Fatty Acids

Fatty acids are carboxylic acids that are structural components of fats, oils, and all other categories of lipids, except steroids. More than 70 have been identified in nature. They usually contain an even number of carbon atoms (typically 12–20), are generally unbranched, and can be classified by the presence and number of carbon double bonds. Thus, saturated fatty acids contain no carbon-to-carbon double bonds, monounsaturated fatty acids contain one carbon-to-carbon double bond, and polyunsaturated fatty acids contain two or more carbon-to-carbon double bond. Table 17.1 lists some common fatty acids and one important source for each. The atoms or groups around the double bonds in unsaturated fatty acids can be arranged in either the cis or trans isomeric form. Naturally occurring fatty acids are generally in the cis configuration.

Table 17.1 Some Common Fatty Acids Found in Natural Fats

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviated Structural Formula</th>
<th>Condensed Structural Formula</th>
<th>Melting Point (°C)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>lauric acid</td>
<td>C_{12}H_{23}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{10})COOH</td>
<td>44</td>
<td>palm kernel oil</td>
</tr>
<tr>
<td>myristic acid</td>
<td>C_{13}H_{27}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{12})COOH</td>
<td>58</td>
<td>oil of nutmeg</td>
</tr>
<tr>
<td>palmitic acid</td>
<td>C_{15}H_{31}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{14})COOH</td>
<td>63</td>
<td>palm oil</td>
</tr>
<tr>
<td>palmitoleic acid</td>
<td>C_{15}H_{29}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{12})CH=CH(CH(<em>2))(</em>{7})COOH</td>
<td>0.5</td>
<td>macadamia oil</td>
</tr>
<tr>
<td>stearic acid</td>
<td>C_{17}H_{35}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{16})COOH</td>
<td>70</td>
<td>cocoa butter</td>
</tr>
<tr>
<td>oleic acid</td>
<td>C_{17}H_{33}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{14})CH=CH(CH(<em>2))(</em>{7})COOH</td>
<td>16</td>
<td>olive oil</td>
</tr>
<tr>
<td>linoleic acid</td>
<td>C_{17}H_{31}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{12})(CH(_2))(_2)(CH(_2))(_7)COOH</td>
<td>−5</td>
<td>canola oil</td>
</tr>
<tr>
<td>α-linolenic acid</td>
<td>C_{17}H_{29}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{12})(CH(_2))(_2)(CH(_2))(_7)COOH</td>
<td>−11</td>
<td>flaxseed</td>
</tr>
<tr>
<td>arachidonic acid</td>
<td>C_{19}H_{31}COOH</td>
<td>CH(_3)(CH(<em>2))(</em>{14})(CH(_2))(_2)(CH(_2))(_7)COOH</td>
<td>−50</td>
<td>liver</td>
</tr>
</tbody>
</table>

Two polyunsaturated fatty acids—linoleic and α-linolenic acids—are termed essential fatty acids because humans must obtain them from their diets. Both substances are required for normal growth and development, but the human body does not synthesize them. The body uses linoleic acid to synthesize many of the other unsaturated fatty acids, such as arachidonic acid, a precursor for the synthesis of prostaglandins. In addition, the essential fatty acids are necessary for the
efficient transport and metabolism of cholesterol. The average daily diet should contain about 4–6 g of the essential fatty acids.

**Prostaglandins**

Prostaglandins are chemical messengers synthesized in the cells in which their physiological activity is expressed. They are unsaturated fatty acids containing 20 carbon atoms, characterized by a 5 carbon ring. They are synthesized from arachidonic acid when needed by a particular cell. They are synthesized in nearly all mammalian tissues and affect almost all organs in the body. The classes of prostaglandins are designated as PGA, PGB, PGE, etc.

The prostaglandins are among the most potent biological substances known. Slight structural differences give them highly distinct biological effects; however, all prostaglandins exhibit some ability to induce smooth muscle contraction, lower blood pressure, and contribute to the inflammatory response.

Aspirin and other nonsteroidal anti-inflammatory agents, such as ibuprofen, obstruct the synthesis of prostaglandins by inhibiting cyclooxygenase, the enzyme needed for the initial step in the conversion of arachidonic acid to prostaglandins.

Their wide range of physiological activity has led to the synthesis of hundreds of prostaglandins and their analogs. Prostaglandins have been employed clinically to induce labor, lower or increase blood pressure, inhibit stomach secretions, relieve nasal congestion, relieve asthma, and prevent the formation of blood clots, which are associated with heart attacks and strokes.
Viewed as a whole, the saturated fatty acid molecule is relatively straight. Such molecules pack closely together into a crystal lattice, maximizing the strength of dispersion forces (i.e. cohesive forces, Van der Waals forces) and causing fatty acids and the fats derived from them to have relatively high melting points.

