

Lipid Metabolism

Most of the lipids found in the body fall into the categories of fatty acids and triacylglycerols; glycerophospholipids and sphingolipids; eicosanoids; cholesterol, bile salts, and steroid hormones; and fat-soluble vitamins. These lipids have very diverse chemical structures and functions. However, they are related by a common property: their relative insolubility in water.

Fatty acids, which are stored as triacylglycerols, serve as fuels, providing the body with its major source of energy (Fig. VI.1). Glycerophospholipids and sphingolipids, which contain esterified fatty acids, are found in membranes and in blood lipoproteins at the interfaces between the lipid components of these structures and the surrounding water. These membrane lipids form hydrophobic barriers between subcellular compartments and between cellular constituents and the extracellular milieu. Polyunsaturated fatty acids containing 20 carbons form the eicosanoids, which regulate many cellular processes (Fig. VI.2).

Cholesterol adds stability to the phospholipid bilayer of membranes. It serves as the precursor of the bile salts, detergent-like compounds that function in the process of lipid digestion and absorption (Fig. VI.3). Cholesterol also serves as the precursor of the steroid hormones, which have many actions, including the regulation of metabolism, growth, and reproduction.

The fat-soluble vitamins are lipids that are involved in such varied functions as vision, growth, and differentiation (vitamin A), blood clotting (vitamin K), prevention of oxidative damage to cells (vitamin E), and calcium metabolism (vitamin D).

Triacylglycerols, the major dietary lipids, are digested in the lumen of the intestine (Fig. VI.4). The initial digestive products, free fatty acids and 2-monoacylglycerol, are reconverted to triacylglycerols in intestinal epithelial cells, packaged in lipoproteins known as chylomicrons (so they can safely enter the circulation), and secreted into the lymph. Ultimately, chylomicrons enter the blood, serving as one of the major blood lipoproteins.

Very low density lipoprotein (VLDL) is produced in the liver, mainly from dietary carbohydrate. Lipogenesis is an insulin-stimulated process through which glucose is converted to fatty acids, which are subsequently esterified to glycerol to form the triacylglycerols that are packaged in VLDL and secreted from the liver. Thus, chylomicrons primarily transport dietary lipids, and VLDL transports endogenously synthesized lipids.

The triacylglycerols of chylomicrons and VLDL are digested by lipoprotein lipase (LPL), an enzyme found attached to capillary endothelial cells (see Fig. VI.4). The fatty acids that are released are taken up by muscle and many other tissues and oxidized to CO_2 and water to produce energy (see Chapter 23). After a meal, these fatty acids are taken up by adipose tissue and stored as triacylglycerols.

LPL converts chylomicrons to chylomicron remnants and VLDL to intermediate density lipoprotein (IDL). These products, which have a relatively low triacylglycerol content, are taken up by the liver by the process of endocytosis and degraded by lysosomal action. IDL may also be converted to low density lipoprotein (LDL) by further digestion of triacylglycerol. Endocytosis of LDL occurs in peripheral tissues as well as the liver (Table VI.1), and is the major means of cholesterol transport and delivery to peripheral tissues.

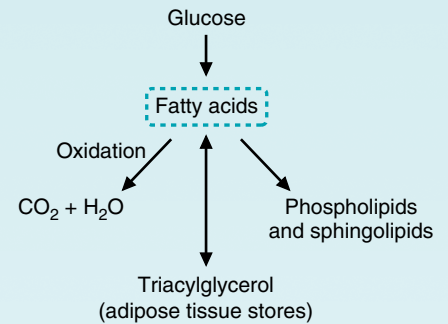


Fig. VI.1. Summary of fatty acid metabolism.

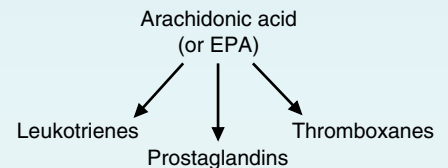


Fig. VI.2. Summary of eicosanoid synthesis. EPA = eicosapentenoic acid.

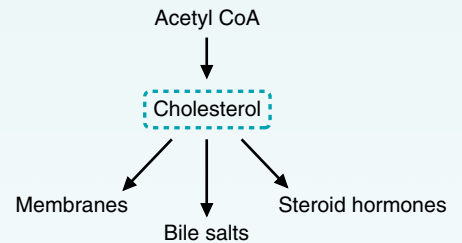


Fig. VI.3. Summary of cholesterol metabolism.

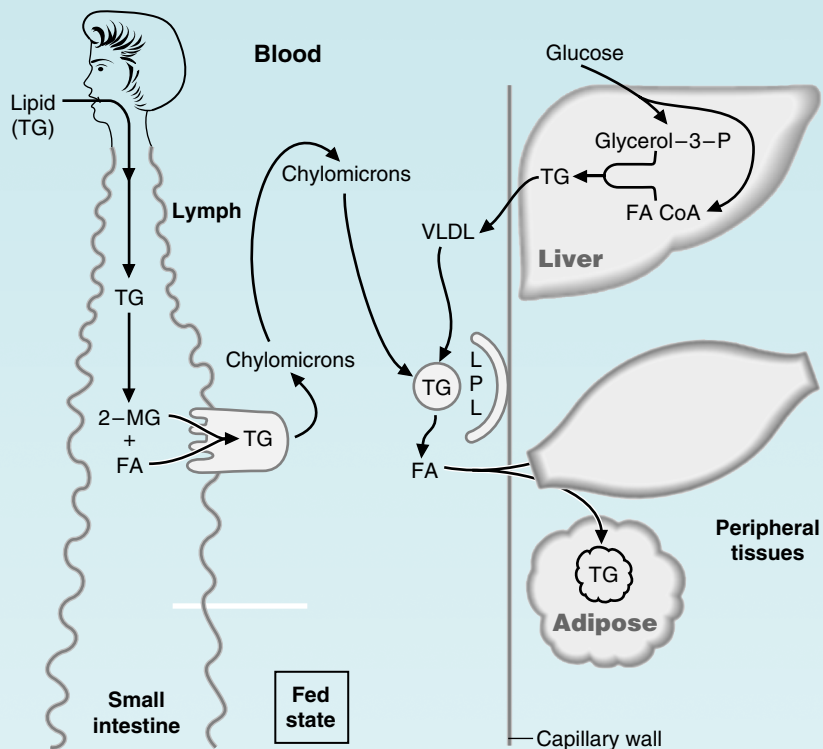


Fig. VI.4. Overview of triacylglycerol metabolism in the fed state. TG = triacylglycerol; 2-MG = 2-monoacylglycerol; FA = fatty acid; circled TG = triacylglycerols of VLDL and chylomicrons; LPL = lipoprotein lipase.

The principal function of high density lipoprotein (HDL) is to transport excess cholesterol obtained from peripheral tissues to the liver and to exchange proteins and lipids with chylomicrons and VLDL. The protein exchange converts "nascent" particles to "mature" particles.

