Lipids I: Fatty Acids and Eicosanoids

Lipids (or fats) are a heterogeneous group of organic compounds defined by their solubility in nonpolar solvents such as chloroform, ether, and benzene and by their poor solubility in water.

Lipids may be polar or nonpolar (amphipathic). Polar lipids have limited solubility in water because they are amphipathic, i.e., they possess hydrophilic and hydrophobic regions in the same molecule. Major polar lipids include fatty acids, cholesterol, glycerophosphatides, and glycosphingolipids. Very short chain fatty acids and ketone bodies are readily soluble in water. Nonpolar lipids serve principally as storage and transport forms of lipid and include triacylglycerols (also called triglycerides) and cholesteryl esters.

Lipids have numerous functions including the following: thermal insulation, energy storage (as triacylglycerol), metabolic fuels, membrane components (phospholipids and cholesterol; Chapter 10), hormones (steroids and vitamin D metabolites; Chapters 32 and 37, respectively), precursors of prostanoids (discussed on p. 391) and leukotrienes, (vitamins A, C, D, E, and K; Chapters 36–38), emulsifying agents in the digestion and absorption of lipids (bile acids; Chapters 12 and 19), and surfactants in the alveolar membrane (phosphatidylcholine; Chapter 19). The metabolism of fatty acids (saturated and unsaturated) is discussed in this chapter. The metabolism of phospholipids, glycosphingolipids, and cholesterol is considered in Chapter 19.

Fatty acids that contain no carbon-carbon double bonds are known as saturated and those with carbon-carbon double bonds as unsaturated. Fatty acids that contain an even number of carbon atoms and are acyclic, unbranched, nonhydroxylated, and monocarboxylic make up the largest group. The most abundant saturated fatty acids in animals are palmitic and stearic acids (Table 18-1). The melting point of fatty acids rises with increase in chain length, the even-numbered saturated fatty acids having higher melting points than the odd-numbered. Among the even-numbered, the presence of cis double bonds lowers the melting point significantly. Free fatty acids at physiological pH are ionized (pK ~4.85) and exist only in small quantities; in plasma, they typically are bound to albumin. They are usually present as esters or amides.

Digestion and absorption of lipids are discussed in Chapter 12. The Western diet contains about 40% fat, mostly as triacylglycerol (100–150 g/day). Triacylglycerols packaged as chylomicrons in the intestinal epithelial cell are delivered to the blood circulation via the lymphatic system and are hydrolyzed to glycerol and fatty acids by endothelial lipoprotein lipase. Fatty acids are taken up by the cells of the tissue where the hydrolysis occurs, whereas glycerol is metabolized in the liver and kidney (Chapter 15). Another means of triacylglycerol transport is very-low-density lipoprotein (VLDL), which is synthesized in the liver. Its triacylglycerol is also hydrolyzed by endothelial lipoprotein lipase. The metabolism of plasma
TABLE 18-1
Naturally Occurring Saturated Fatty Acids

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Systematic Name*</th>
<th>Molecular Formula</th>
<th>Structural Formula</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capric</td>
<td>n-Decanoic</td>
<td>C₁₀H₂₀O₂</td>
<td>CH₃(CH₂)₉COOH</td>
<td>31</td>
</tr>
<tr>
<td>Lauric</td>
<td>n-Dodecanoic</td>
<td>C₁₂H₂₄O₂</td>
<td>CH₃(CH₂)₁₀COOH</td>
<td>44</td>
</tr>
<tr>
<td>Myristic</td>
<td>n-Tetradecanoic</td>
<td>C₁₄H₂₈O₂</td>
<td>CH₃(CH₂)₁₂COOH</td>
<td>58</td>
</tr>
<tr>
<td>Palmitic†</td>
<td>n-Hexadecanoic</td>
<td>C₁₆H₃₂O₂</td>
<td>CH₃(CH₂)₁₄COOH</td>
<td>63</td>
</tr>
<tr>
<td>Stearic</td>
<td>n-Octadecanoic</td>
<td>C₁₈H₃₆O₂</td>
<td>CH₃(CH₂)₁₆COOH</td>
<td>70</td>
</tr>
<tr>
<td>Arachidic</td>
<td>n-Eicosanoic</td>
<td>C₂₀H₄₀O₂</td>
<td>CH₃(CH₂)₂₀COOH</td>
<td>80</td>
</tr>
<tr>
<td>Behenic</td>
<td>n-Docosanoic</td>
<td>C₂₂H₄₄O₂</td>
<td>CH₃(CH₂)₂₂COOH</td>
<td>84</td>
</tr>
<tr>
<td>Lignoceric</td>
<td>n-Tetracosanoic</td>
<td>C₂₄H₄₈O₂</td>
<td>CH₃(CH₂)₂₄COOH</td>
<td>88</td>
</tr>
<tr>
<td>Cerotic</td>
<td>n-Hexacosanoic</td>
<td>C₂₆H₅₂O₂</td>
<td>CH₃(CH₂)₂₆COOH</td>
<td>92</td>
</tr>
<tr>
<td>Montanic</td>
<td>n-Octacosanoic</td>
<td>C₂₈H₅₆O₂</td>
<td>CH₃(CH₂)₂₈COOH</td>
<td></td>
</tr>
</tbody>
</table>

*Systematic name is based on replacing the final letter "e" of the parent hydrocarbon with "oic."
†Most abundant fatty acids present in animal lipids.

Interrelationships of tissues in lipid metabolism are discussed in Chapter 22.

18.1 Oxidation of Fatty Acids

The overall fatty acid oxidation process in mitochondria consists of uptake of fatty acids, their activation to acyl-CoA, then to thioesters, and finally translocation into mitochondria which involves a carnitine transesterification shuttle and β-oxidation. Fatty acids released from chylomicrons and VLDLs are transferred across cell membranes by passive diffusion, which depends on the concentration gradient. Fatty acids are also obtained from the hydrolysis of triacylglycerol stored in adipose tissue which are bound to albumin and transported in blood. Fatty acids serve as substrates for energy production in liver, skeletal and cardiac muscle during periods of fasting. Although the brain does not utilize fatty acids for generating energy directly, brain cells can utilize ketone bodies synthesized from acetyl-CoA and acetoacetyl-CoA. The latter two are obtained from β-oxidation of fatty acids in the liver. All of the enzymes involved in mitochondrial fatty acid β-oxidation are encoded by nuclear genes. After their synthesis in the cytosolic endoplasmic reticulum, the enzymes are transported to mitochondria. The transport of the enzymes into mitochondria, in many instances, requires the presence of N-terminal extensions to guide the protein across the mitochondrial membrane, receptor-mediated ATP-dependent uptake, and proteolytic processing to form fully assembled, mature enzymes. During β-oxidation of acyl-CoA, the chain length of the substrate is shortened by two carbon atoms (acetyl-CoA) each cycle. Thus, β-oxidation requires a group of enzymes with chain length specificity.

Activation of Fatty Acids

At least three acetyl-CoA synthases, each specific for a particular size of fatty acid, exist: acetyl-CoA synthase acts on acetate and other low-molecular-weight carboxylic acids, medium-chain acyl-CoA synthase on fatty acids with 4–11 carbon atoms, and acyl-CoA synthase on fatty acids with 6–20 carbon atoms. The activity of acetyl-CoA synthase in muscle is restricted to the mitochondrial matrix. Medium-chain acyl-CoA synthase occurs only in liver mitochondria, where medium-chain fatty acids obtained from digestion of dietary triacylglycerols and transported by the portal blood are metabolized. Acyl-CoA synthase, the major activating enzyme, occurs on the outer mitochondrial membrane surface and in endoplasmic reticulum. The overall reaction of activation is as follows:

\[
\text{RCOO}^- + \text{ATP}^{4-} + \text{CoASH} \rightleftharpoons \text{RCO-CoA} + \text{AMP}^{2-} + \text{PPi}^{3-}
\]

The reaction favors the formation of fatty acyl-CoA, since the pyrophosphate formed is hydrolyzed by pyrophosphatase: \( \text{PP}_1 + \text{H}_2\text{O} \rightarrow 2\text{Pi} \). Thus, activation of a fatty
acids molecule requires expenditure of two high-energy phosphate bonds. The reaction occurs in two steps (E = enzyme):

\[
\text{RCOO}^- + \text{ATP} + E \\
\xrightarrow{\text{Step 1}} \\
\text{E} \rightarrow \text{AMP} + \text{C} \rightarrow \text{R} + \text{PP}_i
\]

\[
\text{E} + \text{R} \rightarrow \text{C} \rightarrow \text{SCoA} + \text{AMP}
\]

A mitochondrial acyl-CoA synthase, which utilizes GTP, has also been identified:

\[
\text{R} \cdot \text{COO}^- + \text{CoASH} + \text{GTP}^{4-} \rightarrow \text{RCO} \cdot \text{SCoA} + \text{GDP}^{3-} + \text{P}_i^{2-}
\]

Its role is not known.

**Transport of Acyl-CoA to Mitochondrial Matrix**

This transport is accomplished by carnitine (L-β-hydroxyγ-trimethylammonium butyrate), which is required in catalytic amounts for the oxidation of fatty acids (Figure 18-1). Carnitine also participates in the transport of acetyl-CoA for cytosolic fatty acid synthesis. Two carnitine acyltransferases are involved in acyl-CoA transport: carnitine palmitoyltransferase I (CPTI), located on the outer surface of the inner mitochondrial membrane, and carnitine palmitoyltransferase II (CPTII), located on the inner surface.

The overall translocation reaction is as follows:

\[
\begin{align*}
\text{R} - \text{C} & \rightarrow \text{SCoA} + \text{H}_3\text{C} - \text{N} & \rightarrow \text{CH}_2 \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{COOH} \\
\text{Acyl-CoA} & \rightarrow \text{Carnitine} \\
\text{H}_3\text{C} - \text{N} & \rightarrow \text{CH}_2 \rightarrow \text{C} \rightarrow \text{CH}_2 \rightarrow \text{COOH} + \text{CoASH} \\
\text{C} & \rightarrow \text{O} & \rightarrow \text{Acyl group}
\end{align*}
\]

The standard free-energy change of this reaction is about zero, and therefore the O-ester bond of acylcarnitine may be considered as a high-energy linkage. Malonyl-CoA, a precursor in the synthesis of fatty acids, is an allosteric inhibitor of CPTII in liver and thus prevents a futile cycle of simultaneous fatty acid oxidation and synthesis.

Carnitine is synthesized from two essential amino acids, lysine and methionine. S-Adenosylmethionine donates three methyl groups to a lysyl residue of a protein with the formation of a protein-bound trimethyllysyl. Proteolysis yields trimethyllysine, which is converted to carnitine (Figure 18-2). In humans, liver and kidney are major sites of carnitine production; from there it is transported to skeletal and cardiac muscle, where it cannot be synthesized.