In contrast, each cis carbon-to-carbon double bond in an unsaturated fatty acid produces a pronounced bend in the molecule, so that these molecules do not stack neatly. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.

(a) Ball-and-stick model of a palmitic acid molecule. (b) The Space-filling model of palmitic acid shows the overall straightness of a saturated fatty acid molecule.

Waxes

Waxes are esters formed from long-chain fatty acids and long-chain alcohols. Most natural waxes are mixtures of such esters. Plant waxes on the surfaces of leaves, stems, flowers, and fruits protect the plant from dehydration and invasion by harmful microorganisms. Carnauba wax, used extensively in floor waxes, automobile waxes, and furniture polish, is largely myricyl cerotate, obtained from the leaves of certain Brazilian palm trees. Animals also produce waxes that serve as protective coatings, keeping the surfaces of feathers, skin, and hair pliable and water repellent.

Key Takeaways:
- Fatty acids are carboxylic acids that are the structural components of many lipids. They may be saturated or unsaturated.
- Most fatty acids are unbranched and contain an even number of carbon atoms.
- Unsaturated fatty acids have lower melting points than saturated fatty acids containing the same number of carbon atoms.
Triglycerides

Fats and oils are the most abundant lipids in nature. They provide energy for living organisms, insulate body organs, and transport fat-soluble vitamins through the blood.

Fats and oils are called triglycerides (or triacylglycerols) because they are esters composed of three fatty acid units joined to glycerol, a trihydroxy alcohol:

If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a simple triglyceride. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a mixed triglyceride.

A triglyceride is called a fat if it is a solid at 25°C; it is called an oil if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation and number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils.

Table 2 shows the fatty acid compositions of some common fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors. To cite just one example, lard from corn-fed hogs is more highly saturated than lard from peanut-fed hogs. Palmitic acid is the most abundant of the saturated fatty acids, while oleic acid is the most abundant unsaturated fatty acid.
### Table 2 Average Fatty Acid Composition of Some Common Fats and Oils (%)*

<table>
<thead>
<tr>
<th></th>
<th>Lauric</th>
<th>Myristic</th>
<th>Palmitic</th>
<th>Stearic</th>
<th>Oleic</th>
<th>Linoleic</th>
<th>Linolenic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fats</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>butter (cow)</td>
<td>3</td>
<td>11</td>
<td>27</td>
<td>12</td>
<td>29</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>tallow</td>
<td>3</td>
<td>24</td>
<td>19</td>
<td>43</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>lard</td>
<td>2</td>
<td>26</td>
<td>14</td>
<td>44</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oils</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>canola oil</td>
<td></td>
<td></td>
<td>4</td>
<td>2</td>
<td>62</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>coconut oil*</td>
<td>47</td>
<td>18</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>corn oil</td>
<td></td>
<td></td>
<td>11</td>
<td>2</td>
<td>28</td>
<td>58</td>
<td>1</td>
</tr>
<tr>
<td>olive oil</td>
<td></td>
<td></td>
<td>13</td>
<td>3</td>
<td>71</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>peanut oil</td>
<td></td>
<td></td>
<td>11</td>
<td>2</td>
<td>48</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>soybean oil</td>
<td></td>
<td></td>
<td>11</td>
<td>4</td>
<td>24</td>
<td>54</td>
<td>7</td>
</tr>
</tbody>
</table>

*Totals less than 100% indicate the presence of fatty acids with fewer than 12 carbon atoms or more than 18 carbon atoms.

*Coconut oil is highly saturated. It contains an unusually high percentage of the low-melting C₈, C₁₀, and C₁₂ saturated fatty acids.

Terms such as *saturated fat* or *unsaturated oil* are often used to describe the fats or oils obtained from foods. Saturated fats contain a high proportion of saturated fatty acids, while unsaturated oils contain a high proportion of unsaturated fatty acids. The high consumption of saturated fats is a factor, along with the high consumption of cholesterol, in increased risks of heart disease.

### Physical Properties of Triglycerides

Pure triglycerides are colorless, odorless, and tasteless. The characteristic colors, odors, and flavors that we associate with some of them are imparted by foreign substances that are lipid soluble and have been absorbed by these lipids. For example, the yellow color of butter is due to the presence of the pigment carotene; the taste of butter comes from two compounds—diacetyl and 3-hydroxy-2-butanone—produced by bacteria in the ripening cream from which the butter is made.

![Chemical structures of diacetyl and 3-hydroxy-2-butanone](image)

Fats and oils are lighter than water, having densities of about 0.8 g/cm³. They are poor conductors of heat and electricity and therefore serve as excellent insulators for the body, slowing the loss of heat through the skin.
Chemical Reactions of Triglycerides

Because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [50 atm or 5,000 kPa and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts.

