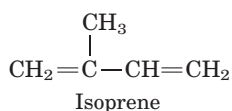


21.4 Biosynthesis of Cholesterol, Steroids, and Isoprenoids

Cholesterol is doubtless the most publicized lipid, notorious because of the strong correlation between high levels of cholesterol in the blood and the incidence of human cardiovascular diseases. Less well advertised is cholesterol's crucial role as a component of cellular membranes and as a precursor of steroid hormones and bile acids. Cholesterol is an essential molecule in many animals, including humans, but is not required in the mammalian diet—all cells can synthesize it from simple precursors.

The structure of this 27-carbon compound suggests a complex biosynthetic pathway, but all of its carbon atoms are provided by a single precursor—acetate (Fig. 21–32). The **isoprene** units that are the essential intermediates in the pathway from acetate to cholesterol are also precursors to many other natural lipids, and the mechanisms by which isoprene units are polymerized are similar in all these pathways.



We begin with an account of the main steps in the biosynthesis of cholesterol from acetate, then discuss the transport of cholesterol in the blood, its uptake by cells, the normal regulation of cholesterol synthesis, and its regulation in those with defects in cholesterol uptake or transport. We next consider other cellular components derived from cholesterol, such as bile acids and steroid hormones. Finally, an outline of the biosynthetic pathways to some of the many compounds derived from isoprene units, which share early steps with the pathway to cholesterol, illustrates the extraordinary versatility of isoprenoid condensations in biosynthesis.

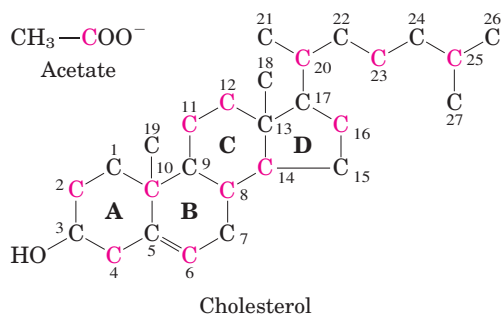


FIGURE 21–32 Origin of the carbon atoms of cholesterol. This can be deduced from tracer experiments with acetate labeled in the methyl carbon (black) or the carboxyl carbon (red). The individual rings in the fused-ring system are designated A through D.

Cholesterol Is Made from Acetyl-CoA in Four Stages

Cholesterol, like long-chain fatty acids, is made from acetyl-CoA, but the assembly plan is quite different. In early experiments, animals were fed acetate labeled with ¹⁴C in either the methyl carbon or the carboxyl carbon. The pattern of labeling in the cholesterol isolated from the two groups of animals (Fig. 21–32) provided the blueprint for working out the enzymatic steps in cholesterol biosynthesis.

Synthesis takes place in four stages, as shown in Figure 21–33: ① condensation of three acetate units to form a six-carbon intermediate, mevalonate; ② conversion of mevalonate to activated isoprene units; ③ polymerization of six 5-carbon isoprene units to form the 30-carbon linear squalene; and ④ cyclization of squalene to form the four rings of the steroid nucleus, with a further series of changes (oxidations, removal or migration of methyl groups) to produce cholesterol.

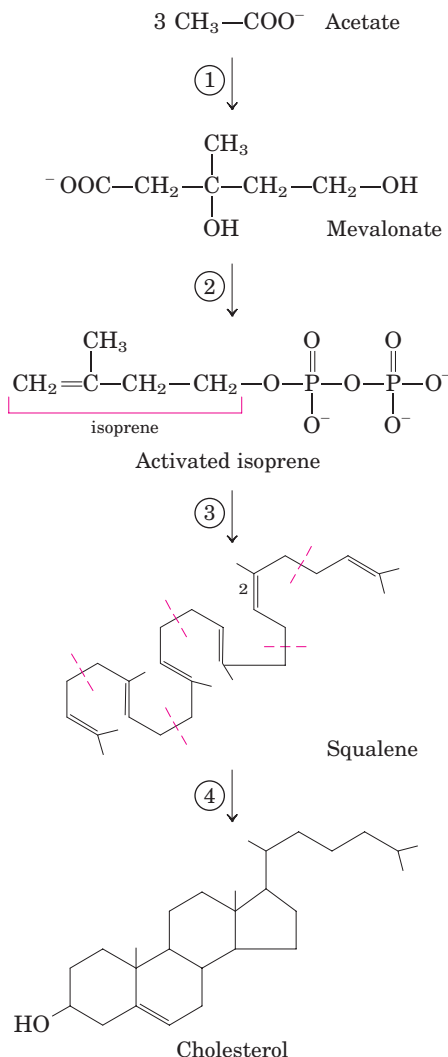


FIGURE 21–33 Summary of cholesterol biosynthesis. The four stages are discussed in the text. Isoprene units in squalene are set off by red dashed lines.

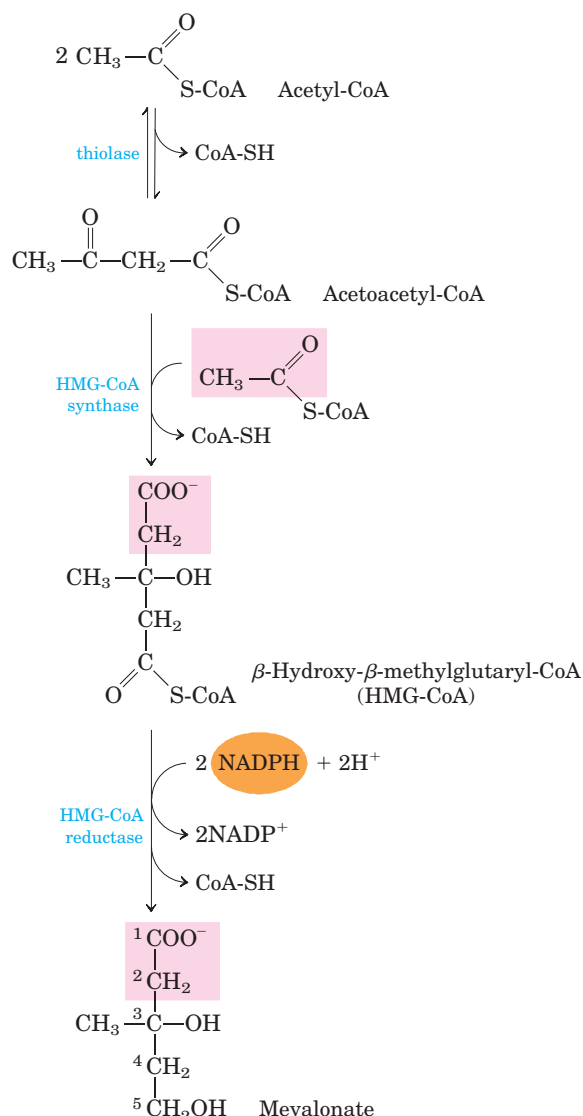


FIGURE 21-34 Formation of mevalonate from acetyl-CoA. The origin of C-1 and C-2 of mevalonate from acetyl-CoA is shown in pink.

Stage ① Synthesis of Mevalonate from Acetate The first stage in cholesterol biosynthesis leads to the intermediate **mevalonate** (Fig. 21-34). Two molecules of acetyl-CoA condense to form acetoacetyl-CoA, which condenses with a third molecule of acetyl-CoA to yield the six-carbon compound **β -hydroxy- β -methylglutaryl-CoA (HMG-CoA)**. These first two reactions are catalyzed by **thiolase** and **HMG-CoA synthase**, respectively. The cytosolic HMG-CoA synthase in this pathway is distinct from the mitochondrial isozyme that catalyzes HMG-CoA synthesis in ketone body formation (see Fig. 17-18).

The third reaction is the committed and rate-limiting step: reduction of HMG-CoA to mevalonate, for which each of two molecules of NADPH donates two electrons. **HMG-CoA reductase**, an integral membrane protein of the smooth ER, is the major point of regulation on the pathway to cholesterol, as we shall see.

Stage ② Conversion of Mevalonate to Two Activated Isoprenes

In the next stage of cholesterol synthesis, three phosphate groups are transferred from three ATP molecules to mevalonate (Fig. 21-35). The phosphate attached to the C-3 hydroxyl group of mevalonate in the intermediate 3-phospho-5-pyrophosphomevalonate is a good