Four inherited defects of carnitine metabolism lead to impaired utilization of long-chain fatty acids for energy production. These include defects of plasma
Carnitine biosynthesis in humans. A lysyl residue is trimethylated by S-adenosylmethionine, with subsequent proteolytic release of trimethyllysine, the starting material. The reactions are catalyzed by (1) trimethyllysine β-hydroxylase, (2) β-hydroxy-trimethyllysine aldolase (pyridoxal phosphate), (3) γ-trimethylaminobutyraldehyde dehydrogenase, and (4) γ-butyrobetaine hydroxylase.

β-Oxidation

The major pathway for fatty acid oxidation, β-oxidation (Figure 18-3), involves oxidation of acyl-CoA at the β-carbon and removal of two carbon fragments as acetyl-CoA and takes place entirely in the mitochondrial matrix. Oxidation of a saturated acyl-CoA with an even number of carbon atoms to acetyl-CoA requires repeated sequential action of four enzymes.

1. Acyl-CoA dehydrogenase dehydrogenates acyl-CoA at the α- and β-carbon atoms to yield the α,β-unsaturated acyl-CoA (or Δ^2-unsaturated acyl-CoA). Each one of four distinct dehydrogenases is specific for a given range of fatty acid chain length. All four are flavoproteins and contain a tightly bound molecule of flavin adenine dinucleotide (FAD). The electrons from the acyl-CoA dehydrogenase are transferred to the main respiratory chain (Chapter 14) through mitochondrial electron transfer flavoprotein (ETF) and ETF-ubiquinone oxidoreductase (ETF-QO) (Figure 18-4). Both ETF and ETF-ubiquinone oxidoreductase are nuclear encoded proteins. They also mediate transfer of electrons from dimethylglycine dehydrogenase and sarcosine dehydrogenase. Inherited defects in ETF and ETF-QO cause accumulation of organic acids (acidemia) and their excretion in the urine (acidurias). Examples of these disorders are glutaric acidemia type I and type II which are inherited as autosomal recessive traits. Glutaric acid is an intermediate in the metabolism of lysine, hydroxy lysine, and tryptophan. Glutaric acidemia type I is caused by deficiency of glutaryl-CoA dehydrogenase which catalyzes the conversion of glutaryl-CoA to crotonyl-CoA. Glutaric acidemia type II is caused by defects in the ETF/ETF-QO proteins. The clinical manifestations of these disorders are similar to medium-chain acyl-CoA dehydrogenase deficiency (discussed later). The Δ^2 double bond formed by the acyl-CoA dehydrogenase has a trans configuration. The double bonds in naturally occurring fatty acids are generally in the cis configuration. The oxidation of unsaturated cis-fatty acids requires two auxiliary enzymes, enoyl-CoA isomerase and 2,4-dienoyl-CoA reductase.

Acyl-CoA dehydrogenase (especially butyryl-CoA dehydrogenase) is irreversibly inactivated by methylene cyclopropylacetyl-CoA through the formation of covalent adduct with the FAD of the enzyme. The inhibitor is derived by transamination
SECTION 18.1 Oxidation of Fatty Acids

and oxidative decarboxylation of the amino acid hypoglycin (Chapter 15). Ingestion of hypoglycin causes severe hypoglycemia due to the inhibition of β-oxidation and corresponding decrease in ATP synthesis. Gluconeogenesis, which is important in maintaining fasting glucose levels, is dependent on adequate supplies of ATP. The action of hypoglycin thus serves to emphasize the importance of β-oxidation in gluconeogenesis under normal circumstances.

Among the fatty acid oxidation disorders, medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is the most common and its frequency is similar to that of phenylketonuria. The disorder can be identified by mutant alleles and some key abnormal metabolites. An A → G transition mutation occurs at position 985 of MCAD-cDNA in about 90% of cases. This mutation leads to replacement of lysine with glutamate at position 329 (K329E) of the polypeptide.
The MCAD deficiency primarily affects hepatic fatty acid oxidation and the most common clinical presentation is episodic hypoketotic hypoglycemia initiated by fasting. The major metabolic derangement in MCAD is an inadequate supply of acetyl-CoA (Figure 18-4). The deficiency of acetyl-CoA leads to a decreased flux through the tricarboxylic acid (TCA) cycle causing diminished ATP production, decreased ketone body formation (the ketone bodies are metabolites used by the extrahepatic tissues), decreased citrate synthesis, and decreased oxaloacetate synthesis from pyruvate catalyzed by pyruvate carboxylase for which acetyl-CoA is the primary activator. The decreased flux through the TCA cycle during deficiency of acetyl-CoA causes a diminished synthesis of citrate from oxaloacetate and acetyl-CoA, as well as inhibition of α-ketoglutarate dehydrogenase due to an elevated ratio of fatty acyl-CoA to CoA. The formation of oxaloacetate is crucial for gluconeogenesis (Chapter 15). Accumulation of octanoate, which occurs in MCAD, may be responsible for encephalopathy and cerebral edema. In Reye's syndrome, octanoate also is elevated and may be responsible for its phenotypical similarity with MCAD. MCAD is managed with avoidance of fasting, stress, and treatment with intravenous glucose during acute episodes.

2. Enoyl-CoA hydratase catalyses the hydration of Δ² unsaturated acyl-CoA. This enzyme has broad specificity and can act on α-, β- (or Δ²-) unsaturated CoA in trans or cis configuration. The products formed are

\[2-\text{trans-Enoyl-CoA} \rightarrow \text{L}(+)-\beta\text{-hydroxyacyl-CoA} \]
\[\text{or L}(+)-3\text{-hydroxyacyl-CoA}\]

\[2-\text{cis-Enoyl-CoA} \rightarrow \text{D}(-)-\beta\text{-hydroxyacyl-CoA} \]
\[\text{or D}(-)-3\text{-hydroxyacyl-CoA}\]
The latter reaction occurs in the oxidation of natural unsaturated fatty acids, and an epimerase converts the product to the L-isomer, which is the substrate of the next enzyme.

3. \(\beta\)-Hydroxyacyl-CoA dehydrogenase oxidizes \(\beta\)-hydroxyacyl-CoA by an NAD\(^+\)-linked reaction that is absolutely specific for the \(\alpha\)-stereoisomer. The electrons from the NADH generated are passed on to NADH dehydrogenase of the respiratory chain.

4. 3-Ketoacyl-CoA thiolase (\(\beta\)-ketothiolase) catalyzes a thiolytic cleavage, has broad specificity, and yields acetyl-CoA and acyl-CoA shortened by two carbon atoms. The reaction is highly exergonic \((\Delta G^o = -6.7 \text{kcal/mol})\) and favors thiolysis. The enzyme has a reactive \(-\text{SH}\) group on a cysteinyl residue, which participates as follows (E = enzyme):

\[
\begin{align*}
\text{R}-\text{C} & \iff \text{CH}_2 \iff \text{C} 
\iff \text{SCoA} + \text{HS} \iff \text{E} \rightarrow \text{RC} \iff \text{S} \iff \text{E} + \text{CH}_3 \iff \text{C} \iff \text{SCoA} \\
\text{\(\beta\)-Ketoacyl-CoA} & \\
\iff \text{R} & \iff \text{C} \iff \text{S} \iff \text{E} + \text{HS} \iff \text{CoA} \rightarrow \text{R} \iff \text{C} \iff \text{SCoA} + \text{HS} \iff \text{E} \\
\text{Acetyl-CoA} & \\
\text{Acyl-CoA} & \\
\text{(with two} & \iff \text{less carbon} \iff \text{atoms)} & \iff \\
\text{Regenerated} & \\
\text{enzyme) }
\end{align*}
\]

\[
\begin{align*}
\text{R} & \iff \text{C} \iff \text{CH}_2 \iff \text{C} 
\iff \text{SCoA} + \text{HS} \iff \text{E} \\
\text{\(\beta\)-Ketoacyl-CoA} & \\
\iff \text{R} & \iff \text{C} \iff \text{S} \iff \text{E} + \text{HS} \iff \text{CoA} \\
\text{Acetyl-CoA} & \\
\text{(with two} & \iff \text{less carbon} \iff \text{atoms)} & \iff \\
\text{Regenerated} & \\
\text{enzyme) }
\end{align*}
\]

Three enzyme activities—long-chain enoyl-CoA hydratase, \(\beta\)-hydroxyacyl-CoA dehydrogenase, and long-chain \(\beta\)-ketoacyl-CoA thiolase (reactions 2–4, Figure 18-3)—are associated with a trifunctional protein complex consisting of four \(\alpha\)- and four \(\beta\)-subunits bound to inner mitochondrial membrane. Each of the four \(\alpha\)-subunits possesses hydratase and dehydrogenase enzyme activities at the N-terminal and C-terminal domains, respectively. The active site for the thiolase activity resides in the four \(\beta\)-subunits of the protein complex. Deficiencies of the dehydrogenase activity or all of the three enzyme activities for oxidation of long-chain fatty acids have been described. These deficiencies can cause nonketotic hypoglycemia during fasting, hepatic encephalopathy, and cardiac and skeletal myopathy. In some instances, women carrying fetuses with a deficiency of long-chain \(\beta\)-hydroxyacyl-CoA dehydrogenase may themselves develop acute liver disease, hemolysis, and a low platelet count. This clinical disorder is associated with a high risk of maternal and neonatal morbidity and mortality, and is known as HELLP (hemolysis, elevated liver enzyme levels and low platelet count). A change of Glu 474 to Gln (E474Q) in the \(\alpha\)-subunits of the trifunctional protein has been identified in three unrelated children whose mothers had an acute fatty liver episode or HELLP syndrome during pregnancy.

The fetal-maternal interaction that leads to toxic effects in women during pregnancy may be due to transport of long-chain \(\beta\)-hydroxyacyl metabolites produced by the fetus and placenta to the maternal liver.

Other inborn errors of fatty acid oxidation include defects in short-chain \(\beta\)-hydroxy acyl-CoA dehydrogenase and medium-chain \(\beta\)-ketoacyl-CoA thiolase. The spectrum of clinical findings in these and other fatty acid oxidation defects are variable; typical symptoms include fasting intolerance, cardiomyopathy, and sudden death. Children with long-chain fatty acid oxidation disorders are treated with frequent feeding of a low-fat diet consisting of medium-chain triglycerides. This dietary regimen can prevent hypoketotic hypoglycemic liver dysfunction.

**Energetics of \(\beta\)-Oxidation**

Palmitoyl-CoA yields 8 acetyl-CoA molecules and 14 pairs of hydrogen atoms, by seven cycles through the \(\beta\)-oxidation system. Acetyl-CoA can be oxidized in the TCA cycle, used for the synthesis of fatty acid or cholesterol, or used for the formation of ketone bodies in liver. \(\beta\)-Oxidation of an acyl-CoA with an uneven number of carbon atoms also yields a propionyl-CoA during the acetyl-CoA acyltransferase reaction of the last cycle.

