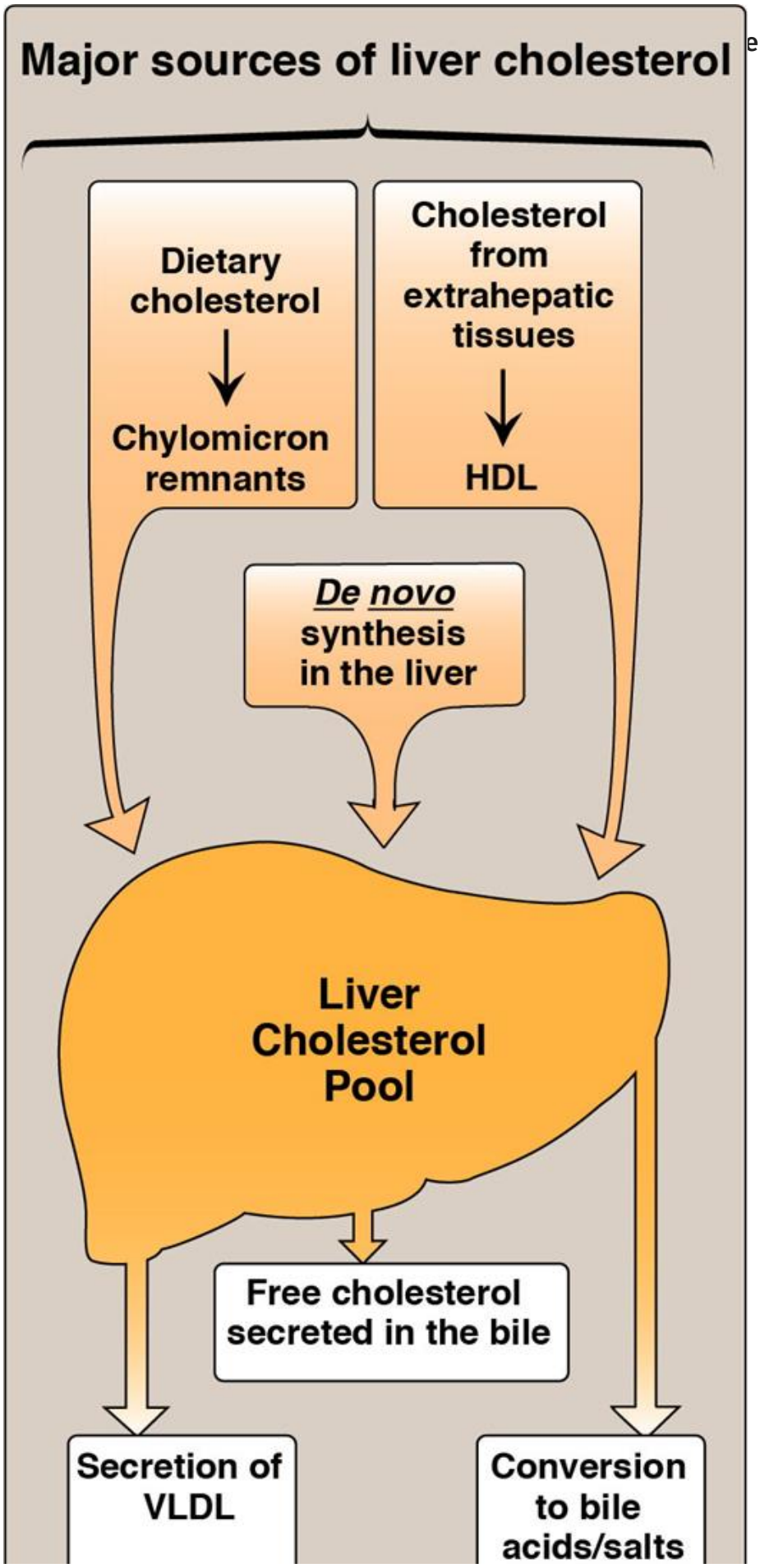
18: Cholesterol, Lipoprotein, and Steroid Metabolism

Overview

Cholesterol, the major steroid alcohol in animals, performs a number of essential functions in the body. For example, cholesterol is a structural component of all cell membranes, modulating their fluidity, and, in specialized tissues, cholesterol is a precursor of bile acids, steroid hormones, and vitamin D. Therefore, it is critically important that the cells of the body be assured an appropriate supply of cholesterol. To meet this need, a complex series of transport, biosynthetic, and regulatory mechanisms has evolved. The liver plays a central role in the regulation of the body's cholesterol homeostasis. For example, cholesterol enters the hepatic cholesterol pool from a number of sources including dietary cholesterol as well as cholesterol synthesized *de novo* by extrahepatic tissues and by the liver itself. Cholesterol is eliminated from the liver as unmodified cholesterol in the bile, or it can be converted to bile salts that are secreted into the intestinal lumen. It can also serve as a component of plasma lipoproteins that carry lipids to the peripheral tissues. In humans, the balance between cholesterol influx and efflux is not precise, resulting in a gradual deposition of cholesterol in the tissues, particularly in the endothelial linings of blood vessels. This is a potentially life-threatening occurrence when the lipid deposition leads to plaque formation, causing the narrowing of blood vessels (atherosclerosis) and increased risk of cardio-, cerebro-, and peripheral vascular disease. Figure 18.1 summarizes the major sources of liver cholesterol and the routes by which cholesterol leaves the liver.

FIGURE 18.1



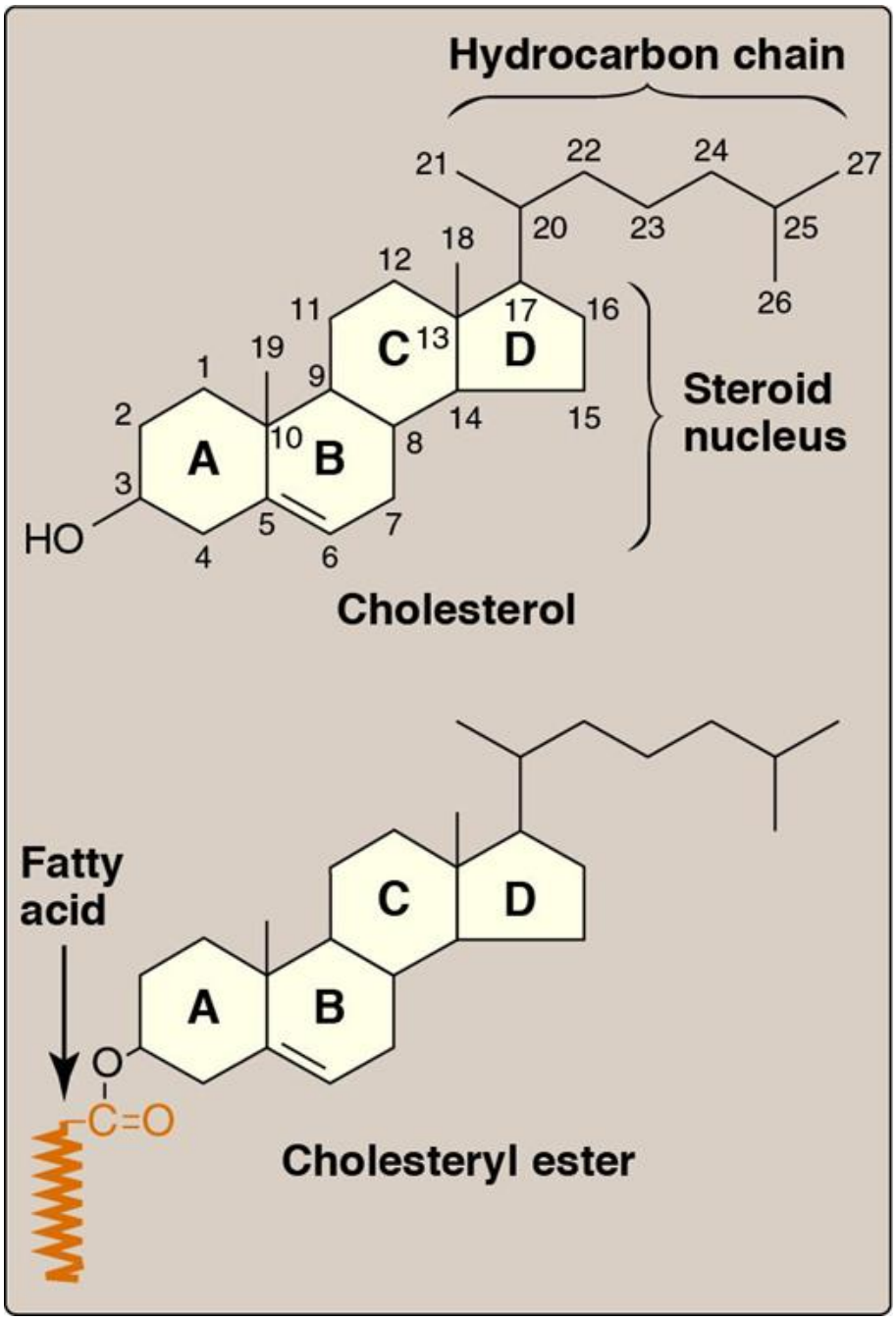
erol leaves the liver (efflux).

Cholesterol Structure

Listen

Cholesterol is a very hydrophobic compound. It consists of four fused hydrocarbon rings (A–D) called the steroid nucleus, and it has an eight-carbon, branched hydrocarbon chain attached to carbon 17 of the D ring. Ring A has a hydroxyl group at carbon 3, and ring B has a double bond between carbon 5 and carbon 6 (Fig. 18.2).

FIGURE 18.2



Sterols

Steroids with 8 to 10 carbon atoms in the side chain at carbon 17 and a hydroxyl group at carbon 3 are classified as sterols. Cholesterol is the major sterol in animal tissues. It arises from *de novo* synthesis and absorption of dietary cholesterol. Intestinal uptake of cholesterol is mediated by the Niemann–Pick C1-like 1 protein, the target of the drug ezetimibe that reduces absorption of dietary cholesterol (see Chapter 15). (Note: Plant sterols [phytosterols], such as β-sitosterol, are poorly absorbed by humans [5% absorbed as compared to 40% for cholesterol]. After entering the enterocytes, they are actively transported back into the intestinal lumen. Defects in the efflux transporter [ABCG5/8] result in the rare condition of sitosterolemia in which plant sterols accumulate in the blood and tissues reducing blood flow and increasing the risk of a heart attack, stroke, or sudden death. Because some cholesterol is transported back as well, plant sterols reduce the absorption of dietary cholesterol. Daily ingestion of plant sterol esters supplied, e.g., in spreads, is one of a number of dietary strategies to reduce plasma cholesterol levels [see Chapter 27].)

Cholesteryl esters

Most plasma cholesterol is in an esterified form (with a fatty acid [FA] attached at carbon 3, as shown in Fig. 18.2), which makes the structure even more hydrophobic than free (nonesterified) cholesterol. Cholesteryl esters are not found in membranes and are normally present only in low levels in most cells. Because of their hydrophobicity, cholesterol and its esters must be transported in association with protein as a component of a lipoprotein particle or be solubilized by phospholipids and bile salts in the bile.

Cholesterol Synthesis

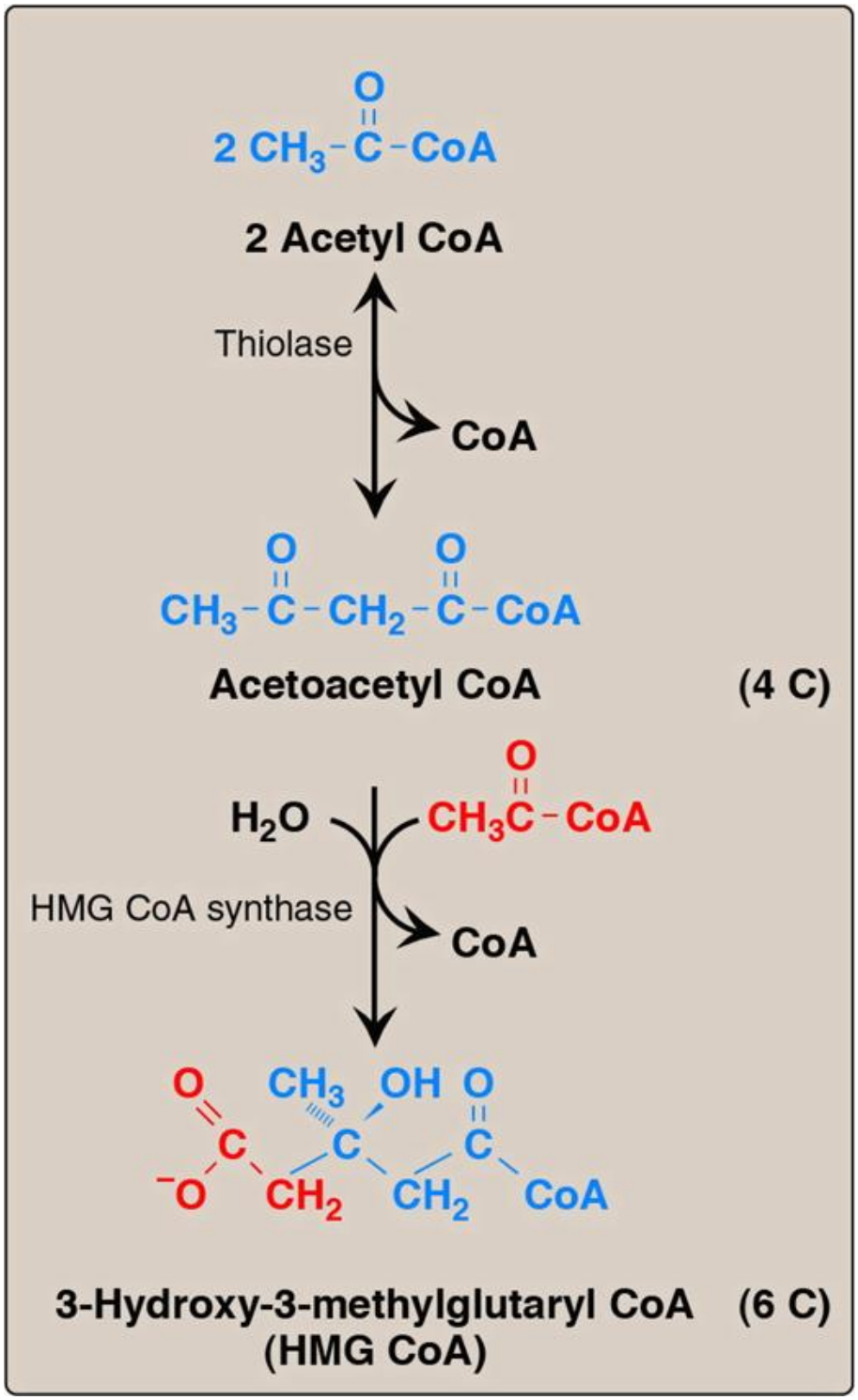
Listen

Cholesterol is synthesized by virtually all tissues in humans, although liver, intestine, adrenal cortex, and reproductive tissues, including ovaries, testes, and placenta, make the largest contributions to the cholesterol pool. As with FA, all the carbon atoms in cholesterol are provided by acetyl coenzyme A (CoA), and nicotinamide adenine dinucleotide phosphate (NADPH) provides the reducing equivalents. The pathway is endergonic, being driven by hydrolysis of the high-energy thioester bond of acetyl CoA and the terminal phosphate bond of ATP. Synthesis requires enzymes in the cytosol, the membrane of the smooth endoplasmic reticulum (SER), and the peroxisome. The pathway is responsive to changes in cholesterol concentration, and regulatory mechanisms exist to balance the rate of cholesterol synthesis against the rate of cholesterol excretion. An imbalance in this regulation can lead to an elevation in circulating levels of plasma cholesterol, with the potential for vascular disease.

3-Hydroxy-3-methylglutaryl coenzyme A synthesis

The first two reactions in the cholesterol biosynthetic pathway are similar to those in the pathway that produces ketone bodies (see Fig. 16.22). They result in the production of 3-hydroxy-3-methylglutaryl CoA ([HMG CoA], Fig. 18.3). First, two acetyl CoA molecules condense to form acetoacetyl CoA. Next, a third molecule of acetyl CoA is added by HMG CoA synthase, producing HMG CoA, a six-carbon compound. (Note: Liver parenchymal cells contain two isoenzymes of the synthase. The cytosolic enzyme participates in cholesterol synthesis, whereas the mitochondrial enzyme functions in the pathway for ketone body synthesis.)

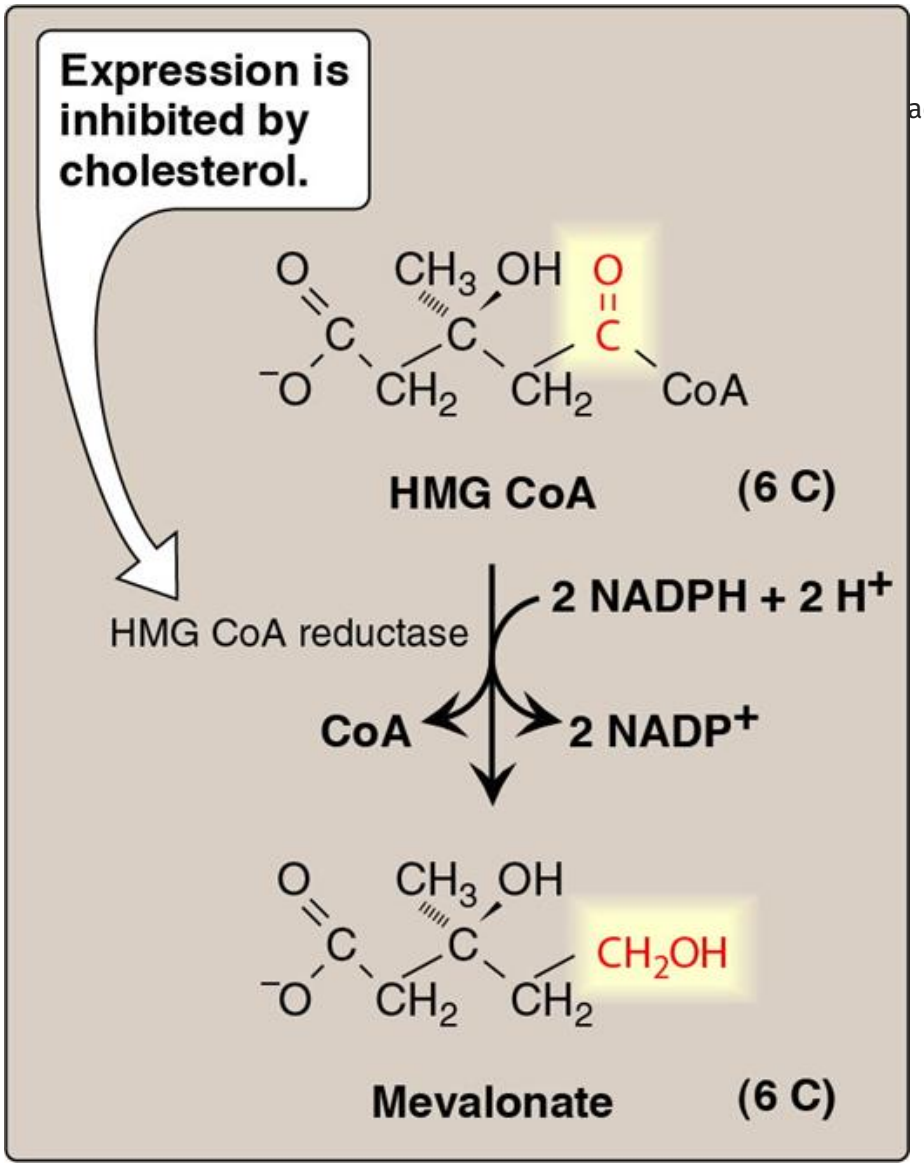
FIGURE 18.3



Mevalonate synthesis

HMG CoA is reduced to mevalonate by HMG CoA reductase. This is the rate-limiting and key regulated step in cholesterol synthesis. It occurs in the cytosol, uses two molecules of NADPH as the reducing agent, and releases CoA, making the reaction irreversible (Fig. 18.4). (Note: HMG CoA reductase is an integral membrane protein of the SER, with its catalytic domain projecting into the cytosol. Regulation of reductase activity is discussed in D. below.)