Dirt and grime usually adhere to skin, clothing, and other surfaces by combining with body oils, cooking fats, lubricating greases, and similar substances that act like glues. Because these substances are not miscible in water, washing with water alone does little to remove them. Soap removes them, however, because soap molecules have a dual nature. One end, called the head, carries an ionic charge (a carboxylate anion) and therefore dissolves in water; the other end, the tail, has a hydrocarbon structure and dissolves in oils. The hydrocarbon tails dissolve in the soil; the ionic heads remain in the aqueous phase, and the soap breaks the oil into tiny soap-enclosed droplets called micelles, which disperse throughout the solution. The droplets repel each other because of their charged surfaces and do not coalesce. With the oil no longer “gluing” the dirt to the soiled surface (skin, cloth, dish), the soap-enclosed dirt can easily be rinsed away.

The double bonds in fats and oils can undergo hydrogenation and also oxidation. The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry.
In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats.

In the preparation of margarine, for example, partially hydrogenated oils are mixed with water, salt, and nonfat dry milk, along with flavoring agents, coloring agents, and vitamins A and D, which are added to approximate the look, taste, and nutrition of butter. (Preservatives and antioxidants are also added.)

Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the trans fatty acids. Studies have shown that trans fatty acids also raise cholesterol levels and increase the incidence of heart disease. Trans fatty acids do not have the bend in their structures, which occurs in cis fatty acids and thus pack closely together in the same way that the saturated fatty acids do.

Fats and oils that are in contact with moist air at room temperature eventually undergo oxidation and hydrolysis reactions that cause them to turn rancid, acquiring a characteristic disagreeable odor. One cause of the odor is the release of volatile fatty acids by hydrolysis of the ester bonds. Butter, for example, releases foul-smelling butyric, caprylic, and capric acids. Microorganisms present in the air furnish lipases that catalyze this process. Another cause of volatile, odorous compounds is the oxidation of the unsaturated fatty acid components, particularly the readily oxidized structural unit

$$\sim\text{CH}==\text{CH}==\text{CH}_{2}==\text{CH}==\text{CH}\sim$$

in polyunsaturated fatty acids, such as linoleic and linolenic acids. One particularly offensive product, formed by the oxidative cleavage of both double bonds in this unit, is a compound called malonaldehyde.

[Rancidity is a major concern of the food industry, which is why food chemists are always seeking new and better antioxidants, substances added in very small amounts (0.001%–0.01%) to prevent oxidation and thus suppress rancidity. Antioxidants are compounds whose affinity for oxygen is greater than that of the lipids in the food; thus they function by preferentially depleting the supply of oxygen absorbed into the product. Because vitamin E has antioxidant properties, it helps reduce damage to lipids in the body, particularly to unsaturated fatty acids found in cell membrane lipids.](image)
Key Takeaways:

- Fats and oils are composed of molecules known as triglycerides, which are esters composed of three fatty acid units linked to glycerol.
- An increase in the percentage of shorter-chain fatty acids and/or unsaturated fatty acids lowers the melting point of a fat or oil.
- The hydrolysis of fats and oils in the presence of a base makes soap (saponification reaction).
- Double bonds present in unsaturated triglycerides can be hydrogenated to convert oils (liquid) into margarine (solid).
- The oxidation of fatty acids can form compounds with disagreeable odors. This oxidation can be minimized by the addition of antioxidants.

Phospholipids and Membranes

All living cells are surrounded by a cell membrane. Plant cells and animal cells contain a cell nucleus that is also surrounded by a membrane and holds the genetic information for the cell. Everything between the cell membrane and the nuclear membrane—including intracellular fluids and various subcellular components such as the mitochondria and ribosomes—is called the cytoplasm.

The membranes of all cells have a fundamentally similar structure, but membrane function varies tremendously from one organism to another and even from one cell to another within a single organism. This diversity arises mainly from the presence of different proteins and lipids in the membrane.

The lipids in cell membranes have dual characteristics: part of the lipid is ionic and therefore dissolves in water, whereas the rest has a hydrocarbon structure and therefore dissolves in nonpolar substances.

When allowed to float freely in water, polar lipids spontaneously cluster together in any one of three arrangements: micelles, monolayers, and bilayers according to their concentration.

Micelles are aggregations in which the lipids’ hydrocarbon tails—are hydrophobic—are directed toward the center of the assemblage and away from the surrounding water while the hydrophilic heads are directed outward, in contact with the water. Each micelle may contain thousands of lipid molecules.

Polar lipids may also form a monolayer, a layer one molecule thick on the surface of the water. The polar heads face into water, and the nonpolar tails stick up into the air.