Two high-energy bonds are consumed in the activation of a fatty acid molecule. Every mole of fatty acyl-CoA that cycles through reactions 1–4 produces 1 mol of FADH\(_2\), 1 mol of NADH, and 1 mol of acetyl-CoA. On the last pass of an even-chain-length fatty acid, 2 mol of acetyl-CoA are formed; and the final pass of an odd-chain-length molecule releases 1 mol of propionyl-CoA. The amount of ATP formed from complete oxidation of a hexanoic acid is calculated as shown in Table 18-2.

Fatty acid oxidation produces more moles of ATP per mole of CO\(_2\) formed than does carbohydrate oxidation. In this case, oxidation of 1 mol of hexose produces at most (assuming malate shuttle operation exclusively) 38 mol of ATP.

Complete oxidation of one molecule of palmitic acid yields 129 ATP molecules:

\[
\begin{align*}
\text{C}_{15}\text{H}_{31}\text{COOH} + 8\text{CoASH} + \text{ATP} + 7\text{FAD} + \\
7\text{NAD}^+ + 7\text{H}_2\text{O} & \rightarrow 8\text{CH}_3\text{COSCoA} + \text{AMP} + \\
\text{PPi} + 7\text{FADH}_2 + 7\text{NADH} + 7\text{H}^+ \\
\end{align*}
\]

Each molecule of acetyl-CoA yields 12 ATP (12 \times 8 = 96); FADH\(_2\) yields 2 ATP (7 \times 2 = 14); NADH yields 3ATP (7 \times 3 = 21); and two high-energy bonds are consumed (-2; ATP \rightarrow \text{AMP} + \text{PPi}). Thus, net ATP production is 129. The energy yield from total combustion of palmitic acid in a bomb calorimeter (Chapter 5) is
### CHAPTER 18 Lipids I: Fatty Acids and Eicosanoids

#### TABLE 18-2

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Direct Consequences of the Reaction</th>
<th>Moles of ATP Gained or Lost per Mole of Hexanoic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation reaction</td>
<td>Hexanoic acid → Hexanoyl-CoA</td>
<td>−2</td>
</tr>
<tr>
<td>First dehydrogenation</td>
<td>Dehydrogenation of acyl-CoA; 2(FAD → FADH\textsubscript{2})</td>
<td>+4</td>
</tr>
<tr>
<td>Hydration</td>
<td>Hydration of α, β-unsaturated fatty acyl-CoA</td>
<td>0</td>
</tr>
<tr>
<td>Second dehydrogenation</td>
<td>Dehydrogenation of β-hydroxy-acyl-CoA; 2(NAD\textsuperscript{+} → NADH + H\textsuperscript{+})</td>
<td>+6</td>
</tr>
<tr>
<td>Oxidation of acetyl-CoA</td>
<td>Formation of 3 mol of acetyl-CoA, and their oxidation in the TCA cycle and electron transport system</td>
<td>+ (3 × 12) = +36</td>
</tr>
</tbody>
</table>

Total ATP = +44

\[ -2380 \text{ kcal/mol:} \]

\[ \text{C}_{16}\text{H}_{32}\text{O}_2 + 23\text{O}_2 \rightarrow 16\text{CO}_2 + 16\text{H}_2\text{O at } 20^\circ\text{C}, \]

\[ \Delta H^\circ = -2380 \text{ kcal/mol} \]

In biological oxidation, the energy conserved as ATP is about 942 kcal/mol (129 × 7.3). Thus, the percentage of standard free energy of oxidation of palmitic acid conserved as high-energy phosphate is about 40% (942/2380 × 100).

### Regulation of Fatty Acid Oxidation

Regulation of fatty acid oxidation involves diet, cofactors, competing substrates and hormones of fatty acid mobilization. Adipose tissue triacylglycerol lipolysis is one of the major sites of regulation. The other site is CPTI. The latter is inhibited by malonyl-CoA which is involved in fatty acid biosynthesis (discussed later). Thus, fatty acid oxidation and synthesis do not occur simultaneously. Insulin inhibits fatty acid oxidation by blocking lipolysis in adipose tissue, and it stimulates lipogenesis and synthesis of malonyl-CoA. Glucagon stimulates fatty acid oxidation by inhibiting synthesis of acetyl-CoA carboxylase which leads to decreased synthesis of malonyl-CoA. This causes enhanced activity of CPTI, and promotion of fatty acid oxidation. In the fed state, the glucagon/insulin ratio is low, and fatty acid synthesis is promoted in the liver. In the fasting state, the glucagon/insulin ratio is high and mobilization of free fatty acids from adipose tissue and mitochondrial fatty acid oxidation are augmented.

### Peroxisomal Fatty Acid Oxidation

Peroxisomes have a single membrane and contain a fairly homogeneous, moderately electron-dense matrix. They are present in many mammalian cells and are particularly abundant in liver and kidney. A normal hepatocyte contains about a thousand peroxisomes, whose proliferation is inducible by hypolipidemic drugs such as clofibrate (Chapter 20). Peroxisomes contain H\textsubscript{2}O\textsubscript{2}-producing oxidases and also H\textsubscript{2}O\textsubscript{2}-inactivating catalase. Oxidation of very long-chain, saturated, unbranched fatty acids (C\textsubscript{24}–C\textsubscript{26}) appears to take place mainly, if not exclusively, in peroxisomes after the acyl-CoA derivatives are transported across the membrane without involvement of carnitine. Oxidation is mediated by flavoprotein dehydrogenases that yield H\textsubscript{2}O\textsubscript{2} and acetyl-CoA and terminates with octanoyl-CoA. Octanoyl- and acetyl-CoA are transferred to mitochondria for further oxidation. Phytic acid monoxygenase, which initiates the catabolism of phytic acid (a 20-carbon branched chain fatty acid of dietary origin), is probably a peroxisomal enzyme. Peroxisomal oxidation does not yield ATP. All the energy produced appears as heat.

Three genetic disorders (Zellweger's syndrome, neontal adrenoleukodystrophy, and childhood adrenoleukodystrophy) exhibit defective formation of peroxisomes (in Zellweger's syndrome no morphologically detectable peroxisomes are present) or deficiency of one or more constituent enzymes. All three disorders are characterized by a marked accumulation of very long chain, saturated, unbranched fatty acids (tetracosanoic and hexacosanoic acids) in liver and central nervous system tissues, severe neurological symptoms, and early death.

Peroxisomes contain dihydroxyacetone phosphate acyltransferase and alkylidihydroxyacetone phosphate synthase, which are involved in synthesis of the plasmalogens (Chapter 19). Peroxisomes may also participate in the biosynthesis of bile acids. The conversion of trihydroxy-cholestanolic acid to cholic acid (Chapter 19) has been localized to peroxisomes.
SECTION 18.1 Oxidation of Fatty Acids

Other Pathways of Fatty Acid Oxidation

Propionyl-CoA Oxidation

\( \beta \)-Oxidation of fatty acids with an odd number of carbon atoms yields propionyl-CoA. Since the concentration of such fatty acids in the diet is small, little propionyl-CoA is produced. Important sources of propionyl-CoA are the catabolism of isoleucine, valine, methionine, and threonine (Chapter 17). Cholesterol side chain oxidation also yields propionyl-CoA. Thus, propionyl-CoA is derived from the catabolism of lipids and proteins. In ruminants, propionate is largely derived from bacterial fermentation in the rumen.

Propionyl-CoA is converted to succinyl-CoA, which is oxidized or converted to glucose by way of oxaloacetate and pyruvate (gluconeogenesis; Chapter 15). Succinyl-CoA may also form \( \delta \)-aminolevulinate, a precursor of porphyrin biosynthesis (Chapter 29). Formation of succinyl-CoA from propionyl-CoA requires three mitochondrial enzymes and two vitamins (Figure 18-5).

1. Propionyl-CoA carboxylase is a tetramer of nonidentical subunits, \( \alpha \) and \( \beta \). The native enzyme (M.W. \( \sim 540,000 \)) appears to have the structure \((\alpha \beta)_4\). Biotin is bound through an amide linkage to an \( \varepsilon \)-amino group of a lysyl residue in the \( \alpha \)-subunit. Carboxylation is a two-step reaction similar to that of acetyl-CoA carboxylase (see below). The first step requires ATP and \( \text{Mg}^{2+} \) and fixes CO\(_2\) with the formation of an apoenzyme-biotin-CO\(_2\) complex. In the second step, the carboxyl group from the biotinyl complex is transferred to propionyl-CoA to form \( \delta \)-methylmalonyl-CoA.

2. Methylmalonyl-CoA racemase converts \( \delta \)-methylmalonyl-CoA to the L-isomer by labilization of an \( \alpha \)-hydrogen atom, followed by uptake of a proton from the medium.

3. Methylmalonyl-CoA mutase utilizes 5'-deoxyadenosylcobalamin (Chapter 38) to catalyze intramolecular isomerization by the migration of the \(-\text{COSCoA}\) group. The only other cobalamin-dependent reaction in the mammalian system is methylation of homocysteine to methionine (Chapters 17, 27, and 38).

Inborn errors of metabolism may be due to propionyl-CoA carboxylase deficiency, defects in biotin transport or metabolism, methylmalonyl-CoA mutase deficiency, or defects in adenosylcobalamin synthesis. The former two defects result in propionic acidemia, the latter two in methylmalonic acidemia. All cause metabolic acidosis and developmental retardation. Organic acidemias often exhibit hyperammonemia, mimicking ureagenesis disorders, because they inhibit the formation of N-acetylglutamate, an obligatory cofactor for carbamoyl phosphate synthase (Chapter 17). Some of these disorders can be partly corrected by administration of pharmacological doses of the vitamin involved (Chapter 38). Dietary protein restriction is therapeutically useful (since propionate is primarily derived from amino acids). Propionic and methylmalonyl acidemia (and aciduria) results from vitamin B\(_{12}\) deficiency (e.g., pernicious anemia; Chapter 38).

\( \alpha \)-Oxidation

\( \alpha \)-Oxidation is important in the catabolism of branched-chain fatty acids. The general reaction, catalyzed by a monoxygenase, requires \( \text{O}_2\), \( \text{Fe}^{2+}\), and either ascorbate or tetrahydropteridine. It has been demonstrated in plants and in microsomes from brain and other tissues.

\[
R \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH} + \frac{\text{Reduced cofactor} + \text{O}_2}{\text{Monoxygenase}} \rightarrow \text{OH} \]

\[
R \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{COOH} + \frac{\text{O}_{\text{H}_2}}{} \quad \alpha \text{-Hydroxy fatty acid}
\]

This reaction is also a route for the synthesis of hydroxy fatty acids. The \( \alpha \)-hydroxy fatty acid can be further
oxidized and decarboxylated to a fatty acid one carbon shorter than the original. Thus, if an odd-chain-length compound is used initially, an even-chain-length acid is produced that can be further oxidized by \(\beta\)-oxidation.