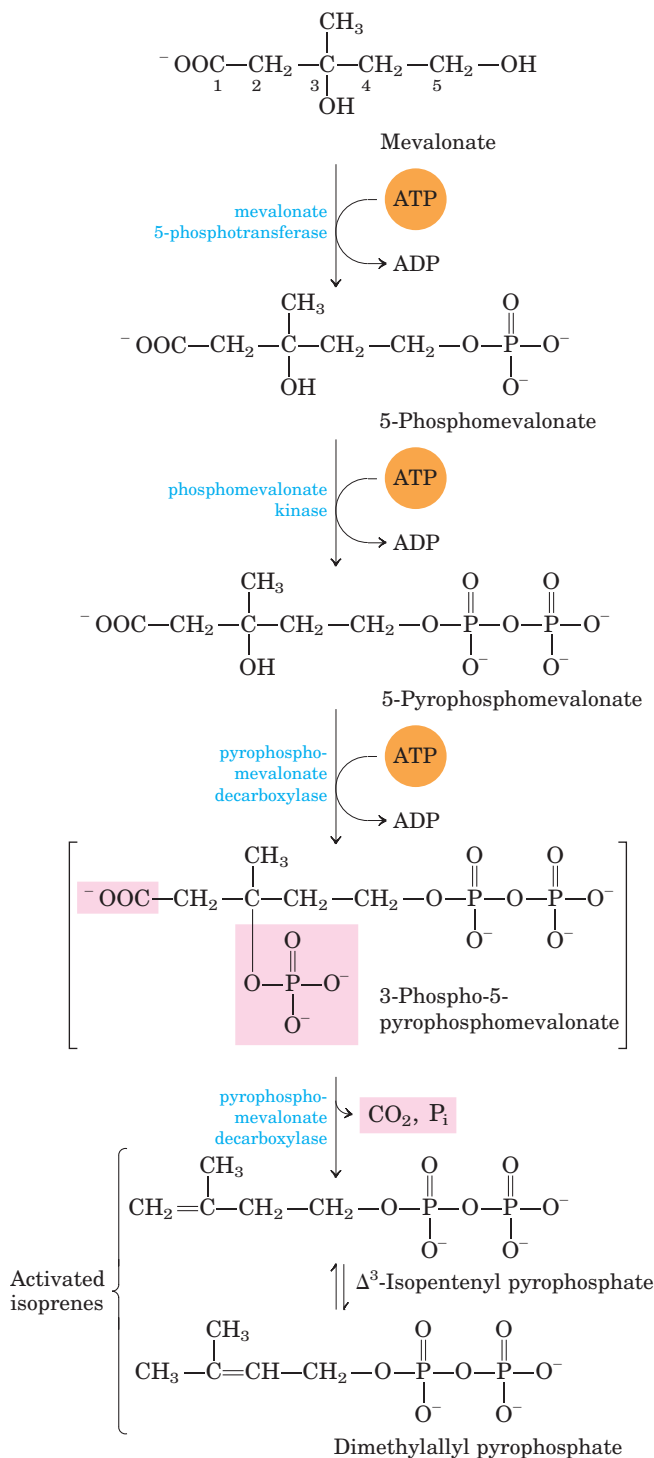


FIGURE 21-35 Conversion of mevalonate to activated isoprene units. Six of these activated units combine to form squalene (see Fig. 21-36). The leaving groups of 3-phospho-5-pyrophosphomevalonate are shaded pink. The bracketed intermediate is hypothetical.

leaving group; in the next step, both this phosphate and the nearby carboxyl group leave, producing a double bond in the five-carbon product, Δ^3 -isopentenyl pyrophosphate. This is the first of the two activated isoprenes central to cholesterol formation. Isomerization of Δ^3 -isopentenyl pyrophosphate yields the second activated isoprene, **dimethylallyl pyrophosphate**. Synthesis of isopentenyl pyrophosphate in the cytoplasm of plant cells follows the pathway described here. However, plant chloroplasts and many bacteria use a mevalonate-independent pathway. This alternative pathway does not

occur in animals, so it is an attractive target for the development of new antibiotics.

Stage ③ Condensation of Six Activated Isoprene Units to Form Squalene Isopentenyl pyrophosphate and dimethylallyl pyrophosphate now undergo a head-to-tail condensation, in which one pyrophosphate group is displaced and a 10-carbon chain, **geranyl pyrophosphate**, is formed (Fig. 21–36). (The “head” is the end to which pyrophosphate is joined.) Geranyl pyrophosphate undergoes another head-to-tail condensation with isopentenyl pyro-

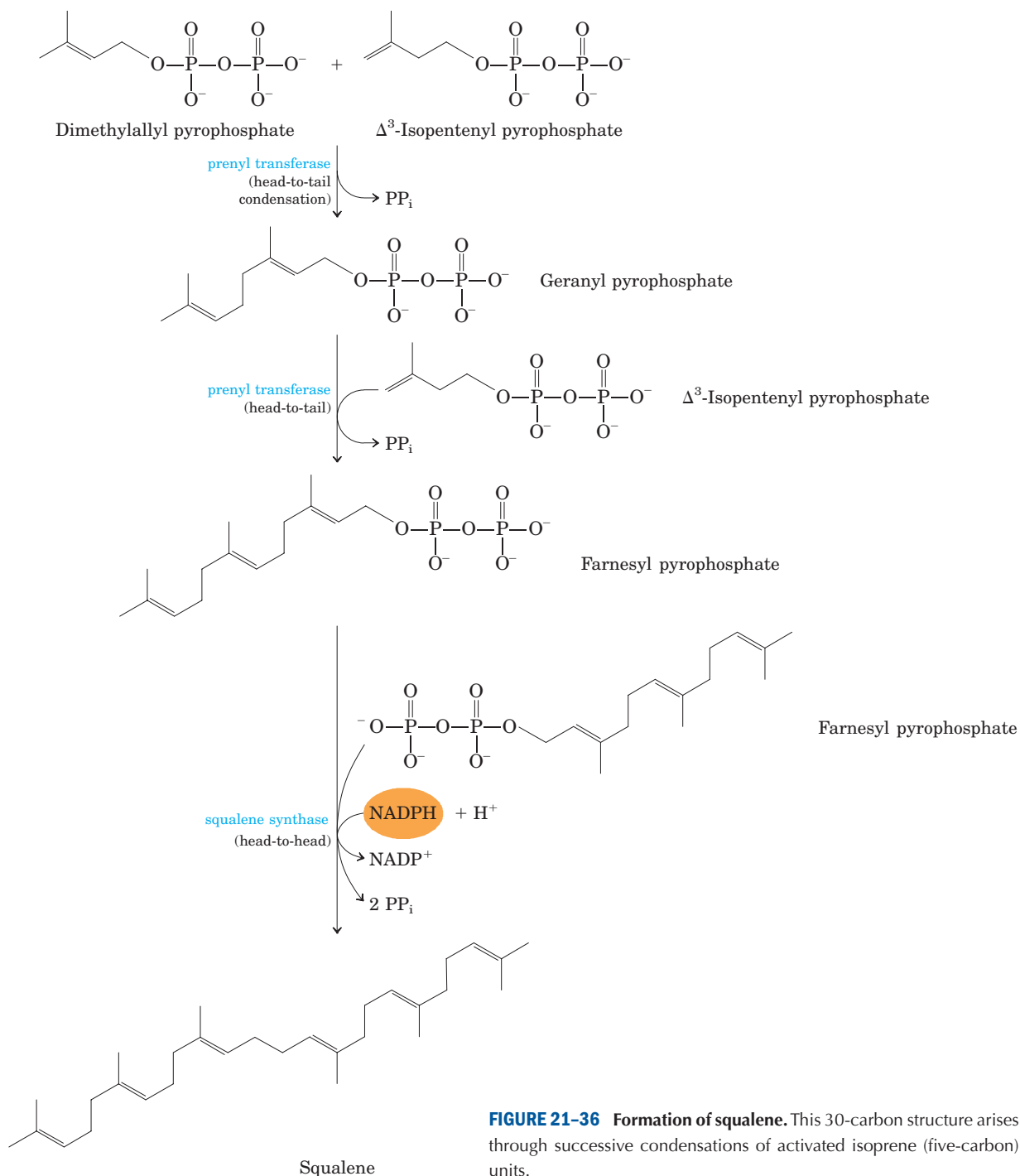


FIGURE 21–36 Formation of squalene. This 30-carbon structure arises through successive condensations of activated isoprene (five-carbon) units.

phosphate, yielding the 15-carbon intermediate **farnesyl pyrophosphate**. Finally, two molecules of farnesyl pyrophosphate join head to head, with the elimination of both pyrophosphate groups, to form **squalene**.

The common names of these intermediates derive from the sources from which they were first isolated. Geraniol, a component of rose oil, has the aroma of geraniums, and farnesol is an aromatic compound found in the flowers of the Farnese acacia tree. Many natural

scent of plant origin are synthesized from isoprene units. Squalene, first isolated from the liver of sharks (genus *Squalus*), has 30 carbons, 24 in the main chain and 6 in the form of methyl group branches.

Stage ④ Conversion of Squalene to the Four-Ring Steroid Nucleus When the squalene molecule is represented as in Figure 21–37, the relationship of its linear structure to the cyclic structure of the sterols becomes apparent. All