FIGURE 18.4



adenine dinucleotide phosphate.

Cholesterol synthesis from mevalonate

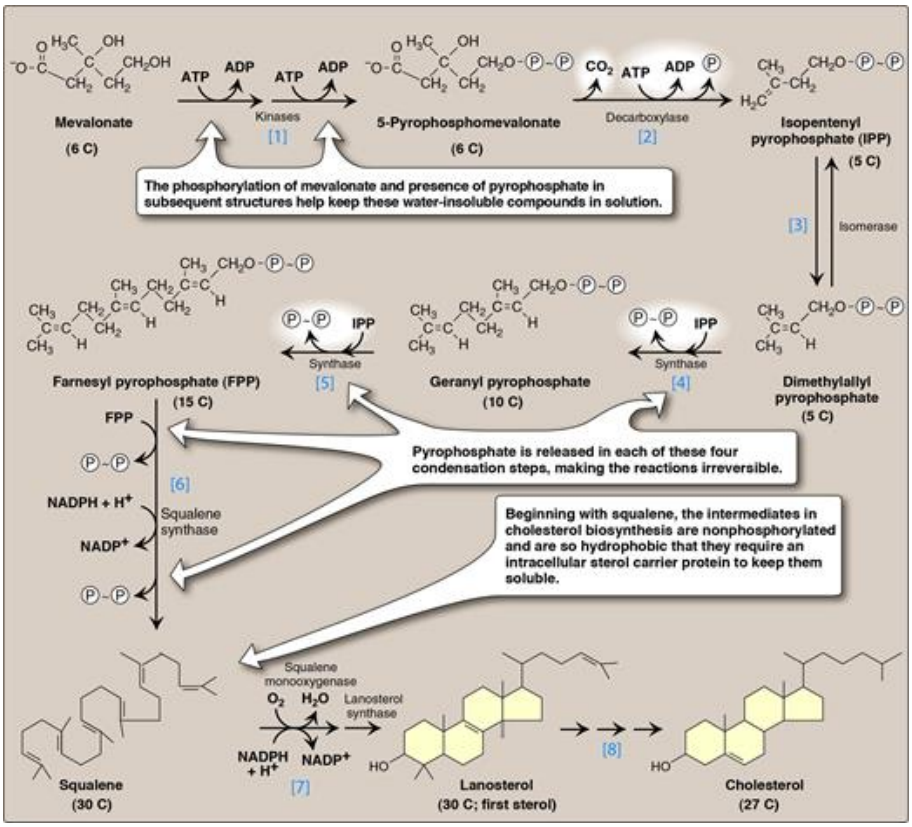
The reactions and enzymes involved in the synthesis of cholesterol from mevalonate are illustrated in Figure 18.5. (Note: The numbers shown in brackets below correspond to numbered reactions shown in this figure.)

1. Mevalonate is converted to 5-pyrophosphomevalonate in two steps, each of which transfers a phosphate group from ATP.
2. A five-carbon isoprene unit, isopentenyl pyrophosphate (IPP), is formed by the decarboxylation of 5-pyrophosphomevalonate. The reaction requires ATP. (Note: IPP is the precursor of a family of molecules with diverse functions, the isoprenoids. Cholesterol is a sterol isoprenoid. Nonsterolisoprenoids include dolichol and ubiquinone [or, coenzyme Q].)
3. IPP is isomerized to 3,3-dimethylallyl pyrophosphate (DPP).
4. IPP and DPP condense to form 10-carbon geranyl pyrophosphate (GPP).
5. A second molecule of IPP then condenses with GPP to form 15-carbon farnesyl pyrophosphate (FPP). (Note: Covalent attachment of farnesyl to proteins, a process known as prenylation, is one mechanism for anchoring proteins [e.g., ras] to the inner face of plasma membranes.)
6. Two molecules of FPP combine, releasing pyrophosphate, and are reduced, forming the 30-carbon compound squalene. (Note: Squalene is formed from six isoprenoid units. Because 3 ATP are hydrolyzed per mevalonate residue converted to IPP, a total of 18 ATP are required to make the polyisoprenoid squalene.)
7. Squalene is converted to the sterol lanosterol by a sequence of two reactions catalyzed by SER-associated enzymes that use molecular oxygen (O_2) and NADPH. The hydroxylation of linear squalene triggers the cyclization of the structure to lanosterol.
8. The conversion of lanosterol to cholesterol is a multistep process involving shortening of the side chain, oxidative removal of methyl groups, reduction of double bonds, and migration of a double bond. Smith–Lemli–Opitz syndrome (SLOS), an autosomal-recessive disorder of cholesterol biosynthesis, is caused by a partial deficiency in 7-dehydrocholesterol-7-reductase, the enzyme that reduces the double bond in 7-dehydrocholesterol (7-DHC), thereby converting it to cholesterol. SLOS is one of several multisystem, embryonic malformation syndromes associated with impaired cholesterol synthesis. (Note: 7-DHC is converted to vitamin D_3 in the skin [see Chapter 28].)

FIGURE 18.5

Synthesis of cholesterol from mevalonate.

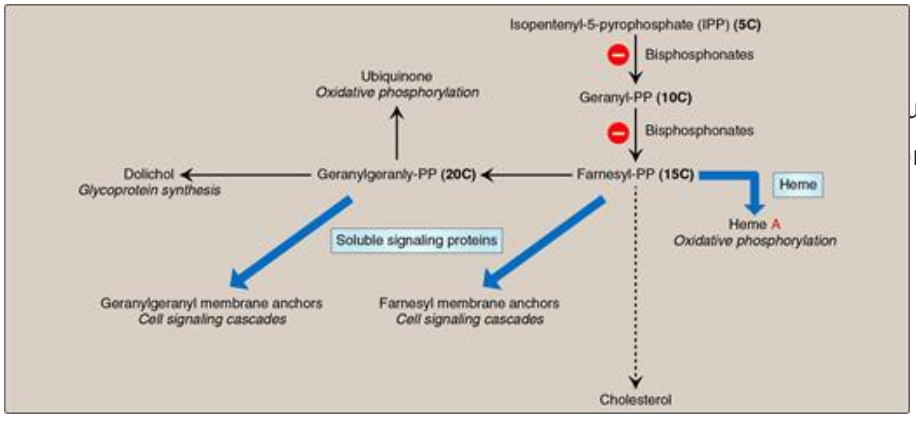
ADP = adenosine diphosphate; Ⓟ = phosphate; Ⓟ ~ Ⓟ = pyrophosphate; NADP(H) = nicotinamide adenine dinucleotide phosphate.



Branch-point reactions in the biosynthesis of cholesterol

The intermediates of cholesterol synthesis are shunted for modification of other molecules. The first branch point starts with step 2 above, the synthesis of IPP **(5C)** (Fig. 18.6). Subsequent addition of 5-carbon isoprene units results in the synthesis of geranyl-PP **(10C)**, farnesyl-PP **(15C),** and geranylgeranyl-PP **(20C)**, respectively**.** These molecules can modify proteins so that they can be anchored into the membrane lipids. Farnesylation of heme creates heme A, a specialized heme in cytochrome *a* of the electron transport chain. Farnesylation and geranylgeranylation of proteins such as ras oncogene can lead to activation of cellular signaling pathways for proliferation. Geranylgeranylation also produces dolichol, which is important for sugar transfer during glycoprotein synthesis, and ubiquinone, a lipid-soluble electron carrier in oxidative phosphorylation.

FIGURE 18.6



uct. *Thick arrows* indicate protein rocesses that the products are

Biphosphonates are used to inhibit bone resorption in osteoporosis and Paget disease. The new generation of bisphosphonates has been shown to kill cancer cells by inhibiting the synthesis of farnesyl-PP and geranylgeranyl-PP.

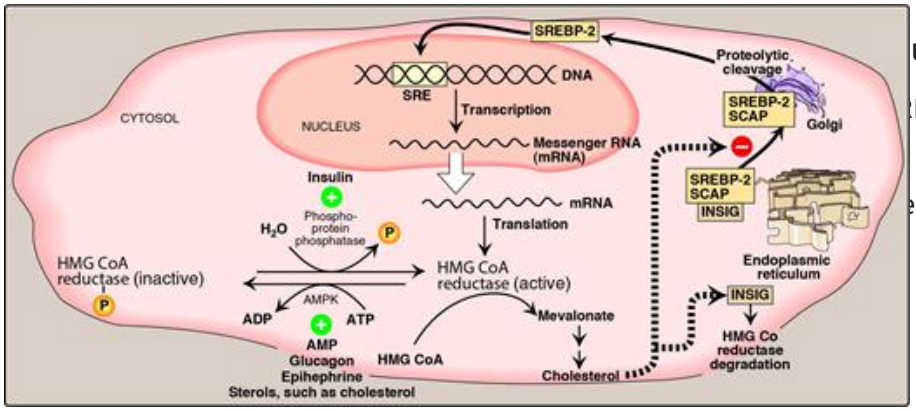
Cholesterol synthesis regulation

HMG CoA reductase is the major control point for cholesterol biosynthesis and is subject to different kinds of metabolic control.

Sterol-dependent regulation of gene expression

Expression of the gene for HMG CoA reductase is controlled by the transacting factor, sterol regulatory element–binding protein-2 (SREBP-2), which binds DNA at the cis-acting sterol regulatory element (SRE) upstream of the *reductase* gene. Inactive SREBP-2 is an integral protein of the SER membrane and associates with a second SER membrane protein, SREBP cleavage–activating protein (SCAP). When sterol levels in the SER are low, the SREBP-2–SCAP complex moves from the ER to the Golgi. In the Golgi membrane, SREBP-2 is sequentially acted upon by two proteases, which generate a soluble fragment that enters the nucleus, binds the SRE, and functions as a transcription factor. This results in increased synthesis of HMG CoA reductase and, therefore, increased cholesterol synthesis (Fig. 18.7). However, if sterols are abundant, they bind SCAP at its sterol-sensing domain and induce the binding of SCAP to yet other ER membrane proteins, the insulin-induced gene proteins (INSIGs). This results in the retention of the SCAP–SREBP complex in the SER, thereby preventing the activation of SREBP-2 and leading to downregulation of cholesterol synthesis. (Note: SREBP-1c upregulates expression of enzymes involved in FA synthesis in response to insulin.)

FIGURE 18.7



uctase.

EBP cleavage–activating protein; AMPK

diphosphate; P = phosphate;

Sterol-accelerated enzyme degradation

The reductase itself is a sterol-sensing integral protein of the SER membrane. When sterol levels in the SER are high, the enzyme binds to INSIG proteins (see Fig. 18.7). Binding leads to cytosolic transfer, ubiquitination, and proteasomal degradation of the reductase (see Chapter 19).

Sterol-independent phosphorylation/dephosphorylation

HMG CoA reductase activity is controlled covalently through the actions of adenosine monophosphate (AMP)–activated protein kinase (AMPK) and a phosphoprotein phosphatase (see Fig. 18.7). The phosphorylated form of the enzyme is inactive, whereas the dephosphorylated form is active. (Note: Because AMPK is activated by AMP, cholesterol synthesis, like FA synthesis, is decreased when ATP availability is decreased.)

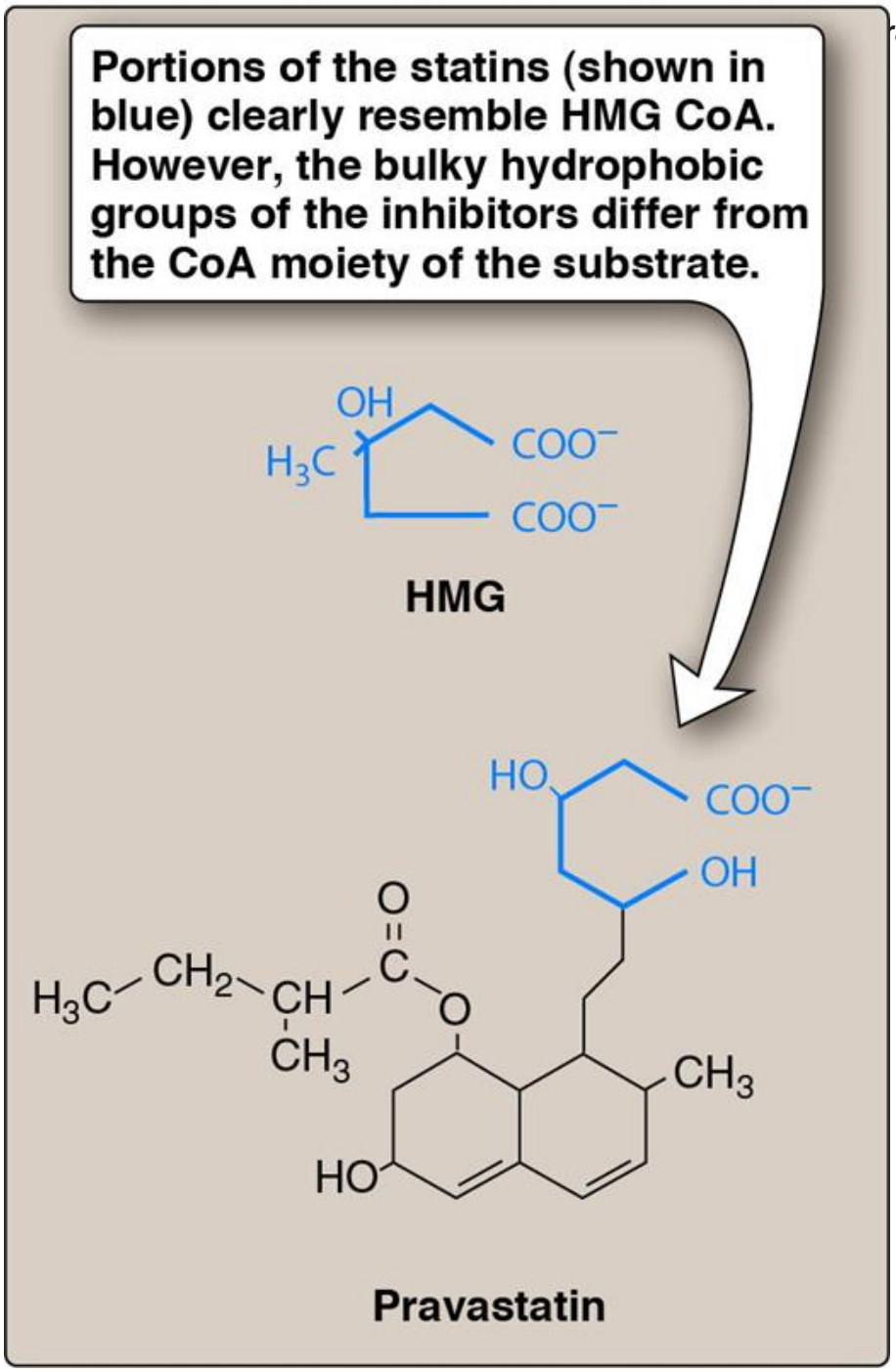
Hormonal regulation

The activity of HMG CoA reductase is controlled hormonally. An increase in insulin favors dephosphorylation (activation) of the reductase, whereas an increase in glucagon and epinephrine and elevated levels of cholesterol has the opposite effect (see Fig. 18.7).

Drug inhibition

The statin drugs (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) are structural analogs of HMG CoA and are (or are metabolized to) reversible, competitive inhibitors of HMG CoA reductase (Fig. 18.8). They are used to decrease plasma cholesterol levels in patients with hypercholesterolemia. The best recognized adverse effects of statins include muscle pain, fatigue, weakness, and rhabdomyolysis. These effects may be due to the inhibition of heme A and ubiquinone synthesis, which are both essential for oxidative phosphorylation for energy (Fig. 18.6). Genetic polymorphisms also influence the physiologic response to statins. For example, organic anion transporting polypeptide (OATP1B1, also known as SLCO1B1) has a polymorphism at nucleotide 521 T>C that is used as a biomarker for simvastatin myopathy.

FIGURE 18.8



ravastatin, a clinically useful

Cholesterol Degradation

Listen

Humans cannot metabolize the cholesterol ring structure to carbon dioxide and water. Rather, the intact steroid nucleus is eliminated from the body by conversion to bile acids and bile salts, a small percentage of which is excreted in the feces, and by secretion of cholesterol into the bile, which transports it to the intestine for elimination. (Note: Some of the cholesterol in the intestine is modified by bacteria before excretion. The primary compounds made are the isomers coprostanol and cholestanol, which are reduced derivatives of cholesterol. Together with cholesterol, these compounds make up the bulk of neutral fecal sterols.)

Bile Acids and Bile Salts

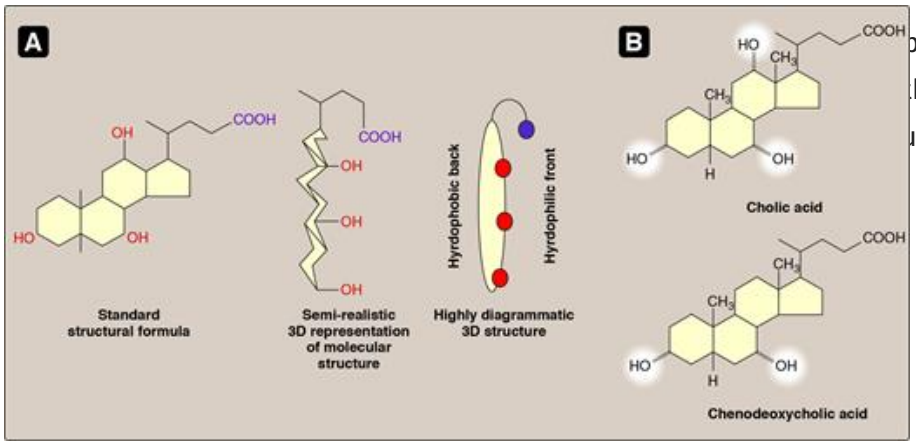
Listen

Bile consists of a watery mixture of organic and inorganic compounds. Phosphatidylcholine (PC), or lecithin (see Chapter 17), and conjugated bile salts are quantitatively the most important organic components of bile. Bile can either pass directly from the liver, where it is synthesized, into the duodenum through the common bile duct, or be stored in the gallbladder when not immediately needed for digestion.