**\(\omega\)-Oxidation**

\(\omega\)-Oxidation is oxidation of the carbon atom most remote from the carboxyl group in a fatty acid. The basic reaction, catalyzed by a monoxygenase that requires NADPH, \(O_2\), and cytochrome P-450, is shown below. It has been observed in liver microsomes and some bacteria.

\[
\text{H}_3\text{C}-(\text{CH}_2)_n-\text{COOH} + \text{O}_2 + \text{NADPH} + \text{H}^+ \xrightarrow{\omega\text{-oxidation}} \text{HO-CH}_2-(\text{CH}_2)_n-\text{COOH} + \text{NADP}^+ + \text{H}_2\text{O}
\]

Further oxidation of the \(\omega\)-hydroxy acids produces dicarboxylic acids, which can be \(\beta\)-oxidized from either end.

**Oxidation of Mono- and Polyunsaturated Fatty Acids**

Oxidation of unsaturated fatty acids requires \(\Delta^3\)-cis-, \(\Delta^2\)-trans-enoyl-CoA isomerase and NADPH-dependent 2,4-dienoyl-CoA reductase, in addition to the enzymes of \(\beta\)-oxidation. The enoyl-CoA isomerase produces the substrate for the hydration step. The reductase catalyzes the reduction of \(\Delta^2\)-trans-, \(\Delta^4\)-cis-decadienoyl-CoA to \(\Delta^3\)-trans-decenoyl-CoA. The latter is isomerized to \(\Delta^2\)-trans-decenoyl isomerase, which is a normal \(\beta\)-oxidation intermediate. These reactions are illustrated for oxidation of oleic and linoleic acids in Figures 18-7 and 18-8.

**18.2 Metabolism of Ketone Bodies**

Ketone bodies consist of acetoacetate, \(D-\beta\)-hydroxybutyrate (\(D-3\)-hydroxybutyrate), and acetone. They are

---

In Refsum's disease, an autosomal recessive disorder, the defect is probably in the \(\alpha\)-hydroxylation of phytanic acid. Phytanic acid is a 20-carbon, branched-chain fatty acid derived from the plant alcohol phytol, which is present as an ester in chlorophyll. Thus, its origin in the body is from dietary sources. The oxidation of phytanic acid is shown in Figure 18-6. The clinical characteristics of Refsum's disease include peripheral neuropathy and ataxia, retinitis pigmentosa, and abnormalities of skin and bones. Significant improvement has been observed when patients are kept on low-phytanic acid diets for prolonged periods (e.g., diets that exclude dairy and ruminant fat).
synthesized in liver mitochondria. The overall steps involved in the formation of ketone bodies include the mobilization of fatty acids by lipolysis from adipose tissue triacylglycerol by hormone-sensitive triacylglycerol lipase, plasma fatty acid transport, fatty acid activation, fatty acid transport into mitochondria (with acylcarnitine as an intermediate), and β-oxidation. The regulatory reactions are those of lipolysis and of acyl-CoA transport across the mitochondrial membrane (CPTI).

Synthesis of ketone bodies from acetyl-CoA consists of three steps: formation of acetoacetyl-CoA, formation of acetoacetate, and reduction of acetoacetate to α-hydroxybutyrate. Nonenzymatic decarboxylation of acetoacetate yields acetone, which is eliminated via the lungs.

The pathways of formation of ketone bodies are shown in Figure 18-9. The major pathway of production of acetoacetate is from β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). Hydrolysis of acetoacetyl-CoA to acetoacetate by acetoacetyl-CoA hydrolase is of minor importance because the enzyme has a high $K_m$ for acetoacetyl-CoA. HMG-CoA is also produced in the cytosol, where it is essential for the synthesis of several isoprenoid compounds and cholesterol (Chapter 19). The reduction of acetoacetyl-CoA to β-hydroxybutyrate depends on the mitochondrial \([\text{NAD}^+] / [\text{NADH}]\) ratio.

Ketone bodies are oxidized primarily in extrahepatic tissues (e.g., skeletal muscle, heart, kidney, intestines, brain) within mitochondria. β-Hydroxybutyrate is oxidized to acetoacetate by NAD$^+$-dependent β-hydroxybutyrate dehydrogenase by reversal of the reaction that occurred during ketogenesis:

$$\text{CH}_3\text{CH(OH)CH}_2\text{CO}^- + \text{NAD}^+ \rightarrow \text{CH}_3\text{COCH}_2\text{COO}^- + \text{NADH} + \text{H}^+$$

Activation of acetoacetate requires transfer of coenzyme A from succinyl-CoA, derived from the TCA cycle, by succinyl-CoA-acetoacetate-CoA transferase (thiophorase):

$$\text{CH}_3\text{COSCoA + CH}_2\text{COO}^- \rightarrow \text{CH}_3\text{COCH}_3 \text{CoA}$$

The activation occurs at the expense of conversion of succinyl-CoA to succinate in the TCA cycle and formation of GTP (Chapter 13). Acetoacetyl-CoA is cleaved to two molecules of acetyl-CoA by acetyl-CoA acetyltransferase, the same enzyme involved in the synthesis of acetoacetyl-CoA (Figure 18-9). Acetyl-CoA is oxidized in the TCA cycle. Thus, formation of ketone bodies in the liver and their oxidation in extrahepatic tissues are dictated by the ratio \([\text{substrates}] / [\text{products}]\).
Physiological and Pathological Aspects of Metabolism of Ketone Bodies

Acetoacetate and $\beta$-hydroxybutyrate are products of normal metabolism of fatty acid oxidation and serve as metabolic fuels in extrahepatic tissues. Their level in blood depends on the rates of production and utilization. Oxidation increases as their plasma level increases. Some extrahepatic tissues (e.g., muscle) oxidize them in preference to glucose and fatty acid. Normally, the serum concentration of ketone bodies is less than 0.3 mM/L.

The rate of formation of ketone bodies depends on the concentration of fatty acids derived from hydrolysis of adipose tissue triacylglycerol by hormone-sensitive lipase. Insulin depresses lipolysis and promotes triacylglycerol synthesis and storage, while glucagon has the opposite effects. Thus, insulin is antiketogenic and glucagon is ketogenic (Chapter 22). Uncontrolled insulin-dependent diabetes may result in fatal ketoacidosis (Chapter 39). Although ketonemia and ketonuria are generally assumed to be due to increased production of ketone bodies in the liver, studies with depancreatized rats have shown that ketosis may also arise from their diminished oxidation.

Ketosis can occur in starvation, in ethanol abuse, and following exercise, the last because of a switch in blood
FIGURE 18-9
Ketogenesis in the liver. All reactions occur in mitochondria; the rate-controlling reactions (not shown) are release of fatty acids from adipose tissue and uptake of acyl-CoA into mitochondria, in particular, the CPTI reaction (see Figure 18-1). Acetoacetyl-CoA may regulate ketogenesis by inhibiting the transferase and the synthase.
*This enzyme is similar to citrate synthase (Chapter 13) which catalyzes an analogous reaction.

flow. During sustained exercise, the blood flow to the liver, intestines, and kidneys is substantially decreased, with a corresponding increase in blood flow to working muscles, so that more fatty acids mobilized from adipose tissue are delivered to the muscle. Thus, the formation of ketone bodies is severely curtailed. But during the postexercise period, with the resumption of normal blood flow to liver, ketone bodies are generated as a result of increased mobilization of fatty acids. Reduced ketone body utilization in the extrahepatic tissues can occur due to deficiency of either succinyl-CoA-acetoacetate-CoA transferase or acetyl-CoA acetyltransferase. These patients are susceptible to attacks of ketoacidosis and the presence of persistent ketone bodies in the urine.

18.3 Metabolism of Ethanol

Ethanol is consumed widely. Microbial fermentation in the large intestine of humans can produce about 3 g of ethanol per day. Ethanol is rapidly absorbed throughout the gastrointestinal tract or, when inhaled, through the lungs. It is metabolized in the liver by a process having zero-order kinetics; i.e., the rate of oxidation is constant with time. The amount metabolized per unit time depends on liver size (or body weight); the average rate in an adult is about 30 mL in 3 hours. The energy content of alcohol is about 7 kcal/g.

Ethanol oxidation begins with conversion to acetaldehyde by alcohol dehydrogenase (M.W. ~85,000), a zinc-containing, NAD+-dependent enzyme that is a relatively nonspecific cytoplasmic enzyme with a $K_m$ of about 1 mM/L:

$$\text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ \rightarrow \text{CH}_3\text{CHO} + \text{NADH} + \text{H}^+$$

Acetaldehyde is rapidly converted to acetate by NAD+-dependent aldehyde dehydrogenase:

$$\text{CH}_3\text{CHO} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{NADH} + \text{H}^+$$

Ethanol is also oxidized by the mixed-function oxidase of smooth endoplasmic reticulum, which requires NADPH, oxygen, and a cytochrome P-450 electron transport system (Chapter 14):

$$\text{CH}_3\text{CH}_2\text{OH} + \text{NADPH} + \text{H}^+ + 2\text{O}_2 \rightarrow \text{CH}_3\text{CHO} + 2\text{H}_2\text{O}_2 + \text{NADP}^+$$

Many drugs are metabolized by this enzyme, hence the competition between ethanol and other drugs (e.g.,
barbiturates). Peroxisomal catalase catalyzes the reaction:

\[ \text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{O}_2 \rightarrow \text{CH}_3\text{CHO} + 2\text{H}_2\text{O} \]

The \( K_m \) for this catalase and for the mixed-function oxidase is about 10 mM/L. The extent to which these two enzymes metabolize ethanol is not known.

Acetaldehyde is converted to acetate in the liver by NAD\(^+\)-linked aldehyde dehydrogenases, one in the cytosol (\( K_m = 1 \) mM/L) and another in mitochondria (\( K_m = 0.01 \) mM/L):

\[ \text{CH}_3\text{CHO} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COO}^- + \text{NADH} + 2\text{H}^+ \]

Disulfiram (tetraethylthiuram disulfide)

\[
\begin{array}{c}
\text{H}_5\text{C}_2 \\
\text{N} \\
\text{C} \\
\text{S} \\
\text{S} \quad \\
\text{S} \\
\text{C}_2\text{H}_5 \\
\end{array}
\]

causes irreversible inactivation of these aldehyde dehydrogenases by reacting with sulfhydryl groups, with a buildup of acetaldehyde that produces the acetaldehyde syndrome (vasodilation, intense throbbing, pulsating headache, respiratory difficulties, copious vomiting, sweating, thirst, hypotension, vertigo, blurred vision, and confusion). Disulfiram by itself is relatively nontoxic. It is used in the treatment of chronic alcoholism but does not cure it. Disulfiram provides a willing patient with a deterrent to consumption of alcohol. A shorter acting reversible inhibitor of aldehyde dehydrogenase is calcium carbimide, which causes accumulation of acetaldehyde and unpleasant symptoms. Thus, calcium carbimide can also be used as a deterrent to alcohol consumption.