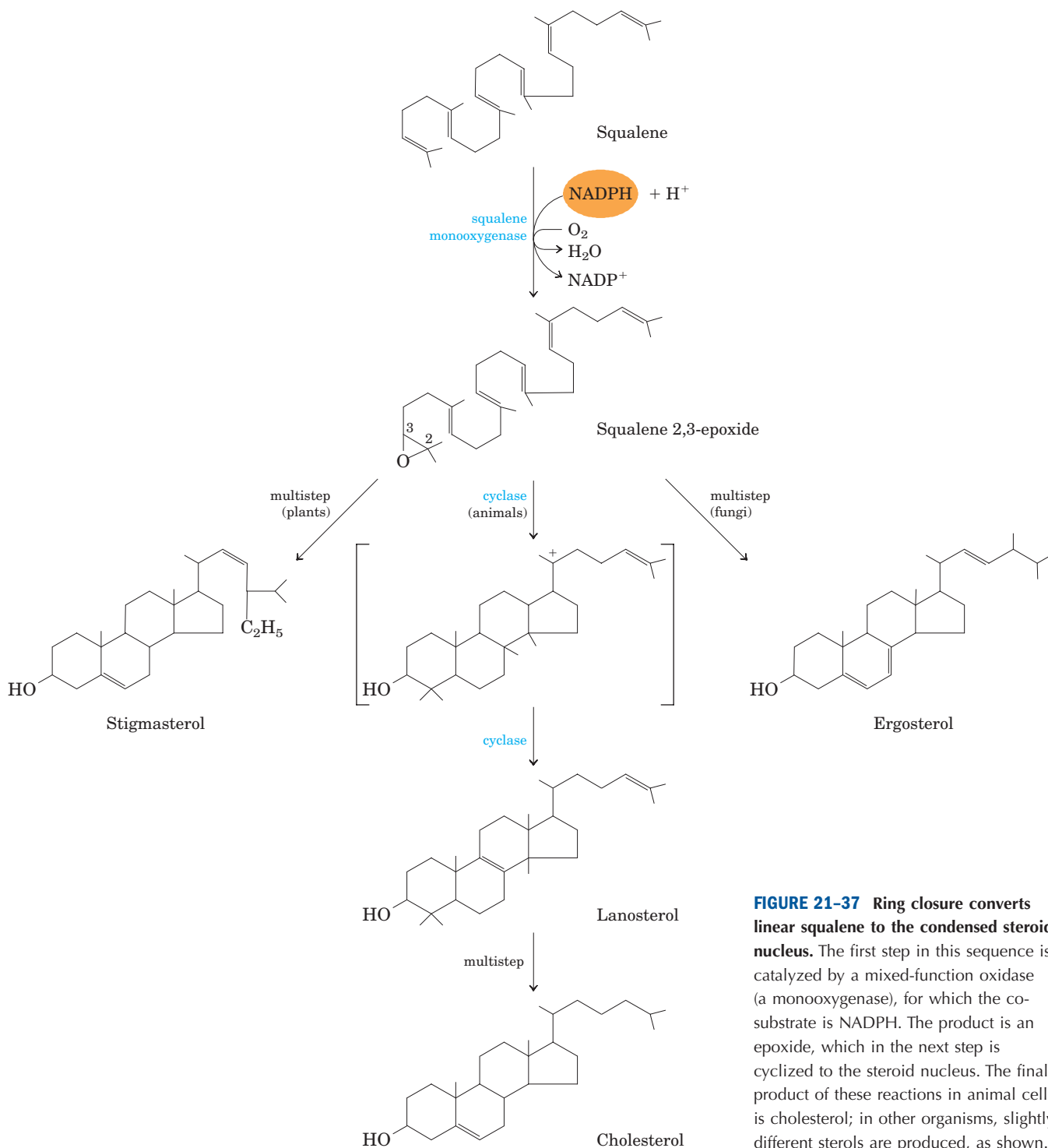


FIGURE 21–37 Ring closure converts linear squalene to the condensed steroid nucleus. The first step in this sequence is catalyzed by a mixed-function oxidase (a monoxygenase), for which the co-substrate is NADPH. The product is an epoxide, which in the next step is cyclized to the steroid nucleus. The final product of these reactions in animal cells is cholesterol; in other organisms, slightly different sterols are produced, as shown.

sterols have the four fused rings that form the steroid nucleus, and all are alcohols, with a hydroxyl group at C-3—thus the name “sterol.” The action of **squalene monoxygenase** adds one oxygen atom from O_2 to the end of the squalene chain, forming an epoxide. This enzyme is another mixed-function oxidase (Box 21-1); NADPH reduces the other oxygen atom of O_2 to H_2O . The double bonds of the product, **squalene 2,3-epoxide**, are positioned so that a remarkable concerted reaction can convert the linear squalene epoxide to a cyclic structure. In animal cells, this cyclization results in the formation of **lanosterol**, which contains the four rings characteristic of the steroid nucleus. Lanosterol is finally converted to cholesterol in a series of about 20 reactions that include the migration of some methyl groups and the removal of others. Elucidation of this extraordinary biosynthetic pathway, one of the most complex known, was accomplished by Konrad Bloch, Feodor Lynen, John Cornforth, and George Popják in the late 1950s.

Cholesterol is the sterol characteristic of animal cells; plants, fungi, and protists make other, closely related sterols instead. They use the same synthetic pathway as far as squalene 2,3-epoxide, at which point the pathways diverge slightly, yielding other sterols, such as stigmasterol in many plants and ergosterol in fungi (Fig. 21-37).

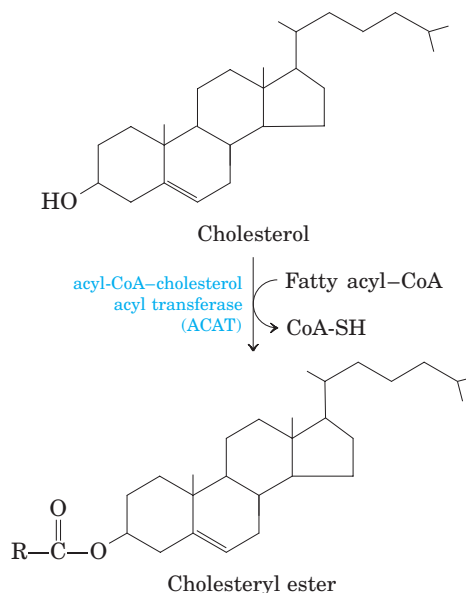


FIGURE 21-38 Synthesis of cholesteryl esters. Esterification converts cholesterol to an even more hydrophobic form for storage and transport.

Cholesterol Has Several Fates

Much of the cholesterol synthesis in vertebrates takes place in the liver. A small fraction of the cholesterol made there is incorporated into the membranes of hepatocytes, but most of it is exported in one of three forms: biliary cholesterol, bile acids, or cholesteryl esters. **Bile acids** and their salts are relatively hydrophilic cholesterol derivatives that are synthesized in the liver and aid in lipid digestion (see Fig. 17-1). **Cholesteryl esters** are formed in the liver through the action of **acyl-CoA-cholesterol acyl transferase (ACAT)**. This enzyme catalyzes the transfer of a fatty acid from coenzyme A to the hydroxyl group of cholesterol (Fig. 21-38), converting the cholesterol to a more hydrophobic form. Cholesteryl esters are transported in secreted lipoprotein particles to other tissues that use cholesterol, or they are stored in the liver.

All growing animal tissues need cholesterol for membrane synthesis, and some organs (adrenal gland and gonads, for example) use cholesterol as a precursor for steroid hormone production (discussed below). Cholesterol is also a precursor of vitamin D (see Fig. 10-20a).

Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins

Cholesterol and cholesteryl esters, like triacylglycerols and phospholipids, are essentially insoluble in water, yet must be moved from the tissue of origin to the tissues in which they will be stored or consumed. They are carried in the blood plasma as **plasma lipoproteins**,



Konrad Bloch,
1912–2000



Feodor Lynen,
1911–1979



John Cornforth



George Popják

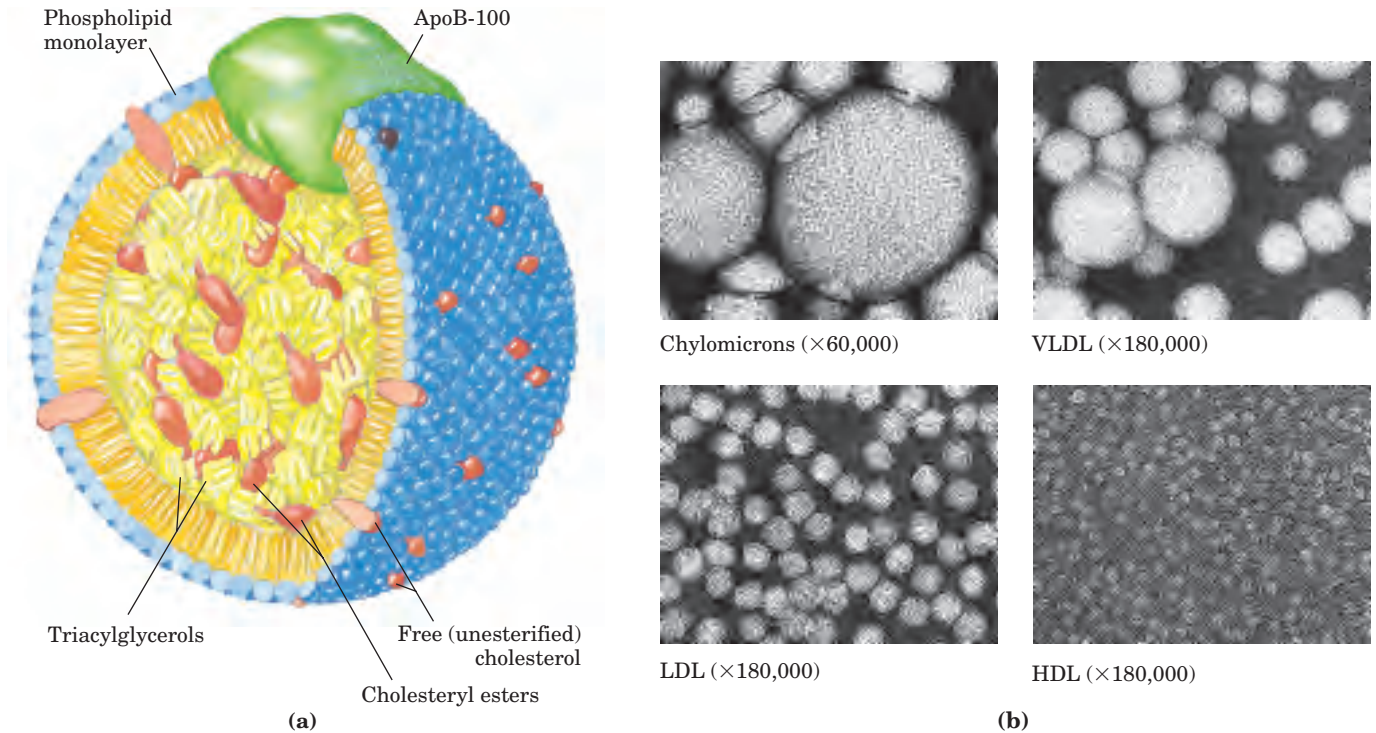


FIGURE 21-39 Lipoproteins. (a) Structure of a low-density lipoprotein (LDL). Apolipoprotein B-100 (apoB-100) is one of the largest single polypeptide chains known, with 4,636 amino acid residues (M_r 513,000). (b) Four classes of lipoproteins, visualized in the electron

microscope after negative staining. Clockwise from top left: chylomicrons, 50 to 200 nm in diameter; VLDL, 28 to 70 nm; HDL, 8 to 11 nm; and LDL, 20 to 25 nm. For properties of lipoproteins, see Table 21-2.

macromolecular complexes of specific carrier proteins, **apolipoproteins**, with various combinations of phospholipids, cholesterol, cholesteryl esters, and triacylglycerols.