Structure

The bile acids contain 24 carbons, with two or three hydroxyl groups and a side chain that terminates in a carboxyl group (Fig. 18.9A). The carboxyl group has a pK_a of ~6. In the duodenum (pH~6), this group will be protonated in half of the molecules (the bile acids) and deprotonated in the rest (the bile salts). The terms bile acid and bile salt are frequently used interchangeably, however. Both forms have hydroxyl groups that are α in orientation (they lie below the plane of the rings) and methyl groups that are β (they lie above the plane of the rings). Therefore, the molecules have both a polar and a nonpolar surface and can act as emulsifying agents in the intestine, helping prepare dietary fat (triacylglycerol [TAG]) and other complex lipids for degradation by pancreatic digestive enzymes (Fig. 18.9B).

FIGURE 18.9

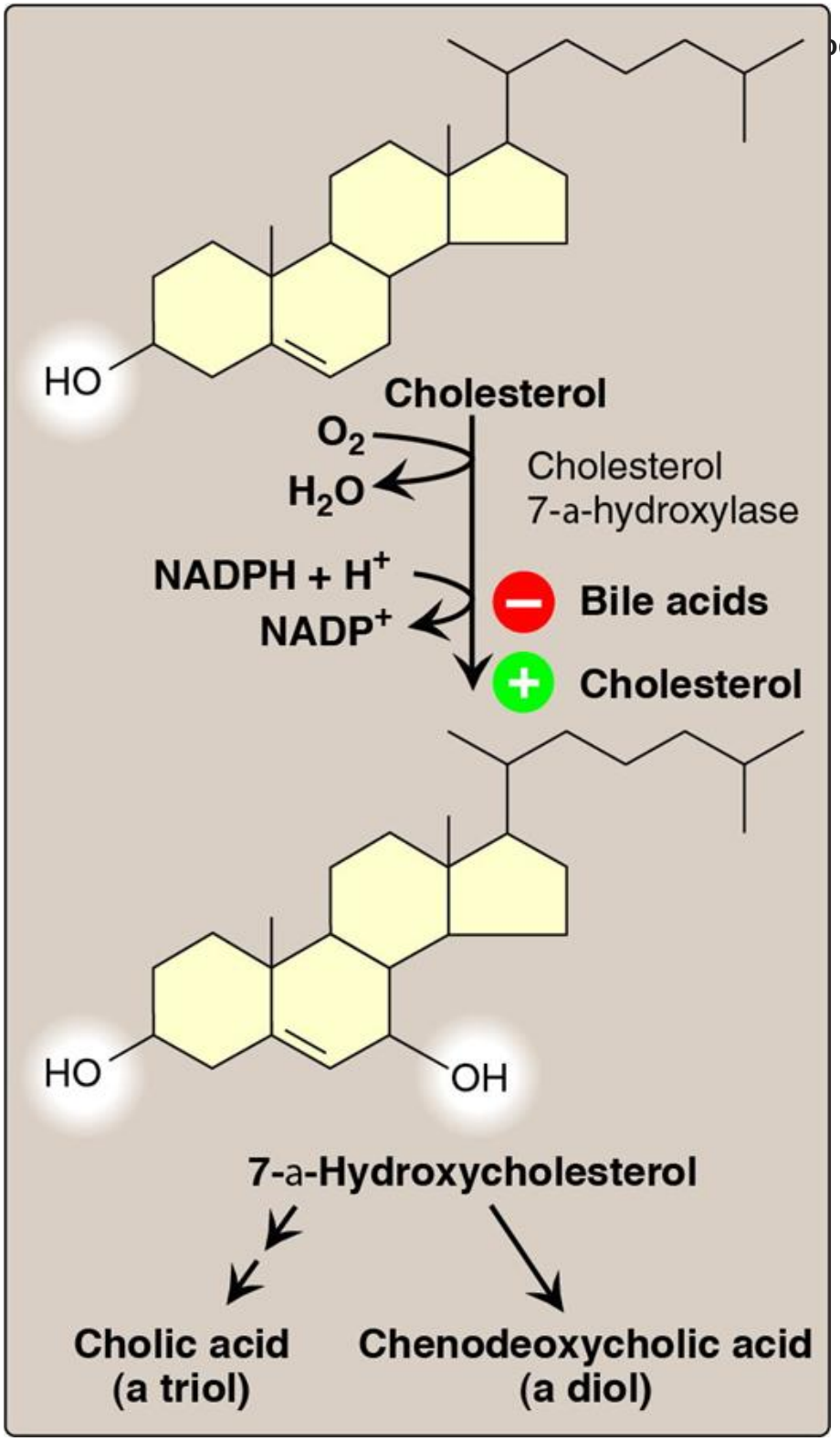


polar) surfaces help emulsifying and
he cholesterol backbone. The *red balls*
up. **B:** The most abundant bile acids in

Synthesis

Bile acids are synthesized in the liver by a multistep, multiorganelle pathway in which hydroxyl groups are inserted at specific positions on the steroid structure; the double bond of the cholesterol B ring is reduced; and the hydrocarbon chain is shortened by three carbons, introducing a carboxyl group at the end of the chain. The most common resulting compounds, cholic acid (a triol) and chenodeoxycholic acid (a diol), as shown in Figure 18.9B, are called primary bile acids. The rate-limiting step in bile acid synthesis is the introduction of a hydroxyl group at carbon 7 of the steroid nucleus by 7-α-hydroxylase, an SER-associated cytochrome P450 (CYP) monooxygenase found only in liver. Expression of the enzyme is downregulated by bile acids and cholesterol (Fig. 18.10). Expression of cholesterol-7-alpha hydroxylase is upregulated by cholesterol and downregulated by bile acids. Elevated levels of cholesterol in the liver stimulate the nuclear receptor liver X factor (LXR), which increases the transcription of cholesterol-7-alpha hydroxylase. Elevated levels of bile acids activate another nuclear receptor bile acid receptor (BAR, also known as farnesoid X receptor [FXR]) which downregulates the transcription of cholesterol-7-alpha hydroxylase.

FIGURE 18.10

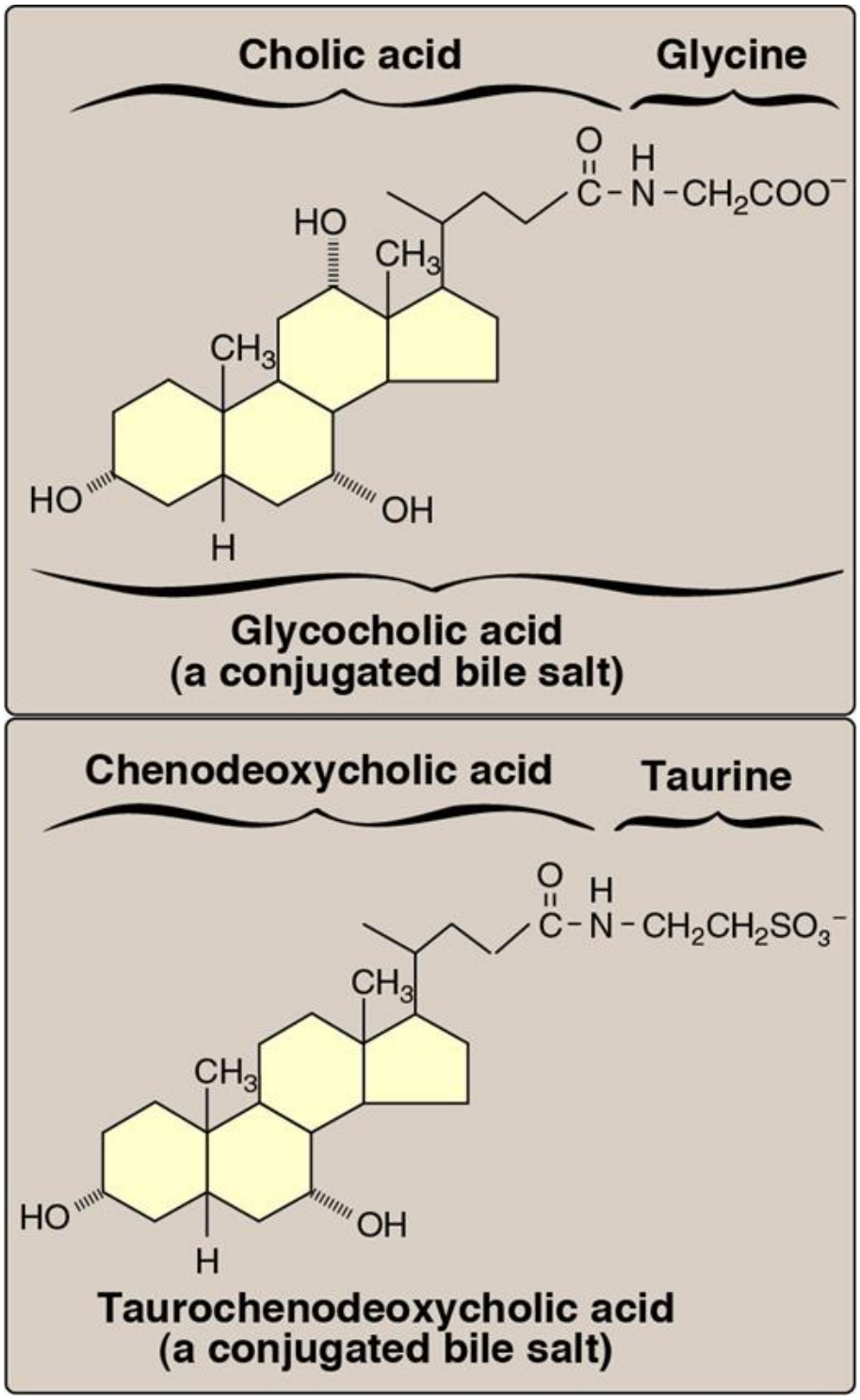


odeoxycholic acid from

Conjugation

Before the bile acids leave the liver, they are conjugated to a molecule of either glycine or taurine (an end product of cysteine metabolism) by an amide bond between the carboxyl group of the bile acid and the amino group of the added compound. These new structures include glycocholic and glycochenodeoxycholic acids and taurocholic and taurochenodeoxycholic acids (Fig. 18.11). The ratio of glycine to taurine forms in the bile is ~3/1. Addition of glycine or taurine results in the presence of a carboxyl group with a lower pK_a (from glycine) or a sulfonate group (from taurine), both of which are fully ionized (negatively charged) at the alkaline pH of bile and the duodenum. The conjugated, ionized bile salts are more effective detergents than the unconjugated ones because of their enhanced amphipathic nature. Therefore, only the conjugated forms are found in the bile. Individuals with genetic deficiencies in the conversion of cholesterol to bile acids are treated with exogenously supplied chenodeoxycholic acid.

FIGURE 18.11

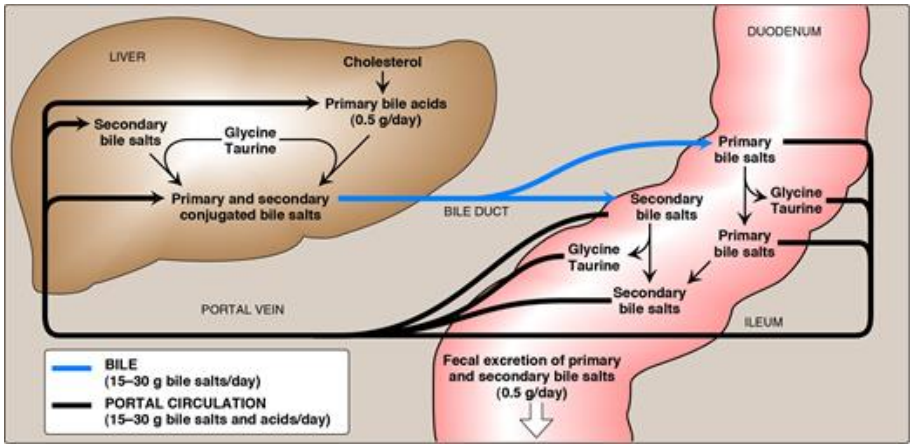


Bile salts provide the only significant mechanism for cholesterol excretion, both as a metabolic product of cholesterol and as a solubilizer of cholesterol in bile.

Enterohepatic circulation

Bile salts secreted into the intestine are efficiently reabsorbed (>95%) and reused. The liver actively secretes bile salts via the bile salt export pump. In the intestine, they are reabsorbed in the terminal ileum via the apical sodium (Na^+)-bile salt cotransporter and returned to the blood via a separate transport system. (Note: Lithocholic acid is only poorly absorbed.) They are efficiently taken up from the blood by the hepatocytes via an isoform of the cotransporter. (Note: Albumin binds bile salts and transports them through the blood as was seen with FA.) The continuous cycle of bile salt secretion into the bile, passage through the duodenum (where some are deconjugated then dehydroxylated to secondary bile salts), uptake in the ileum, and subsequent return to the liver (as a mixture of primary and secondary forms) is termed the enterohepatic circulation (Fig. 18.12). Between 15 and 30 g of bile salts are secreted from the liver into the duodenum each day, yet only ~0.5 g (<3%) is lost daily in the feces. Approximately 0.5 g/day is synthesized from cholesterol in the liver to replace the amount lost. Bile acid sequestrants, such as cholestyramine, bind bile salts in the gut and prevent their reabsorption, thereby promoting their excretion. They are used in the treatment of hypercholesterolemia, because the removal of bile salts relieves the inhibition on bile acid synthesis in the liver, thereby diverting additional cholesterol into that pathway. (Note: Dietary fiber also binds bile salts and increases their excretion [see Chapter 27].)

FIGURE 18.12



Bacterial action on bile salts

After enterohepatic circulation, a small amount of secreted bile salts reaches the colon where the salts are exposed to bacterial modification by the gut microbiome. Bacteria of the intestinal microbiota can deconjugate (remove glycine and taurine) bile salts. They can also dehydroxylate carbon 7, producing secondary bile acids such as deoxycholic acid from cholic acid and lithocholic acid from chenodeoxycholic acid. A small proportion of these secondary bile acids are absorbed by the colonic epithelium and may be conjugated and hydroxylated by the liver enzymes to produce secondary bile salts. The rest are eliminated in the feces.

Bile salt deficiency: Cholelithiasis

The movement of cholesterol from the liver into the bile must be accompanied by the simultaneous secretion of phospholipid and bile salts. If this dual process is disrupted and more cholesterol is present than can be solubilized by the bile salts and PC present, the cholesterol may precipitate in the gallbladder, leading to cholesterol gallstone disease or cholelithiasis (Fig. 18.13). This disorder is typically caused by a decrease of bile acids in the bile. Cholelithiasis also may result from increased secretion of cholesterol into bile, as seen with the use of fibrates (e.g., gemfibrozil) to reduce cholesterol (and TAG) in the blood. Laparoscopic cholecystectomy (surgical removal of the gallbladder through a small incision) is currently the treatment of choice. However, for patients who are unable to undergo surgery, oral administration of chenodeoxycholic acid to supplement the body's supply of bile acids results in a gradual (months to years) dissolution of the gallstones. (Note: Cholesterol stones account for >85% of cases of cholelithiasis, with bilirubin and mixed stones accounting for the rest).

FIGURE 18.13

athology. 4th ed. Wolters Kluwer; 2016,

Plasma Lipoproteins

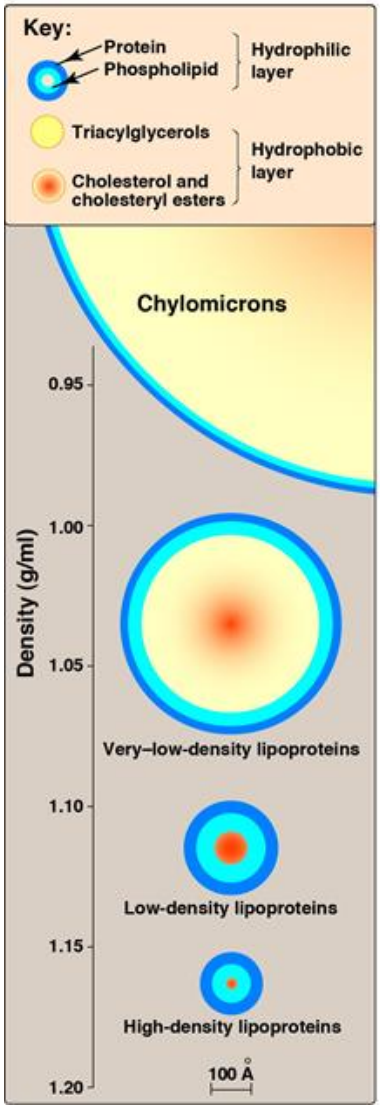
Listen

The plasma lipoproteins are spherical macromolecular complexes of lipids and proteins (apolipoproteins). The lipoprotein particles include chylomicrons, chylomicron remnants, very–low-density lipoproteins (VLDLs), VLDL remnants, also known as intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), high-density lipoproteins (HDLs) and lipoprotein (a) (Lp[a]). They differ in lipid and protein composition, size, density (Fig. 18.14), and site of origin. (Note: Because lipoprotein particles constantly interchange lipids and apolipoproteins, the actual apolipoprotein and lipid content of each class of particles is somewhat variable.) Lipoproteins function both to keep their component lipids soluble as they transport them in the plasma and to provide an efficient mechanism for transporting their lipid contents to (and from) the tissues. In humans, there is a gradual deposition of lipid (especially cholesterol) in tissues.

FIGURE 18.14

es, and typical values are shown.

gh cholesterol and its esters are shown
is on the surface, whereas cholesteryl



Composition

Lipoproteins are composed of a neutral lipid core (containing TAG and cholesteryl esters) surrounded by a shell of amphipathic apolipoproteins, phospholipid, and nonesterified (free) cholesterol (Fig. 18.15). These amphipathic compounds are oriented such that their polar portions are exposed on the surface of the lipoprotein, thereby rendering the particle soluble in aqueous solution. The TAG and cholesterol carried by the lipoproteins are obtained either from the diet (exogenous source) or from *de novo* synthesis (endogenous source). (Note: The cholesterol [C] content of plasma lipoproteins is now routinely measured in fasting blood. Friedewald equation [LDL-C = Total C – HDL-C – TAG/5] is used to calculate LDL-C once the total C, HDL, and TAG are measured in serum. This formula assumes the TAG/cholesterol ratio in VLDL is 5:1 The goal value for total cholesterol is <200 mg/dl.)

Size and density

Chylomicrons are the lipoprotein particles lowest in density and largest in size and that contain the highest percentage of lipid (as TAG) and the lowest percentage of protein. VLDLs and LDLs are successively denser, having higher ratios of protein to lipid. HDL particles are the smallest and densest. Plasma lipoproteins can be separated on the basis of their electrophoretic mobility, as shown in Figure 18.16, or on the basis of their density by ultracentrifugation.

Apolipoproteins

The apolipoproteins associated with lipoprotein particles have a number of diverse functions, such as providing recognition sites for cell-surface receptors and serving as activators or coenzymes for enzymes involved in lipoprotein metabolism. Some of the apolipoproteins are required as essential structural components of the particles and cannot be removed (in fact, the particles cannot be produced without them), whereas others are transferred freely between lipoproteins. Apolipoproteins are divided by structure and function into several major classes, denoted by letters, with each class having subclasses (e.g., apolipoprotein [apo] C-I, apo C-II, and apo C-III). (Note: The functions of all the apolipoproteins are not yet known.)