Symptoms similar to the disulfiram-ethanol reaction occur in high proportion in certain ethnic groups (e.g., Asians and Native Americans) who are extremely sensitive to ethanol consumption. The ethanol sensitivity in these populations is accompanied by a higher acetaldehyde steady-state concentration in the blood, which may be due to a rapid rate of formation of acetaldehyde by alcohol dehydrogenase or to a decreased rate of its removal by aldehyde dehydrogenase. Both of these dehydrogenases are present in several isozyme forms and exhibit extensive polymorphism among racial groups. An alcohol dehydrogenase variant found in the ethanol-sensitive populations has a relatively higher rate of activity at physiological pH and may account for more rapid oxidation of ethanol to acetaldehyde. However, a more important cause of acetaldehyde accumulation appears to be deficiency of an isozyme of aldehyde dehydrogenase, which has a low \( K_m \) for acetaldehyde. Thus, the cause of ethanol sensitivity may be impaired rate of removal of acetaldehyde rather than its excessive formation. Individuals who are predisposed to ethanol sensitivity should avoid ethanol intake in any form.

Acetate produced from ethanol is converted to acetyl-CoA by acetyl-CoA synthase in hepatic and extrahepatic tissues.

\[ \text{CH}_3\text{COO}^- + \text{ATP}^4^- + \text{CoASH} \rightarrow \]

\[ \text{CH}_3\text{COSCoA} + \text{AMP}^2^- + \text{PP}_i^3^- \]

Acetyl-CoA is oxidized in the TCA cycle and is used in liver and adipose tissue for biosynthesis of fatty acids and triacylglycerol.

Alcoholism affects about 10% of the drinking population and alcohol (ethanol) abuse has been implicated in at least 20% of admissions to general hospitals. This chronic disease exhibits high mortality due to a wide variety of factors. Ethanol produces effects in virtually every organ system. The biochemical effects of ethanol are due to increased production of NADH that decreases the [NAD\(^+\)]/[NADH] ratio in the cytoplasm of liver cells at least tenfold from the normal value of about 1000. Increased production of lactate and inhibition of gluconeogenesis (Chapter 15) result. The hyperuricemia associated with ethanol consumption has been attributed to accelerated turnover of adenine nucleotides and their catabolism to uric acid (Chapter 27). Alcohol increases hepatic fatty acid and triacylglycerol synthesis and mobilization of fat from adipose tissue, which can lead to fatty liver, hepatitis, and cirrhosis. These effects are complicated by a deficiency of B vitamins and protein.

Alcohol increases the plasma level of VLDL and of HDL cholesterol (Chapter 20). Many actions of ethanol may be attributed to a membrane-disordering effect. Changes in membrane fluidity can affect membrane-bound enzymes (e.g., Na\(^+\), K\(^+\)-ATPase, adenylate cyclase) and phospholipid architecture. Alcohol also affects several neurotransmitter systems in the brain. These include dopamine (mediates pleasurable effects), \( \gamma \)-aminobutyric acid (GABA), glutamate, serotonin, adenosine, norepinephrine, and opioid peptides. Potential drug therapy for alcohol dependence consists of the use of antagonists and agonists of alcohol affected neurotransmitter systems. For example, naltrexone, a \( \mu \)-opioid antagonist, inhibits alcohol-induced dopamine release, thus minimizing the pleasurable effect of alcohol and reducing the desire to consume alcohol. Another drug, acamprosate, reduces the craving for alcohol presumably by an agonist activity at GABA receptors.
and an inhibitory activity at N-methyl-D-aspartate receptors. A selective antagonist of serotonin receptor 5-HT₃, ondansetron, reduces alcohol consumption in patients with early onset alcoholism. The 5-HT₃ receptors are densely distributed in mesocorticolimbic neuronal terminals and regulate dopamine release. Attenuation of dopamine release reduces alcohol consumption.

In chronic alcoholics, heavy drinking and decreased food intake lead to ketoacidosis. Accelerated lipolysis arising from reduced insulin and increased glucagon secretion caused by hypoglycemia leads to ketosis with a high [β-hydroxybutyrate]/[acetoacetate] ratio. Treatment requires normalization of fluid and electrolyte balance (Chapter 39) and of glucose level. Administration of glucose provokes insulin release and depresses glucagon release, thus suppressing the stimuli for ketogenesis. The distinction between diabetic ketoacidosis and alcoholic ketoacidosis may be difficult to determine, and in some patients plasma glucose levels may not discriminate between the two entities (although in diabetic ketoacidosis plasma glucose levels are usually high, whereas in alcoholic ketoacidosis these levels may be low, normal, or marginally elevated). Fluid and electrolyte replacement and glucose administration in ketoacidosis are essential regardless of etiology.

Ethanol is a teratogen partly because it inhibits embryonic cellular proliferation. Maternal alcoholism causes fetal alcohol syndrome, which is characterized by abnormal function of the central nervous system, microcephaly, cleft palate, and micrognathia.

18.4 Synthesis of Long-Chain Saturated Fatty Acids

The reactions of de novo fatty acid biosynthesis are shown in Figure 18-10. They are carried out by two multienzyme systems functioning in sequence. The first is acetyl-CoA carboxylase, which converts acetyl-CoA to malonyl-CoA. The second is fatty acid synthase, which sequentially joins two-carbon units of malonyl-CoA, eventually producing palmitic acid. Both complexes consist of multifunctional subunits. The various catalytic functions can be readily separated in plant cells and prokaryotes, but in yeasts, birds, and mammals, attempts to subdivide catalytic functions lead to loss of activity. Important features of this system are as follows:

1. De novo synthesis takes place in the cytosol (whereas fatty acid oxidation occurs in mitochondria).
2. All carbon atoms are derived from acetyl-CoA (obtained from carbohydrates or amino acids), and palmitate (C₁₆) is the predominant fatty acid produced. Fatty acids longer than 16 carbons, those that are unsaturated, and hydroxy fatty acids are obtained by separate processes of chain elongation, desaturation, or α-hydroxylation, respectively.
3. The committed (rate-controlling) step is the biotin-dependent carboxylation of acetyl-CoA by acetyl-CoA carboxylase. Important allosteric effectors are citrate (positive) and long-chain acyl-CoA derivatives (negative).
4. Although the initial step requires CO₂ fixation, CO₂ is not incorporated into fatty acids. The labeled carbon in ¹⁴CO₂ (as H¹⁴CO₃⁻) is not incorporated into the carbons of fatty acids synthesized.
5. Synthesis is initiated by a molecule of acetyl-CoA that functions as a primer. Its two carbons become C₁₅ and C₁₆ of palmitate. The acetyl group is extended by successive addition of the two carbons of malonate originally derived from acetyl-CoA, the unesterified carboxylic acid group being removed as CO₂. In mammalian liver and mammary gland, butyryl-CoA is a more active primer than acetyl-CoA.
6. Release of the finished fatty acid occurs when the chain length reaches C₁₆ by action of thioester hydrolase, which is specific for long-chain acyl-CoA derivatives. A thioester hydrolase of mammary gland is specific for acyl residues of C₈, C₁₀, or C₁₂.

The overall reaction for palmitate synthesis from acetyl-CoA is

\[8\text{Acetyl-CoA} + 14\text{NADPH} + 14\text{H}^+ + 7\text{ATP} + H_2O \rightarrow \text{palmitate} + 8\text{CoASH} + 14\text{NADP}^+ + 7\text{ADP} + 7\text{Pi}\]

The reducing equivalents of NADPH are derived largely from the pentose phosphate pathway.

Acetyl-CoA carboxylase is a biotin-dependent enzyme. It has been purified from microorganisms, yeasts, plants, and animals. In animal cells, it exists as an inactive protomer (M.W. ~400,000) and as an active polymer (M.W. 4–8 million). The protomer contains the activity of biotin carboxylase, biotin carboxyl carrier protein (BCCP), transcarboxylase, and a regulatory allosteric site. Each protomer contains a biotinyl group bound in amide linkage to the ε-amino group of a lysyl residue.

Citrate shifts the equilibrium from inactive protomer to active polymer. The polymeric form appears as long filaments in electron micrographs.
CHAPTER 18 Lipids I: Fatty Acids and Eicosanoids

[Diagram of fatty acid synthesis]

FIGURE 18-10 Synthesis of fatty acid. ACP = Functional unit of acyl-carrier-protein segment of fatty acid synthase. The cysteinyI-SH group of β-ketoacyl synthase accepts the acetyl group or the acyl group, and its catalytic site, which is adjacent to the –SH group, catalyzes the condensation reaction.
The mechanism of the carboxylation reaction consists of two half-reactions:

\[ \text{ATP} + \text{HCO}_3^- + \text{BCCP} \xrightarrow{\text{biotin carboxylase}} \text{ADP} + \text{P}_i + \text{BCCP-COO}^- \]

and

\[ \text{BCCP-COO}^- + \text{acetyl-CoA} \rightleftharpoons \text{BCCP} + \text{malonyl-CoA} \]

The overall reaction is

\[ \text{ATP} + \text{HCO}_3^- + \text{acetyl-CoA} \rightleftharpoons \text{malonyl-CoA} + \text{ADP} + \text{P}_i \]

The presumed reaction mechanisms are shown in Figure 18-11.

Other biotin-dependent enzymes include propionyl-CoA carboxylase and pyruvate carboxylase (Chapter 15). The latter, like acetyl-CoA carboxylase, is subject to allosteric regulation. Pyruvate carboxylase, a mitochondrial enzyme, is activated by acetyl-CoA and converts pyruvate to oxaloacetate which, in turn, is converted to glucose via the gluconeogenic pathway or combines with acetyl-CoA to form citrate. Some of the citrate is transported to the cytosol, where it activates the first step of fatty acid synthesis and provides acetyl-CoA as substrate (see below). Other carboxylation reactions use bicarbonate but are dependent on vitamin K, the acceptor being glutamyl residues of glycoprotein clotting factors II, VI, IX, and X and anticlotting factors Protein C and Protein S (Chapter 36).

Acetyl-CoA carboxylase is under short- and long-term control. Allosteric modulation functions as a short-term regulator. Positive modulators are citrate and isocitrate; negative modulators are long-chain acyl-CoA derivatives. The binding of citrate increases the activity by polymerization of the protomers, whereas negative modulators favor dissociation of active polymers into inactive monomers. Acetyl-CoA carboxylase is also regulated by covalent modification by phosphorylation, which inhibits activity, and by dephosphorylation, which restores activity. Phosphorylation can occur by action of cAMP-dependent protein kinase through β-adrenergic agonists and glucagon or by action of calcium-dependent protein kinase through α-adrenergic agonists. It is not known whether the
kinases act at different sites. Insulin suppresses cAMP levels and promotes activity of acetyl-CoA carboxylase. Insulin may also increase the activity of acetyl-CoA carboxylase phosphatase, which is complexed with the carboxylase. This phosphatase also dephosphorylates glycogen synthase, phosphorylase a, and HMG-CoA reductase. Thus, common mediators (e.g., insulin, glucagon, and catecholamines) regulate fatty acid synthesis and carbohydrate metabolism.