Apolipoproteins (“apo” designates the protein in its lipid-free form) combine with lipids to form several classes of lipoprotein particles, spherical complexes with hydrophobic lipids in the core and hydrophilic amino acid side chains at the surface (Fig. 21-39a). Different combinations of lipids and proteins produce particles of different densities, ranging from chylomicrons to high-density lipoproteins. These particles can be separated by ultracentrifugation (Table 21-2) and visualized by electron microscopy (Fig. 21-39b).

Each class of lipoprotein has a specific function, determined by its point of synthesis, lipid composition, and apolipoprotein content. At least nine different apolipoproteins are found in the lipoproteins of human plasma (Table 21-3), distinguishable by their size, their reactions with specific antibodies, and their characteristic distribution in the lipoprotein classes. These protein components act as signals, targeting lipoproteins to specific tissues or activating enzymes that act on the lipoproteins.

Chylomicrons, discussed in Chapter 17 in connection with the movement of dietary triacylglycerols from the intestine to other tissues, are the largest of the lipoproteins and the least dense, containing a high

TABLE 21-2 Major Classes of Human Plasma Lipoproteins: Some Properties

| Lipoprotein | Density (g/mL) | Composition (wt %) | | | | |
|--------------|----------------|--------------------|---------------|------------------|--------------------|------------------|
| | | Protein | Phospholipids | Free cholesterol | Cholesteryl esters | Triacylglycerols |
| Chylomicrons | <1.006 | 2 | 9 | 1 | 3 | 85 |
| VLDL | 0.95–1.006 | 10 | 18 | 7 | 12 | 50 |
| LDL | 1.006–1.063 | 23 | 20 | 8 | 37 | 10 |
| HDL | 1.063–1.210 | 55 | 24 | 2 | 15 | 4 |

Source: Modified from Kritchevsky, D. (1986) Atherosclerosis and nutrition. *Nutr. Int.* **2**, 290-297.

proportion of triacylglycerols (see Fig. 17–2). Chylomicrons are synthesized in the ER of epithelial cells that line the small intestine, then move through the lymphatic system and enter the bloodstream via the left subclavian vein. The apolipoproteins of chylomicrons include apoB-48 (unique to this class of lipoproteins), apoE, and apoC-II (Table 21–3). ApoC-II activates lipoprotein lipase in the capillaries of adipose, heart, skeletal muscle, and lactating mammary tissues, allowing the release of free fatty acids to these tissues. Chylomicrons thus carry dietary fatty acids to tissues where they will be consumed or stored as fuel (Fig. 21–40). The remnants of chylomicrons (depleted of most of their triacylglycerols but still containing cholesterol, apoE, and apoB-48) move through the bloodstream to the liver. Receptors in the liver bind to the apoE in the chylomicron remnants and mediate their uptake by endocytosis. In the liver, the remnants release their cholesterol and are degraded in lysosomes.

When the diet contains more fatty acids than are needed immediately as fuel, they are converted to triacylglycerols in the liver and packaged with specific apolipoproteins into **very-low-density lipoprotein (VLDL)**. Excess carbohydrate in the diet can also be converted to triacylglycerols in the liver and exported as VLDLs (Fig. 21–40a). In addition to triacylglycerols, VLDLs contain some cholesterol and cholesteryl esters, as well as apoB-100, apoC-I, apoC-II, apoC-III, and apoE (Table 21–3). These lipoproteins are transported in the blood from the liver to muscle and adipose tissue, where activation of lipoprotein lipase by apoC-II causes the release of free fatty acids from the VLDL triacylglycerols. Adipocytes take up these fatty acids, reconvert them to triacylglycerols, and store the products in intracellular lipid droplets; myocytes, in contrast, primarily oxidize the fatty acids to supply energy. Most VLDL remnants are removed from the circulation by hepatocytes. The uptake, like that for chylomicrons, is

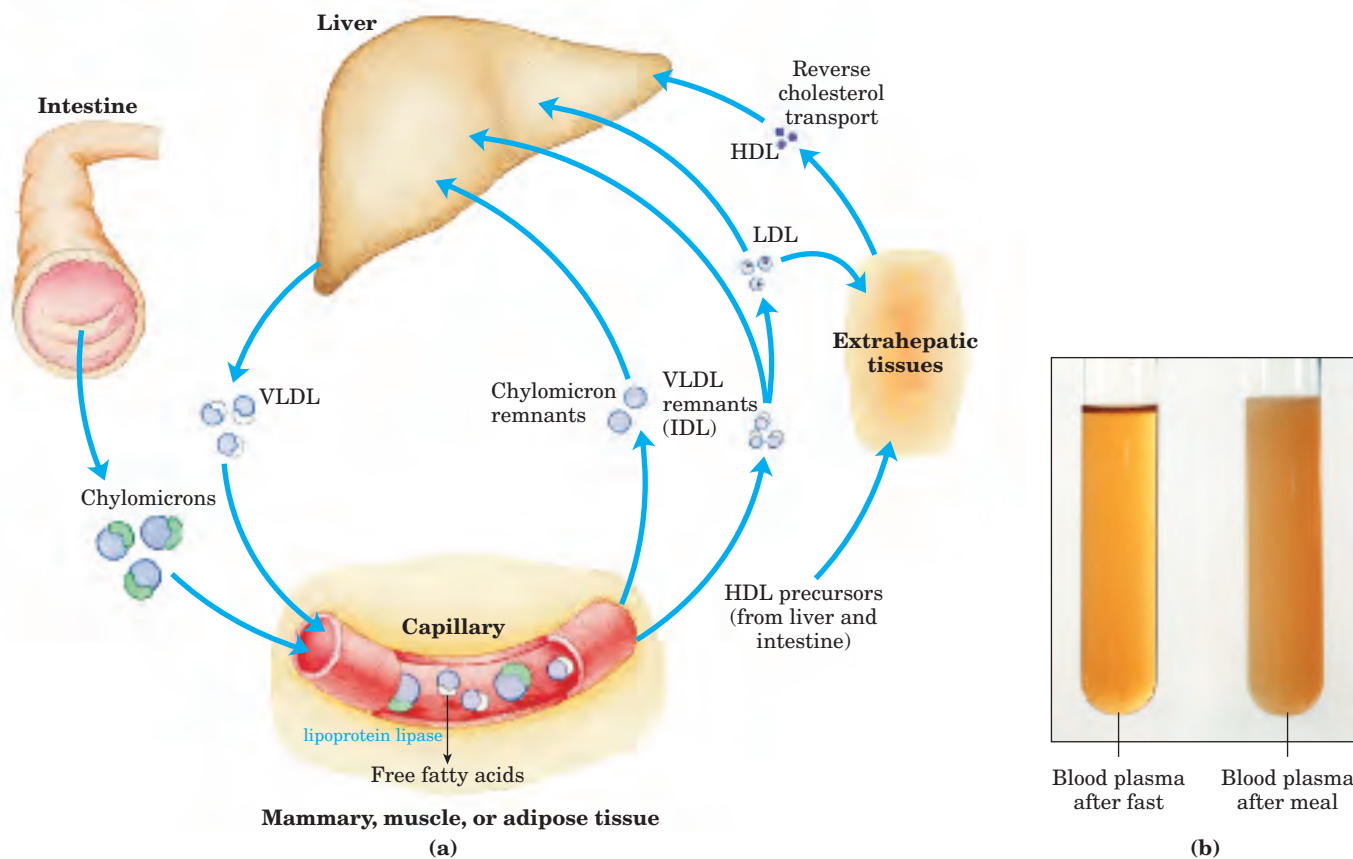


FIGURE 21–40 Lipoproteins and lipid transport. (a) Lipids are transported in the bloodstream as lipoproteins, which exist as several variants that have different functions, different protein and lipid compositions (see Tables 21–2, 21–3), and thus different densities. Dietary lipids are packaged into chylomicrons; much of their triacylglycerol content is released by lipoprotein lipase to adipose and muscle tissues during transport through capillaries. Chylomicron remnants (containing largely protein and cholesterol) are taken up by the liver. Endogenous lipids and cholesterol from the liver are delivered to adipose and muscle tissue by VLDL. Extraction of lipid

from VLDL (along with loss of some apolipoproteins) gradually converts some of it to LDL, which delivers cholesterol to extrahepatic tissues or returns to the liver. The liver takes up LDL, VLDL remnants, and chylomicron remnants by receptor-mediated endocytosis. Excess cholesterol in extrahepatic tissues is transported back to the liver as HDL. In the liver, some cholesterol is converted to bile salts.

(b) Blood plasma samples collected after a fast (left) and after a high-fat meal (right). Chylomicrons produced after a fatty meal give the plasma a milky appearance.