During fasting, fatty acids and glycerol are released from adipose triacylglycerol stores (Fig. VI.5). The glycerol travels to the liver and is used for gluconeogenesis. Only the liver contains glycerol kinase, which is required for glycerol metabolism.

Table VI.1. Blood Lipoproteins

Chylomicrons

- produced in intestinal epithelial cells from dietary fat
- carries triacylglycerol in blood

VLDL (very low density lipoprotein)

- produced in liver mainly from dietary carbohydrate
- carries triacylglycerol in blood

IDL (intermediate density lipoprotein)

- produced in blood (remnant of VLDL after triacylglycerol digestion)
- endocytosed by liver or converted to LDL

LDL (low density lipoprotein)

- produced in blood (remnant of IDL after triacylglycerol digestion; endproduct of VLDL)
- contains high concentration of cholesterol and cholesterol esters
- endocytosed by liver and peripheral tissues

HDL (high density lipoprotein)

- produced in liver and intestine
- exchanges proteins and lipids with other lipoproteins
- functions in the return of cholesterol from peripheral tissues to the liver

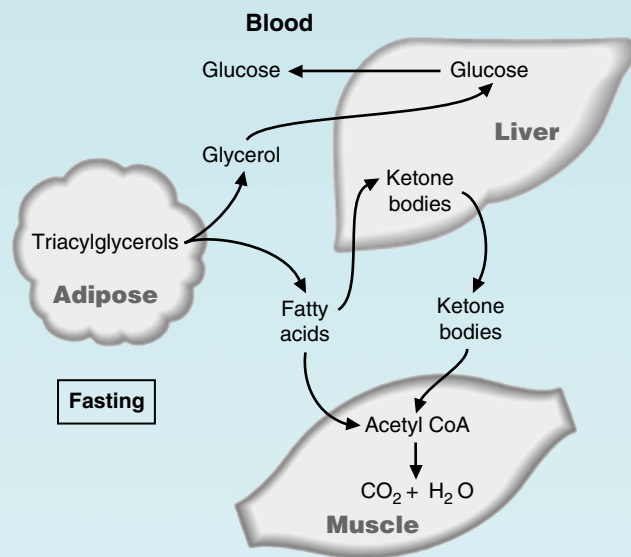


Fig. VI.5. Overview of triacylglycerol metabolism during fasting.

The fatty acids form complexes with albumin in the blood and are taken up by muscle, kidney, and other tissues, where ATP is generated by their oxidation to CO₂ and water. Liver also converts some of the carbon to ketone bodies, which are released into the blood. Ketone bodies are oxidized for energy in muscle, kidney, and other tissues during fasting, and in the brain during prolonged starvation (see Chapter 23).

32 Digestion and Transport of Dietary Lipids

Triacylglycerols are the major fat in the human diet, consisting of three **fatty acids** esterified to a **glycerol** backbone. Limited digestion of these lipids occurs in the mouth (**lingual lipase**) and stomach (**gastric lipase**) because of the low solubility of the substrate. In the intestine, however, the fats are emulsified by **bile salts** that are released from the gallbladder. This increases the available surface area of the lipids for **pancreatic lipase and colipase** to bind and to digest the triglycerides. Degradation products are **free fatty acids** and **2-monoacylglycerol**. When partially digested food enters the intestine, the hormone **cholecystokinin** is secreted by the intestine, which signals the gallbladder to contract and release bile acids, and the pancreas to release digestive enzymes.

In addition to triacylglycerols, phospholipids, cholesterol, and cholesterol esters (cholesterol esterified to fatty acids) are present in the foods we eat. Phospholipids are hydrolyzed in the intestinal lumen by **phospholipase A2**, and cholesterol esters are hydrolyzed by **cholesterol esterase**. Both of these enzymes are secreted from the pancreas.

The products of enzymatic digestion (free fatty acids, glycerol, **lysophospholipids**, cholesterol) form **micelles** with bile acids in the intestinal lumen. The micelles interact with the enterocyte membrane and allow diffusion of the lipid soluble components across the enterocyte membrane into the cell. The bile acids, however, do not enter the enterocyte at this time. They remain in the intestine, travel further down, and are then reabsorbed and sent back to the liver by the **enterohepatic circulation**. This allows the bile salts to be used multiple times in fat digestion.

The intestinal epithelial cells will resynthesize triacylglycerol from free fatty acids and 2-monacylglycerol and will package them with a protein, **apolipoprotein B-48**, phospholipids, and cholesterol esters into a soluble lipoprotein particle known as a **chylomicron**. The chylomicrons are secreted into the **lymph** and eventually end up in the circulation, where they can distribute dietary lipids to all tissues of the body.

Once in circulation, the newly released (“nascent”) chylomicrons interact with another lipoprotein particle, **HDL** (high-density lipoprotein) and acquire two **apoproteins** from HDL, apoprotein **CII** and **E**. This converts the nascent chylomicron to a “mature” chylomicron. The apoCII on the mature chylomicron activates the enzyme **lipoprotein lipase (LPL)**, which is located on the inner surface of the capillary endothelial cells of muscle and adipose tissue. The **LPL** digests the triglyceride in the chylomicron, producing free fatty acids and glycerol. The fatty acids enter the adjacent organs either for energy production (muscle) or fat storage (adipocyte). The glycerol that is released is metabolized in the liver.

As the chylomicron loses triglyceride, its density increases and it becomes a **chylomicron remnant**, which is taken up by the liver by receptors that recognize apolipoprotein E. In the liver, the chylomicron remnant is degraded into its component parts for further disposition by the liver.



The lymph system is a network of vessels that surround interstitial cavities in the body. Cells secrete various compounds into the lymph, and the lymph vessels transport these fluids away from the interstitial spaces in the body tissues and into the bloodstream. In the case of the intestinal lymph system, the lymph enters the bloodstream through the thoracic duct. These vessels are designed such that under normal conditions the contents of the blood cannot enter the lymphatic system. The lymph fluid is similar in composition to that of the blood but lacks the cells found in blood.



THE WAITING ROOM



Will Sichel had several episodes of mild back and lower extremity pain over the last year, probably caused by minor sickle cell crises. He then developed severe right upper abdominal pain radiating to his lower right chest and his right flank 36 hours before admission to the emergency room. He states that the pain is not like his usual crisis pain. Intractable vomiting began 12 hours after the onset of these new symptoms. He reports that his urine is the color of iced tea and his stool now has a light clay color.

On physical examination, his body temperature is slightly elevated, and his heart rate is rapid. The whites of his eyes (the sclerae) are obviously jaundiced (a yellow discoloration caused by the accumulation of bilirubin pigment). He is exquisitely tender to pressure over his right upper abdomen.

The emergency room physician suspects that Michael is not in sickle cell crisis but instead has either acute cholecystitis (gallbladder inflammation) or a gallstone lodged in his common bile duct, causing cholestasis (the inability of the bile from the liver to reach his small intestine). His hemoglobin level was low at 7.6 mg/dL (reference range = 12–16) but unchanged from his baseline 3 months earlier. His serum total bilirubin level was 3.2 mg/dL (reference range = 0.2–1.0), and his direct (conjugated) bilirubin level was 0.9 mg/dL (reference range = 0–0.2).