FIGURE 18.15

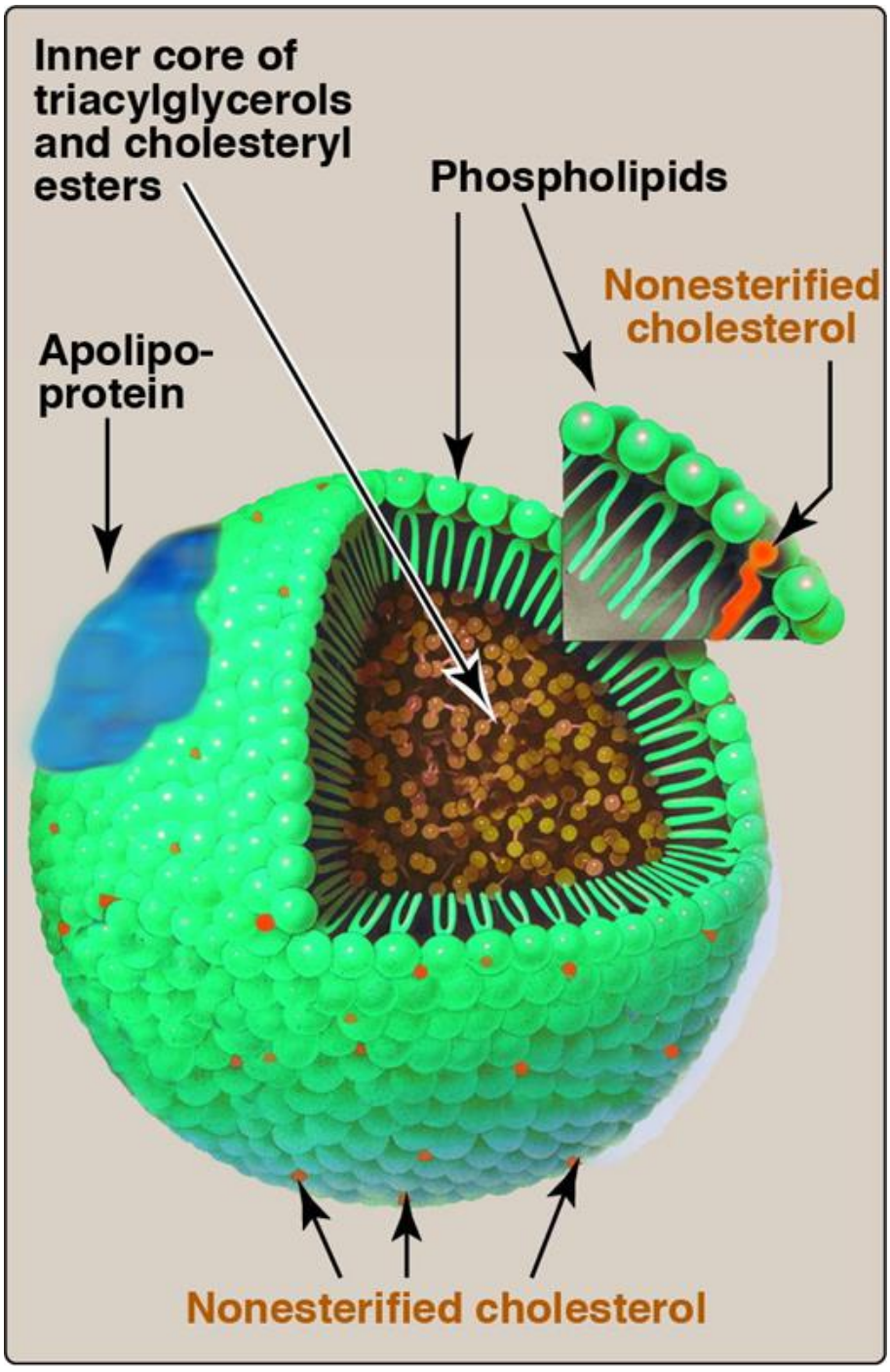
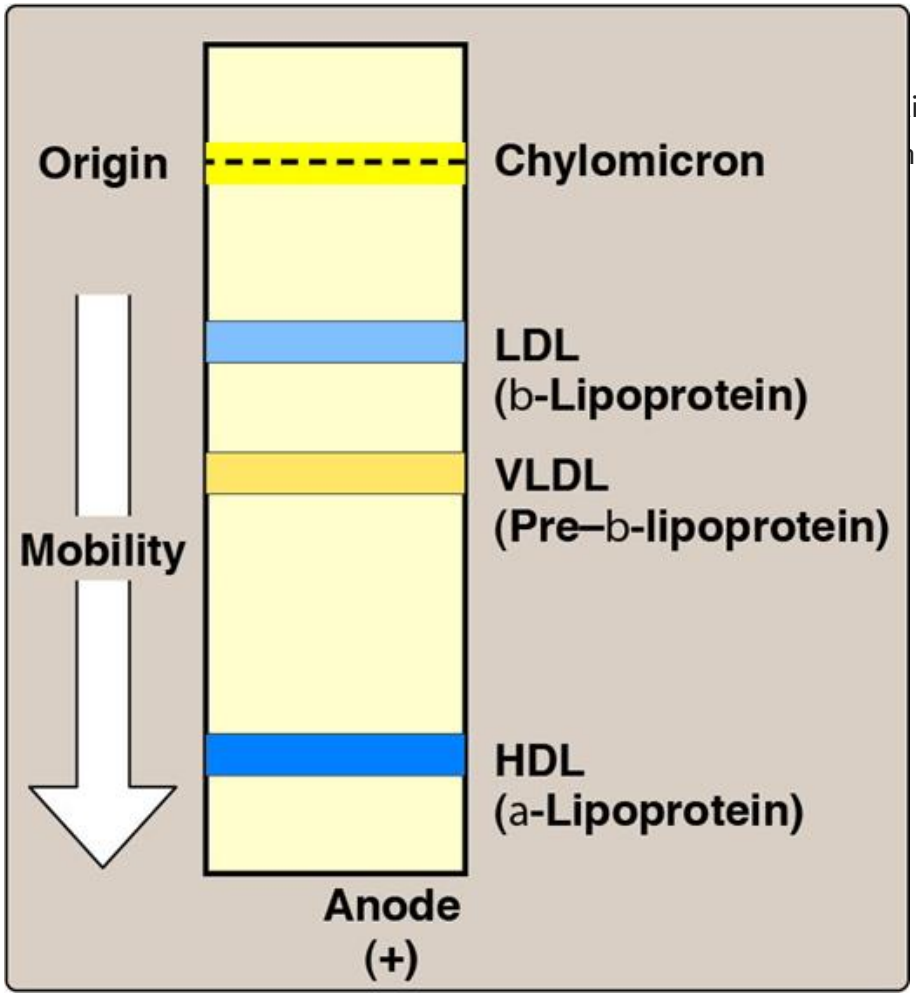

Inner core of triacylglycerols and cholesteryl esters
Phospholipids
Nonesterified cholesterol
Apolipo-protein
Nonesterified cholesterol

FIGURE 18.16



ipoprotein [VLDL] is reversed if
sity lipoprotein.

Chylomicron metabolism

Chylomicrons are assembled in intestinal mucosal cells and carry dietary (exogenous) TAG, cholesterol, fat-soluble vitamins, and cholesteryl esters to the peripheral tissues (Fig. 18.17). (Note: TAGs account for close to 90% of the lipids in a chylomicron.)

Apolipoprotein synthesis

Apo B-48 is unique to chylomicrons. Its synthesis begins on the rough ER (RER), and it is glycosylated as it moves through the RER and Golgi. (Note: Apo B-48 is so named because it constitutes the N-terminal 48% of the protein encoded by the gene for apo B. Apo B-100, which is synthesized by the liver and found in VLDL and LDL, represents the entire protein encoded by this gene. Posttranscriptional editing [see Chapter 33] of a cytosine to a uracil in intestinal apo B-100 messenger RNA [mRNA] creates a nonsense [stop] codon [see Chapter 33], allowing translation of only 48% of the mRNA.)

Chylomicron assembly

Many enzymes involved in TAG, cholesterol, and phospholipid synthesis are located in the SER. Assembly of the apolipoprotein and lipid into chylomicrons requires microsomal triglyceride transfer protein (MTP), which loads apo B-48 with lipid. This occurs before transition from the ER to the Golgi, where the particles are packaged in secretory vesicles. These fuse with the plasma membrane releasing the lipoproteins, which then enter the lymphatic system and, ultimately, the blood. (Note: Chylomicrons leave the lymphatic system via the thoracic duct that empties into the left subclavian vein.)

Nascent chylomicron modification

The particle released by the intestinal mucosal cell is called a nascent chylomicron because it is functionally incomplete. When it reaches the plasma, the particle is rapidly modified, receiving apo E (which is recognized by hepatic receptors) and apo C. The latter includes apo C-II, which is necessary for the activation of lipoprotein lipase (LPL), the enzyme that degrades the TAG contained in the chylomicron. The source of these apolipoproteins is circulating HDL (see Fig. 18.17). (Note: Apo C-III on TAG-rich lipoproteins inhibits LPL.)

Triacylglycerol degradation by lipoprotein lipase

LPL is an extracellular enzyme that is anchored to the capillary walls of most tissues but predominantly those of adipose tissue and cardiac and skeletal muscle. The adult liver does not express this enzyme. (Note: A hepatic lipase is found on the surface of endothelial cells of the liver. It plays a role in TAG degradation in chylomicrons and VLDL and is important in HDL metabolism.) LPL, activated by apo C-II on circulating chylomicrons, hydrolyzes the TAG in these particles to FA and glycerol. The FA are stored (in adipose) or used for energy (in muscle). The glycerol is taken up by the liver, converted to dihydroxyacetone phosphate (an intermediate of glycolysis), and used in lipid synthesis or gluconeogenesis. (Note: Patients with a deficiency of LPL or apo C-II [type I hyperlipoproteinemia or familial chylomicronemia] show a dramatic accumulation [≥1,000 mg/dl] of chylomicron-TAG in the plasma [hypertriacylglycerolemia] even in the fasted state. They are at increased risk for acute pancreatitis. Treatment is the reduction of dietary fat.)

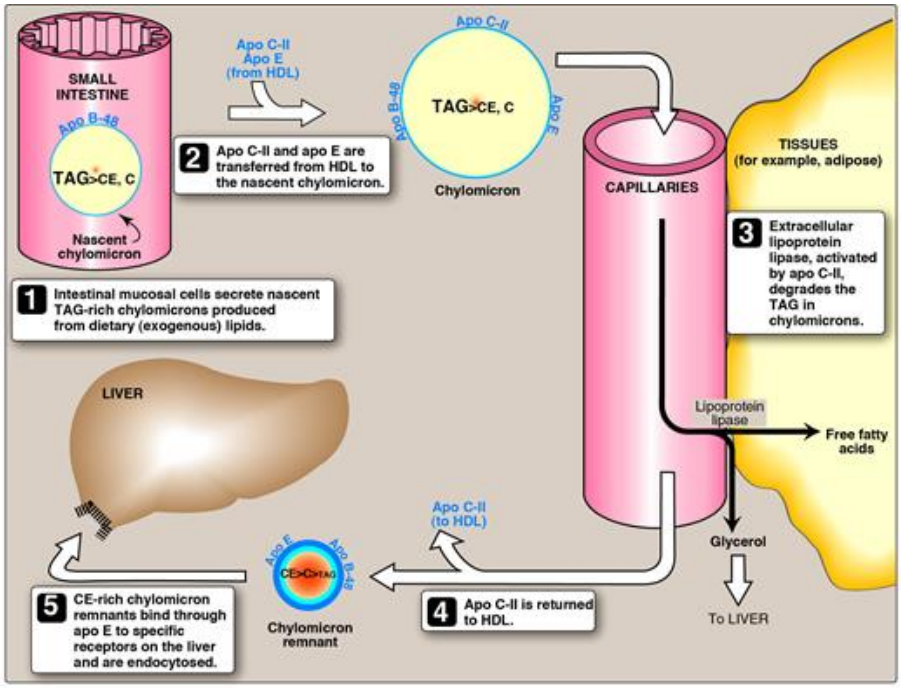
Lipoprotein lipase expression

LPL is synthesized by adipose tissue and by cardiac and skeletal muscle. Expression of the tissue-specific isozymes is regulated by nutritional state and hormonal level. For example, in the fed state (elevated insulin levels), LPL synthesis is increased in adipose but decreased in muscle tissue. Fasting (decreased insulin) favors LPL synthesis in muscle. (Note: The highest concentration of LPL is in cardiac muscle, reflecting the use of FA to provide much of the energy needed for cardiac function.)

Chylomicron remnant formation

As the chylomicron circulates, and >90% of the TAG in its core is degraded by LPL, the particle decreases in size and increases in density. In addition, the C apolipoproteins (but not apo B or E) are returned to HDL. The remaining particle, called a remnant, is rapidly removed from the circulation by the liver, whose cell membranes contain lipoprotein receptors that recognize apo E (see Fig. 18.17). Chylomicron remnants bind to these receptors and are taken into the hepatocytes by endocytosis. The endocytosed vesicle then fuses with a lysosome, and the apolipoproteins, cholesteryl esters, and other components of the remnant are hydrolytically degraded, releasing amino acids, free cholesterol, and FA. The receptor is recycled. (Note: The mechanism of receptor-mediated endocytosis is illustrated for LDL in Fig. 18.21.)

FIGURE 18.17



of plasma lipoprotein particles. The d density). TAG = triacylglycerol; C =

Very–low-density lipoprotein metabolism

VLDLs are produced in the liver (Fig. 18.18). They are composed predominantly of endogenous TAG (~60%), and their function is to carry this lipid from the liver (site of synthesis) to the peripheral tissues. There, the TAG is degraded by LPL, as discussed for chylomicrons. (Note: Nonalcoholic fatty liver [hepatic steatosis] occurs in conditions in which there is an imbalance between hepatic TAG synthesis and the secretion of VLDL. Such conditions include obesity and type 2 diabetes mellitus [see Chapter 25].)

Release from the liver

VLDLs are secreted directly into the blood by the liver as nascent particles containing apo B-100. They must obtain apo C-II and apo E from circulating HDL (see Fig. 18.18). As with chylomicrons, apo C-II is required for activation of LPL. (Note: Abetalipoproteinemia is a rare hypolipoproteinemia caused by a defect in MTP, leading to an inability to load apo B with lipid. Consequently, few VLDLs or chylomicrons are formed, and TAG accumulates in the liver and intestine. Absorption of fat-soluble vitamins is decreased. LDLs are low.)

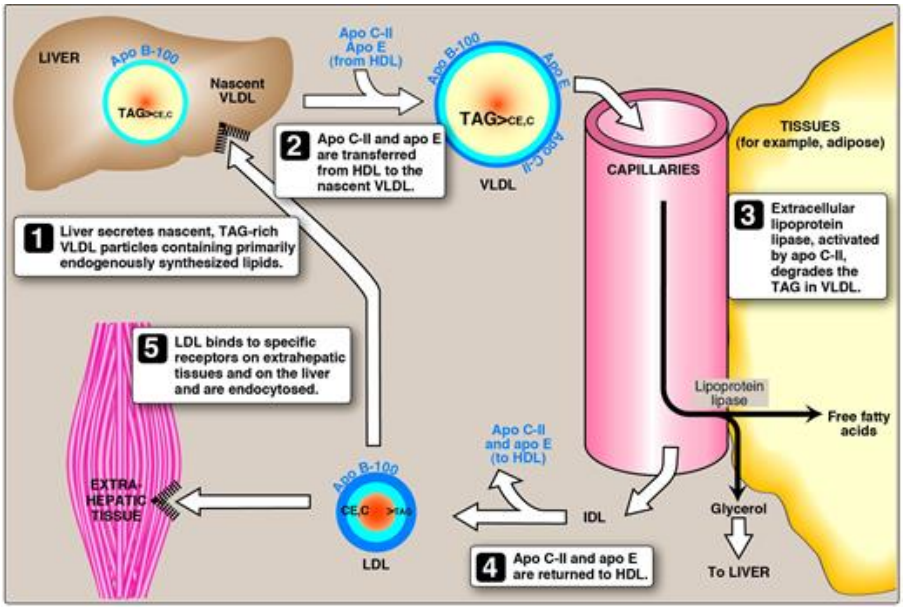
Modification in the circulation

As VLDL passes through the circulation, TAG is degraded by LPL, causing the VLDL to decrease in size and become denser. Surface components, including the C and E apolipoproteins, are returned to HDL, but the particles retain apo B-100. Additionally, some TAGs are transferred from VLDL to HDL in an exchange reaction that concomitantly transfers cholesteryl esters from HDL to VLDL. This exchange is accomplished by cholesteryl ester transfer protein (CETP), as shown in Figure 18.19.

Conversion to low-density lipoproteins

With these modifications, the VLDL is converted in the plasma to LDL. IDLs of varying sizes are formed during this transition. IDL can also be taken up by liver cells through receptor-mediated endocytosis that uses apo E as the ligand. Apo E is normally present in three isoforms, E-2 (the least common), E-3 (the most common), and E-4. Apo E-2 binds poorly to receptors, and patients who are homozygotic for apo E-2 are deficient in the clearance of IDL and chylomicron remnants. These individuals have familial type III hyperlipoproteinemia (familial dysbetalipoproteinemia or broad beta disease), with hypercholesterolemia and premature atherosclerosis. (Note: The apo E-4 isoform confers increased susceptibility to an earlier age of onset of the late-onset form of Alzheimer disease. The effect is dose dependent, with homozygotes being at greatest risk. Estimates of the risk vary.)