TABLE 21-3 Apolipoproteins of the Human Plasma Lipoproteins

| Apolipoprotein | Molecular weight | Lipoprotein association | Function (if known) |
|----------------|------------------|-------------------------|---|
| ApoA-I | 28,331 | HDL | Activates LCAT; interacts with ABC transporter |
| ApoA-II | 17,380 | HDL | |
| ApoA-IV | 44,000 | Chylomicrons, HDL | |
| ApoB-48 | 240,000 | Chylomicrons | |
| ApoB-100 | 513,000 | VLDL, LDL | Binds to LDL receptor |
| ApoC-I | 7,000 | VLDL, HDL | |
| ApoC-II | 8,837 | Chylomicrons, VLDL, HDL | Activates lipoprotein lipase |
| ApoC-III | 8,751 | Chylomicrons, VLDL, HDL | Inhibits lipoprotein lipase |
| ApoD | 32,500 | HDL | |
| ApoE | 34,145 | Chylomicrons, VLDL, HDL | Triggers clearance of VLDL and chylomicron remnants |

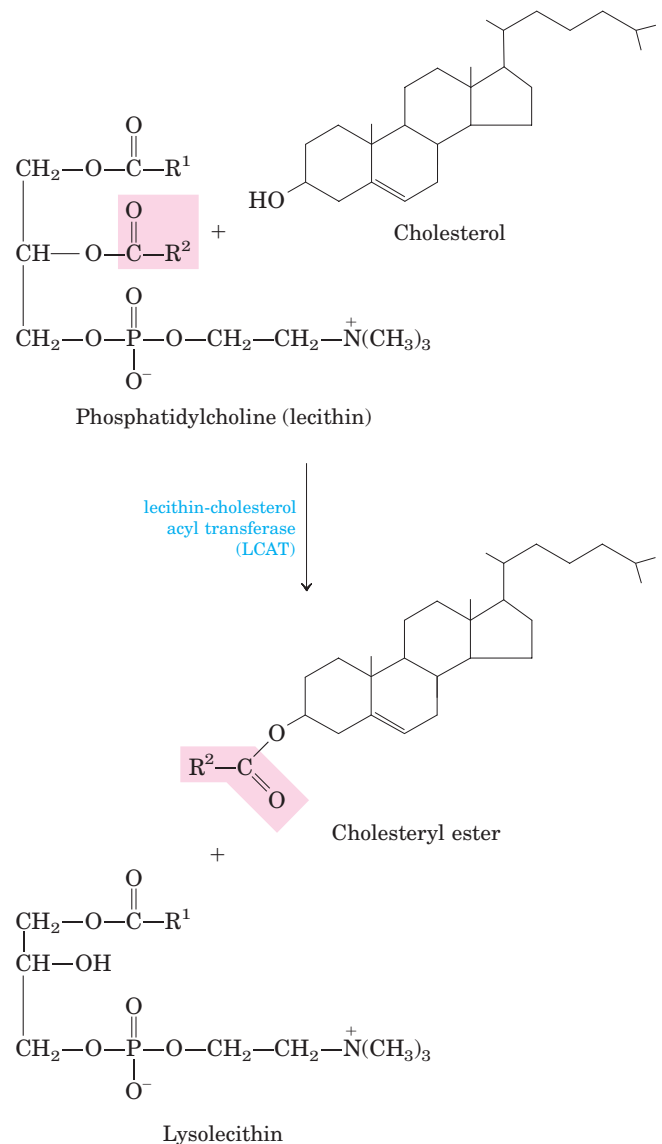
Source: Modified from Vance, D.E. & Vance, J.E. (eds) (1985) *Biochemistry of Lipids and Membranes*. The Benjamin/Cummings Publishing Company, Menlo Park, CA.

receptor-mediated and depends on the presence of apoE in the VLDL remnants (Box 21-3 describes a link between apoE and Alzheimer's disease).

The loss of triacylglycerol converts some VLDL to VLDL remnants (also called intermediate density lipoprotein, IDL); further removal of triacylglycerol from VLDL produces **low-density lipoprotein (LDL)** (Table 21-2). Very rich in cholesterol and cholesteryl esters and containing apoB-100 as their major apolipoprotein, LDLs carry cholesterol to extrahepatic tissues that have specific plasma membrane receptors that recognize apoB-100. These receptors mediate the uptake of cholesterol and cholesteryl esters in a process described below.

The fourth major lipoprotein type, **high-density lipoprotein (HDL)**, originates in the liver and small intestine as small, protein-rich particles that contain relatively little cholesterol and no cholesteryl esters (Fig. 21-40). HDLs contain apoA-I, apoC-I, apoC-II, and other apolipoproteins (Table 21-3), as well as the enzyme **lecithin-cholesterol acyl transferase (LCAT)**, which catalyzes the formation of cholesteryl esters from lecithin (phosphatidylcholine) and cholesterol (Fig. 21-41). LCAT on the surface of nascent (newly forming) HDL particles converts the cholesterol and phosphatidylcholine of chylomicron and VLDL remnants to cholesteryl esters, which begin to form a core, transforming the disk-shaped nascent HDL to a mature, spherical HDL particle. This cholesterol-rich lipoprotein then returns to the liver, where the cholesterol is unloaded; some of this cholesterol is converted to bile salts.

FIGURE 21-41 Reaction catalyzed by lecithin-cholesterol acyl transferase (LCAT). This enzyme is present on the surface of HDL and is stimulated by the HDL component apoA-I. Cholesteryl esters accumulate within nascent HDLs, converting them to mature HDLs.





BOX 21-3 BIOCHEMISTRY IN MEDICINE

ApoE Alleles Predict Incidence of Alzheimer's Disease

In the human population there are three common variants, or alleles, of the gene encoding apolipoprotein E. The most common, accounting for about 78% of human apoE alleles, is *APOE3*; alleles *APOE4* and *APOE2* account for 15% and 7%, respectively. The *APOE4* allele is particularly common in humans with Alzheimer's disease, and the link is highly predictive. Individuals who inherit *APOE4* have an increased risk of late-onset Alzheimer's disease. Those who are homozygous for *APOE4* have a 16-fold increased risk of developing the disease; for those who do, the mean

age of onset is just under 70 years. For people who inherit two copies of *APOE3*, by contrast, the mean age of onset of Alzheimer's disease exceeds 90 years.

The molecular basis for the association between apoE4 and Alzheimer's disease is not yet known. Speculation has focused on a possible role for apoE in stabilizing the cytoskeletal structure of neurons. The apoE2 and apoE3 proteins bind to a number of proteins associated with neuronal microtubules, whereas apoE4 does not. This may accelerate the death of neurons. Whatever the mechanism proves to be, these observations promise to expand our understanding of the biological functions of apolipoproteins.

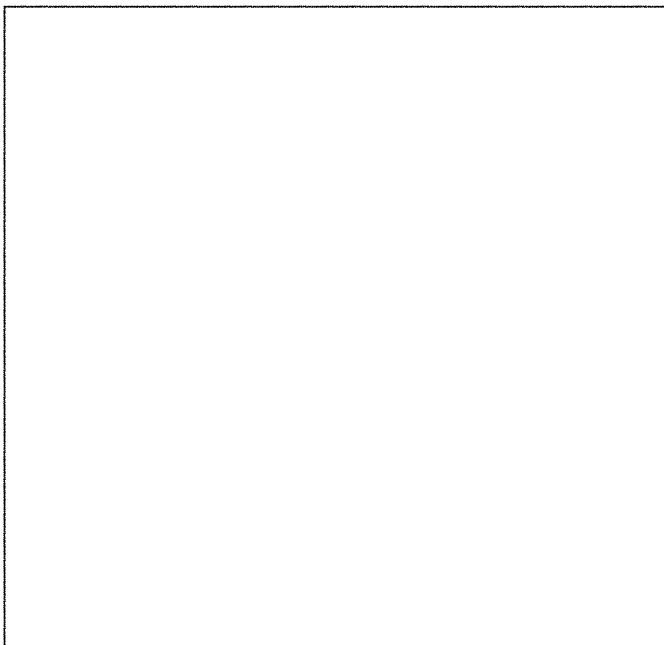
HDL may be taken up in the liver by receptor-mediated endocytosis, but at least some of the cholesterol in HDL is delivered to other tissues by a novel mechanism. HDL can bind to plasma membrane receptor proteins called SR-BI in hepatic and steroidogenic tissues such as the adrenal gland. These receptors mediate not endocytosis but a partial and selective transfer of cholesterol and other lipids in HDL into the cell. Depleted HDL then dissociates to recirculate in the bloodstream and extract more lipids from chylomicron and VLDL remnants. Depleted HDL can also pick up cholesterol stored in extrahepatic tissues and carry it to the liver, in **reverse cholesterol transport** pathways (Fig. 21-40). In one reverse transport path, interaction of nascent HDL with SR-BI receptors in cholesterol-rich cells triggers passive movement of cholesterol from the cell surface into HDL, which then carries it back to the liver. In a second pathway, apoA-I in depleted HDL in-

teracts with an active transporter, the ABC1 protein, in a cholesterol-rich cell. The apoA-I (and presumably the HDL) is taken up by endocytosis, then resecreted with a load of cholesterol, which it transports to the liver.

The ABC1 protein is a member of a large family of multidrug transporters, sometimes called ABC transporters because they all have ATP-binding cassettes; they also have two transmembrane domains with six transmembrane helices (Chapter 11). These proteins actively transport a variety of ions, amino acids, vitamins, steroid hormones, and bile salts across plasma membranes. The CFTR protein that is defective in cystic fibrosis (see Box 11-3) is another member of this ABC family of multidrug transporters.