Intravenous fluids were started, he was not allowed to take anything by mouth, a nasogastric tube was passed and placed on constant suction, and symptomatic therapy was started for pain and nausea. When his condition had stabilized, Michael was sent for an ultrasonographic (ultrasound) study of his upper abdomen.



Al Martini has continued to abuse alcohol and to eat poorly. After a particularly heavy intake of vodka, a steady severe pain began in his upper mid-abdomen. This pain spread to the left upper quadrant and eventually radiated to his mid-back. He began vomiting nonbloody material and was brought to the hospital emergency room with fever, a rapid heart beat, and a mild reduction in blood pressure. On physical examination, he was dehydrated and tender to pressure over the upper abdomen. His vomitus and stool were both negative for occult blood.

Blood samples were sent to the laboratory for a variety of hematologic and chemical tests, including a measurement of serum amylase and lipase, digestive enzymes normally secreted from the exocrine pancreas through the pancreatic ducts into the lumen of the small intestine.



Currently, 38% of the calories (kcal) in the typical American diet come from fat. The content of fat in the diet increased from the early 1900s until the 1960s, and then decreased as we became aware of the unhealthy effects of a high-fat diet. According to current recommendations, fat should provide no more than 30% of the total calories of a healthy diet.

I. DIGESTION OF TRIACYLGLYCEROLS

Triacylglycerols are the major fat in the human diet because they are the major storage lipid in the plants and animals that constitute our food supply. Triacylglycerols contain a glycerol backbone to which three fatty acids are esterified (Fig. 32.1). The main route for digestion of triacylglycerols involves hydrolysis to fatty acids and 2-monoacylglycerols in the lumen of the intestine. However, the route depends to some extent on the chain length of the fatty acids. Lingual and gastric lipases are produced by cells at the back of the tongue and in the stomach, respectively. These lipases preferentially hydrolyze short- and medium-chain fatty acids (containing 12 or fewer carbon atoms) from dietary triacylglycerols. Therefore, they are most active in

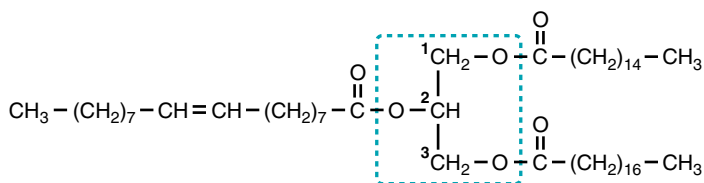


Fig. 32.1. Structure of a triacylglycerol. The glycerol moiety is highlighted, and its carbons are numbered.

infants and young children, who drink relatively large quantities of cow's milk, which contains triacylglycerols with a high percentage of short- and medium-chain fatty acids.

A. Action of Bile Salts

Dietary fat leaves the stomach and enters the small intestine, where it is emulsified (suspended in small particles in the aqueous environment) by bile salts (Fig. 32.2). The bile salts are amphipathic compounds (containing both hydrophobic and hydrophilic components), synthesized in the liver (see Chapter 34 for the pathway) and secreted via the gallbladder into the intestinal lumen. The contraction of the gallbladder and secretion of pancreatic enzymes are stimulated by the gut hormone cholecystokinin, which is secreted by the intestinal cells when stomach contents enter the intestine. Bile salts act as detergents, binding to the globules of dietary fat as they are broken up by the peristaltic action of the intestinal muscle. This emulsified fat, which has an increased surface area as compared with unemulsified fat, is attacked by digestive enzymes from the pancreas (Fig. 32.3).

B. Action of Pancreatic Lipase

The major enzyme that digests dietary triacylglycerols is a lipase produced in the pancreas. Pancreatic lipase is secreted along with another protein, colipase, along with bicarbonate, which neutralizes the acid that enters the intestine with partially digested food from the stomach. Bicarbonate raises the pH of the contents of the intestinal lumen into a range (pH ~ 6) that is optimal for the action of all of the digestive enzymes of the intestine. Bicarbonate secretion from the pancreas is stimulated by the hormone secretin, which is released from the intestine when acid enters the duodenum.



In patients such as **Will Sichel** who have severe and recurrent episodes of increased red blood cell destruction (hemolytic anemia), greater than normal amounts of the red cell pigment heme must be processed by the liver and spleen. In these organs, heme (derived from hemoglobin) is degraded to bilirubin, which is excreted by the liver in the bile.

If large quantities of bilirubin are presented to the liver as a consequence of acute hemolysis, the capacity of the liver to conjugate it, that is, convert it to the water-soluble bilirubin diglucuronide, can be overwhelmed. As a result, a greater percentage of the bilirubin entering the hepatic biliary ducts in patients with hemolysis is in the less water-soluble forms. In the gallbladder, these relatively insoluble particles tend to precipitate as gallstones rich in calcium bilirubinate. In some patients, one or more stones may leave the gallbladder through the cystic duct and enter the common bile duct. Most pass harmlessly into the small intestine and are later excreted in the stool. Larger stones, however, may become entrapped in the lumen of the common bile duct, where they cause varying degrees of obstruction to bile flow (cholestasis) with associated ductal spasm, producing pain. If adequate amounts of bile salts do not enter the intestinal lumen, dietary fats cannot readily be emulsified and digested.



The mammary gland produces milk, which is the major source of nutrients for the breastfed human infant. The fatty acid composition of human milk varies, depending on the diet of the mother. However, long-chain fatty acids predominate, particularly palmitic, oleic, and linoleic acids. Although the amount of fat contained in human milk and cow's milk is similar, cow's milk contains more short- and medium-chain fatty acids and does not contain the long-chain, polyunsaturated fatty acids found in human milk that are important in brain development.

Although the concentrations of pancreatic lipase and bile salts are low in the intestinal lumen of the newborn infant, the fat of human milk is still readily absorbed. This is true because lingual and gastric lipases produced by the infant partially compensate for the lower levels of pancreatic lipase. The human mammary gland also produces lipases that enter the milk. One of these lipases, which requires lower levels of bile salts than pancreatic lipase, is not inactivated by stomach acid and functions in the intestine for a number of hours.

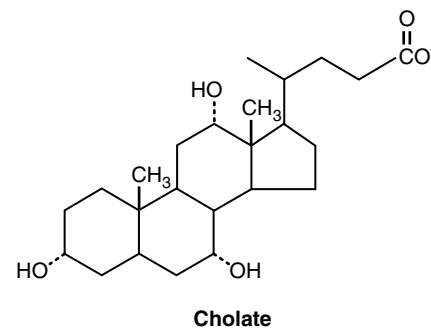


Fig. 32.2. Structure of a bile salt. The bile salts are derived from cholesterol and retain the cholesterol ring structure. They differ from cholesterol in that the rings in bile salts contain more hydroxyl groups and a polar side chain and lack a 5-6 double bond.