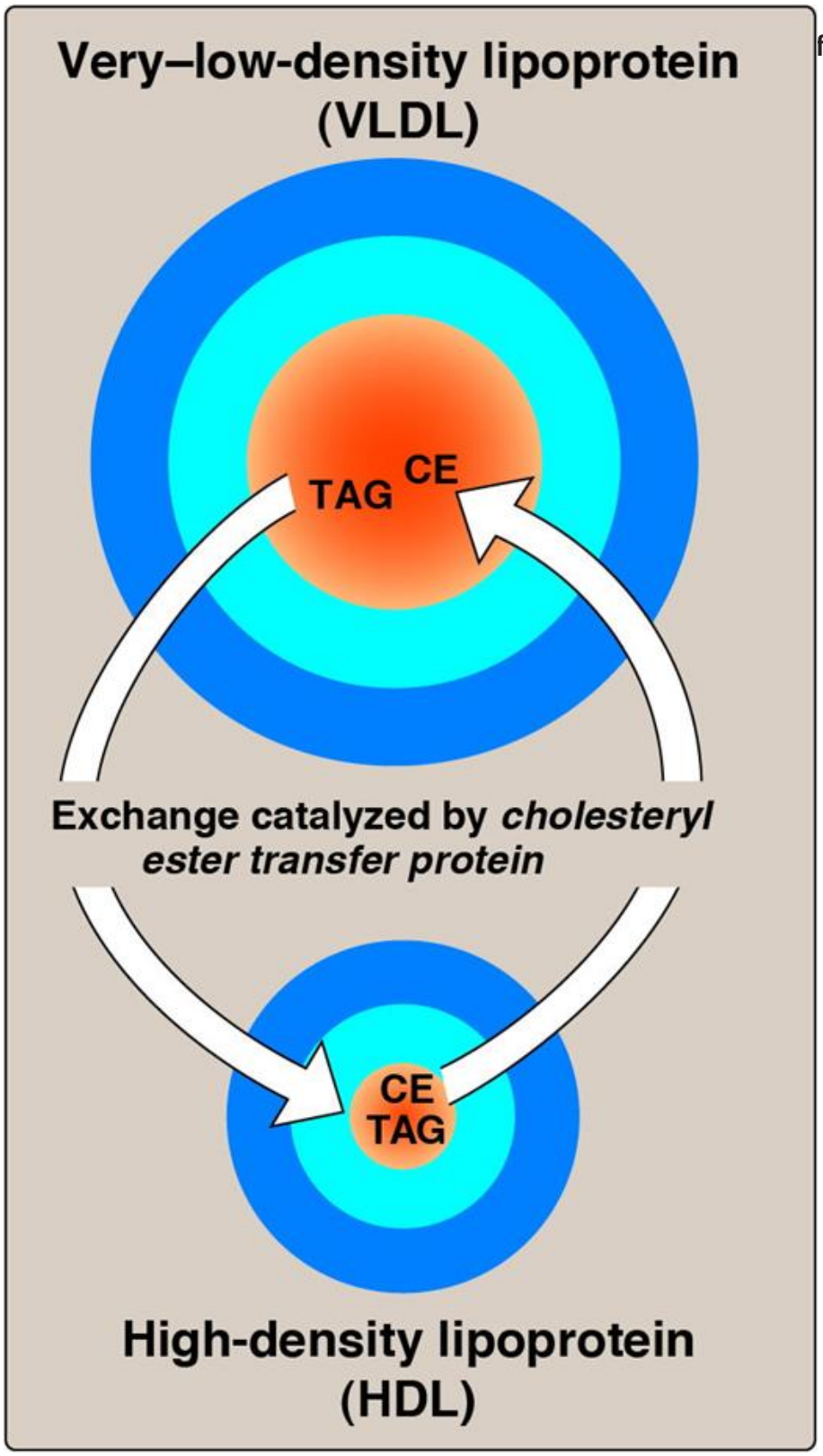
FIGURE 18.18



sity lipoprotein (LDL) particles.

na lipoprotein particles. The particles
). (Note: IDL can also be taken up by
sity lipoproteins; C = cholesterol; CE =

FIGURE 18.19



for triacylglycerol (TAG).

Low-density lipoprotein metabolism

LDL particles contain much less TAG than their VLDL predecessors and have a high concentration of cholesterol and cholesteryl esters (Fig. 18.20). About 70% of plasma cholesterol is in LDL.

Receptor-mediated endocytosis

The primary function of LDL particles is to provide cholesterol to the peripheral tissues (or return it to the liver). They do so by binding to plasma membrane LDL receptors that recognize apo B-100 (but not apo B-48). Because these LDL receptors can also bind apo E, they are known as apo B-100/apo E receptors. A summary of the uptake and degradation of LDL particles is presented in Figure 18.21. (Note: The numbers in brackets below refer to corresponding numbers on that figure.) A similar mechanism of receptor-mediated endocytosis is used for the uptake and degradation of chylomicron remnants and IDLs by the liver.

1. LDL receptors are negatively charged glycoproteins that are clustered in pits on cell membranes. The cytosolic side of the pit is coated with the protein clathrin, which stabilizes the pit.
2. After binding, the LDL–receptor complex is endocytosed. (Note: Defects in the synthesis of functional LDL receptors causes a significant elevation in plasma LDL-C. Patients with such deficiencies have type IIa hyperlipidemia [familial hypercholesterolemia (FH)] and premature atherosclerosis. Autosomal dominant hypercholesterolemia can also be caused by defects in apo B-100 that reduce its binding to the receptor and by increased activity of a protease, proprotein convertase subtilisin/kexin type 9 [PCSK9], which promotes internalization and lysosomal degradation of the receptor. PCSK9 inhibitors are now available for the treatment of hypercholesterolemia.)
3. The vesicle containing LDL loses its clathrin coat and fuses with other similar vesicles, forming larger vesicles called endosomes.
4. The pH of the endosome falls (due to the proton-pumping activity of endosomal ATPase), which allows separation of the LDL from its receptor. The receptors then migrate to one side of the endosome, whereas the LDL stay free within the lumen of the vesicle.
5. The receptors can be recycled, whereas the lipoprotein remnants in the vesicle are transferred to lysosomes and degraded by lysosomal acid hydrolases, releasing free cholesterol, amino acids, FA, and phospholipids. These compounds can be reutilized by the cell. (Note: A few of the lysosomal storage diseases result from rare autosomal-recessive deficiencies in the ability to hydrolyze lysosomal cholesteryl esters [Wolman disease] or to transport free cholesterol out of the lysosome [Niemann–Pick disease, type C].)

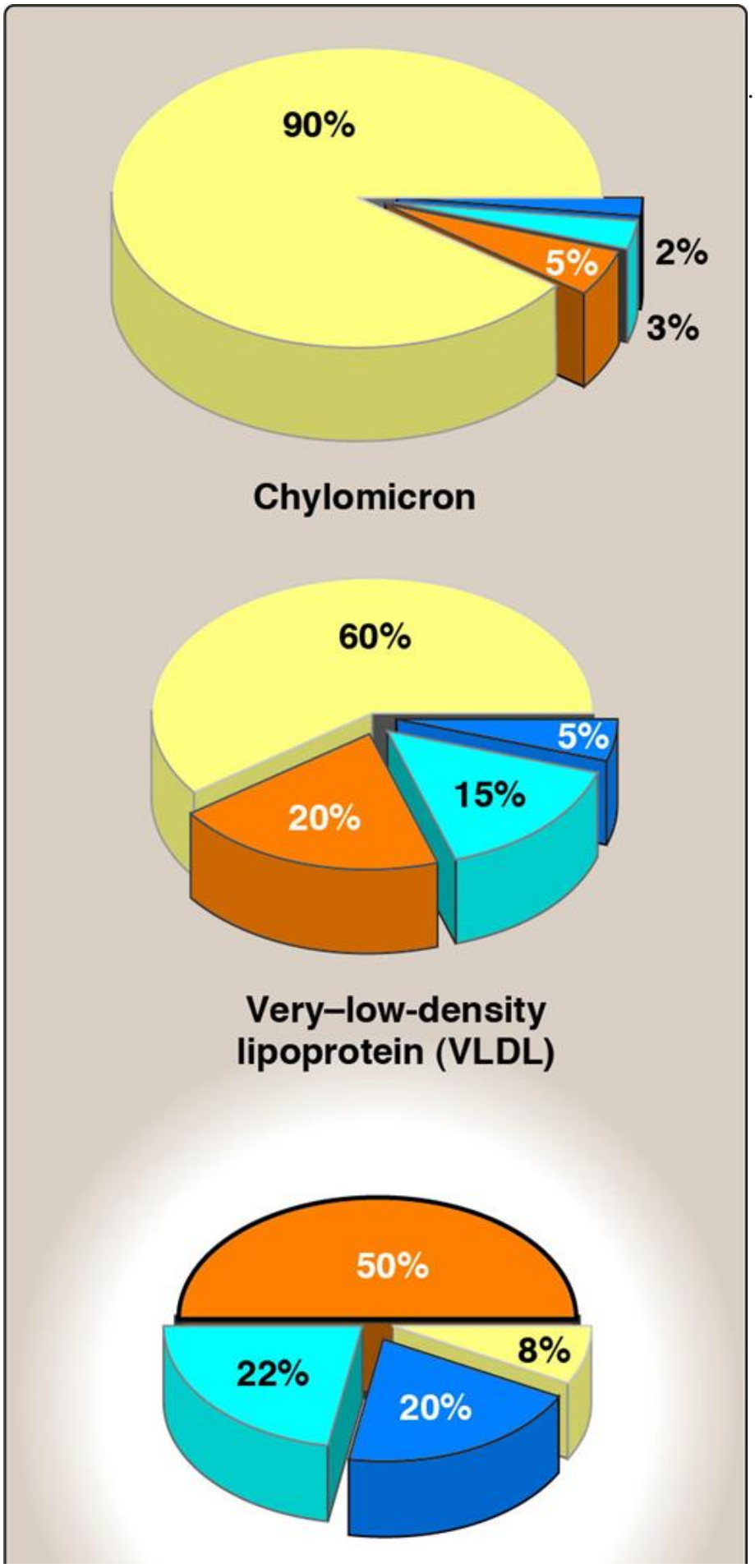
Endocytosed cholesterol and cholesterol homeostasis

The chylomicron remnant-, IDL-, and LDL-derived cholesterol affects cellular cholesterol content in several ways (Fig. 18.21). First, expression of the gene for HMG CoA reductase is inhibited by high cholesterol, and *de novo* cholesterol synthesis decreases as a result. Additionally, degradation of the *reductase* is accelerated. Second, synthesis of new LDL receptor protein is reduced by decreasing the expression of the LDL receptor gene, thus limiting further entry of LDL-C into cells. (Note: As was seen with the *reductase* gene, transcriptional regulation of the LDL receptor gene involves an SRE and SREBP-2. This allows coordinate regulation of the expression of these proteins.) Third, if the cholesterol is not required immediately for some structural or synthetic purpose, it is esterified by acyl CoA:cholesterol acyltransferase (ACAT). ACAT transfers a FA from a fatty acyl CoA to cholesterol, producing a cholesteryl ester that can be stored in the cell (Fig. 18.22). The activity of ACAT is enhanced in the presence of increased intracellular cholesterol.

Uptake by macrophage scavenger receptors

In addition to the highly specific and regulated receptor-mediated pathway for LDL uptake described above, macrophages possess high levels of scavenger receptor (SR) activity. These receptors, known as scavenger receptor class A (SR-A), can bind a broad range of ligands and mediate the endocytosis of chemically modified LDL in which the lipid or apo B component has been oxidized. Unlike the LDL receptor, the SR is not downregulated in response to increased intracellular cholesterol. Cholesteryl esters accumulate in macrophages and cause their transformation into “foam” cells, which participate in the formation of atherosclerotic plaque (Fig. 18.23). LDL-C is the primary cause of atherosclerosis.

FIGURE 18.20


90%
5%
2%
3%
Chylomicron
60%
5%
15%
20%
Very–low-density lipoprotein (VLDL)
50%
8%
22%
20%

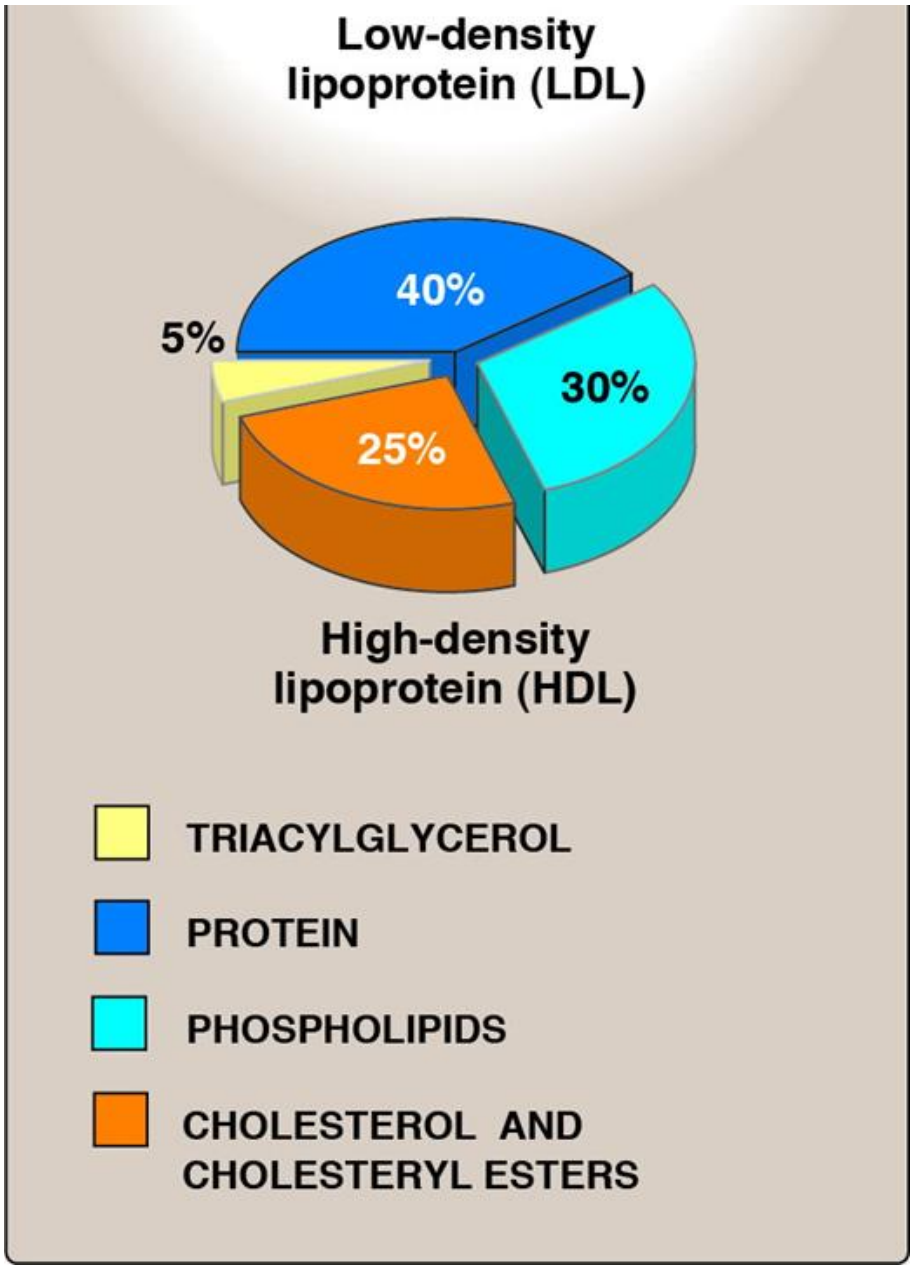
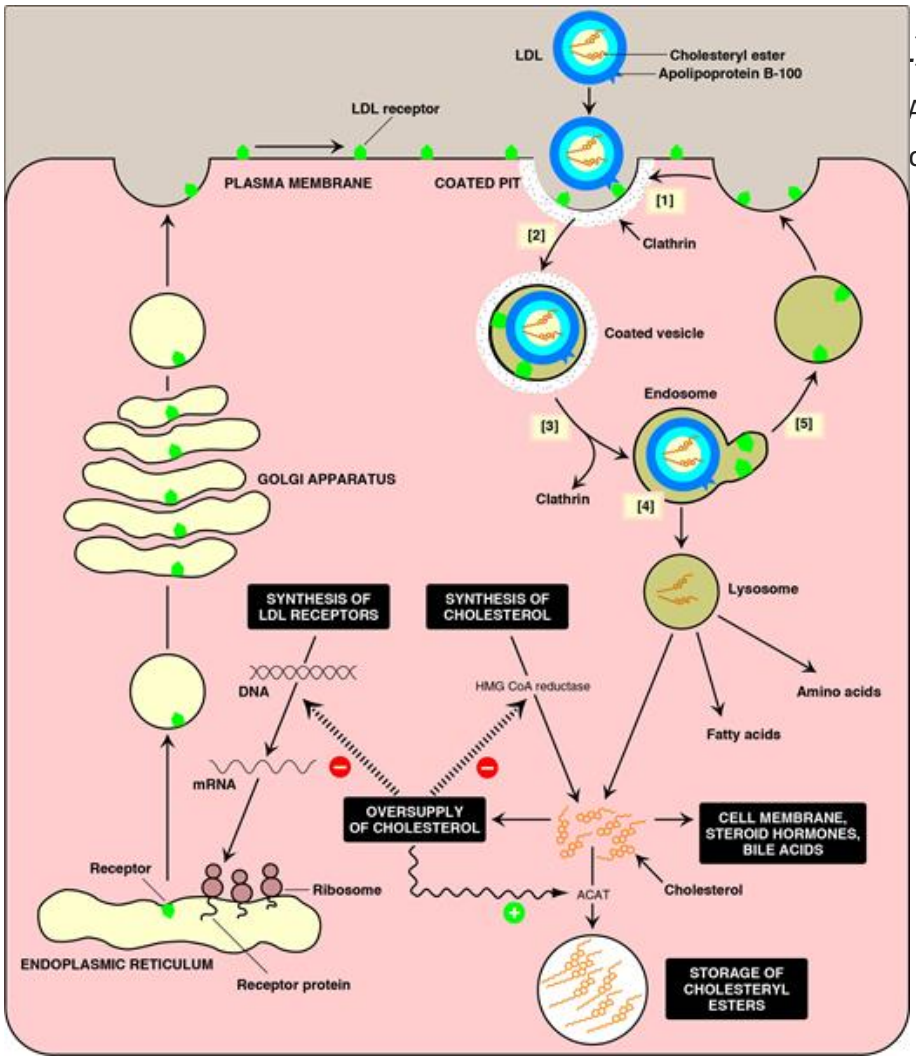

Low-density lipoprotein (LDL)
40%
5%
30%
25%
High-density lipoprotein (HDL)
TRIACYLGLYCEROL
PROTEIN
PHOSPHOLIPIDS
CHOLESTEROL AND CHOLESTERYL ESTERS

FIGURE 18.21

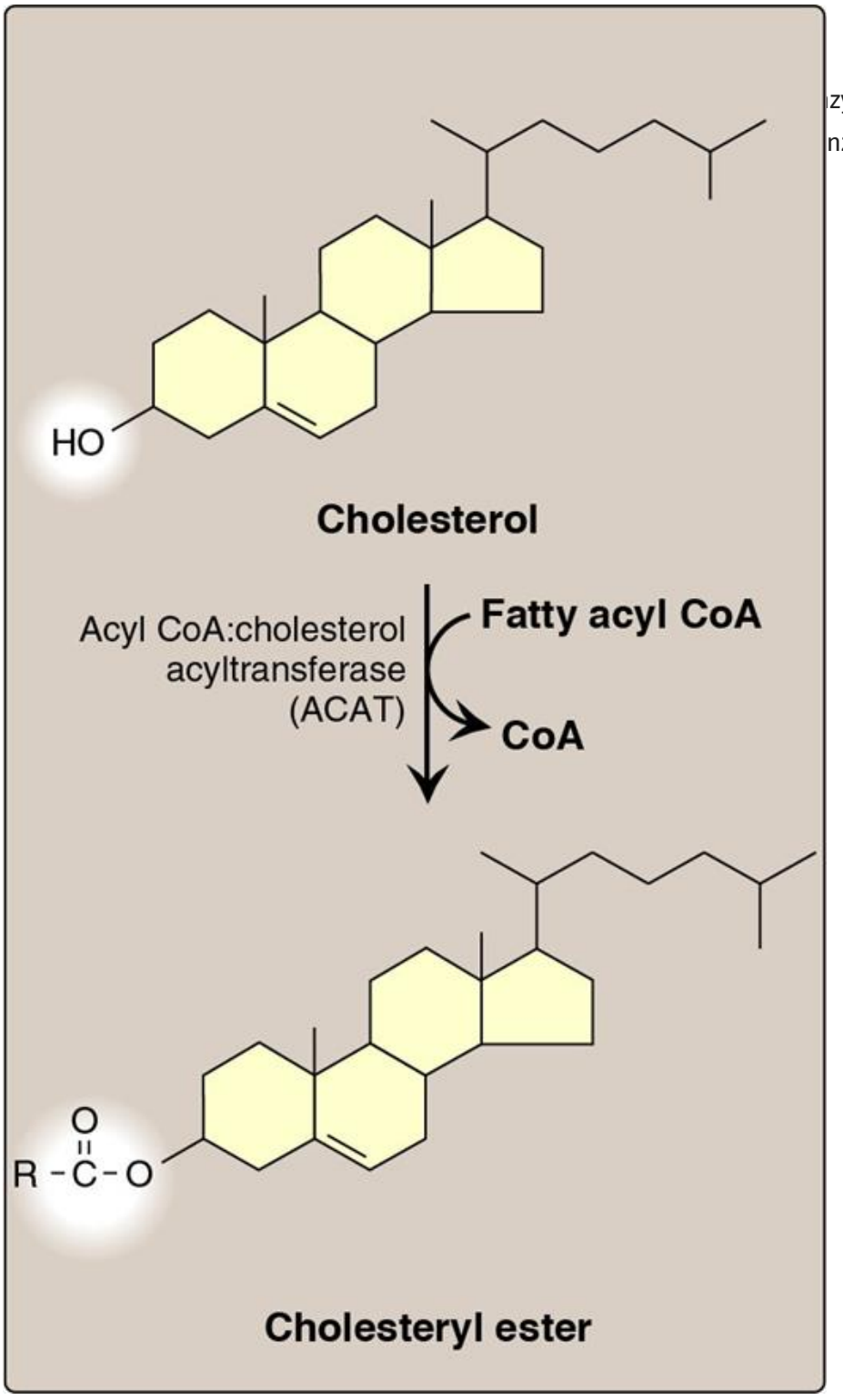


.) particles.