Cholesteryl Esters Enter Cells by Receptor-Mediated Endocytosis

Each LDL particle in the bloodstream contains apoB-100, which is recognized by specific surface receptor proteins, **LDL receptors**, on cells that need to take up cholesterol. The binding of LDL to an LDL receptor initiates endocytosis, which conveys the LDL and its receptor into the cell within an endosome (Fig. 21-42). The endosome eventually fuses with a lysosome, which contains enzymes that hydrolyze the cholesteryl esters, releasing cholesterol and fatty acid into the cytosol. The apoB-100 of LDL is also degraded to amino acids that are released to the cytosol, but the LDL receptor escapes degradation and is returned to the cell surface, to function again in LDL uptake. ApoB-100 is also present in VLDL, but its receptor-binding domain is not available for binding to the LDL receptor; conversion of VLDL to LDL exposes the receptor-binding domain of apoB-100. This pathway for the transport of cholesterol in blood and its **receptor-mediated endocytosis** by target tissues was elucidated by Michael Brown and Joseph Goldstein.



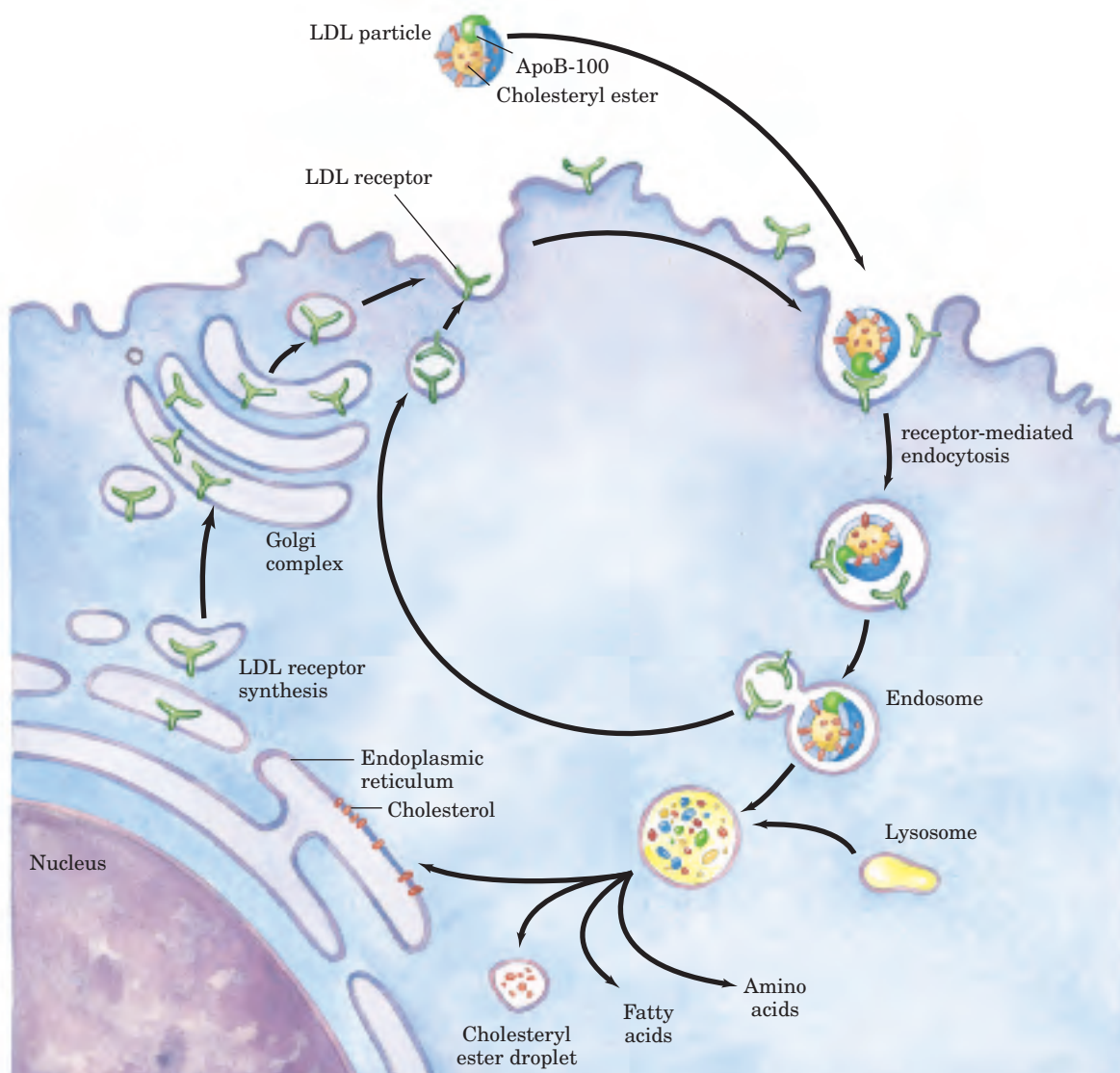


FIGURE 21-42 Uptake of cholesterol by receptor-mediated endocytosis.

Cholesterol that enters cells by this path may be incorporated into membranes or reesterified by ACAT (Fig. 21-38) for storage within cytosolic lipid droplets. Accumulation of excess intracellular cholesterol is prevented by reducing the rate of cholesterol synthesis when sufficient cholesterol is available from LDL in the blood.

The LDL receptor also binds to apoE and plays a significant role in the hepatic uptake of chylomicrons and VLDL remnants. However, if LDL receptors are unavailable (as, for example, in a mouse strain that lacks the gene for the LDL receptor), VLDL remnants and chylomicrons are still taken up by the liver even though LDL is not. This indicates the presence of a back-up system for receptor-mediated endocytosis of VLDL remnants and chylomicrons. One back-up receptor is *lipoprotein receptor-related protein* (LRP), which binds to apoE as well as to a number of other ligands.

Cholesterol Biosynthesis Is Regulated at Several Levels

Cholesterol synthesis is a complex and energy-expensive process, so it is clearly advantageous to an organism to regulate the biosynthesis of cholesterol to complement dietary intake. In mammals, cholesterol production is regulated by intracellular cholesterol concentration and by the hormones glucagon and insulin. The rate-limiting step in the pathway to cholesterol (and a major site of regulation) is the conversion of HMG-CoA to mevalonate (Fig. 21-34), the reaction catalyzed by HMG-CoA reductase.

Regulation in response to cholesterol levels is mediated by an elegant system of transcriptional regulation of the gene encoding HMG-CoA reductase. This gene, along with more than 20 other genes encoding enzymes that mediate the uptake and synthesis of cholesterol and

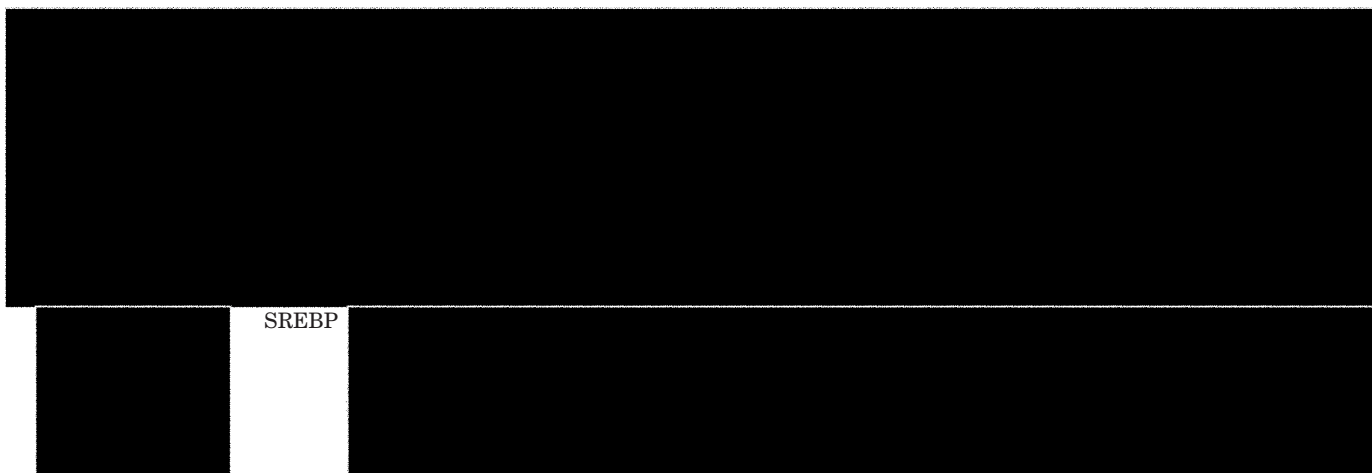


FIGURE 21-43 SREBP activation. Sterol regulatory element-binding proteins (SREBPs, shown in green) are embedded in the ER when first synthesized, in a complex with the protein SREBP cleavage-activating protein (SCAP, red). (N and C represent the amino and carboxyl termini of the proteins.) When bound to SCAP, SREBPs are inactive. When

unsaturated fatty acids, is controlled by a small family of proteins called sterol regulatory element-binding proteins (SREBPs). When newly synthesized, these proteins are embedded in the ER. Only the soluble amino-terminal domain of an SREBP functions as a transcriptional activator, using mechanisms discussed in Chapter 28. However, this domain has no access to the nucleus and cannot participate in gene activation while it remains part of the SREBP molecule. To activate transcription of the HMG-CoA reductase gene and other genes, the transcriptionally active domain is separated from the rest of the SREBP by proteolytic cleavage. When cholesterol levels are high, SREBPs are inactive, secured to the ER in a complex with another protein called SREBP cleavage-activating protein (SCAP) (Fig. 21-43). It is SCAP that binds cholesterol and a number of other sterols, thus acting as a sterol sensor. When sterol levels are high, the SCAP-SREBP complex probably interacts with another protein that retains the entire complex in the ER. When the level of sterols in the cell declines, a conformational change in SCAP causes release of the SCAP-SREBP complex from the ER-retention activity, and the complex migrates within vesicles to the Golgi complex. In the Golgi complex, SREBP is cleaved twice by two different proteases, the second cleavage releasing the amino-terminal domain into the cytosol. This domain travels to the nucleus and activates transcription of its target genes. The amino-terminal domain of SREBP has a short half-life and is rapidly degraded by proteasomes (see Fig. 27-42). When sterol levels increase sufficiently, the proteolytic release of SREBP amino-terminal domains is again blocked, and proteasome degradation of the existing active domains results in a rapid shut-down of the gene targets.