Al Martini's serum levels of pancreatic amylase (which digests dietary starch) and pancreatic lipase were elevated, a finding consistent with a diagnosis of acute and possibly chronic pancreatitis. The elevated levels of these enzymes in the blood are the result of their escape from the inflamed exocrine cells of the pancreas into the surrounding pancreatic veins. The cause of this inflammatory pancreatic process in this case was related to the toxic effect of acute and chronic excessive alcohol ingestion.

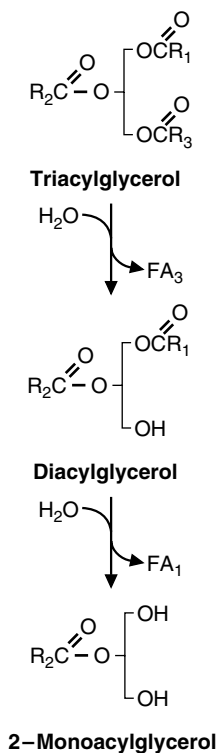


Fig. 32.4. Action of pancreatic lipase. Fatty acids (FA) are cleaved from positions 1 and 3 of the triacylglycerol, and a monoacylglycerol with a fatty acid at position 2 is produced.

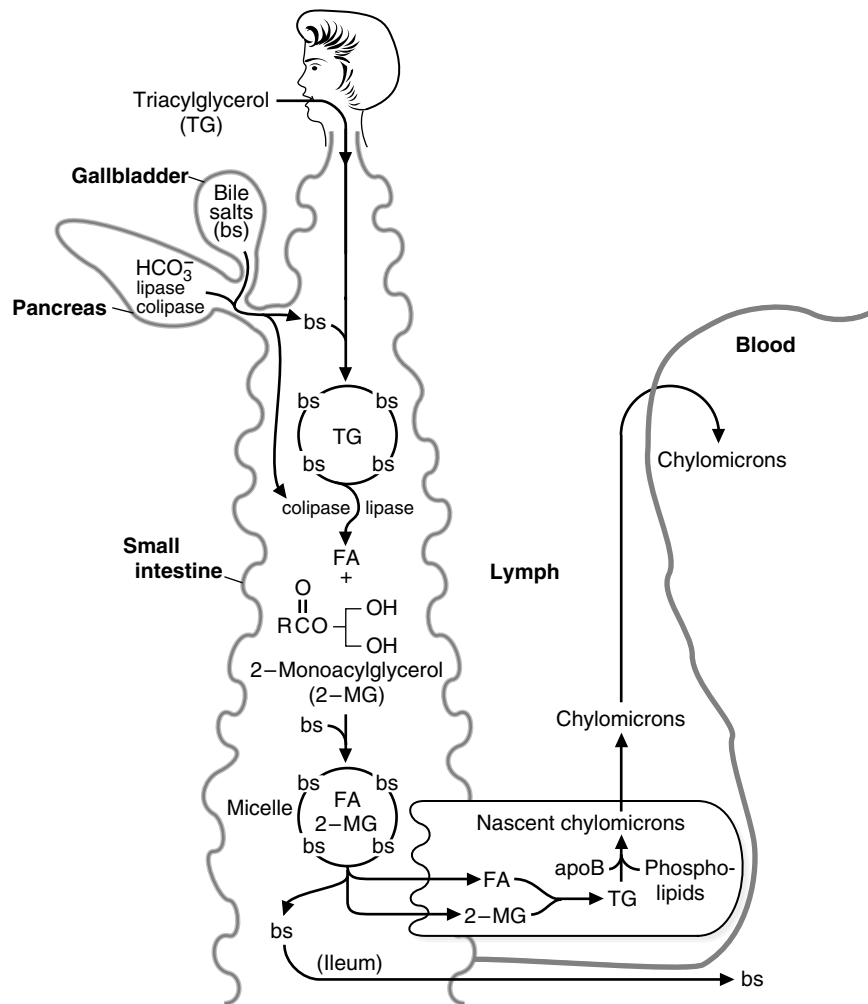


Fig. 32.3. Digestion of triacylglycerols in the intestinal lumen. TG = triacylglycerol; bs = bile salts; FA = fatty acid; 2-MG = 2-monoacylglycerol.



Bile salts inhibit pancreatic lipase activity by coating the substrate and not allowing the enzyme access to the substrate. The colipase relieves the bile salt inhibition, and allows the triglyceride to enter the active site of the lipase.



The exocrine pancreas secretes phospholipase A2 in an inactive zymogen form, pro-phospholipase A2. The enzyme is activated in the intestinal lumen by proteolytic cleavage by trypsin. Pancreatic lipase, however, is secreted in its active form, and only needs to bind colipase and substrate to be active.



When he was finally able to tolerate a full diet, **Al Martini's** stools became bulky, glistening, yellow-brown, and foul smelling. They floated on the surface of the toilet water. What caused this problem?

The colipase binds to the dietary fat and to the lipase, thereby increasing lipase activity. Pancreatic lipase hydrolyzes fatty acids of all chain lengths from positions 1 and 3 of the glycerol moiety of the triacylglycerol, producing free fatty acids and 2-monoacylglycerol, i.e., glycerol with a fatty acid esterified at position 2 (Fig. 32.4). The pancreas also produces esterases that remove fatty acids from compounds (such as cholesterol esters) and phospholipase A2 that digests phospholipids to a free fatty acid and a lysophospholipid (Fig. 32.5).

II. ABSORPTION OF DIETARY LIPIDS

The fatty acids and 2-monoacylglycerols produced by digestion are packaged into micelles, tiny microdroplets emulsified by bile salts (see Fig. 32.3). Other dietary lipids, such as cholesterol, lysophospholipids, and fat-soluble vitamins, are also packaged in these micelles. The micelles travel through a layer of water (the unstirred water layer) to the microvilli on the surface of the intestinal epithelial cells, where the fatty acids, 2-monoacylglycerols, and other dietary lipids are absorbed, but the bile salts are left behind in the lumen of the gut.

The bile salts are extensively resorbed when they reach the ileum. Greater than 95% of the bile salts are recirculated, traveling through the enterohepatic circulation

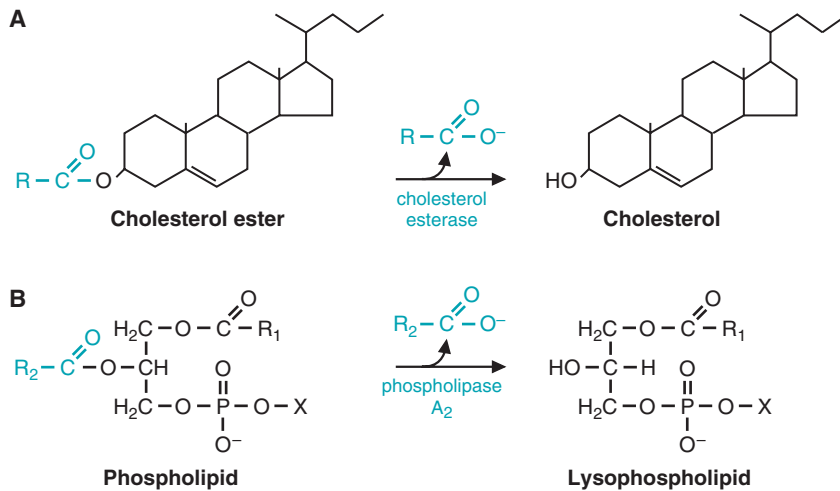


Fig. 32.5. Action of pancreatic esterases (A) and phospholipase A₂ (B).

to the liver, which secretes them into the bile for storage in the gallbladder and ejection into the intestinal lumen during another digestive cycle (Fig. 32.6).