Bilayers are double layers of lipids arranged so that the hydrophobic tails are sandwiched between an inner surface and an outer surface consisting of hydrophilic heads. The hydrophilic heads are in contact with water on either side of the bilayer, whereas the tails, sequestered inside the bilayer, are prevented from having contact with the water. Bilayers like this make up every cell membrane.

![Schematic Diagram of a Cell Membrane](image)

**Figure 17.5 Spontaneously Formed Polar Lipid Structures in Water: Monolayer, Micelle, and Bilayer**

![Monolayer](image)  ![Bilayer](image)  ![Micelle](image)
The membrane enclosing a typical animal cell is a phospholipid bilayer with embedded cholesterol and protein molecules. Short oligosaccharide chains are attached to the outer surface.

In the bilayer interior, the hydrophobic tails (that is, the fatty acid portions of lipid molecules) interact by means of dispersion forces (Van der Waals forces). The interactions are weakened by the presence of unsaturated fatty acids. As a result, the membrane components are free to mill about to some extent, and the membrane is described as fluid.

In 1972 S. J. Singer and G. L. Nicolson proposed the fluid mosaic model to give account of some properties of the cell membranes. According to this model, biological membranes can be considered as a two-dimensional liquid in which lipid and protein molecules diffuse more or less easily. Although the lipid bilayers that form the basis of the membranes do indeed form two-dimensional liquids by themselves, the plasma membrane also contains a large quantity of proteins, which provide more structure.

The plasma membranes of cells contain combinations of glycosphingolipids and protein receptors organized in glycolipoprotein microdomains termed lipid rafts. These specialized membrane microdomains compartmentalize cellular processes by serving as organizing centres for the assembly of signalling molecules, influencing membrane fluidity and membrane protein trafficking, and regulating neurotransmission and receptor trafficking. Lipid rafts are more ordered and tightly packed than the surrounding bilayer, but they float freely in the membrane bilayer in response to external stresses.
The lipids found in cell membranes can be categorized in various ways:

- **Phospholipids** are lipids containing phosphorus.
- **Glycolipids** are sugar-containing lipids. They are found exclusively on the outer surface of the cell membrane, acting as distinguishing surface markers for the cell and thus serving in cellular recognition and cell-to-cell communication.
- **Sphingolipids** are phospholipids or glycolipids that contain the unsaturated amino alcohol sphingosine rather than glycerol.

*Phosphoglycerides* (also known as glycerophospholipids) are the most abundant phospholipids in cell membranes. They consist of a glycerol unit with fatty acids attached to the first two carbon atoms, while a phosphoric acid unit, esterified with an alcohol molecule (usually an amino alcohol, as in part (a) of figure) is attached to the third carbon atom of glycerol (part (b) of figure).

If there is no esterification on the phosphoric group, the molecule is names phosphatidic acid. Notice that the phosphoglyceride molecule is identical to a triglyceride up to the phosphoric acid unit.
Amino alcohols commonly found in phosphoglycerides, which are evident in its structural formula (b).

There are two common types of phosphoglycerides. Phosphoglycerides containing ethanolamine as the amino alcohol are called cephalins or phosphatidylethanolamines. Cephalins are found in brain tissue and nerves and also have a role in blood clotting. Phosphoglycerides containing choline as the amino alcohol unit are called phosphatidylcholines or lecithins. Lecithins occur in all living organisms. Like cephalins, they are important constituents of nerve and brain tissue. Egg yolks are especially rich in lecithins. Commercial-grade lecithins isolated from soybeans are widely used in foods as emulsifying agents. An emulsifying agent is used to stabilize an emulsion—a dispersion of two liquids that do not normally mix, such as oil and water. Many foods are emulsions. Milk is an emulsion of butterfat in water. The emulsifying agent in milk is a protein called casein. Mayonnaise is an emulsion of salad oil in water, stabilized by lecithins present in egg yolk.

**Sphingolipids** are phospholipids not containing glycerol but sphingosine (a), an amino-alcohol with a long hydrocarbon chain (17 C atoms). **Sphingomyelins** (b) are the simplest sphingolipids. Each of them contains a fatty acid, a phosphoric acid, sphingosine, and choline. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.
Most animal cells contain sphingolipids called **cerebrosides**. Cerebrosides are sphingolipids that contain a sugar unit. They are composed of sphingosine, a fatty acid, and galactose or glucose. They therefore resemble sphingomyelins but have a sugar unit in place of the choline phosphate group. Cerebrosides are important constituents of the membranes of nerve and brain cells.