Several other mechanisms also regulate cholesterol synthesis (Fig. 21-44). Hormonal control is mediated

sterol levels decline, the complex migrates to the Golgi complex, and SREBP is cleaved by two different proteases in succession. The liberated amino-terminal domain of SREBP migrates to the nucleus, where it activates transcription of sterol-regulated genes.

by covalent modification of HMG-CoA reductase itself. The enzyme exists in phosphorylated (inactive) and dephosphorylated (active) forms. Glucagon stimulates phosphorylation (inactivation), and insulin promotes dephosphorylation, activating the enzyme and favoring cholesterol synthesis. High intracellular concentrations of cholesterol activate ACAT, which increases esterification of cholesterol for storage. Finally, a high cellular cholesterol level diminishes transcription of the gene that encodes the LDL receptor, reducing production of the receptor and thus the uptake of cholesterol from the blood.

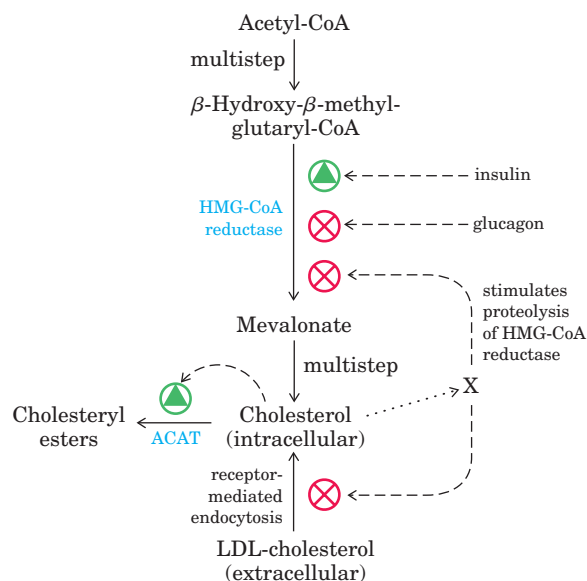



FIGURE 21-44 Regulation of cholesterol formation balances synthesis with dietary uptake. Glucagon promotes phosphorylation (inactivation) of HMG-CoA reductase; insulin promotes dephosphorylation (activation). X represents unidentified metabolites of cholesterol that stimulate proteolysis of HMG-CoA reductase.

 Unregulated cholesterol production can lead to serious human disease. When the sum of cholesterol synthesized and cholesterol obtained in the diet exceeds the amount required for the synthesis of membranes, bile salts, and steroids, pathological accumulations of cholesterol in blood vessels (atherosclerotic plaques) can develop, resulting in obstruction of blood vessels (**atherosclerosis**). Heart failure due to occluded coronary arteries is a leading cause of death in industrialized societies. Atherosclerosis is linked to high levels of cholesterol in the blood, and particularly to high levels of LDL-bound cholesterol; there is a *negative* correlation between HDL levels and arterial disease.

In familial hypercholesterolemia, a human genetic disorder, blood levels of cholesterol are extremely high and severe atherosclerosis develops in childhood. These individuals have a defective LDL receptor and lack receptor-mediated uptake of cholesterol carried by LDL. Consequently, cholesterol is not cleared from the blood; it accumulates and contributes to the formation of atherosclerotic plaques. Endogenous cholesterol synthesis continues despite the excessive cholesterol in the blood, because extracellular cholesterol cannot enter the cell to regulate intracellular synthesis (Fig. 21–44). Two products derived from fungi, **lovastatin** and **compactin**, are used to treat patients with familial hypercholesterolemia. Both these compounds, and several synthetic analogs, resemble mevalonate (Fig. 21–45) and are competitive inhibitors of HMG-CoA reductase, thus inhibiting cholesterol synthesis. Lovastatin treatment lowers serum cholesterol by as much as 30% in individuals having one defective copy of the gene for the LDL receptor. When combined with an edible resin that binds bile acids and prevents their reabsorption from the intestine, the drug is even more effective.

In familial HDL deficiency, HDL levels are very low; they are almost undetectable in Tangier disease. Both genetic disorders are the result of mutations in the ABC1 protein. Cholesterol-depleted HDL cannot take up cholesterol from cells that lack ABC1 protein, and

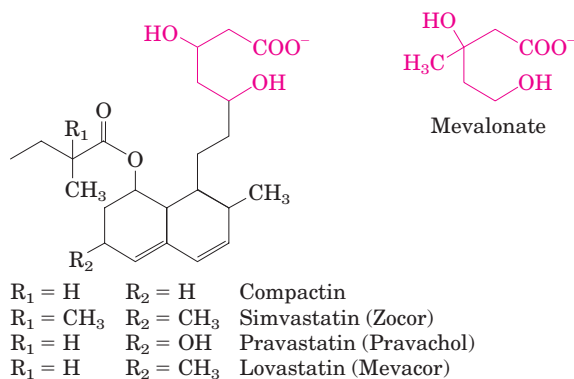


FIGURE 21–45 Inhibitors of HMG-CoA reductase. A comparison of the structures of mevalonate and four pharmaceutical compounds that inhibit HMG-CoA reductase.

cholesterol-poor HDL is rapidly removed from the blood and destroyed. Both familial HDL deficiency and Tangier disease are very rare (worldwide, fewer than 100 families with Tangier disease are known), but the existence of these diseases establishes a role for ABC1 protein in the regulation of plasma HDL levels. Because low plasma HDL levels correlate with a high incidence of coronary artery disease, the ABC1 protein may prove a useful target for drugs to control HDL levels. ■

Steroid Hormones Are Formed by Side-Chain Cleavage and Oxidation of Cholesterol

Humans derive all their steroid hormones from cholesterol (Fig. 21–46). Two classes of steroid hormones are synthesized in the cortex of the adrenal gland: **mineralocorticoids**, which control the reabsorption of inorganic ions (Na^+ , Cl^- , and HCO_3^-) by the kidney, and **glucocorticoids**, which help regulate gluconeogenesis and reduce the inflammatory response. Sex hormones are produced in male and female gonads and the placenta. They include **progesterone**, which regulates the female reproductive cycle, and **androgens** (such as testosterone) and **estrogens** (such as estradiol), which influence the development of

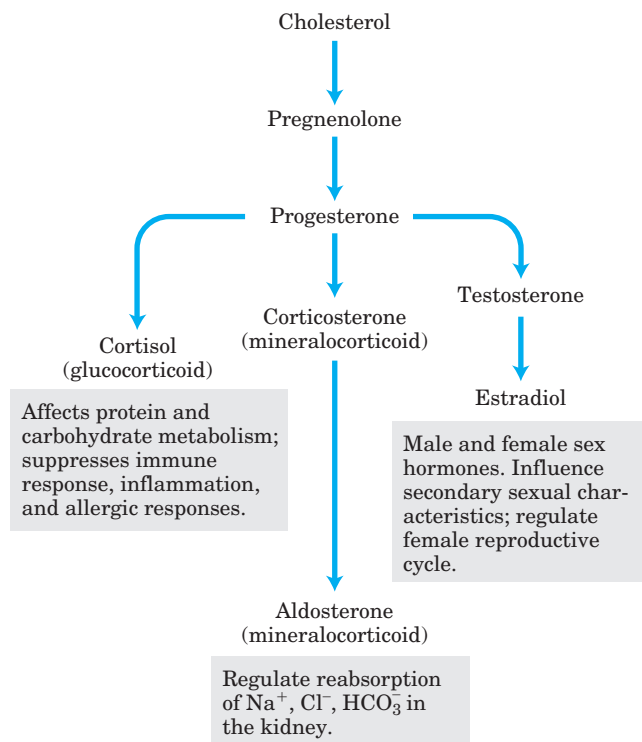
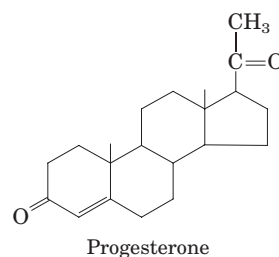


FIGURE 21–46 Some steroid hormones derived from cholesterol. The structures of some of these compounds are shown in Figure 10–19.

secondary sexual characteristics in males and females, respectively. Steroid hormones are effective at very low concentrations and are therefore synthesized in relatively small quantities. In comparison with the bile salts, their production consumes relatively little cholesterol.