Short- and medium-chain fatty acids (C₄ to C₁₂) do not require bile salts for their absorption. They are absorbed directly into intestinal epithelial cells. Because they do not need to be packaged to increase their solubility, they enter the portal blood (rather than the lymph) and are transported to the liver bound to serum albumin.

III. SYNTHESIS OF CHYLOMICRONS

Within the intestinal epithelial cells, the fatty acids and 2-monoacylglycerols are condensed by enzymatic reactions in the smooth endoplasmic reticulum to form triacylglycerols. The fatty acids are activated to fatty acyl CoA by the same process



Al Martini's stool changes are characteristic of steatorrhea (fat-laden stools caused by malabsorption of dietary fats), in this case caused by a lack of pancreatic secretions, particularly pancreatic lipase, which normally digests dietary fat.

Steatorrhea also may be caused by insufficient production or secretion of bile salts. Therefore, **Michael Sichel** might also develop this condition.



For bile salt micelles to form, the concentration of bile salts in the contents of the intestinal lumen must reach 5–15 $\mu\text{mol/mL}$. This critical concentration of bile salts is therefore required for optimal lipid absorption.

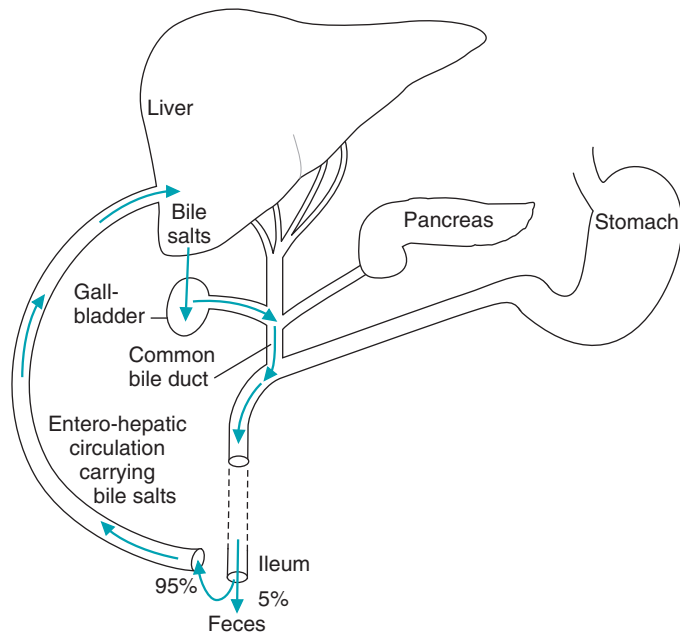


Fig. 32.6. Recycling of bile salts. Bile salts are synthesized in the liver, stored in the gallbladder, secreted into the small intestine, resorbed in the ileum, and returned to the liver via the enterohepatic circulation. Five percent or less of luminal bile acids are excreted in the stool under normal circumstances.

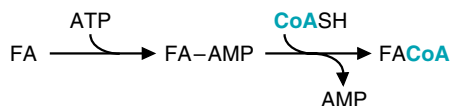
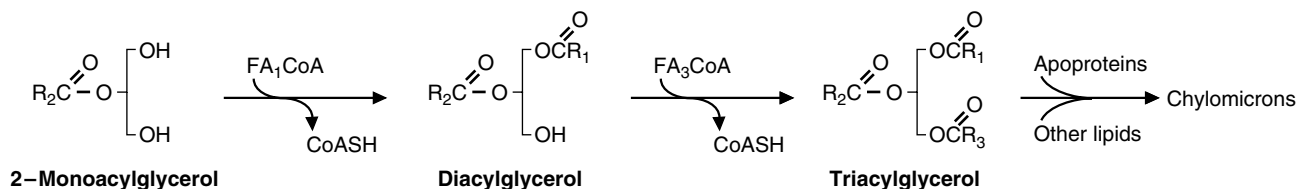
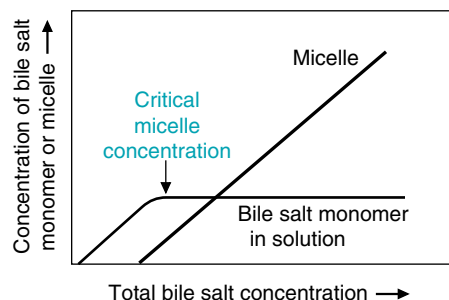
Activation of fatty acids**Triacylglycerol synthesis**

Fig. 32.7. Resynthesis of triacylglycerols in intestinal epithelial cells. Fatty acids (FA), produced by digestion, are activated in intestinal epithelial cells and then esterified to the 2-monoacylglycerol produced by digestion. The triacylglycerols are packaged in chylomicrons and secreted into the lymph.



Because the fat-soluble vitamins (A, D, E, and K) are absorbed from micelles along with the long-chain fatty acids and 2-monoacylglycerols, prolonged obstruction of the duct that carries exocrine secretions from the pancreas and the gallbladder into the intestine (via the common duct) could lead to a deficiency of these metabolically important substances. If the obstruction of **Michael Sichel's** common duct continues, he will eventually suffer from a fat-soluble vitamin deficiency. (Graph from Devlin T. *Textbook of Biochemistry*, 3rd Ed. 1992:1084. Copyright © John Wiley & Sons, Inc.)

used for activation of fatty acids before β -oxidation (see Chapter 23). A fatty acyl CoA then reacts with a 2-monoacylglycerol to form a diacylglycerol, which reacts with another fatty acyl CoA to form a triacylglycerol (Fig. 32.7). The reactions for triacylglycerol synthesis in intestinal cells differ from those in liver and adipose cells in that 2-monoacylglycerol is an intermediate in triacylglycerol in intestinal cells, whereas phosphatidic acid is the necessary intermediate in other tissues.

Triacylglycerols are transported in lipoprotein particles because they are insoluble in water. If triacylglycerols directly entered the blood, they would coalesce, impeding blood flow. Intestinal cells package triacylglycerols together with proteins and phospholipids in chylomicrons, which are lipoprotein particles that do not readily coalesce in aqueous solutions (Figs. 32.8 and 32.9). Chylomicrons also contain cholesterol and fat-soluble vitamins. The protein constituents of the lipoproteins are known as apoproteins.