The sphingolipids called **gangliosides** are more complex, usually containing a branched chain of three to eight monosaccharides and/or substituted sugars. Because of considerable variation in their sugar components, about 130 varieties of gangliosides have been identified. Most cell-to-cell recognition and communication processes (e.g., blood group antigens) depend on differences in the sequences of sugars in these compounds. Gangliosides are most prevalent in the outer membranes of nerve cells, although they also occur in smaller quantities in the outer membranes of most other cells. Because cerebrosides and gangliosides contain sugar groups, they are also classified as glycolipids.

**Membrane Proteins**

If membranes were composed only of lipids, very few ions or polar molecules could pass through their hydrophobic “sandwich filling” to enter or leave any cell. However, certain charged and polar species do cross the membrane. They are aided by some proteins that move about in the lipid bilayer.

The two major classes of proteins in the cell membrane are:
• integral proteins, which span the hydrophobic interior of the bilayer,
• peripheral proteins, which are more loosely associated with the surface of the lipid bilayer. Peripheral proteins may be attached to integral proteins, to the polar head groups of phospholipids, or to both by hydrogen bonding and electrostatic forces.

Small ions and molecules soluble in water enter and leave the cell by way of channels through the integral proteins. Their membrane crossing can be active (if it requires energy) or passive (if it does not). Those proteins are called channels (passive) or pumps (active).

Some proteins, called carrier proteins, facilitate the passage of certain molecules, such as hormones and neurotransmitters, by specific interactions between the protein and the molecule being transported. Other proteins links to small molecules on the outer surface of the membrane, undergo conformational changes and activate another molecule (called second messengers) inside the cell. They are called G-proteins.

Key Takeaways

• Lipids are important components of biological membranes. These lipids have dual characteristics: part of the molecule is hydrophilic, and part of the molecule is hydrophobic.
• Membrane lipids may be classified as phospholipids, glycolipids, and/or sphingolipids.
• Proteins are another important component of biological membranes. Integral proteins span the lipid bilayer, while peripheral proteins are more loosely associated with the surface of the membrane.

Steroids

All the lipids discussed so far are saponifiable, reacting with aqueous alkali to yield simpler components, such as glycerol, fatty acids, amino alcohols, and sugars.

Lipid samples extracted from cellular material, however, also contain a small but important fraction that does not react with alkali. The most important nonsaponifiable lipids are the steroids. These compounds include the bile salts, cholesterol and related compounds, and certain hormones (such as cortisone and the sex hormones).

Steroids occur in plants, animals, yeasts, and molds but not in bacteria.
They may exist in free form or combined with fatty acids or carbohydrates. All steroids have a characteristic structural component consisting of four fused rings. Chemists identify the rings by capital letters and number the carbon atoms. Slight variations in this structure or in the atoms or groups attached to it produce profound differences in biological activity.

**Cholesterol**

Cholesterol is an extremely important biological molecule that has roles in membrane structure as well as being a precursor for the synthesis of the steroid hormones, the bile acids, and vitamin D. Both dietary cholesterol and that synthesized *de novo* are transported through the circulation in lipoprotein particles. The same is true of cholesteryl esters, the form in which cholesterol is stored in cells. Due to its important role in membrane function, all cells express the enzymes of cholesterol biosynthesis.

The synthesis and utilization of cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body. The abnormal deposition of cholesterol and cholesterol-rich lipoproteins in the coronary arteries is of particular clinical importance. Such deposition, eventually leading to atherosclerosis, is the leading contributory factor in diseases of the coronary arteries.

**Biosynthesis of Cholesterol**

Slightly less than half of the cholesterol in the body derives from biosynthesis *de novo*. Biosynthesis in the liver accounts for approximately 10%, and in the intestines approximately 15%, of the amount produced each day. Synthesis of cholesterol, like that of most biological lipids, begins from the two-carbon acetate group of acetyl-CoA.

The acetyl-CoA utilized for cholesterol biosynthesis derives mainly from an oxidation reaction (e.g., fatty acids or pyruvate) in the mitochondria and it is transported to the cytoplasm by the same process as that described for fatty acid synthesis. All the reduction reactions of cholesterol biosynthesis use NADPH as a cofactor.

The process of cholesterol synthesis is composed of five major steps:

1. Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
2. HMG-CoA is converted to mevalonate
3. Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO₂
4. IPP is converted to squalene
5. Squalene is converted to cholesterol.

Synthesis of cholesterol begins with the transport of acetyl-CoA from within the mitochondria to the cytosol.

The phosphorylation reactions are required to solubilize the isoprenoid intermediates in the pathway.

Intermediates in the pathway are used for the synthesis of prenylated proteins, glycoproteins, coenzyme Q and the side chain of heme a.
1. The pathway begins when two moles of acetyl-CoA are condensed in a reversal of the thiolase reaction, forming acetoacetyl-CoA. The cytoplasmic enzyme involved in cholesterol biosynthesis is acetoacetyl-CoA thiolase.