Long-term regulation of acetyl-CoA carboxylase involves nutritional, hormonal (e.g., insulin, thyroxine), and other factors. In animals on high-carbohydrate diets, fat-free diets, choline deprivation, or vitamin B₁₂ deprivation, the activity is enhanced. However, fasting, high intake of fat or polyunsaturated fatty acids, and prolonged biotin deficiency leads to decreased activity. In diabetes, the enzyme activity is low, but insulin administration raises it to normal levels.

Fatty acid synthesis is also carried out by a multienzyme complex and leads from acetyl-CoA, malonyl-CoA, and NADPH to palmitic acid. The overall process is as follows:

\[
\begin{align*}
\text{Acetyl-CoA} & \quad + \quad 7\text{HOOC--CH}_2\text{C}--\text{SCoA} + 14\text{NADPH} + 14\text{H}^+ \\
\end{align*}
\]

The condensation occurs with release of CO₂:

\[
\begin{align*}
\text{Acetyl-CoA} & \quad + \quad \text{Malonyl-CoA} \\
\end{align*}
\]

β-Ketoacyl-ACP reductase catalyzes the first reduction reaction:

\[
\begin{align*}
\text{CH}_3\text{CHC}_2\text{C}--\text{ACP} + \text{NADPH} + \text{H}^+ \\
\end{align*}
\]

It is stereospecific, and the product formed is D(--)-β-hydroxybutyryl-ACP (or D(--)-β-hydroxyacyl-ACP, in subsequent reactions).

β-Hydroxyacyl-ACP dehydratase catalyzes the reaction:

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{C}--\text{ACP} + \text{NADP}^+ + \text{H}^+ \\
\end{align*}
\]

In this stereospecific reaction, the D(--)-isomer is converted to a trans-α,β-unsaturated acyl-ACP derivative.

Enoyl-ACP reductase catalyzes the second reduction with NADPH.

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{C}--\text{ACP} + \text{NADPH} + \text{H}^+ \\
\end{align*}
\]

The product formed is a saturated acyl-thioester of ACP.
FIGURE 18-12
Diagram of a fatty acid synthase dimer with its head-to-tail association of the two multifunctional polypeptides.


Thioester hydrolase catalyzes the removal of palmitate from the 4'-phosphopantetheine arm of the acyl carrier site.

\[
\begin{align*}
\text{CH}_3\text{(CH}_2\text{)}_{14}\text{C} & \quad \text{ACP} + \text{H}_2\text{O} \\
\text{CH}_3\text{(CH}_2\text{)}_{14}\text{COOH} + \text{ACP} & \quad \text{ACP} - \text{SH}
\end{align*}
\]

The enzyme has an active serine residue and is specific for long-chain acyl derivatives.

Functional Organization of Fatty Acid Synthase

In animal cells, fatty acid synthase (FAS) consists of two subunits, each having a molecular weight of 250,000. Evidence from negative-stain electron microscopy indicates that FAS is a linear polypeptide with a series of globular domains representing areas of catalytic activity. Fatty acid synthase mRNA is large enough to code for the ~2300 amino acids required. Animal FAS is the largest known multifunctional protein. Although each subunit contains all of the catalytic activities required to synthesize palmitate, the monomer lacks β-ketoacyl synthase activity. The two subunits must be juxtaposed head to tail to bring the cysteine-SH of the β-ketoacyl synthase of one close to the 4'-phosphopantetheine-SH of the acyl carrier site of the other to obtain a fully functional dimer.

Figure 18-12 presents schematically the active FAS homodimer complex. Synthesis may proceed from either end of the active complex.

The assembly of rat liver FAS involves three stages: synthesis of the multifunctional polypeptide chains, formation of the dimer, and attachment of a 4'-phosphopantetheine group by an enzyme-catalyzed reaction. This assembly process is influenced by changes in developmental, hormonal, and nutritional states. The FAS complex provides considerable catalytic efficiency, since free intermediates do not accumulate and the individual activities are present in equal amounts.

The central role of the acyl carrier domain is to carry acyl groups from one catalytic site to the next. The
4'-phosphopantetheine (20 nm long) derived from coenzyme A is bound as a phosphodiester through the hydroxyl group of a specific seryl residue. The acyl intermediates are in thioester linkage with the -SH of the prosthetic group, which serves as a swinging arm to carry acyl groups from one catalytic site to the next.

The structure of 4'-phosphopantetheine attached to the serine residue of ACP is

![Diagram](https://example.com/structure.png)

Sources of NADPH for Fatty Acid Synthesis

The reducing agent for fatty acid synthesis is NADPH. It is mostly supplied by the pentose phosphate pathway (Chapter 15) in the reactions

\[
\text{Glucose 6-phosphate} \quad \text{Glucose-6-phosphate dehydrogenase} \quad \text{NADP}^+ \quad \text{NADPH} + H^+
\]

and

\[
\text{6-Phosphogluconate} \quad \text{6-Phosphogluconate dehydrogenase} \quad \text{NADP}^+ \quad \text{CO}_2 \quad \text{NADPH} + H^+
\]

Oxidation of malate also provides NADPH:

\[
\text{Malate} \quad \text{Malic enzyme} \quad \text{Pyruvate} \quad \text{NADP}^+ \quad \text{NADPH} + H^+
\]

These three enzymes, like the fatty acid synthase complex, are located in the cytosol. Active lipogenesis occurs in liver, adipose tissue, and lactating mammary glands, which contain a correspondingly high activity of the pentose phosphate pathway. Thus, lipogenesis is closely linked to carbohydrate oxidation. The rate of lipogenesis is high in humans on carbohydrate-rich diets. Restricted energy intake, a high-fat diet, and insulin deficiency decrease fatty acid synthesis.

Source and Transport of Acetyl-CoA

Acetyl-CoA is synthesized in mitochondria by a number of reactions: oxidative decarboxylation of pyruvate, catabolism of some amino acids (e.g., phenylalanine, tyrosine, leucine, lysine, and tryptophan; see Chapter 17), and β-oxidation of fatty acids (see above). Since acetyl-CoA cannot be transported directly across the inner mitochondrial membrane to the cytosol, its carbon atoms are transferred by two transport mechanisms.

1. Transport dependent upon carnitine: Carnitine participates in the transport of long-chain acyl-CoA into the mitochondria and plays a similar role in the transport of acetyl-CoA out of mitochondria. However, carnitine acetyl transferases have a minor role in acetyl-CoA transport.

2. Cytosolic generation of acetyl-CoA (“citrate shuttle”): This pathway is shown in Figure 18-13. Citrate synthesized from oxaloacetate and acetyl-CoA is transported to the cytosol via the tricarboxylate anion carrier system and cleaved to yield acetyl-CoA and oxaloacetate.

\[
\text{Citrate}^{3-} + \text{ATP}^{4-} + \text{CoA} \quad \text{ATP citrate-lyase} \quad \text{ADP}^{3-} + \text{P}^{2-}
\]

Thus, citrate not only modulates the rate of fatty acid synthesis but also provides carbon atoms for the synthesis. The oxaloacetate formed from pyruvate may eventually be converted (via malate) to glucose by the gluconeogenic pathway. The glucose oxidized via the pentose phosphate pathway augments fatty acid synthesis by providing NADPH. Pyruvate generated from oxaloacetate can enter mitochondria and be converted to oxaloacetate, which is required for the formation of citrate.

Regulation of Fatty Acid Synthase

Like acetyl-CoA carboxylase, FAS is under short- and long-term control. The former is due to negative or positive allosteric modulation or to changes in the concentrations of substrate, cofactor, and product. The latter usually consists of changes in enzyme content as a result of protein synthesis or decreased protein degradation. Variation in levels of hormones (e.g., insulin, glucagon, epinephrine, thyroid hormone, and prolactin) and in the nutritional state affect fatty acid synthesis through short- and long-term mechanisms. In the diabetic state, hepatic fatty acid synthesis is severely impaired but is corrected by administration of insulin. The impairment may be due to defects in glucose metabolism that lead to a reduced level of an inducer or increased level of a repressor of transcription of the FAS gene, or both. Glucagon and epinephrine raise intracellular levels of cAMP, and their inhibitory effect on fatty acid synthesis may be due to phosphorylation or dephosphorylation of acetyl-CoA carboxylase. They also stimulate the action of hormone-sensitive triacylglycerol lipase and raise intracellular levels of long-chain acyl-CoA.
As a result, acetyl-CoA carboxylase and citrate synthase are inhibited. The stimulatory effect of prolactin is confined to the mammary gland and may involve synthesis of the enzyme.

**Fatty Acid Elongation**

Cytoplasmic fatty acid synthase yields palmitate. Human triacylglycerol contains fatty acids with 18, 20, 22, and 24 carbon atoms, which are synthesized by elongation of palmitate in endoplasmic reticulum or mitochondria. Elongation in the endoplasmic reticulum occurs mainly in liver and involves C_{10-16}-saturated and C_{18}-unsaturated fatty acids by successive addition of two-carbon groups derived from malonyl-CoA (Figures 18-14 and 18-15). The reductant is NADPH. The intermediates, however, are CoA thioesters.

Mitochondrial fatty acid elongation occurs primarily when the [NADH]/[NAD^+] ratio is high (e.g., anaerobiosis, excessive ethanol oxidation).

**FIGURE 18-13**


**FIGURE 18-14**

Synthesis of arachidonic acid from linoleic acid. The desaturation and chain elongation occur in microsomes.
\[ \alpha\text{-Linolenic acid, C18:3(9,12,15) (from the diet)} \]

- Activation
  - \(\alpha\text{-Linolenoyl-CoA, C18:3(9,12,15)}\)
- Desaturation
  - Octadecatetraenoyl-CoA, C18:4(6,9,12,15)
    - Chain-elongation system
  - Eicosatetraenoyl-CoA, C20:4(8,11,14,17)
    - Desaturation
  - Eicosapentaenoyl-CoA, C20:5(5,8,11,14,17)
    - Chain-elongation system
  - Docosapentaenoyl-CoA, C22:5(7,10,13,16,19)
    - Desaturation
  - Docosahexaenoyl-CoA, C22:6(4,7,10,13,16,19)

**FIGURE 18-15**
Synthesis of docosahexaenoic acid from \(\alpha\text{-linolenic acid}\. Desaturation and chain elongation are similar to the use described in Figure 18-13.

### 18.5 Metabolism of Unsaturated Fatty Acids

**Structure and Nomenclature of Unsaturated Fatty Acids**

Unsaturated fatty acids contain one or more double bonds. A common method for designating fatty acids gives the carbon chain length, number of double bonds, and double-bond positions (in parentheses). Thus, palmitoleic acid is designated C16:1(9) and linoleic acid is C18:2(9,12). The location of the double bond is sometimes indicated by \(\Delta\); for example, \(\Delta^\gamma\) signifies that the double bond is between carbon 9 and carbon 10. In both methods, the carboxyl carbon is carbon 1. The double-bond position can also be related to the \(\omega\)-end of the fatty acid molecule (i.e., the methyl carbon farthest from the carboxyl end); oleic acid is an \(\omega\)-9 acid; linoleic acid has double bonds at \(\omega\)-6 and \(\omega\)-9 carbons. The structures and names of some naturally occurring unsaturated fatty acids are given in Table 18-3.