A reductase. It also decreases

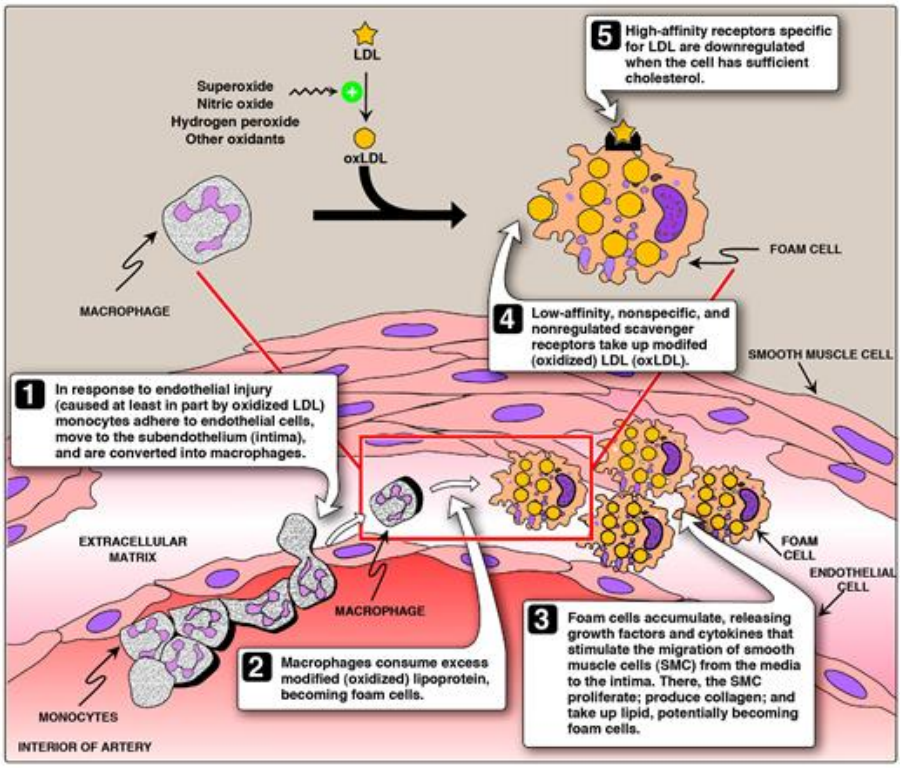
cholesterol acyltransferase; HMG CoA =

FIGURE 18.22



zyme that esterifies cholesterol using
nzyme A.

FIGURE 18.23



e formation in an arterial wall.

High-density lipoprotein metabolism

HDLs comprise a heterogeneous family of lipoproteins with a complex metabolism that is not yet completely understood. HDL particles are formed in the blood by the addition of lipid to apo A-1, an apolipoprotein made and secreted by the liver and intestine. Apo A-1 accounts for ~70% of the apolipoproteins in HDL. HDLs perform a number of important functions, including the following.

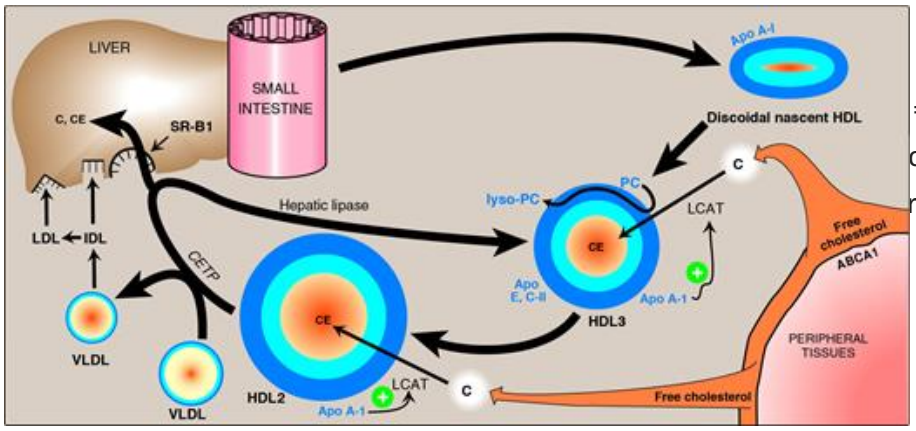
Apolipoprotein supply

HDL particles serve as a circulating reservoir of apo C-II (the apolipoprotein that is transferred to VLDL and chylomicrons and is an activator of LPL) and apo E (the apolipoprotein required for the receptor-mediated endocytosis of IDLs and chylomicron remnants).

Nonesterified cholesterol uptake

Nascent HDLs are disc-shaped particles containing primarily phospholipid (largely PC) and apo A, C, and E. They take up cholesterol from nonhepatic (peripheral) tissues and return it to the liver as cholesteryl esters (Fig. 18.24). (Note: HDL particles are excellent acceptors of nonesterified cholesterol as a result of their high concentration of phospholipids, which are important solubilizers of cholesterol.)

FIGURE 18.24



= cholesterol; CE = cholesteryl ester; ow–, intermediate-, and low-density r receptor B1.

Cholesterol esterification

The cholesterol taken up by HDL is immediately esterified by the plasma enzyme lecithin:cholesterolacyltransferase (LCAT, also known as PCAT, in which P stands for PC, the source of the FA). This enzyme is synthesized and secreted by the liver. LCAT binds to nascent HDL and is activated by apo A-I. LCAT transfers the FA from carbon 2 of PC to cholesterol. This produces a hydrophobic cholesteryl ester, which is sequestered in the core of the HDL, and lysophosphatidylcholine, which binds to albumin. (Note: Esterification maintains the cholesterol concentration gradient, allowing continued efflux of cholesterol to HDL.) As the discoidal nascent HDL accumulates cholesteryl esters, it first becomes a spherical, relatively cholesteryl ester–poor HDL3 and, eventually, a cholesteryl ester–rich HDL2 particle that carries these esters to the liver. Hepatic lipase, which degrades TAG and phospholipids, participates in the conversion of HDL2 to HDL3 (see Fig. 18.24). CETP transfers some of the cholesteryl esters from HDL to VLDL in exchange for TAG, relieving product inhibition of LCAT. Because VLDLs are catabolized to LDLs, the cholesteryl esters transferred by CETP are ultimately taken up by the liver.

Reverse cholesterol transport

The selective transfer of cholesterol from peripheral cells to HDL and from HDL to the liver for bile acid synthesis or disposal via the bile is a key component of cholesterol homeostasis. This process of reverse cholesterol transport (RCT) is, in part, the basis for the inverse relationship seen between plasma HDL concentration and atherosclerosis and for the designation of HDL as the “good” cholesterol carrier. (Note: Exercise and estrogen raise HDL levels.) RCT involves efflux of cholesterol from peripheral cells to HDL, esterification of the cholesterol by LCAT, binding of the cholesteryl ester–rich HDL (HDL2) to liver (and, perhaps, steroidogenic cells), selective transfer of the cholesteryl esters into these cells, and release of lipid-depleted HDL (HDL3). The efflux of cholesterol from peripheral cells is mediated primarily by the transport protein ABCA1. (Note: Tangier disease is a very rare deficiency of ABCA1 and is characterized by the virtual absence of HDL particles due to degradation of lipid-poor apo A-1.) Cholesteryl ester uptake by the liver is mediated by the cell-surface receptor scavenger receptor class B type 1 (SR-B1) that binds HDL (see Section VI D3 for SR-A receptors). The HDL particle itself is not taken up. Instead, there is selective uptake of the cholesteryl ester from the HDL particle. (Note: Low HDL-C is a risk factor for atherosclerosis.)

ABCA1 is an ATP-binding cassette (ABC) protein. ABC proteins use energy from ATP hydrolysis to transport materials, including lipids, in and out of cells and across intracellular compartments. In addition to Tangier disease, defects in specific ABC proteins result in sitosterolemia, cystic fibrosis, X-linked adrenoleukodystrophy, respiratory distress syndrome due to decreased surfactant secretion, and liver disease due to decreased bile salt secretion.

Lipoprotein (a) and heart disease

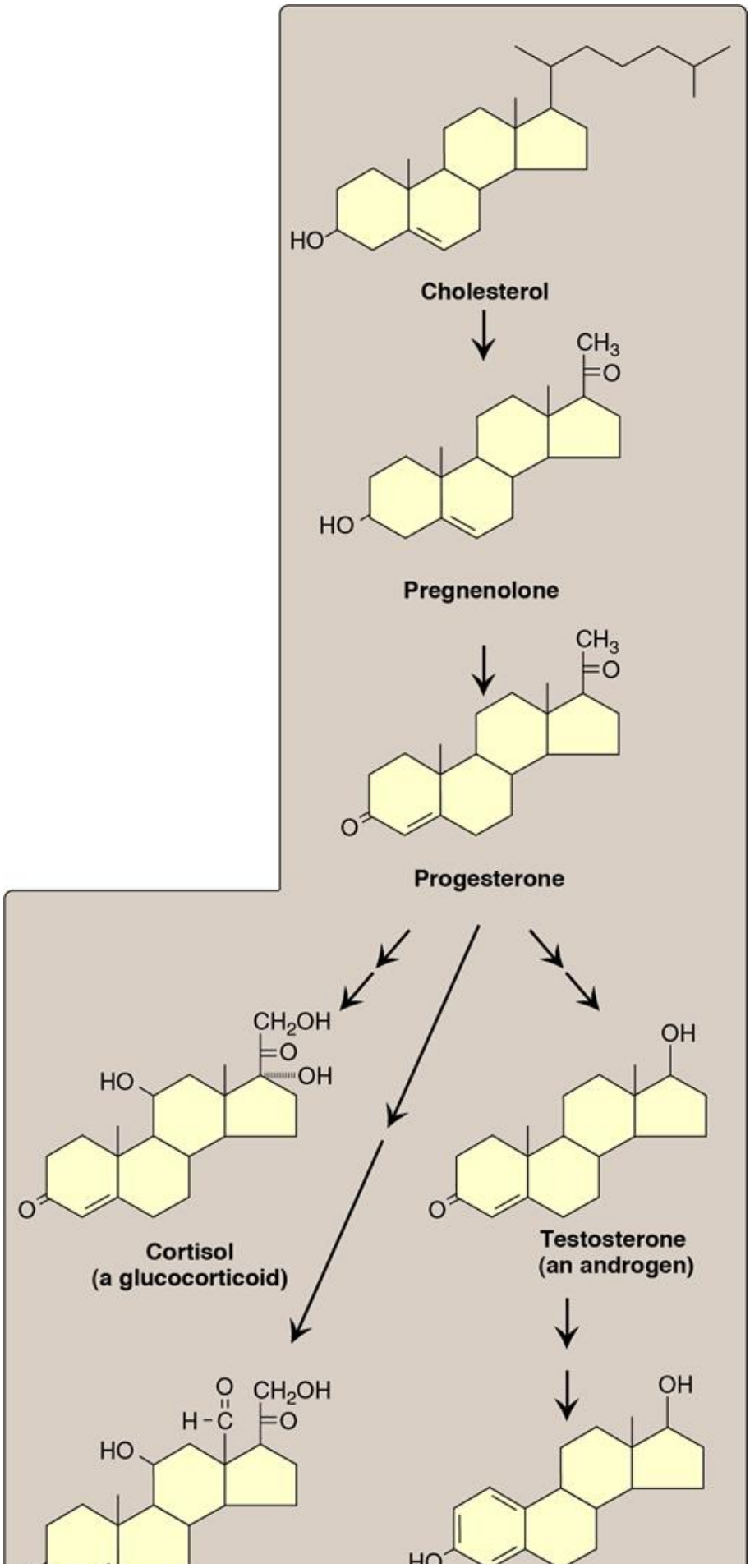
Lp(a), is nearly identical in structure to an LDL particle. Its distinguishing feature is the presence of an additional apolipoprotein molecule, apo(a), which is covalently linked at a single site to apo B-100. Apo(a) is structurally homologous to plasminogen, the precursor of a blood protease whose target is fibrin. Fibrin is the main protein component of blood clots (see Chapter 35). Lp(a) is an independent risk factor for coronary heart disease. The apo(a) component of Lp(a) particles is indicated to promote atherogenesis. Circulating levels of Lp(a) are determined primarily by genetics. However, diet may play some role, as trans FA have been reported to increase Lp(a). On the other hand, niacin reduces Lp(a), as well as LDL-C and TAG, but raises HDL-C.

Steroid Hormones

Listen

Cholesterol is the precursor of all classes of steroid hormones: glucocorticoids (e.g., cortisol), mineralocorticoids (e.g., aldosterone), and the sex hormones (i.e., androgens, estrogens, and progestins), as shown in Figure 18.25. (Note: Glucocorticoids and mineralocorticoids are collectively called corticosteroids.) Synthesis and secretion occur in the adrenal cortex (cortisol, aldosterone, and androgens), ovaries and placenta (estrogens and progestins), and testes (testosterone). Steroid hormones are transported by the blood from their sites of synthesis to their target organs. Because of their hydrophobicity, they must be complexed with a plasma protein. Albumin can act as a nonspecific carrier and does carry aldosterone. However, specific steroid-carrier plasma proteins bind the steroid hormones more tightly than does albumin (e.g., corticosteroid-binding globulin, or transcortin, is responsible for transporting cortisol). A number of genetic diseases are caused by deficiencies in specific steps in the biosynthesis of steroid hormones. Some representative diseases are described in Figure 18.26.

FIGURE 18.25


HO
Cholesterol
CH3
O
HO
Pregnenolone
CH3
O
O
Progesterone
CH2OH
O
HO
OH
O
Cortisol
(a glucocorticoid)
OH
O
Testosterone
(an androgen)
O
H-C
CH2OH
O
HO
OH
HO

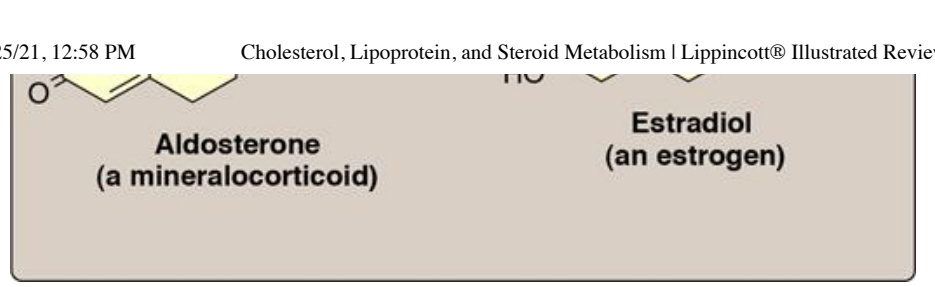
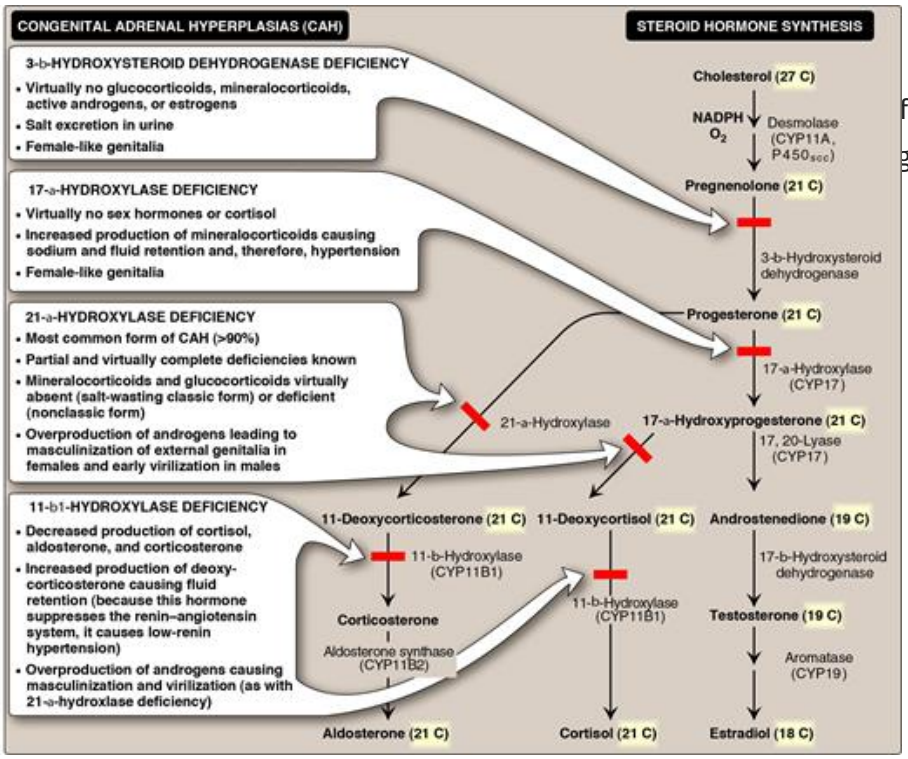


FIGURE 18.26



functional enzymes. Synthesis of gland.) NADPH = nicotinamide adenine

Synthesis

Synthesis involves shortening the hydrocarbon chain of cholesterol and hydroxylating the steroid nucleus. The initial and rate-limiting reaction converts cholesterol to the 21-carbon pregnenolone. It is catalyzed by the cholesterol side-chain cleavage enzyme, a cytochrome P450 (CYP) mixed function oxidase of the inner mitochondrial membrane that is also known as $P450_{scc}$ and desmolase. NADPH and O_2 are required for the reaction. The cholesterol substrate can be newly synthesized, taken up from lipoproteins, or released by an esterase from cholesteryl esters stored in the cytosol of steroidogenic tissues. The cholesterol moves to the outer mitochondrial membrane. An important control point is the subsequent movement from the outer to the inner mitochondrial membrane. This process is mediated by steroidogenic acute regulatory (StAR) protein. Pregnenolone is the parent compound for all steroid hormones (see Fig. 18.26). It is oxidized and then isomerized to progesterone, which is further modified to the other steroid hormones by CYP protein–catalyzed hydroxylation reactions in the SER and mitochondria. A defect in the activity or amount of an enzyme in this pathway can lead to a deficiency in the synthesis of hormones beyond the affected step and to an excess in the hormones or metabolites before that step. Because all members of the pathway have potent biologic activity, serious metabolic imbalances occur with enzyme deficiencies (see Fig. 18.26). Collectively, these disorders are known as the congenital adrenal hyperplasia (CAH), because they result in enlarged adrenals. (Note: Addison disease, due to autoimmune destruction of the adrenal cortex, is characterized by adrenocortical insufficiency.)

