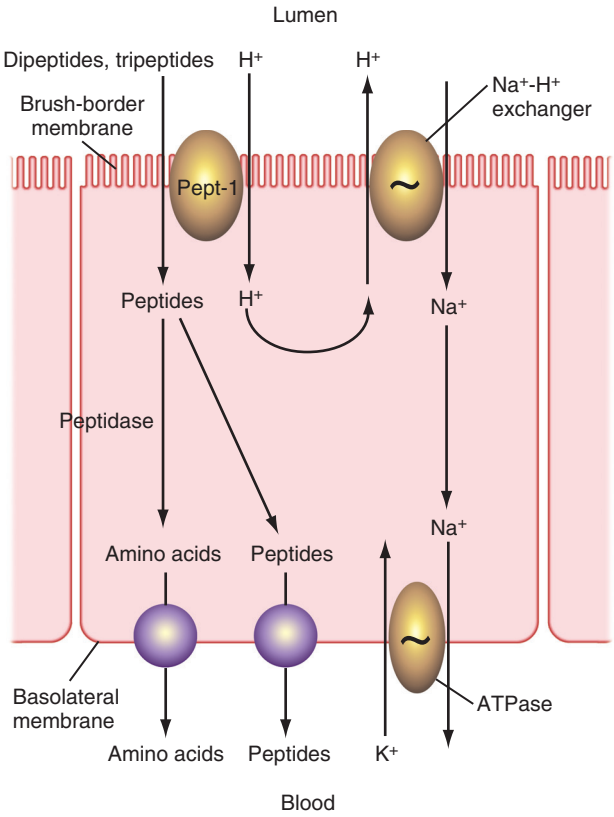

FIGURE 102-17. Peptide transport across the intestinal epithelium. The transport process uses a transmembrane H^+ gradient rather than a transmembrane electrochemical Na^+ gradient as the driving force. An acid pH microclimate on the luminal surface of the intestinal brush border membrane (BBM) is generated and maintained by the combined action of Na^+/H^+ exchanger in the BBM and Na^+, K^+-ATPase in the basolateral membrane of the enterocyte. The mechanism of the transport process is a simultaneous translocation of H^+ and peptide substrate involving a single H^+ binding site on the protein. Pept-1, Peptide transporter-1.

Amino Acids

Whereas there appears to be only 1 type of oligopeptide transporter in the BBM, there is a multiplicity of transport mechanisms for the 20 individual amino acids. In adults, these are situated on villus enterocytes and involve carrier-mediated active transport or facilitated diffusion processes, which are typically dependent on the Na^+ gradient as the driving force; a small proportion may be absorbed by simple diffusion, independent of any ion gradient.

In addition to their stereospecificity (L-amino acids are preferentially transported), amino acid transporters exhibit broad/overlapping substrate specificity; consequently there has been some difficulty in defining the number and types of transporters. Several amino acids utilize a number of different transport systems (Table 102-6). On the basis of kinetic studies, at least 4 active processes for transport of neutral amino acids across the apical cell membrane have been identified. Each is electrogenic and sodium dependent: 1 has broad specificity for a number of neutral amino acids (NBB system or B^0 system), a second provides another route for phenylalanine and methionine (PHE system), a third provides a mechanism for imino acid absorption (IMINO system), and the fourth transports beta amino acids. Separate sodium-dependent, active transport processes for basic and acidic amino acids also have been demonstrated, and there is some evidence to suggest that facilitated diffusion of these types of amino acids also occurs, although this is likely to be a minor pathway.[242,383,400,401]

TABLE 102-6 Major Amino Acid Transport Systems Detected in Intestinal Epithelial Cells

Transport System	Substrates
Brush Border Membrane *Neutral Amino Acids*	
SLC6A19	Broad specificity for neutral amino acids
SLC36A1	Imino acids; proline, hydroxyproline
SLC6A20	Imino acids
SLC6A14	Neutral and cationic amino acids
SLC1A5	Ala, Ser, Cys, Gln, Asn
SLC7A9/SLC3A1	Neutral amino acids, cationic amino acids, cystine
Basic Amino Acids	Lysine, Cys, basic amino acids
Acidic Amino Acids	
SLC1A1 ($X\text{-}GA^-$)	Glutamate, aspartate
Basolateral Membrane	
L	Broad selectivity
A	Broad selectivity
SLC1A5 (ASC)	Neutral amino acids, Ala, Ser, Cys
N	Glutamine, histidine, Asn

Ala, alanine; Asn, asparagine; Cys, cysteine; Gln, glycine; Ser, serine.