The presence of a double bond in the hydrocarbon chain gives rise to geometrical isomerism, which is due to restricted rotation around carbon–carbon double bonds and is exemplified by fumaric and maleic acids.

**FIGURE 18-16**
Geometry of saturated, trans monounsaturated, and cis monounsaturated chains.

Almost all naturally occurring, unsaturated, long-chain fatty acids exist as the cis isomers, which are less stable than the trans isomers. The cis configuration introduces a bend (of about 30°) in the molecule, whereas the trans isomer resembles the extended form of the saturated chain (Figure 18-16). Arachidonic acid with four cis double bonds is a U-shaped molecule. Some cis isomers are biologically active as essential fatty acids. The trans isomers cannot substitute for them but are metabolized like the saturated fatty acids.

**Functions of Unsaturated Fatty Acids**

The cis unsaturated fatty acids provide fluidity of triacylglycerol reserves and phospholipid membranes and many serve as precursors of eicosanoids (prostaglandins, prosta-cyclins, thromboxanes, and leukotrienes). The importance of membrane fluidity and its relationship to the membrane constituent phospholipids are discussed in Chapter 10. Eicosanoids have numerous functions (see below).

### 18.6 Nonessential Fatty Acids

Palmitoleic and oleic acids, the two most abundant monounsaturated fatty acids of animal lipids, can be
<table>
<thead>
<tr>
<th>Common Name</th>
<th>Systematic Name*</th>
<th>Molecular Formula</th>
<th>Structural Formula</th>
<th>$\omega$-Series$^+$</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitoleic$^\dagger$</td>
<td>9-Hexadecenoic</td>
<td>$\text{C}<em>{16}\text{H}</em>{30}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_5\text{CH}==\text{CH}(\text{CH}_2)_7\text{COOH}$</td>
<td>$\omega-7$</td>
<td>0.5</td>
</tr>
<tr>
<td>Oleic$^\dagger$</td>
<td>9-Octadecenoic</td>
<td>$\text{C}<em>{18}\text{H}</em>{34}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_7\text{CH}==\text{CH}(\text{CH}_2)_7\text{COOH}$</td>
<td>$\omega-9$</td>
<td>13</td>
</tr>
<tr>
<td>Vaccenic</td>
<td>trans-11-Octadecenoic</td>
<td>$\text{C}<em>{18}\text{H}</em>{34}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_5\text{CH}==\text{CH}(\text{CH}_2)_9\text{COOH}$</td>
<td>$\omega-7$</td>
<td>43</td>
</tr>
<tr>
<td>Linoleic$^\ddagger$</td>
<td>9,12-Octadecadienoic</td>
<td>$\text{C}<em>{18}\text{H}</em>{32}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_4\text{CH}==\text{CHCH}_2\text{CH}==\text{CH}(\text{CH}_2)_7\text{COOH}$</td>
<td>$\omega-6$</td>
<td>-5</td>
</tr>
<tr>
<td>$\omega$-Linolenic</td>
<td>9,12,15-Octadecatrienoic</td>
<td>$\text{C}<em>{18}\text{H}</em>{30}\text{O}_2$</td>
<td>$\text{CH}_3\text{CH}_2\text{CH}==\text{CHCH}_2\text{CH}==\text{CHCH}_2\text{CH}==\text{CH}(\text{CH}_2)_7\text{COOH}$</td>
<td>$\omega-3$</td>
<td>-11</td>
</tr>
<tr>
<td>$\gamma$-Linolenic</td>
<td>6,9,12-Octadecatrienoic</td>
<td>$\text{C}<em>{18}\text{H}</em>{30}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_4\text{CH}==\text{CHCH}_2\text{CH}==\text{CHCH}_2\text{CH}==\text{CH}(\text{CH}_2)_4\text{COOH}$</td>
<td>$\omega-6$</td>
<td>-11</td>
</tr>
<tr>
<td>Arachidonic$^\ddagger$</td>
<td>5,8,11,14-Eicosatetraenoic</td>
<td>$\text{C}<em>{20}\text{H}</em>{32}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_4(\text{CH}==\text{CH}==\text{CH}_2)_4(\text{CH}_2)_2\text{COOH}$</td>
<td>$\omega-6$</td>
<td>-50</td>
</tr>
<tr>
<td>Nervonic</td>
<td>15-Tetracosenoic</td>
<td>$\text{C}<em>{24}\text{H}</em>{46}\text{O}_2$</td>
<td>$\text{CH}_3(\text{CH}_2)_7\text{CH}==\text{CH}(\text{CH}<em>2)</em>{13}\text{COOH}$</td>
<td>$\omega-9$</td>
<td>39</td>
</tr>
</tbody>
</table>

*All double bonds are in the cis geometric configuration, except where indicated.

$^\dagger$This series is based on the number of carbon atoms present between the terminal methyl group and the nearest double bond; $\omega-3$ and $\omega-6$ are essential fatty acids.

$^\ddagger$Most abundant unsaturated fatty acids in animal lipids.
synthesized from the respective saturated fatty acid coenzyme-A esters. Desaturase is a monooxygenase system present in endoplasmic reticulum of liver and adipose tissue. The overall reaction for palmitoleic acid synthesis is

\[
\text{Palmitoyl-CoA + NAD(P)H + H^+ + O}_2 \rightarrow \text{palmitoleyl-CoA + NAD(P)^+ + 2H}_2\text{O}
\]

One molecule of oxygen accepts two pairs of electrons, one from palmitoyl-CoA and the other from NADPH or NADH. The electrons NAD(P)H are transported via cytochrome-b\(_5\) reductase to cytochrome b\(_5\) (microsomal electron transport; Chapter 14). An enzyme-bound superoxide radical is responsible for the oxidation of acyl-CoA. Four desaturases specific for introducing cis double bonds at C\(_9\), C\(_6\), C\(_5\), and C\(_4\), respectively, are known. If the substrate is saturated, the first double bond introduced is C\(_9\). With an unsaturated substrate, other double bonds are introduced between the carboxyl group and the double bond nearest the carboxyl group. Desaturation yields a divinylmethane arrangement of double bonds (\(-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-\)). Usually desaturation alternates with chain elongation. Desaturation is inhibited by fasting and diabetes. The oxidation of unsaturated fatty acids occurs in mitochondria.

### 18.7 trans-Fatty Acids

Trans-Fatty acid metabolism is similar to that of saturated fatty acids. During the partial dehydrogenation of vegetable oils (e.g., in the manufacture of margarine), the cis fatty acids are isomerized to trans-fatty acid forms. The “hydrogenated” margarines contain 15–40% of trans-fatty acids.

The hypercholesterolemic effect of trans-fatty acids may be due to impairment of the first step in the formation of bile acids from cholesterol. Since the steady-state level of cholesterol depends on its conversion to bile acid (Chapter 19), any perturbation in this process affects cholesterol levels. Both metabolic and epidemiological studies have shown that the consumption of trans-fatty acids increases the risk of coronary heart disease. This risk appears to be even higher when compared on a per-gram basis with saturated fatty acids. The adverse effects of trans-fatty acids are attributed to the elevation of atherogenic low-density lipoprotein (LDL) cholesterol and a decrease in the antiatherogenic (or cardioprotective) high-density lipoprotein (HDL) cholesterol level. Thus, the ratio of LDL cholesterol to HDL cholesterol is significantly higher with the trans-fatty acid diet compared to a saturated-fat diet. A diet rich in oleic acid has a lower ratio of LDL cholesterol to HDL cholesterol compared to either of the other diets. The metabolism of lipoproteins and their role in atherosclerosis are discussed in Chapter 20.

### 18.8 Essential Fatty Acids

Polyunsaturated fatty acids not synthesized in the body but required for normal metabolism are essential fatty acids (EFAs). EFAs are linoleic acid, linolenic acids (\(\omega-6\) and \(\omega-3\)), and arachidonic acid. All contain at least one double bond located beyond C-9 or within the terminal seven carbon atoms (Table 18-3).

A double bond within the terminal seven carbon atoms can be present at \(\omega-3\) or \(\omega-6\). \(\gamma\)-Linolenic acid is an \(\omega-6\) EFA and \(\alpha\)-linolenic acid an \(\omega-3\) EFA. Other \(\omega-3\) EFA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DCHA), both abundant in edible fish tissues. Vegetable oils are rich in \(\omega-6\) EFA (Table 18-4). Plants contain \(\alpha\)-linolenic acid, which can be converted in the body to EPA and DCHA, but it is found within chloroplast membranes and not in seed oils; hence, it may not be available in significant quantities in the diet. The \(\omega-3\) and \(\omega-6\) EFA have different metabolic effects (see below). Particularly rich sources of EPA are fishes (e.g., salmon, mackerel, blue fish, herring, menhaden) that live in deep, cold waters. These fishes have fat in their muscles and their skin. In contrast, codfish, which have a similar habitat, store fat in liver rather than muscle. Thus, cod liver oil is a good source of EPA, but it also contains high amounts of vitamins A and D, which can be toxic in large quantities (Chapters 38 and 37, respectively). Shellfish also contain EPA. Plankton are the ultimate source of EPA.

Linoleic acid can be converted in mammalian liver to \(\gamma\)-linolenic acid and arachidonic acid by the microsomal desaturation and chain elongation process (Figure 18-14). Thus, the requirement for arachidonic acid may be dispensed with when the diet contains adequate amounts of linoleic acid. Similarly, \(\alpha\)-linolenic acid is converted by desaturation and chain elongation to EPA and DCHA (Figure 18-15).
Deficiency of Essential Fatty Acids

The clinical manifestations of EFA deficiency in humans closely resemble those seen in animals. They include dry, scaly skin, usually erythematous eruptions (generalized or localized and affecting the trunk, legs, and intertriginous areas), diffuse hair loss (seen frequently in infants), poor wound healing, failure of growth, and increased metabolic rate. Abnormalities in ECG patterns may be due to membrane alterations, which may also account for structural and functional abnormalities observed in mitochondria. Surgical patients maintained on glucose-amino acid solutions for prolonged periods develop EFA deficiency, manifested as anemia, thrombocytopenia, hair loss and sparse hair growth, increased capillary permeability, dry scaly skin, desquamating dermatitis, and a shift in the oxygen-dissociation curve of hemoglobin to the left. Oral or intravenous administration of linoleic acid is necessary to correct these problems. Fat emulsions containing linoleic acid are commercially available for intravenous use. An adult requires 10 g of linoleic acid per day. The recommended dietary allowance for EFA is 1–2% of the total energy intake.