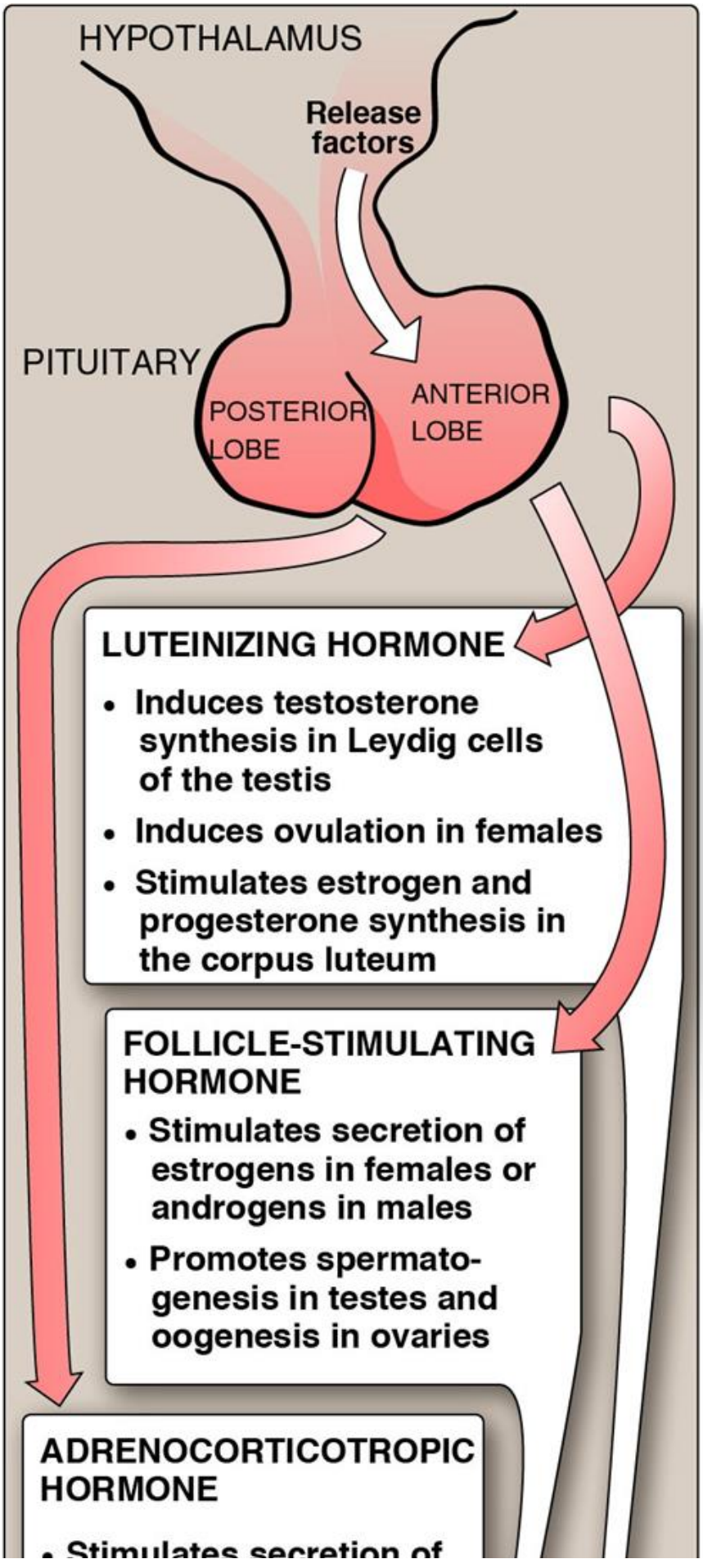
Adrenal cortical steroid hormones

Steroid hormones are synthesized and secreted in response to hormonal signals. The corticosteroids and androgens are made in different regions of the adrenal cortex and are secreted into blood in response to different signals. (Note: The adrenal medulla makes catecholamines [see Chapter 21].)

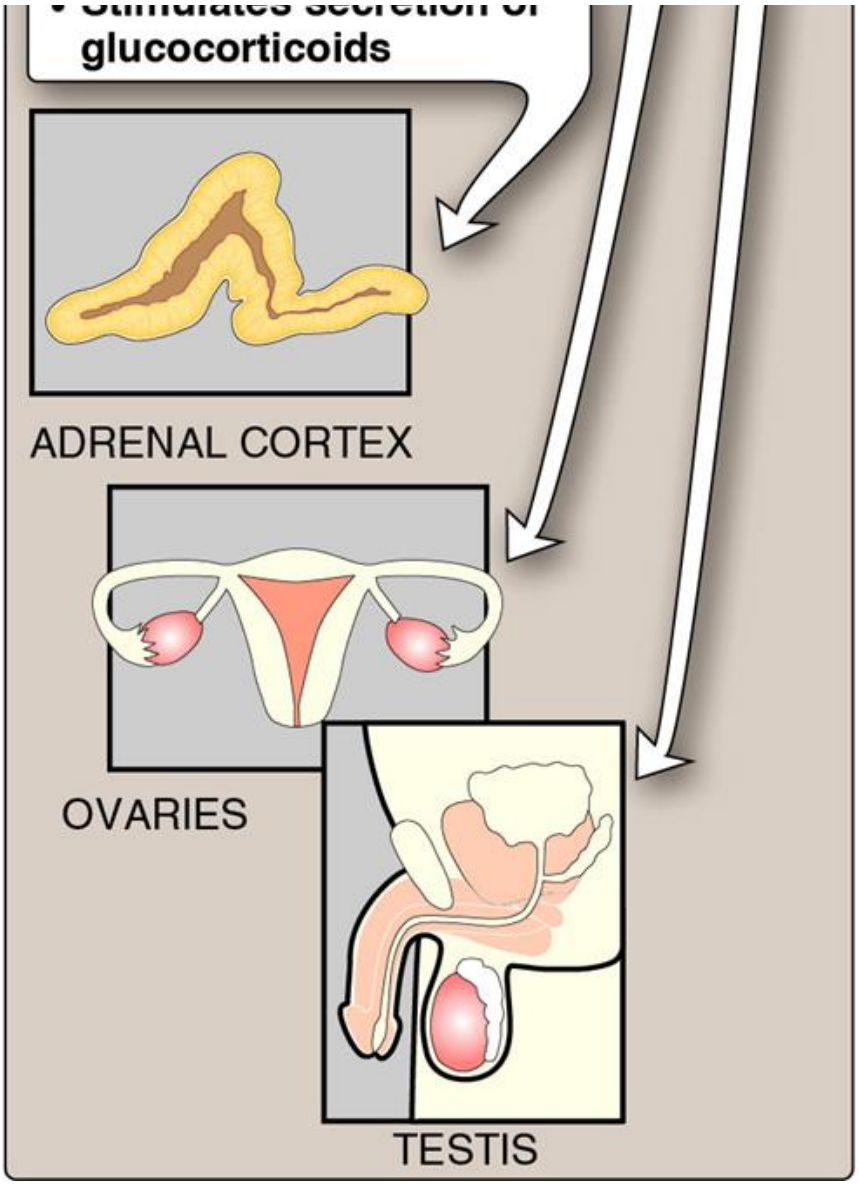
Cortisol

Its production in the middle layer (zona fasciculata) of the adrenal cortex is controlled by the hypothalamus, to which the pituitary gland is attached (Fig. 18.27). In response to severe stress (e.g., infection), corticotropin-releasing hormone (CRH), produced by the hypothalamus, travels through capillaries to the anterior lobe of the pituitary, where it induces the production and secretion of adrenocorticotropic hormone (ACTH), a peptide. ACTH stimulates the adrenal cortex to synthesize and secrete the glucocorticoid cortisol, the stress hormone. (Note: ACTH binds to a membrane G protein–coupled receptor, resulting in cyclic AMP [cAMP] production and activation of protein kinase A [PKA]. PKA phosphorylates and activates both the esterase that converts cholesteryl ester to free cholesterol and StAR protein.) Cortisol allows the body to respond to stress through its effects on intermediary metabolism (e.g., increased gluconeogenesis) and the inflammatory and immune responses (which are decreased). As cortisol levels rise, the release of CRH and ACTH is inhibited. (Note: The reduction of cortisol in CAH results in a rise in ACTH that causes adrenal hyperplasia.)

FIGURE 18.27



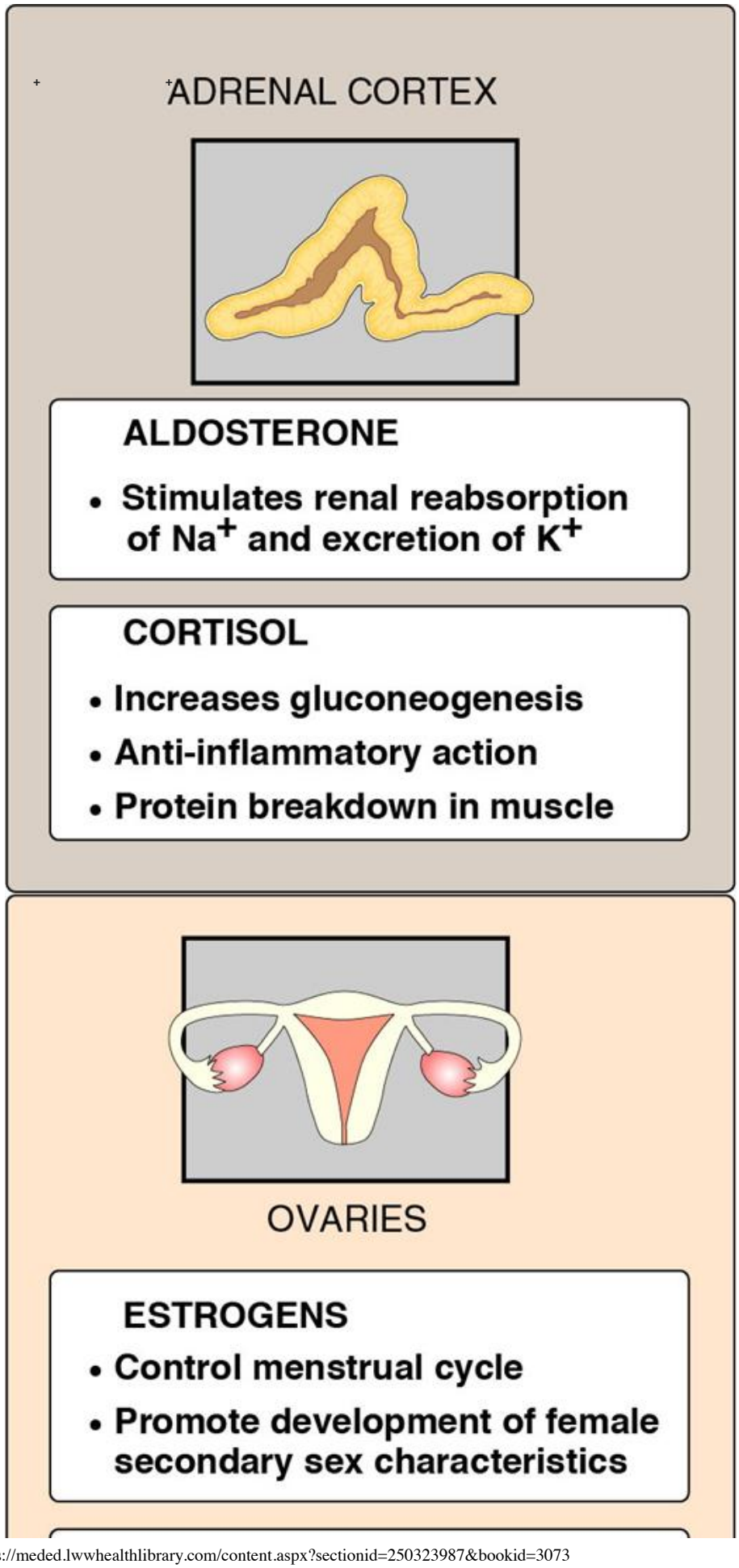
ɪ secretion.

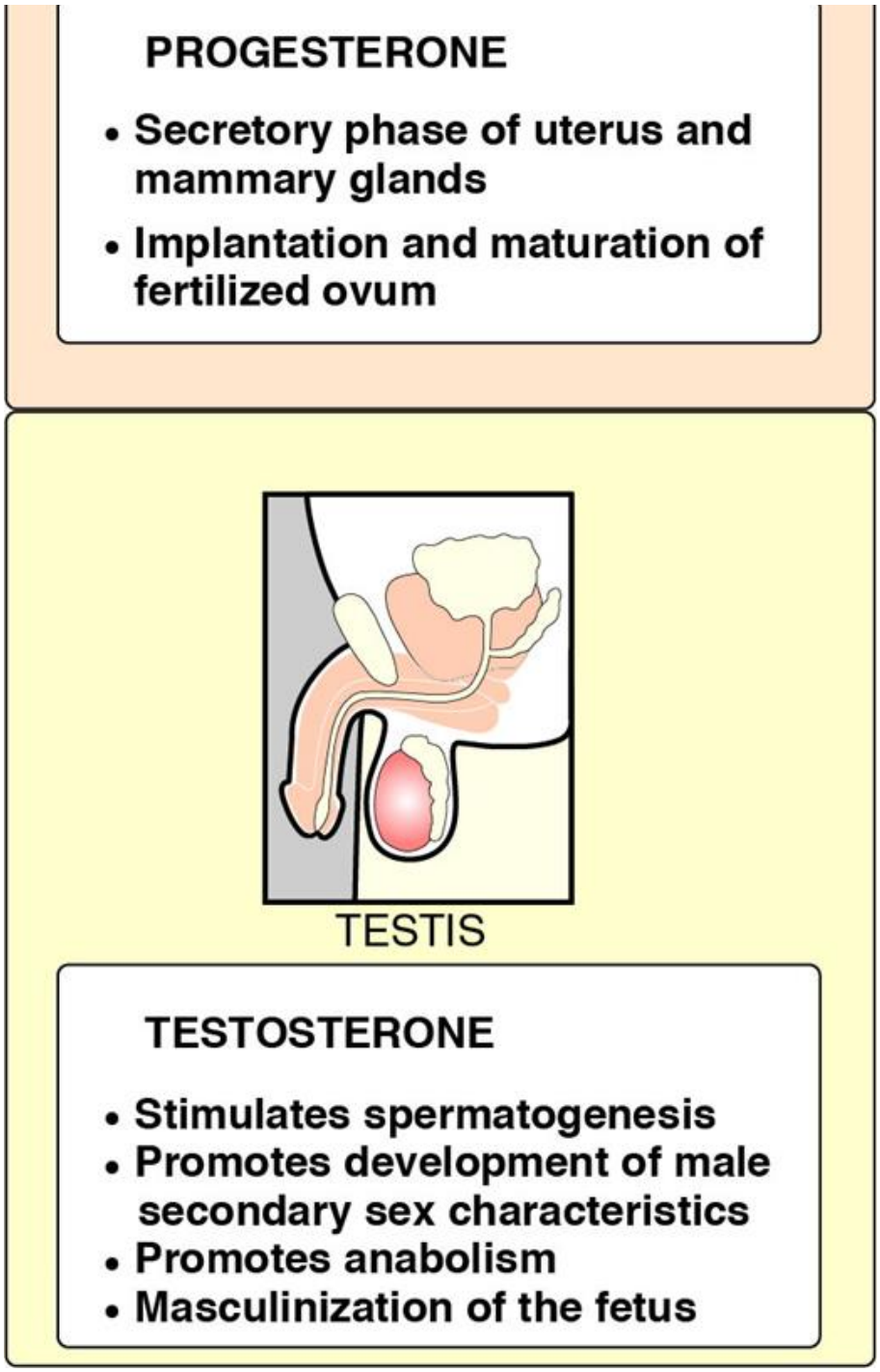


Aldosterone

Its production in the outer layer (zona glomerulosa) of the adrenal cortex is induced by a decrease in the plasma Na^+/potassium (K^+) ratio and by the hormone angiotensin II (Ang-II). Ang-II (an octapeptide) is produced from angiotensin I ([Ang-I] a decapeptide) by angiotensin-converting enzyme (ACE), an enzyme found predominantly in the lungs but also distributed widely in the body. (Note: Ang-I is produced in the blood by cleavage of an inactive precursor, angiotensinogen, secreted by the liver. Cleavage is catalyzed by renin, made and secreted by the kidneys.) Ang-II binds to cell surface receptors. However, in contrast to ACTH, its effects are mediated through the phosphatidylinositol 4,5-bisphosphate pathway and not by cAMP. Aldosterone's primary effect is on the kidney tubules, where it stimulates Na^+ and water uptake and K^+ excretion (Fig. 18.28). (Note: An effect of aldosterone is an increase in blood pressure. Competitive inhibitors of ACE are used to treat renin-dependent hypertension.)

FIGURE 18.28


ADRENAL CORTEX
ALDOSTERONE
• Stimulates renal reabsorption of Na^+ and excretion of K^+
CORTISOL
• Increases gluconeogenesis
• Anti-inflammatory action
• Protein breakdown in muscle
OVARIES
ESTROGENS
• Control menstrual cycle
• Promote development of female secondary sex characteristics



Androgens

Both the inner (zona reticularis) and middle layers of the adrenal cortex produce androgens, primarily dehydroepiandrosterone and androstenedione. Although adrenal androgens themselves are weak, they are converted by aromatase (CYP19) to testosterone, a stronger androgen, in the testes and to estrogens in the ovaries (primarily) of premenopausal women. (Note: Postmenopausal women produce estrogen at extragonadal sites such as the breast. Aromatase inhibitors are used in the treatment of estrogen-responsive breast cancer in these women.)