Synthesis of steroid hormones requires removal of some or all of the carbons in the “side chain” on C-17

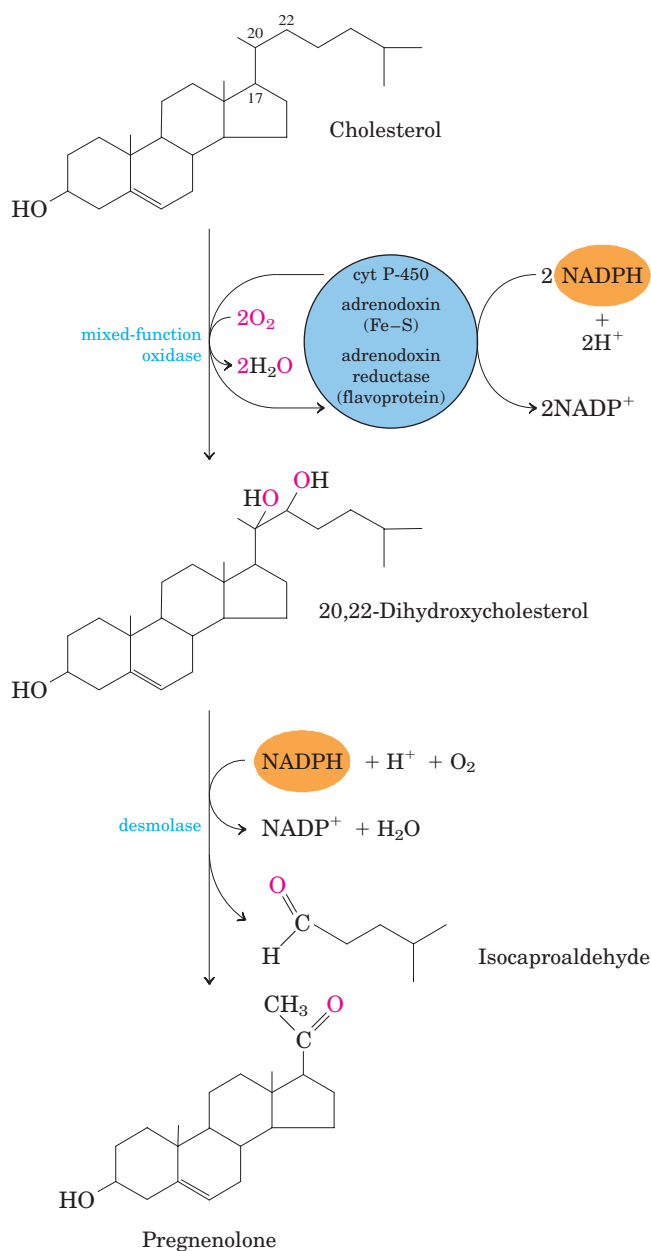


FIGURE 21-47 Side-chain cleavage in the synthesis of steroid hormones. Cytochrome P-450 acts as electron carrier in this mixed-function oxidase system that oxidizes adjacent carbons. The process also requires the electron-transferring proteins adrenodoxin and adrenodoxin reductase. This system for cleaving side chains is found in mitochondria of the adrenal cortex, where active steroid production occurs. Pregnenolone is the precursor of all other steroid hormones (see Fig. 21-46).

of the D ring of cholesterol. Side-chain removal takes place in the mitochondria of steroidogenic tissues. Removal involves the hydroxylation of two adjacent carbons in the side chain (C-20 and C-22) followed by cleavage of the bond between them (Fig. 21-47). Formation of the various hormones also involves the introduction of oxygen atoms. All the hydroxylation and oxygenation reactions in steroid biosynthesis are catalyzed by mixed-function oxidases (Box 21-1) that use NADPH, O₂, and mitochondrial cytochrome P-450.

Intermediates in Cholesterol Biosynthesis Have Many Alternative Fates

In addition to its role as an intermediate in cholesterol biosynthesis, isopentenyl pyrophosphate is the activated precursor of a huge array of biomolecules with diverse biological roles (Fig. 21-48). They include vitamins A, E, and K; plant pigments such as carotene and the phytol chain of chlorophyll; natural rubber; many essential oils (such as the fragrant principles of lemon oil, eucalyptus, and musk); insect juvenile hormone, which controls metamorphosis; dolichols, which serve as lipid-soluble carriers in complex polysaccharide synthesis; and ubiquinone and plastoquinone, electron carriers in mitochondria and chloroplasts. Collectively, these molecules are called isoprenoids. More than

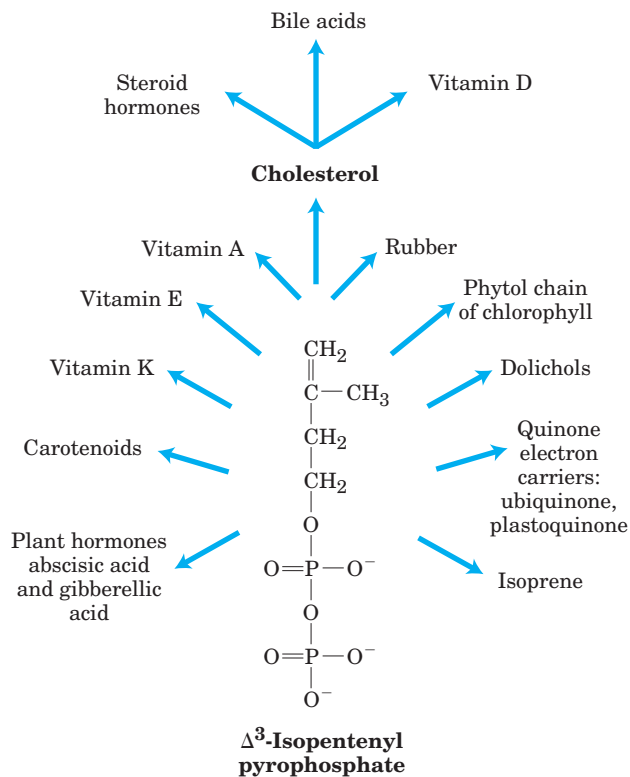


FIGURE 21-48 Overview of isoprenoid biosynthesis. The structures of most of the end products shown here are given in Chapter 10.

20,000 different isoprenoid molecules have been discovered in nature, and hundreds of new ones are reported each year.

Prenylation (covalent attachment of an isoprenoid; see Fig. 27–30) is a common mechanism by which proteins are anchored to the inner surface of cellular membranes in mammals (see Fig. 11–14). In some of these proteins the attached lipid is the 15-carbon farnesyl group; others have the 20-carbon geranylgeranyl group. Different enzymes attach the two types of lipids. It is possible that prenylation reactions target proteins to different membranes, depending on which lipid is attached. Protein prenylation is another important role for the isoprene derivatives of the pathway to cholesterol.

SUMMARY 21.4 Biosynthesis of Cholesterol, Steroids, and Isoprenoids

- Cholesterol is formed from acetyl-CoA in a complex series of reactions, through the intermediates β -hydroxy- β -methylglutaryl-CoA, mevalonate, and two activated isoprenes, dimethylallyl pyrophosphate and isopentenyl pyrophosphate. Condensation of isoprene units produces the noncyclic squalene, which is cyclized to yield the steroid ring system and side chain.
- Cholesterol synthesis is under hormonal control and is also inhibited by elevated concentrations of intracellular cholesterol, which acts through covalent modification and transcriptional regulation mechanisms.
- Cholesterol and cholesteryl esters are carried in the blood as plasma lipoproteins. VLDL carries cholesterol, cholesteryl esters, and triacylglycerols from the liver to other tissues, where the triacylglycerols are degraded by lipoprotein lipase, converting VLDL to LDL. The LDL, rich in cholesterol and its esters, is taken up by receptor-mediated endocytosis, in which the apolipoprotein B-100 of LDL is recognized by receptors in the plasma membrane. HDL removes cholesterol from the blood, carrying it to the liver. Dietary conditions or genetic defects in cholesterol metabolism may lead to atherosclerosis and heart disease.
- The steroid hormones (glucocorticoids, mineralocorticoids, and sex hormones) are produced from cholesterol by alteration of the side chain and introduction of oxygen atoms into the steroid ring system. In addition to cholesterol, a wide variety of isoprenoid compounds are derived from mevalonate through condensations of isopentenyl pyrophosphate and dimethylallyl pyrophosphate.
- Prenylation of certain proteins targets them for association with cellular membranes and is essential for their biological activity.

Key Terms

Terms in bold are defined in the glossary.

| | | | | | |
|---------------------------------------|-----|---|-----|--------------------------------|-----|
| acetyl-CoA carboxylase | 787 | thiazolidinediones | 807 | bile acids | 820 |
| fatty acid synthase | 789 | phosphatidylserine | 811 | cholesteryl esters | 820 |
| acyl carrier protein (ACP) | 790 | phosphatidylglycerol | 811 | apolipoproteins | 821 |
| fatty acyl-CoA desaturase | 798 | phosphatidylethanolamine | 811 | chylomicron | 821 |
| mixed-function oxidases | 799 | cardiolipin | 811 | very-low-density lipoprotein | |
| mixed-function oxygenases | 799 | phosphatidylcholine | 812 | (VLDL) | 822 |
| cytochrome P-450 | 799 | plasmalogen | 813 | low-density lipoprotein (LDL) | 823 |
| essential fatty acids | 800 | platelet-activating factor | 813 | high-density lipoprotein (HDL) | 823 |
| prostaglandins | 800 | cerebroside | 813 | reverse cholesterol transport | 824 |
| cyclooxygenase (COX) | 800 | sphingomyelin | 813 | LDL receptors | 824 |
| prostaglandin H ₂ synthase | 800 | gangliosides | 813 | receptor-mediated endocytosis | 824 |
| thromboxane synthase | 800 | isoprene | 816 | atherosclerosis | 827 |
| thromboxanes | 800 | mevalonate | 817 | lovastatin | 827 |
| leukotrienes | 800 | β -hydroxy- β -methylglutaryl-CoA | | mineralocorticoids | 827 |
| glycerol 3-phosphate | | (HMG-CoA) | 817 | glucocorticoids | 827 |
| dehydrogenase | 804 | thiolase | 817 | progesterone | 827 |
| triacylglycerol cycle | 806 | HMG-CoA synthase | 817 | androgens | 827 |
| glyceroneogenesis | 806 | HMG-CoA reductase | 817 | estrogens | 827 |