The major apoprotein associated with chylomicrons as they leave the intestinal cells is B-48 (Fig. 32.10). The B-48 apoprotein is structurally and genetically

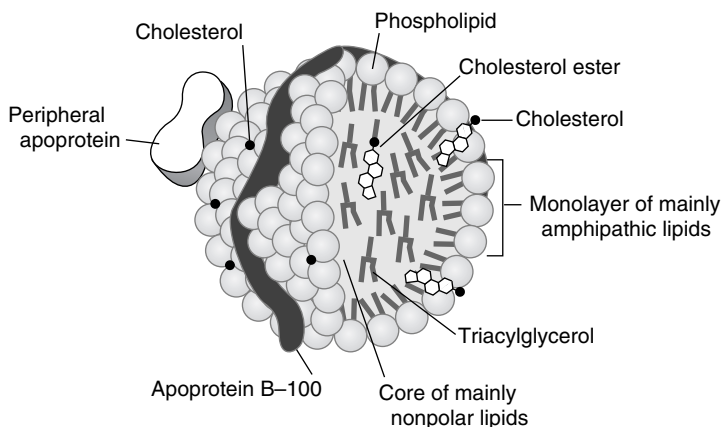


Fig. 32.8. Example of the structure of a blood lipoprotein. VLDL is depicted. Lipoproteins contain phospholipids and proteins on the surface, with their hydrophilic regions interacting with water. Hydrophobic molecules are in the interior of the lipoprotein. The hydroxyl group of cholesterol is near the surface. In cholesterol esters, the hydroxyl group is esterified to a fatty acid. Cholesterol esters are found in the interior of lipoproteins and are synthesized by reaction of cholesterol with an activated fatty acid (see Chapter 33).

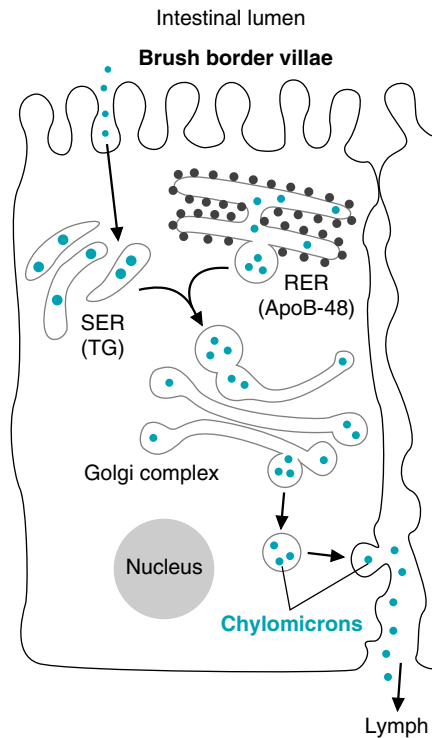


Fig. 32.10. Formation and secretion of chylomicrons. The triacylglycerol is produced in the smooth endoplasmic reticulum (SER) of intestinal epithelial cells from the digestive products, fatty acids, and 2-monoacylglycerols. The protein is synthesized in the rough endoplasmic reticulum (RER). The major apolipoprotein in chylomicrons is B-48. Assembly of the lipoproteins occurs in both the ER and the Golgi complex.

related to the B-100 apolipoprotein synthesized in the liver that serves as a major protein of another lipid carrier, very-low-density lipoprotein (VLDL). These two apolipoproteins are encoded by the same gene. In the intestine, the primary transcript of this gene undergoes RNA editing (Fig. 32.11 and see Chapter 15). A stop codon is generated that causes a protein to be produced in the intestine that is 48% of the size of the protein produced in the liver; hence the designations B-48 and B-100.

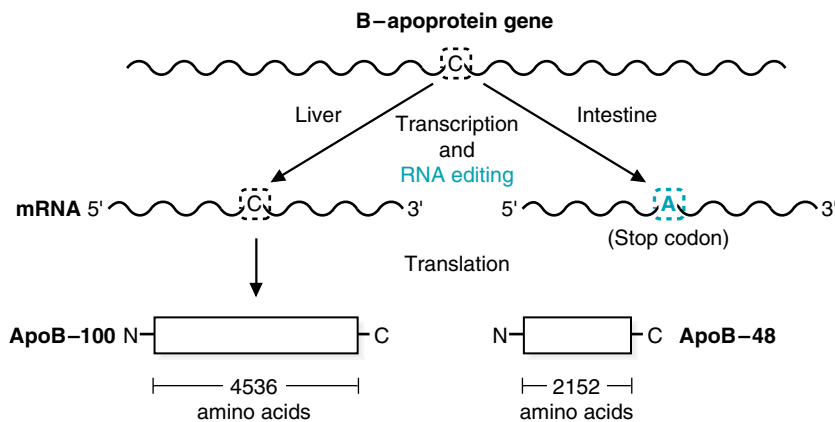


Fig. 32.11. B-apoprotein gene. The gene, located on chromosome 2, is transcribed and translated in liver to produce apoB-100, which is 4,536 amino acids in length (one of the longest single-polypeptide chains). In intestinal cells, RNA editing converts a cytosine (C) to an adenine (A), producing a stop codon. Consequently, the B-apoprotein of intestinal cells (apoB-48) contains only 2,152 amino acids. ApoB-48 is 48% of the size of apoB-100.

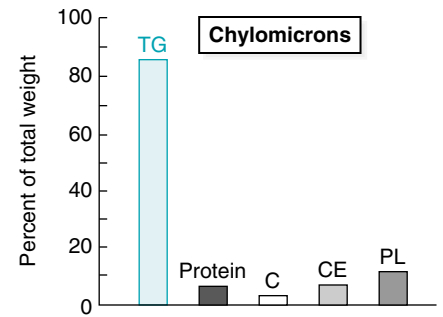
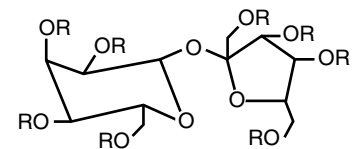


Fig. 32.9. Composition of a typical chylomicron. Although the composition varies to some extent, the major component is triacylglycerol (TG). C = cholesterol; CE = cholesterol ester; PL = phospholipid.



Olestra is an artificial fat substitute designed to allow individuals to obtain the taste and food consistency of fat, without the calories from fat. The structure of Olestra is shown below and consists of a sucrose molecule to which fatty acids are esterified to the hydroxyl groups.



Olestra = octa-acyl sucrose
R = fatty acyl group

The fatty acids attached to sucrose are resistant to hydrolysis by pancreatic lipase, so Olestra passes through the intestine intact and is eliminated in the feces. As a result, no useful calories can be obtained through the metabolism of Olestra.



Because of their high triacylglycerol content, chylomicrons are the least dense of the blood lipoproteins. When blood is collected from patients with certain types of hyperlipoproteinemias (high concentrations of lipoproteins in the blood) in which chylomicron levels are elevated, and the blood is allowed to stand in the refrigerator overnight, the chylomicrons float to the top of the liquid and coalesce, forming a creamy layer.