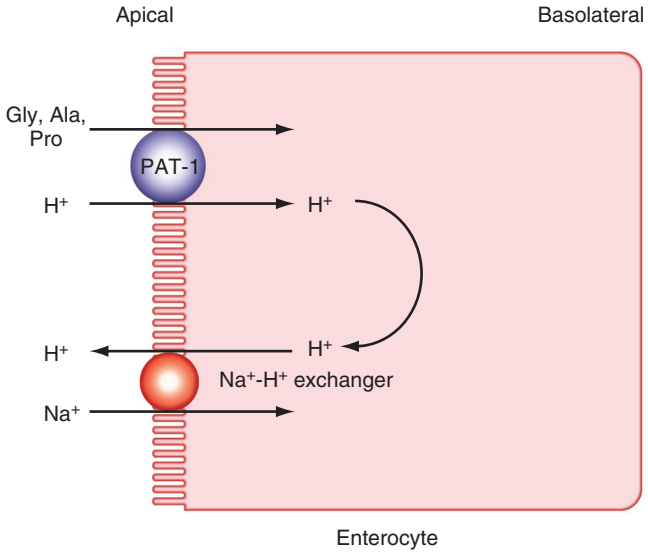

FIGURE 102-18. Intestinal amino acid transport. Human PAT-1 transporter is involved in absorption of small amino acids across the apical membrane. The acid microenvironment generated by the Na^+/H^+ exchanger provides an electrochemical proton gradient that drives amino acids to the cytosol. Ala, alanine; Gly, glycine; PAT-1, Proton-assisted amino acid transporter-1; Pro, proline. *(From Boll M, Daniel H, Gasnier B. The SLC36 family: Proton-coupled transporters for the absorption of selected amino acids from extracellular and intracellular proteolysis. Pflugers Arch 2004; 447:776-9.)*

Genomic advances have allowed most mammalian amino acid transport functions to be attributed to specific gene products: at least 52 amino acid transporter-related gene products are grouped within 12 solute carrier families, with their own new nomenclature.[402] The classic Na^+-dependent imino acid transporter has been identified as the human PAT1 (or human *p*roton-coupled *a*mino acid *t*ransporter 1) or solute carrier SLC36A1. This high-capacity imino acid carrier has been localized to the small intestinal luminal membrane and transports imino and amino acids (glycine, praline, alanine, taurine).[403,404] Human PAT1 mediates 1:1 symport of protons and small neutral amino acids. The acid microclimate of the BBM drives transport of amino acids into the cytosol. Transport activity is independent of Na^+ and Cl^- (Fig. 102-18). In addition, the IMINO system is a Na^+-dependent transporter with specificity toward the imino acids proline and hydroxyproline. The protein responsible for this transport activity is SIT1 (Na^+-coupled imino acid transporter 1).[405,406]

System $B^{0,+}$, also present on the BBM, mediates the Na^+- and Cl^--coupled electrogenic transport of neutral as well as cationic amino acids across the BBM. The gene encoding the protein responsible for this activity, *$ATB^{0,+}$* is located on human chromosome X. A separate Na^+-dependent transport system, X^-_{AG} (*SLC1A1*), is specific for the anionic amino acid aspartate and glutamate. The glutamate transporter expressed in the intestinal BBM is known as the EAAT3. This transporter is defective in the inherited amino acid transport defect known as *dicarboxylic aciduria*.[351]

Hartnup disease is a disorder of renal and GI neutral amino acid transport that is inherited as an autosomal recessive trait.[407] The gene causing Hartnup disease has been localized to chromosome 5p15 (it had previously been localized to chromosome 19), and the gene, *SLC6A19*, a Na^+-dependent and Cl^--independent neutral amino acid transporter, has been suggested as the defective gene by 2 separate groups.[408,409] This transporter has been shown to be expressed in the intestine and has properties of system B^0. *System B^0* refers to a broad range of amino acids with neutral (0) charge. SLC1A5 is the proposed ASC carrier for neutral amino acids: alanine, serine, and cysteine.[410] Whereas the *SLC1A1* carrier co-transports 3 Na^+ and 1 H^+ with countertransport of 1 K^+, the SLC1A5 transporter mediates Na^+-dependent transport.