2. Acetoacetyl-CoA and a third mole of acetyl-CoA are converted to HMG-CoA by the action of the HMG-CoA synthase.

3. HMG-CoA is then converted to mevalonate by HMG-CoA reductase, this enzyme is bound in the endoplasmic reticulum, ER. Two moles of NADPH are consumed during the conversion of HMG-CoA to mevalonate. The reaction catalyzed by HMGR is the rate limiting step of cholesterol biosynthesis, and this enzyme is subject to complex regulatory controls.

4. Mevalonate is then activated by two successive phosphorylations (catalyzed by mevalonate kinase, and phosphomevalonate kinase) yielding, sequentially, mevalonate 5-phosphate and then mevalonate 5-diphosphate (or mevalonate 5-pyrophosphate). In humans, those kinases are peroxisome localized enzymes.

5. Following the formation of mevalonate 5-diphosphate, an ATP-dependent decarboxylation yields isopentenyl pyrophosphate (IPP) which is an activated isoprenoid molecule. The synthesis of IPP is catalyzed by diphosphomevalonate decarboxylase.

6. One molecule of IPP condenses with one molecule of DMPP to generate geranyl pyrophosphate, GPP.

7. GPP further condenses with another IPP molecule to yield farnesyl pyrophosphate, FPP. Synthesis of both GPP and FPP is catalyzed by the enzyme, farnesyl diphosphate synthase.

8. The synthesis of squalene, from FPP, represents the first cholesterol-specific step in the cholesterol synthesis pathway. This is due to the fact that several intermediates in the pathway can be diverted to the production of other biologically relevant molecules. The
synthesis of squalene is catalyzed by the NADPH-reaching enzyme, farnesyl-diphosphate farnesyltransferase 1 (commonly called squalene synthase). This enzyme catalyses the two-step head-to-head condensation of two molecules of FPP, yielding squalene.

9. Squalene then undergoes a two-step cyclization to yield lanosterol. This first reaction in this two-step cyclization is catalyzed by the enzyme, squalene epoxidase (also called squalene monooxygenase). This enzyme uses NADPH as a cofactor to introduce molecular oxygen as an epoxide at the 2,3 position of squalene forming the intermediate, 2,3-oxidosqualene. In the second step, this epoxide intermediate is converted to lanosterol through the action of the enzyme lanosterol cyclase.

10. Through a series of 19 additional reactions, lanosterol is converted to cholesterol. These 19 reaction steps are catalyzed by nine different enzymes that are localized either to the ER or to the peroxisomes.

Regulating Cholesterol Synthesis

Normal healthy adults synthesize cholesterol at a rate of approximately 1g/day and consume approximately 0.3g/day. A relatively constant level of cholesterol in the blood (150–200 mg/dL) is maintained primarily by controlling the level of de novo synthesis. The level of cholesterol synthesis is regulated in part by the dietary intake of cholesterol. Cholesterol from both diet and synthesis is utilized in the formation of membranes and in the synthesis of the steroid hormones and bile acids. The greatest proportion of cholesterol is used in bile acid synthesis.

The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1. Regulation of HMGR activity and levels
2. Regulation of excess intracellular free cholesterol through the activity of sterol O-acyltransferases, SOAT1 and SOAT2.
3. Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse transport.

Regulation of HMGR activity is the primary means for controlling the level of cholesterol biosynthesis. The enzyme is controlled by four distinct mechanisms:

- feed-back inhibition,
- control of gene expression,
- rate of enzyme degradation,
- phosphorylation-dephosphorylation.

The first three control mechanisms are exerted by cholesterol itself.

Cholesterol acts as a feed-back inhibitor of pre-existing HMGR as well as inducing rapid degradation of the enzyme.

The latter is the result of cholesterol-induced polyubiquitination of HMGR and its degradation in the proteosome. This ability of cholesterol is a consequence of the sterol sensing domain of HMGR.

In addition, when cholesterol is in excess the amount of mRNA for HMGR is reduced as a result of decreased expression of the gene.

Regulation of HMGR through covalent modification occurs as a result of phosphorylation and dephosphorylation. The enzyme is most active in its unmodified form. Phosphorylation of the
enzyme decreases its activity.

Phosphorylation of HMGR is catalysed by AMP-activated protein kinase (AMPK) an enzyme whose activity is also regulated by phosphorylation. Phosphorylation of AMPK is catalyzed by at least 2 enzymes (LKB1 and CaMKKβ).

Hormones such as glucagon and epinephrine negatively affect cholesterol biosynthesis by inhibiting the activity HMGR. Conversely, insulin stimulates the removal of phosphates and, thereby, activates HMGR activity.