One manner in which individuals can lose weight is to inhibit the activity of pancreatic lipase. This would result in reduced fat digestion and absorption and a reduced caloric yield from the diet. The drug Orlistat is a chemically synthesized derivative of lipstatin, a natural lipase inhibitor found in certain bacteria. The drug works in the intestinal lumen and forms a covalent bond with the active site serine residue of both gastric and pancreatic lipase, thereby inhibiting their activities. Nondigested triglycerides are not absorbed by the intestine and are eliminated in the feces. Under normal use of the drug, approximately 30% of dietary fat absorption is inhibited. Because excessive nondigested fat in the intestines can lead to gastrointestinal distress related to excessive intestinal gas formation, individuals taking this drug need to follow a reduced daily intake of fat in their diet, which should be evenly distributed amongst the meals of the day.

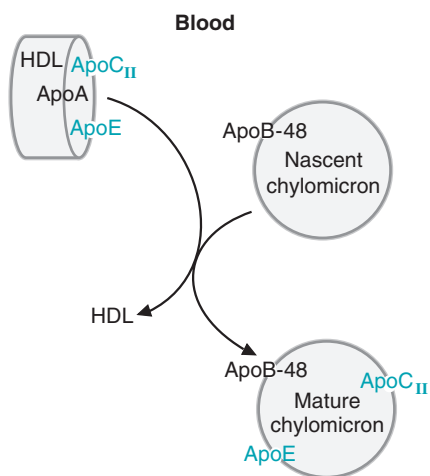


Fig. 32.12. Transfer of proteins from HDL to chylomicrons. Newly synthesized chylomicrons (nascent chylomicrons) mature as they receive apoproteins CII and E from HDL. HDL functions in the transfer of these apoproteins and also in transfer of cholesterol from peripheral tissues to the liver (see Table 1 in the introduction to this section).

The protein component of the lipoproteins is synthesized on the rough endoplasmic reticulum. Lipids, which are synthesized in the smooth endoplasmic reticulum, are complexed with the proteins to form the chylomicrons (see Fig. 32.10).

IV. TRANSPORT OF DIETARY LIPIDS IN THE BLOOD

By the process of exocytosis, chylomicrons are secreted by the intestinal epithelial cells into the chyle of the lymphatic system and enter the blood through the thoracic duct. Chylomicrons begin to enter the blood within 1 to 2 hours after the start of a meal; as the meal is digested and absorbed, they continue to enter the blood for many hours. Initially, the particles are called nascent (newborn) chylomicrons. As they accept proteins from HDL within the lymph and the blood, they become “mature” chylomicrons.

HDL transfers proteins to the nascent chylomicrons, particularly apoprotein E (apoE) and apoprotein CII (apoCII) (Fig. 32.12). ApoE is recognized by membrane receptors, particularly those on the surface of liver cells, allowing ApoE-bearing lipoproteins to enter these cells by endocytosis for subsequent digestion by lysosomes. ApoCII acts as an activator of LPL, the enzyme on capillary endothelial cells, primarily within muscle and adipose tissue, that digests the triacylglycerols of the chylomicrons and VLDL in the blood.

V. FATE OF CHYLOMICRONS

The triacylglycerols of the chylomicrons are digested by LPL attached to the proteoglycans in the basement membranes of endothelial cells that line the capillary walls (Fig. 32.13). LPL is produced by adipose cells, muscle cells (particularly cardiac muscle), and cells of the lactating mammary gland. The isozyme synthesized in adipose cells has a higher K_m than the isozyme synthesized in muscle cells. Therefore, adipose LPL is more active after a meal, when chylomicrons levels are elevated in the blood. Insulin stimulates the synthesis and secretion of adipose LPL, such that after a meal, when triglyceride levels increase in circulation, LPL has been upregulated (through insulin release) to facilitate the hydrolysis of fatty acids from the triglyceride.

The fatty acids released from triacylglycerols by LPL are not very soluble in water. They become soluble in blood by forming complexes with the protein albumin. The major fate of the fatty acids is storage as triacylglycerol in adipose tissue. However, these fatty acids also may be oxidized for energy in muscle and other tissues (see Fig. 32.13). The LPL in the capillaries of muscle cells has a lower K_m than adipose LPL. Thus, muscle cells can obtain fatty acids from blood lipoproteins whenever they are needed for energy, even if the concentration of the lipoproteins is low.

The glycerol released from chylomicron triacylglycerols by LPL may be used for triacylglycerol synthesis in the liver in the fed state.

The portion of a chylomicron that remains in the blood after LPL action is known as a chylomicron remnant. This remnant binds to receptors on hepatocytes (the major cells of the liver), which recognize apoprotein E, and is taken up by the process of endocytosis. Lysosomes fuse with the endocytic vesicles, and the



Heparin is a complex polysaccharide that is a component of proteoglycans (see Chapter 49). Isolated heparin is frequently used as an anticoagulant, because it binds to antithrombin III (ATIII), and the activated ATIII then binds factors necessary for clotting and inhibits them from working. As LPL is bound to the capillary endothelium through binding to proteoglycans, heparin also can bind to LPL and dislodge it from the capillary wall. This leads to loss of LPL activity and an increase of triglyceride content in the blood.

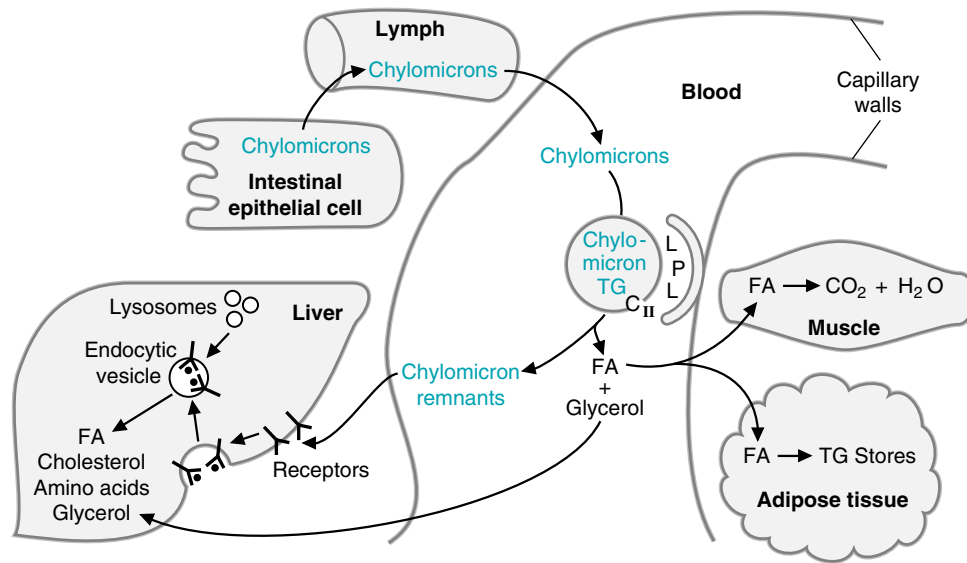


Fig. 32.13. Fate of chylomicrons. Chylomicrons are synthesized in intestinal epithelial cells, secreted into the lymph, pass into the blood, and become mature chylomicrons (see Fig. 32.11). On capillary walls in adipose tissue and muscle, lipoprotein lipase (LPL) activated by ApoC_{II} digests the triacylglycerols (TG) of chylomicrons to fatty acids and glycerol. Fatty acids (FA) are oxidized in muscle or stored in adipose cells as triacylglycerols. The remnants of the chylomicrons are taken up by the liver by receptor-mediated endocytosis. Lysosomal enzymes within the hepatocyte digest the remnants, releasing the products into the cytosol.

chylomicron remnants are degraded by lysosomal enzymes. The products of lysosomal digestion (e.g., fatty acids, amino acids, glycerol, cholesterol, phosphate) can be reused by the cell.