The $B^{0,+}$ is a Na^+-independent transport system that recognizes neutral and cationic amino acids in addition to the disulfide amino acid cystine. It is a heterodimer consisting of a light and heavy chain, with the genes responsible for each chain found on chromosomes 2 and 19, respectively; this transporter is defective in cystinuria.[411,412]

Several hormones have been shown to alter the amino acid and peptide transport process in the intestine. Somatostatin and VIP decrease these transport processes, whereas EGF, neurotensin, CCK, and secretin enhance them.[413-415] Human PEPT1 appears to be inhibited by protein kinase C[416] and cAMP.[417] Expression of the intestinal peptide transporter is also modulated by dietary protein content.[418] Even though the peptide transporter is expressed along the entire small intestine, diet-induced changes in transporter expression are specific to certain regions. A high-protein diet increases the steady-state levels of the transporter-specific messenger RNA in the middle and distal regions of the small intestine. Expression of the brush border peptidases dipeptidylcarboxypeptidase and dipeptidylaminopeptidase IV, which releases dipeptides from oligopeptides, also is enhanced by a high-protein diet.[386] Recent evidence has also demonstrated the potential role the intestinal microbiota plays in the regulation of protein absorption, specifically with respect to enhancing PEPT1 expression.[419-422]

Exit from the Epithelium

Exit through the basolateral membrane operates via a number of different mechanisms that involves active transport and diffusion of both facilitated types.[351] Active Na^+-dependent

processes exist at this membrane for the uptake of neutral amino acids, which presumably supply nutrients for crypt cells and for villus enterocytes during fasting when a luminal source is unavailable. Villus enterocytes normally receive the amino acids necessary for production of their own protein from luminal nutrients; crypt cells obtain their supply from the portal circulation. Of all the amino acids, glutamine appears to be a unique and major source of energy for enterocytes; ammonia is an important metabolic by-product of this process. Active uptake of glutamine at the basolateral membrane, as well as via apical membrane processes, is therefore of particular importance.[423,424]

It has been estimated that approximately 10% of amino acids are utilized in the production of enterocyte protein. Some of these proteins are secreted across the basolateral membrane, specifically by villus enterocytes, including apoA-1 and apo-IV, secretion of which increases many-fold after a fatty meal.[254]

The intestinal basolateral membrane possesses a set of amino acid transport systems that differ from those in the BBM. The amino acid transport systems in the basolateral membrane function to export amino acids from the enterocytes into the portal circulation during feeding. They also participate in the import of amino acids from the portal circulation into the enterocyte for cellular metabolism when amino acids are not available from the intestinal lumen, such as between meals. The intestinal basolateral membrane possesses a peptide transporter system that is probably identical to that in the BBM, and that facilitates the exit of hydrolysis-resistant small peptides from the enterocyte into the portal circulation.[351]

Several well-documented amino acid transport systems have been described in the basolateral membrane. System y^+L is the amino acid exchanger that permits Na^+-independent efflux of cationic amino acids from intestinal cells into the blood, coupled to the Na^+-dependent influx of neutral amino acids from the blood into intestinal cells. System A is a Na^+-coupled transport system for neutral amino acids, including glutamine, that plays a role in the entry of amino acids from the blood into intestinal cells for cellular metabolism. This Na^+-coupled neutral amino acid transporter (SNAT) consists of 3 subtypes, SNAT1, 2, and 4; SNAT2 is expressed in the small intestine.[425-427]

Whereas very small amounts of di- and tripeptides have been detected in the portal circulation after a meal, the great majority of absorbed products of protein digestion that reach the circulation are in the form of single amino acids. A somewhat surprising finding is that digestion of protein continues into the ileum, with about 40% of ingested protein undergoing transport in this segment of small intestine.[428]

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