We can say regulation of cholesterol biosynthesis is hormonally controlled. Insulin leads to a decrease in cAMP, which in turn activates cholesterol synthesis. Alternatively, glucagon and epinephrine, which increase the level of cAMP, inhibit cholesterol synthesis.

The ability of insulin to stimulate, and glucagon to inhibit, HMGR activity is consistent with the effects of these hormones on other metabolic pathways. The basic function of these two hormones is to control the availability and delivery of energy to all cells of the body.

Long-term control of HMGR activity is exerted primarily through control over the synthesis and degradation of the enzyme. When levels of cholesterol are high, the level of expression of the HMGR gene is reduced. Conversely, reduced levels of cholesterol activate expression of the gene. Insulin also brings about long-term regulation of cholesterol metabolism by increasing the level of HMGR synthesis.

Functions

Cholesterol is required to build and maintain membranes; it modulates membrane fluidity over the range of physiological temperatures. The hydroxyl group on cholesterol interacts with the polar head groups of the membrane phospholipids and sphingolipids, while the bulky steroid and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty-acid chain of the other lipids. Through the interaction with the phospholipid fatty-acid chains, cholesterol increases membrane packing, which reduces membrane fluidity. The structure of the tetracyclic ring of cholesterol contributes to the decreased fluidity of the cell membrane as the molecule is in a trans conformation making all but the side chain of cholesterol rigid and planar. In this structural role, cholesterol reduces the permeability of the plasma membrane to neutral solutes, hydrogen ions, and sodium ions.

Within the cell membrane, cholesterol also functions in intracellular transport, cell signalling and nerve conduction. Cholesterol is essential for the structure and function of invaginated caveolae and clathrin-coated pits and, consequently, of endocytosis. Cholesterol is also implicated in cell signalling processes, assisting in the formation of lipid rafts in the plasma membrane. Lipid raft formation brings receptor proteins in close proximity with high concentrations of second messenger molecules. In many neurons, a myelin sheath, rich in cholesterol, since it is derived from compacted layers of Schwann cell membrane, provides insulation for more efficient conduction of impulses.

Within cells, cholesterol is the precursor molecule in several biochemical pathways. In the liver, cholesterol is converted to bile, which is then stored in the gallbladder. Bile contains bile salts, which solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins, A, D, E, and K. Cholesterol is an important precursor molecule for the synthesis of vitamin D and the steroid hormones, including the adrenal gland hormones cortisol and aldosterone, as well as the sex hormones progesterone, estrogens, and testosterone, and their derivatives.
Plasma transport and regulation of absorption

Cholesterol is only slightly soluble in water; it dissolves into the (water-based) bloodstream only at exceedingly small concentrations. Instead, cholesterol is transported inside lipoproteins, complex discoidal particles with exterior amphiphilic proteins and lipids, whose outward-facing surfaces are water-soluble and inward-facing surfaces are lipid-soluble. Triglycerides and cholesterol esters are carried internally. Phospholipids and cholesterol, being amphipathic, are transported in the monolayer surface of the lipoprotein particle.

There are several types of lipoproteins in the blood. In order of increasing density, they are:

- chylomicrons,
- very-low-density lipoprotein (VLDL),
- low-density lipoprotein (LDL),
- intermediate-density lipoprotein (IDL),
- high-density lipoprotein (HDL).

Lower protein/lipid ratios make for less dense lipoproteins. Cholesterol within different lipoproteins is identical, although some is carried as "free" alcohol, while others as fatty acyl esters, known also as cholesterol esters.

Lipoproteins contain apolipoproteins, which bind to specific receptors on cell membranes, directing their lipid payload to specific tissues. Lipoprotein particles thus include these molecular addresses, which determine the start- and end points of cholesterol transport.

Chylomicrons carry fats from the intestine to muscle and other tissues in need of fatty acids for energy or fat production. Unused cholesterol remains in more cholesterol-rich chylomicron remnants, and taken up from here to the bloodstream by the liver.

VLDL molecules are produced by the liver from triacylglycerol and cholesterol which was not used in the synthesis of bile acids. These molecules are degraded by lipoprotein lipase on the blood vessel wall to IDL.

Blood vessels cleave and absorb triacylglycerol from IDL molecules, increasing the concentration of cholesterol. IDL molecules are then consumed in two processes. Half is metabolized by HTGL (hepatic lipase) and taken up by the LDL receptor on the liver cell surfaces. The other half continues to lose triacylglycerols in the bloodstream until they become LDL molecules, with the
highest concentration of cholesterol within them.