CLINICAL COMMENTS



The upper abdominal ultrasound study showed a large gallstone lodged in **Will Sichel's** common duct with dilation of this duct proximal to the stone. Michael was scheduled for endoscopic retrograde cholangiopancreatography (ERCP). (An ERCP involves cannulation of the common bile duct—and, if necessary, the pancreatic duct—through a tube placed through the mouth and stomach and into the upper small intestine.) With this technique, a stone can be snared in the common duct and removed to relieve an obstruction.

If common duct obstruction is severe enough, bilirubin flows back into the venous blood draining from the liver. As a consequence, serum bilirubin levels, particularly the indirect (unconjugated) fraction, increase. Tissues such as the sclerae of the eye take up this pigment, which causes them to become yellow (jaundiced). **Will Sichel's** condition was severe enough to cause jaundice by this mechanism.



Alcohol excess may produce proteinaceous plugs in the small pancreatic ducts, causing back pressure injury and autodigestion of the pancreatic acini drained by these obstructed channels. This process causes one form of acute pancreatitis. **Al Martini** had an episode of acute alcohol-induced pancreatitis superimposed on a more chronic alcohol-related inflammatory process in the pancreas—in other words, a chronic pancreatitis. As a result of decreased secretion of pancreatic lipase through the pancreatic ducts and into the lumen of the small intestine, dietary fat was not absorbed at a normal rate, and steatorrhea (fat-rich

stools) occurred. If abstinence from alcohol does not allow adequate recovery of the enzymatic secretory function of the pancreas, Mr. Martini will have to take a commercial preparation of pancreatic enzymes with meals that contain even minimal amounts of fat.

BIOCHEMICAL COMMENTS



The assembly of chylomicrons within the endoplasmic reticulum of the enterocyte requires the activity of microsomal triglyceride transfer protein (MTP). The protein is a dimer of two nonidentical subunits. The smaller subunit (57 kDa) is protein disulfide isomerase (PDI, see Chapter 7, section IX.A), whereas the larger subunit (97 kDa) contains the triglyceride transfer activity. MTP accelerates the transport of triglycerides, cholesterol esters, and phospholipids across membranes of subcellular organelles. The role of PDI in this complex is not known; the disulfide isomerase activity of this subunit is not needed for triglyceride transport to occur. The lack of triglyceride transfer activity leads to the disease **abetalipoproteinemia**. This disease affects both chylomicron assembly in the intestine and VLDL assembly in the liver. Both particles require a B apoprotein for their assembly (ApoB-48 for chylomicrons, ApoB-100 for VLDL), and MTP binds to the B apoproteins. For both chylomicron and VLDL assembly, a small ApoB-containing particle is first produced within the lumen of the ER. The appropriate apoB is made on the rough endoplasmic reticulum (RER) and is inserted into the ER lumen during its synthesis (see Chapter 15, section IX). As the protein is being translated, lipid (a small amount of triglyceride) begins to associate with the protein, and the lipid association is catalyzed by MTP. This leads to the generation of small ApoB-containing particles; these particles are not formed in patients with abetalipoproteinemia. Thus, it appears as though MTP activity is necessary to transfer triacylglycerol formed within the ER to the ApoB protein. The second stage of particle assembly is the fusion of the initial ApoB particle with triacylglycerol droplets within the ER. MTP also may be required for the transfer of triacylglycerol from the cytoplasm to the lumen of the ER to form this lipid droplet. These steps are depicted in Fig. 32.14.

The symptoms of abetalipoproteinemia include lipid malabsorption (and its accompanying symptoms, such as steatorrhea and vomiting), which can result in caloric deficiencies and weight loss. Because lipid-soluble vitamin distribution occurs through chylomicron circulation, signs and symptoms of deficiencies in the lipid-soluble vitamins may be seen in these patients.

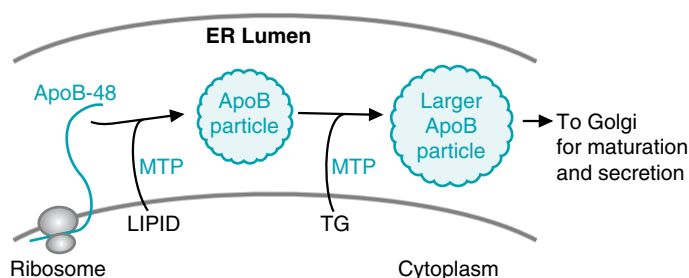


Fig. 32.14. A model of microsomal triglyceride transfer protein (MTP) action. MTP is required to transfer lipid to apoB-48 as it is synthesized, and to transfer lipid from the cytoplasm to the ER lumen.

Suggested References

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REVIEW QUESTIONS—CHAPTER 32

- The most abundant component of chylomicrons is which of the following?
 - ApoB-48
 - Triglyceride
 - Phospholipid
 - Cholesterol
 - Cholesterol ester
- The conversion of nascent chylomicrons to mature chylomicrons requires which of the following?
 - Bile salts
 - 2-Monoacylglycerol
 - Lipoprotein lipase
 - High-density lipoprotein
 - Lymphatic system
- The apoproteins B-48 and B-100 are similar with respect to which of the following?
 - They are synthesized from the same gene.
 - They are derived by alternative splicing of the same hnRNA.
 - ApoB-48 is a proteolytic product of apoB-100.
 - Both are found in mature chylomicrons.
 - Both are found in very-low-density lipoproteins.
- Bile salts must reach a particular concentration within the intestinal lumen before they are effective agents for lipid digestion. This is because of which of the following?
 - The bile salt concentration must be equal to the triglyceride concentration.
 - The bile salt solubility in the lumen is a critical factor.
 - The ability of bile salts to bind lipase is concentration dependant.
 - The bile salts cannot be reabsorbed in the ileum until they reach a certain concentration.
 - The bile salts do not activate lipase until they reach a particular concentration.
- Type III hyperlipidemia is caused by a deficiency of apoprotein E. Analysis of the serum of patients with this disorder would exhibit which of the following?
 - An absence of chylomicrons after eating
 - Above-normal levels of VLDL after eating
 - Normal triglyceride levels
 - Elevated triglyceride levels
 - Below-normal triglyceride levels