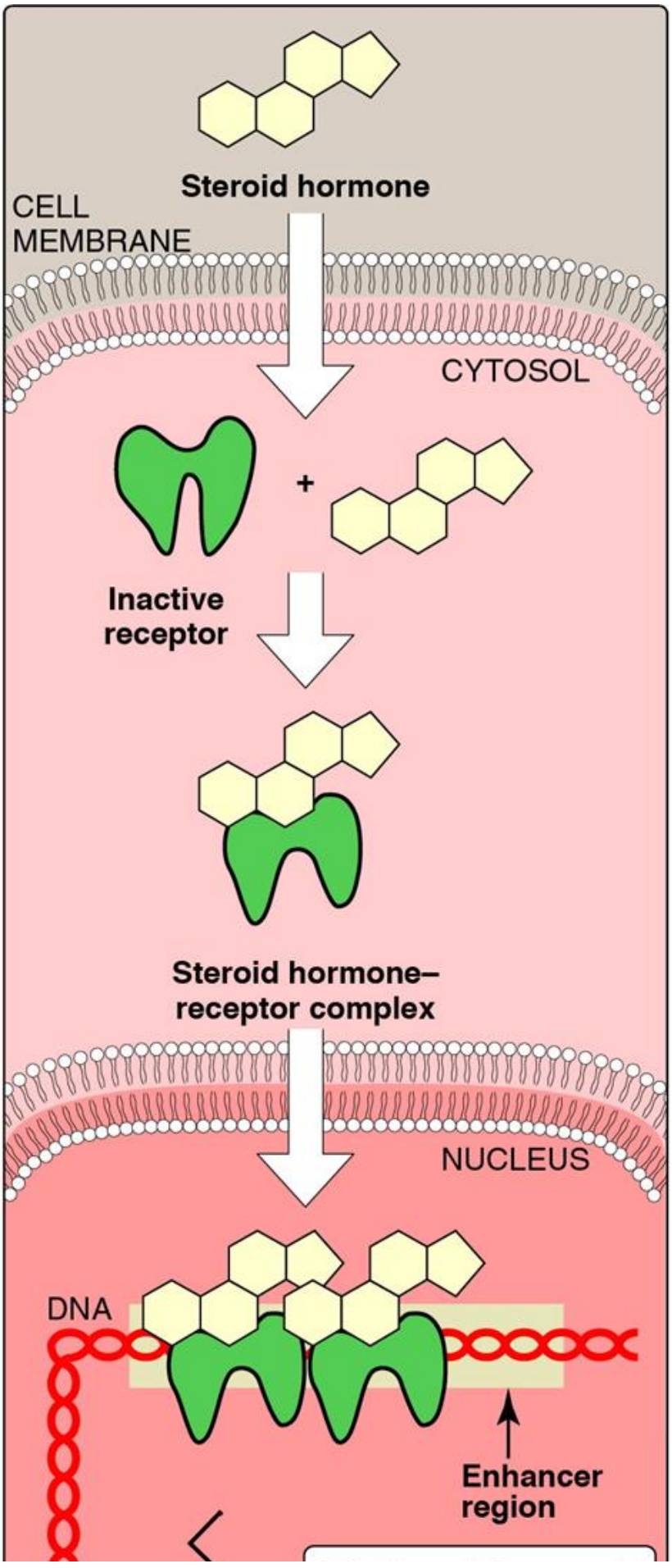
Gonadal steroid hormones

The testes and ovaries (gonads) synthesize hormones necessary for sexual differentiation and reproduction. A single hypothalamic-releasing factor, gonadotropin-releasing hormone, stimulates the anterior pituitary to release the glycoproteins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Like ACTH, LH and FSH bind to surface receptors and cause an increase in cAMP. LH stimulates the testes to produce testosterone and the ovaries to produce estrogens and progesterone (see Fig. 18.28). FSH regulates the growth of ovarian follicles and stimulates testicular spermatogenesis.

Mechanism

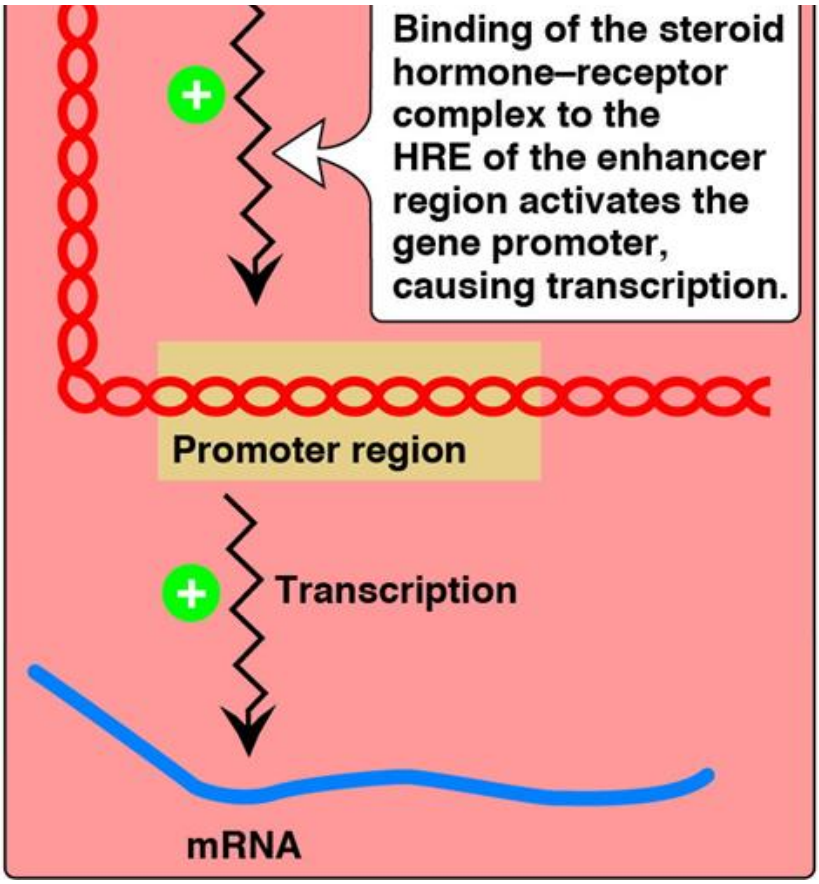
Each steroid hormone diffuses across the plasma membrane of its target cell and binds to a specific cytosolic or nuclear receptor. These receptor–ligand complexes accumulate in the nucleus, dimerize, and bind to specific regulatory DNA sequences (hormone response elements [HREs]) in association with coactivator proteins, thereby causing increased transcription of targeted genes (Fig. 18.29). An HRE is found in the promoter or an enhancer element (see Chapter 31) for genes that respond to a specific steroid hormone, thus ensuring coordinated regulation of these genes. Hormone–receptor complexes can also inhibit transcription in association with corepressors. (Note: The binding of a hormone to its receptor causes a conformational change in the receptor that uncovers its DNA-binding domain, allowing the complex to interact through a zinc finger motif with the appropriate DNA sequence. Receptors for the steroid hormones, plus those for thyroid hormone, retinoic acid, and 1,25-dihydroxycholecalciferol [vitamin D], are members of a superfamily of structurally related gene regulators that function in a similar way.)

FIGURE 18.29



ceptor complex with hormone

ating proteins. mRNA = messenger



Further metabolism

Steroid hormones are generally converted into inactive metabolic excretion products in the liver. Reactions include reduction of unsaturated bonds and the introduction of additional hydroxyl groups. The resulting structures are made more soluble by conjugation with glucuronic acid or sulfate (from 3′-phosphoadenosyl-5′-phosphosulfate). These conjugated metabolites are fairly water soluble and do not need protein carriers. They are eliminated in feces and urine.

Chapter Summary

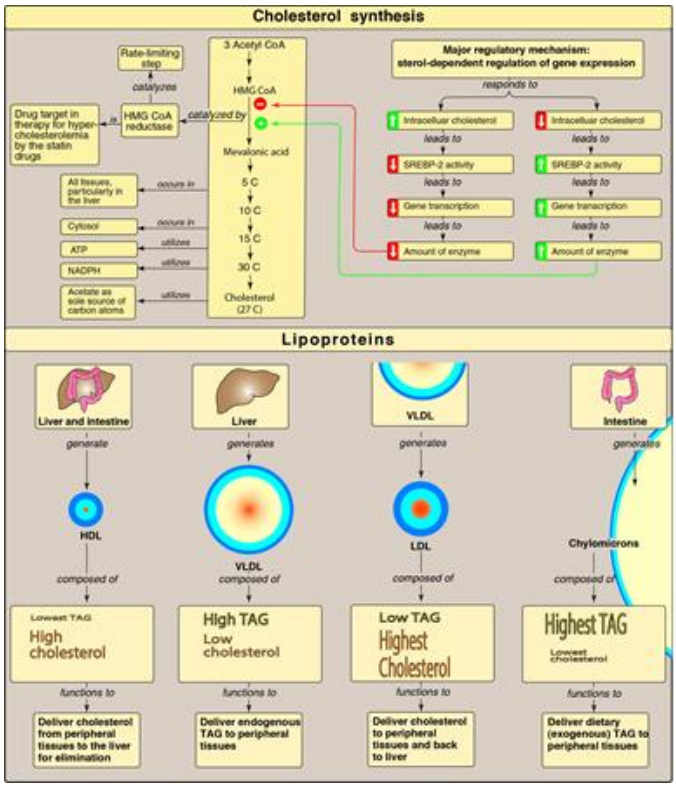
Listen

- **Cholesterol** is a hydrophobic compound, with a single hydroxyl group to which a FA can be attached, producing an even more hydrophobic **cholesteryl ester**.
- Cholesterol is synthesized by virtually all human tissues, although primarily by the **liver**, **intestine**, **adrenal cortex**, and **reproductive tissues.**
- Synthesis requires enzymes of the **cytosol**, **SER**, and **peroxisomes**.
- The rate-limiting and regulated step in cholesterol synthesis is catalyzed **HMG CoA reductase**, which produces **mevalonate** from HMG CoA.
- **HMG CoA reductase** is highly regulated by a number of mechanisms: (1) via the transcription factor, **SREBP-2**; (2) accelerated **degradation** of the **protein** when cholesterol levels are high; (3) **phosphorylation** causing **inactivation** of the enzyme by **AMPK**; and (4) hormonal regulation by **insulin** and **glucagon**.
- **Statins** are **competitive inhibitors** of HMG CoA reductase. These drugs are used to decrease plasma cholesterol in patients with **hypercholesterolemia**.
- The ring structure of cholesterol cannot be degraded in humans. It is eliminated from the body either by conversion to bile salts or by secretion into the **bile**.
- The rate-limiting step in bile acid synthesis is catalyzed by **cholesterol-7-α-hydroxylase**, which is inhibited by **bile acids**.
- Before the bile acids leave the liver, they are conjugated. Conjugated bile acids are known as bile salts which are **more** ionized and **more** water **soluble** than bile acids at the alkaline pH of the bile.
- Intestinal **bacteria** modify bile salts producing the **secondary bile salts.**
- Bile salts are efficiently reabsorbed (>95%) and return to the liver by **enterohepatic circulation.**
- Enterohepatic circulation of bile salts is reduced by **bile acid sequestrants.**
- If more cholesterol enters the bile than can be solubilized by the available bile salts and PC, **cholesterol gallstone disease** (**cholelithiasis**) can occur.
- The plasma lipoproteins (see Fig. 18.30) include **chylomicrons**, **VLDLs**, **IDLs**, **LDLs**, and **HDLs**. They function to keep lipids soluble as they transport them between tissues.

FIGURE 18.30

Concept map for cholesterol and the lipoproteins.

HMG CoA = hydroxymethylglutaryl coenzyme A; SREBP = sterol regulatory element–binding protein; HDLs, LDLs, and VLDLs = high-, low-, and very-low-density lipoproteins; TAG = triacylglycerol; NADPH = nicotinamide adenine dinucleotide phosphate; C = carbon.



- Lipoproteins are composed of **TAG** and **cholesteryl esters** in the core surrounded by a shell of **amphipathic apolipoproteins**, **phospholipid**, and **nonesterified cholesterol**.
- **Chylomicrons** are assembled in **intestinal mucosal cells** from **dietary lipids**. Each nascent chylomicron particle has one molecule of **apo B-48**.
- Due to their large size, **chylomicrons** are released from the cells into the lymphatic system and travel to the blood. Apo C-II activates endothelial **LPL**, which degrades the TAG in chylomicrons to FA and glycerol. The **FA** that are released are stored in **adipose tissue** or used for energy in **muscle**. The **glycerol** is metabolized by the **liver**.
- After most of the TAG is removed, the **chylomicron remnant**, carrying most of the **dietary cholesterol**, binds to a liver receptor that recognizes apo E.
- Patients with a **deficiency** of LPL or apo C-II show a dramatic accumulation of chylomicrons in the plasma (**type I hyperlipoproteinemia** or **familial chylomicronemia**) even if fasted.
- Nascent VLDLs are produced in the liver and are composed predominantly of TAG. They contain a single molecule of **apo B-100**. VLDLs carry hepatic TAG to the peripheral tissues where LPL degrades the lipid.
- The VLDL particle receives **cholesteryl esters** from HDL in exchange for TAG. This process is accomplished by **CETP**.
- VLDL in the plasma is first converted to IDL and then to LDL.
- Apo B-100 on LDL is recognized by the **LDL receptor** which results in the **receptor-mediated endocytosis of LDL. The contents of LDL are** degraded in the **lysosomes and the LDL receptor is recycled**. The protease **PCSK9** prevents receptor recycling.

- Defective uptake of these chylomicron remnants and IDL causes **type III hyperlipoproteinemia** or **dysbetalipoproteinemia**.
- Defects in the synthesis of functional LDL receptors causes **type II ahyperlipoproteinemia** (**FH**).
- HDLs are created by **lipidation** of **apo A-1** synthesized in the liver and intestine. They have a number of functions, including (1) serving as a circulating **reservoir** of apo C-II and apo E for chylomicrons and VLDL; (2) removing **cholesterol** from peripheral tissues via ABCA1 and esterifying it using **LCAT**, a liver-synthesized plasma enzyme that is activated by **apo A-1**; and (3) delivering these cholesteryl esters to the liver (**RCT**) for uptake via **SR-B1**.
- Cholesterol is the precursor of all classes of **steroid hormones**, which include **glucocorticoids**, **mineralocorticoids**, and the **sex hormones**. Synthesis occurs in the **adrenal cortex (the glucocorticoids, the mineralocorticoids, and the androgens)**, **gonads,** and **placenta**.
- The initial and rate-limiting step is the conversion of cholesterol to **pregnenolone** by the side-chain cleavage enzyme **$P450_{scc}$**. Deficiencies in synthesis lead to **CAH**.
- Each steroid hormone binds to a specific intracellular receptor in its target cell. These **receptor–hormone complexes** bind to specific regulatory DNA sequences (**HREs**) in association with coactivator proteins/corepressors, thereby regulating **transcription** of targeted genes.

Study Questions

Listen

Choose the ONE best answer.

18.1. Mice were genetically engineered to contain hydroxymethylglutaryl coenzyme A reductase in which serine 871, a phosphorylation site, was replaced by alanine. Which of the following statements concerning the modified form of the enzyme is most likely to be correct?

A. The enzyme is nonresponsive to ATP depletion.

B. The enzyme is nonresponsive to statin drugs.

C. The enzyme is nonresponsive to the sterol response element–sterol response element–binding protein system.

D. The enzyme is unable to be degraded by the ubiquitin–proteasome system.

Correct answer = A. The reductase is regulated by covalent phosphorylation and dephosphorylation. Depletion of ATP results in a rise in adenosine monophosphate (AMP), which activates AMP kinase (AMPK), thereby phosphorylating and inactivating the reductase. In the absence of the serine, a common phosphorylation site, the enzyme cannot be phosphorylated by AMPK. The enzyme is also regulated physiologically through changes in transcription and degradation and pharmacologically by statin drugs (competitive inhibitors), but none of these depends on serine phosphorylation.

18.2. Calculate the amount of cholesterol in the low-density lipoproteins in an individual whose fasting blood gave the following lipid-panel test results: total cholesterol = 300 mg/dl, high-density lipoprotein cholesterol = 25 mg/dl, triglycerides = 150 mg/dl.

A. 55 mg/dl

B. 95 mg/dl

C. 125 mg/dl

D. 245 mg/dl

Correct answer = D. The total cholesterol in the blood of a fasted individual is equal to the sum of the cholesterol in low-density lipoproteins plus the cholesterol in high-density lipoproteins plus the cholesterol in very–low-density lipoproteins (VLDLs). This last term is calculated by dividing the triacylglycerol value by 5 because cholesterol accounts for about one-fifth of the volume of VLDL in fasted blood.

For Questions 18.3 and 18.4, use the following scenario.

A young female with a history of severe abdominal pain was taken to her local hospital at 5 AM in severe distress. Blood was drawn, and the plasma appeared milky, with the triacylglycerol level >2,000 mg/dl (normal = 4 to 150 mg/dl). The patient was placed on a diet extremely limited in fat but supplemented with medium-chain triglycerides.

18.3. Which of the following lipoprotein particles are most likely responsible for the appearance of the patient's plasma?

A. Chylomicrons

B. High-density lipoproteins

C. Intermediate-density lipoproteins

D. Low-density lipoproteins

E. Very–low-density lipoproteins

Correct answer = A. The milky appearance of her plasma was a result of triacylglycerol-rich chylomicrons. Because 5 AM is presumably several hours after her evening meal, the patient must have difficulty degrading these lipoprotein particles. Intermediate-, low-, and high-density lipoproteins contain primarily cholesteryl esters, and, if one or more of these particles was elevated, it would cause hypercholesterolemia. Very–low-density lipoproteins do not cause the described milky appearance of plasma.

18.4. Which one of the following proteins is most likely to be deficient in this patient?

A. Apolipoprotein A-I

B. Apolipoprotein B-48

C. Apolipoprotein C-II

D. Cholesteryl ester transfer protein

E. Microsomal triglyceride transfer protein

Correct answer = C. The triacylglycerol (TAG) in chylomicrons is degraded by endothelial lipoprotein lipase (LPL), which requires apolipoprotein (apo) C-II as a coenzyme. Deficiency of LPL or apo C-II results in decreased ability to degrade chylomicrons to their remnants, which get cleared (via apo E) by liver receptors. Apo A-I is the coenzyme for lecithin:cholesterolacyltransferase; apo B-48 is the characteristic structural protein of chylomicrons; cholesteryl ester transfer protein catalyzes the cholesteryl ester–TAG exchange between high-density and very–low-density lipoproteins (VLDLs); and microsomal triglyceride transfer protein is involved in the formation, not degradation, of chylomicrons (and VLDLs).

18.5. Complete the table below for an individual with classic 21-α-hydroxylase deficiency relative to a normal individual.

Variable	Increased	Decreased
Aldosterone		
Androstenedione		
Cortisol		
Blood glucose		
Adrenocorticotropic hormone		
Blood pressure		

How might the results be changed if this individual were deficient in 17-α-hydroxylase, rather than 21-α-hydroxylase?

Classic 21-α-hydroxylase deficiency causes mineralocorticoids (aldosterone) and glucocorticoids (cortisol) to be virtually absent. Because aldosterone increases blood pressure, and cortisol increases blood glucose, their deficiencies result in a decrease in blood pressure and blood glucose, respectively. Cortisol normally feeds back to inhibit adrenocorticotropic hormone (ACTH) release by the pituitary, and, so, its absence results in an elevation in ACTH. The loss of 21-α-hydroxylase pushes progesterone and pregnenolone to androgen synthesis and, therefore, causes androstenedione levels to rise. With 17-α-hydroxylase deficiency, sex hormone synthesis would be decreased. Mineralocorticoid production would be increased, leading to hypertension.