LDL particles are the major blood cholesterol carriers. Each one contains approximately 1,500 molecules of cholesterol ester. LDL molecule shells contain just one molecule of apolipoprotein B100, recognized by LDL receptors in peripheral tissues. Upon binding of apolipoprotein B100, many LDL receptors concentrate in clathrin-coated pits. Both LDL and its receptor form vesicles within a cell via endocytosis. These vesicles then fuse with a lysosome, where the lysosomal acid lipase enzyme hydrolyses the cholesterol esters. The cholesterol can then be used for membrane biosynthesis or esterified and stored within the cell, not to interfere with the cell membranes.

LDL receptors are used up during cholesterol absorption, and their synthesis is regulated by SREBP, the same protein that controls the synthesis of cholesterol de novo, according to its presence inside the cell. A cell with abundant cholesterol will have its LDL receptor synthesis blocked, to prevent new cholesterol in LDL molecules from being taken up. Conversely, LDL receptor synthesis proceeds when a cell is deficient in cholesterol.

When this process becomes unregulated, LDL molecules without receptors begin to appear in the blood. These LDL molecules are oxidized and taken up by macrophages, which become engorged and form foam cells. These foam cells often become trapped in the walls of blood vessels and contribute to atherosclerotic plaque formation. Differences in cholesterol homeostasis affect the development of early atherosclerosis. These plaques are the main causes of heart attacks, strokes, and other serious medical problems, leading to the association of so-called LDL cholesterol (actually a lipoprotein) with "bad" cholesterol.

HDL particles are thought to transport cholesterol back to the liver, either for excretion or for other tissues that synthesize hormones, in a process known as reverse cholesterol transport (RCT). Large numbers of HDL particles correlates with better health outcomes, whereas low numbers of HDL particles is associated with atheromatous disease progression in the arteries.

Dietary Sources

Animal fats are complex mixtures of triglycerides, with lesser amounts of phospholipids and cholesterol. As a consequence, all foods containing animal fat contain cholesterol to varying extents. Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp. From a dietary perspective, cholesterol is not found in significant amounts in plant sources. In addition, plant products such as avocado, flax seeds and peanuts contain cholesterol-like compounds called phytosterols, which are believed to compete with cholesterol for absorption in the intestines, thus reducing the absorption of both dietary and bile cholesterol.

The fraction of dietary cholesterol, which is absorbed varies from 15% to 75%, and is about 50% on average, with the remainder excreted in the feces. Free cholesterol is much more likely to be absorbed than esterified cholesterol.
Reductions in circulating cholesterol levels can have profound positive impacts on cardiovascular disease, particularly on atherosclerosis, as well as other metabolic disruptions of the vasculature. Control of dietary intake is one of the easiest and least cost intensive means to achieve reductions in cholesterol.

Drug treatment to lower plasma lipoproteins and/or cholesterol is primarily aimed at reducing the risk of atherosclerosis and subsequent coronary artery disease that exists in patients with elevated circulating lipids. Drug therapy usually is considered as an option only if non-pharmacologic interventions (altered diet and exercise) have failed to lower plasma lipids.

**Steroid Hormones**

_Hormones_ are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (see table below), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

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<th><strong>Table 17.3 Representative Steroid Hormones and Their Physiological Effects</strong></th>
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<td>Cortisol (Hydrocortisone)</td>
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<td>Estradiol (an estrogen)</td>
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<td>Testosterone (an androgen)</td>
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The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands.

Testosterone and androstenedione are the primary male sex hormones, or androgens, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength.

Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs.
Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other. Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Bile Salts

Bile is a yellowish green liquid (pH 7.8–8.6) produced in the liver. The most important constituents of bile are bile salts, which are sodium salts of amidelike combinations of bile acids, such as cholic acid and an amine such as the amino acid glycine. They are synthesized from cholesterol in the liver, stored in the gallbladder, and then secreted in bile into the small intestine. In the gallbladder, the composition of bile gradually changes as water is absorbed and the other components become more concentrated.

Because they contain both hydrophobic and hydrophilic groups, bile salts are highly effective detergents and emulsifying agents; they break down large fat globules into smaller ones and keep those smaller globules suspended in the aqueous digestive environment. Enzymes can then hydrolyze fat molecules more efficiently. Thus, the major function of bile salts is to aid in the digestion of dietary lipids.

Surgical removal is often advised for a gallbladder that becomes infected, inflamed, or perforated. This surgery does not seriously affect digestion because bile is still produced by the liver, but the liver’s bile is more dilute and its secretion into the small intestine is not as closely tied to the arrival of food.

Key Takeaways

- Steroids have a four-fused-ring structure and have a variety of functions.
- Cholesterol is a steroid found in mammals that is needed for the formation of cell membranes, bile acids, and several hormones.
- Bile salts are secreted into the small intestine to aid in the digestion of fats.