EFA deficiency can also occur in infants with highly restricted diets (e.g., primarily skim milk intake), in patients receiving total parenteral hyperalimentation without supplements of unsaturated lipids, and in those with severe malabsorptive defects.

In EFA deficiency, oleic acid can be dehydrogenated to yield polyunsaturated fatty acids (PUFAs) that are nonessential and do not substitute for the essential fatty acids. One such PUFA is 5,8,11-eicosatrienoic acid, which occurs in significant amounts in heart, liver, adipose tissue, and erythrocytes of animals fed diets deficient in EFAs but decreases after supplementation with linoleic or linolenic acids. Its appearance in tissues and plasma has been used in the assessment of EFA deficiency.

Most vegetable oils are relatively rich in EFAs (coconut oil is an exception), low in saturated fatty acids, and lack cholesterol. Animal fats (except those in fish), on the other hand, are generally low in EFAs, high in saturated fats, and contain cholesterol. The EFA content of body and milk fat of ruminants can be increased by the feeding of EFA emulsions of unsaturated lipids, and in those with severe malabsorptive defects.

Table 18-4 summarizes the fatty acid composition of some fats of animal and plant origin. The recommended daily diet does not exceed 30–35% of the total energy intake as fat (current average consumption in North America is 40–45%), with equal amounts of saturated, monounsaturated, and polyunsaturated fats, and a cholesterol intake of no more than 300 mg/day (current average consumption in North America is about 600 mg/day).

Substitution of ω-6 polyunsaturated for saturated fats in the diet lowers plasma cholesterol levels through reduction in levels of VLDL and LDL. Diets rich in polyunsaturated fats lead to higher biliary excretion of sterols, although this effect may not be directly related to reduced levels of plasma lipoproteins. Diets low in EFA (linoleic acid) have been associated with high rates of coronary heart disease. A significantly lower proportion of EFA in the adipose tissue of people dying from coronary heart disease has been reported, and an inverse relationship has been found between the percentage composition of EFA in serum cholesteryl esters and mortality rates from coronary heart disease. Consumption of ω-3 polyunsaturated fatty acids markedly decreases plasma triacylglycerol and, to a lesser extent, cholesterol levels in some hyperlipoproteinemic patients (Chapter 20). Consumption of fish-oil fatty acids decreases the biosynthesis of fatty acids and of VLDL by the liver and also decrease the platelet and monocyte function. These effects of ω-3 fatty acids appear to prevent or delay atherogenesis. Low death rates from coronary heart disease are found among populations with high intake of fish (e.g., Greenland Eskimos, people of fishing villages of Japan, people of Okinawa). Metabolic and functional differences exist between ω-3 and ω-6 fatty acids. They have opposing physiological effects and their balance in the diet is important for homeostasis and normal development.

18.9 Metabolism of Eicosanoids

The eicosanoids—prostaglandins (PGs), thromboxanes (TXs), prostacyclins (PGIs), and leukotrienes (LTs)—are derived from essential fatty acids and act similarly to hormones (Chapter 30). However, they are synthesized in almost all tissues (unlike hormones, which are synthesized in selected tissues) and are not stored to any significant extent; their physiological effects on tissues occur near sites of synthesis rather than at a distance. They function as paracrine messengers and are sometimes referred to as autacoids.

The four groups of eicosanoids are derived, respectively, from a 20-carbon fatty acid with three, four, or five double bonds: 8,11,14-eicosatrienoic acid (dihomo-γ-linolenic acid), 5,8,11,14-eicosatetraenoic acid (arachidonic acid), and 5,8,11,14,17-eicosapentaenoic acid (Figure 18-17). In humans, the most abundant precursor is arachidonic acid. Secretion of eicosanoids in response
TABLE 18-4
Fatty Acid Composition of Some Fats of Animal and Plant Origin

<table>
<thead>
<tr>
<th></th>
<th>Saturated*</th>
<th>Monounsaturated*</th>
<th>Polyunsaturated*, mostly as linoleic acid (C18:2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C14:0; C16:0; C18:0</td>
<td>C16:1; C18:1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(predominantly C16:0 and C18:0)</td>
<td>(predominantly C18:1)</td>
<td></td>
</tr>
<tr>
<td>Animal Fats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td>59</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Beef</td>
<td>54</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Chicken</td>
<td>40</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Pork</td>
<td>40</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>Fish (salmon and tuna)</td>
<td>28</td>
<td>29</td>
<td>23 + 20‡</td>
</tr>
<tr>
<td>Vegetable Oils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safflower</td>
<td>11</td>
<td>11</td>
<td>78</td>
</tr>
<tr>
<td>Corn</td>
<td>14</td>
<td>26</td>
<td>60</td>
</tr>
<tr>
<td>Sesame</td>
<td>14</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Soybean</td>
<td>15</td>
<td>27</td>
<td>58</td>
</tr>
<tr>
<td>Peanut</td>
<td>20</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Cottonseed</td>
<td>29</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>Coconut</td>
<td>92</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Palm</td>
<td>53</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>Olive</td>
<td>16</td>
<td>69</td>
<td>15</td>
</tr>
<tr>
<td>Sunflower</td>
<td>12</td>
<td>18</td>
<td>70</td>
</tr>
</tbody>
</table>

*All values expressed as weight percentages of total fatty acids.
†Other polyenoic acids, e.g., eicosapentaenoic acid, docosahexaenoic acid.

FIGURE 18-17
Precursor and product relationships of eicosanoids: prostaglandins (PGs), prostacyclins (PGIs), thromboxanes (TXs), and leukotrienes (LTs). Arrows arising from each fatty acid indicate two different synthetic pathways: one for prostanoids (PG, PGI, TX) and the other for leukotrienes. The numerical subscript of an eicosanoid indicates the total number of double bonds in the molecule and thus the series to which it belongs. The prostanoids contain two fewer double bonds than does the precursor fatty acid.

FIGURE 18-18
Hydrolysis of phosphoglycerides by phospholipases, whose cleavage sites are shown by vertical arrows.
arachidonic acid is through action of phospholipase A₂. It may also be derived through action of phospholipase C, which liberates diacylglycerol; the latter is then acted on by diacylglycerol lipase. Stimuli that increase the biosynthesis of eicosanoids cause increased mobilization of intracellular calcium, which with calmodulin is thought to activate membrane-bound phospholipases A₂ and C (phagocytosis, Chapter 15; and mechanism of hormone action, Chapter 30).

Glucocorticoids (e.g., cortisol) inhibit phospholipase A₂ activity by induction of synthesis of a phospholipase inhibitor protein, which partly explains their anti-inflammatory effects.

The major metabolites of arachidonic acid (Figure 18-19) arise from the 12-lipoxygenase, the 5-lipoxygenase, and the fatty acid cyclooxygenase pathway. The 5-lipoxygenase pathway yields leukotrienes, and the cyclooxygenase pathway yields cyclic endoperoxides, which are converted to PGs, TXs, and PGI₂.

**Prostaglandins** (PG) were discovered in human semen more than 50 years ago. Their name derives from the prostate gland, but they are produced in many tissues. In fact, the high concentrations found in semen arise in the seminal vesicles rather than the prostate. The chemical parent compound is a 20 carbon unnatural fatty acid known as prostanoic acid that contains a five-membered (cyclopentane) ring. Derivatives that contain this structure (PGs, TXs, and PGI₂) are known collectively as prostanoids.

Differences among various PGs are attributable to differences in substituents and in their positions on the five-membered ring (Figure 18-20). PGs are identified by a letter (e.g., PGE, PGF), characteristic for ring substituents, and by a numerical subscript (e.g., PGE₁, PGF₂), which indicates the number of double bonds (Figure 18-17). The location and type of double bonds are as follows:

- PG₁, trans-C₁₃;
- PG₂, trans-C₁₃ cis-C₅;
- PG₃, trans-C₁₃ cis-C₅C₁₇. All PGs have a hydroxy group at C₁₅ except PGG, which has a hydroperoxy group (−OOH). The hydroxy group at C₁₅ is in the S-configuration in the naturally occurring prostaglandins. The α and β notations (e.g., PGF₂α) designate the configuration of the substituent at C₉ on the cyclopentane moiety, as used in steroid chemistry (α for below and β for above the plane of the projection of the cyclopentane ring). The natural compounds are α-derivatives.

PGs are synthesized in a stepwise manner by microsomal enzymes. The metabolic pathways discussed here use arachidonic acid as an example. Similar pathways are applicable to other polyenoic fatty acids. PG synthesis is started by microsomal prostaglandin endoperoxide
FIGURE 18-20
Ring structures of prostaglandins (PG), prostacyclin (PGI), and thromboxane (TX). Groups that lie behind the plane of
the ring are shown by □ and those that lie above the plane by ●.

**Oxidase, which is a cyclooxygenase and a peroxidase. Cyc-
oxigenase activity (the rate-limiting reaction) results
in 15-hydroperoxy-9,11-endoperoxide (PGG2), which is
converted to a 9,11-endoperoxide (PGH2) by the per-
oxidase activity. There are two isoforms of cyclooxy-
genase (COX), which have been designated as COX1
and COX2. Both forms are membrane-associated en-
zymes. COX1 is constitutively expressed in many tissues,
where arachidonic acid metabolites play a role in pro-
tective "housekeeping" homeostatic functions. Some of
the COX1 mediated normal physiological functions in-
clude gastric cytoprotection and limiting acid secretion
(Chapter 12), maintenance of renal blood flow, vascular
homeostasis, and hemostasis (e.g., antiplatelet effects,
Chapter 36). COX2 activity, on the other hand, is normally
undetectable in most tissues and it is principally an in-
ducible enzyme. In cells such as monocytes, macrophages,
synoviocytes, endothelial cells, and chondrocytes, COX2
is expressed at high levels after induction by inflammatory
mediators (e.g., interleukin-1 and tumor necrosis factor)
and growth factors. COX2 enzymatic activity initiates the
synthesis of arachidonic acid metabolites that mediate
pain, inflammation, cellular differentiation and mitogene-
sis. For example, PGE2 is chemotactic for neutrophils and
PGI2 causes changes in vascular permeability facilitating
eextravasation of leukocytes. Although COX2 is generally
an inducible enzyme, it is constitutively expressed in de-
veloping kidney and brain and, therefore, may be involved
in their normal development and proper maturation.

The two unique isoforms, COX1 and COX2, are struc-
turally similar but they are encoded by separate genes
differing in their tissue distribution and expression. The
COX1 gene contains a promoter region without a TATA
sequence and is constitutively expressed. In contrast, the
COX2 gene contains DNA segments that allow for rapid
up regulation in response to appropriate stimuli. The anti-
inflammatory action of glucocorticoids have no effect on
the regulation of the COX1 gene.
The amino acid sequence homology of COX1 and COX2 is about 60%. However, in the region of the active site the amino acid homology is about 90% and both isoforms contain a long narrow largely hydrophobic channel with a hairpin bend at the end to accommodate the substrate arachidonic acid. A unique single-amino-acid difference in the wall of the hydrophobic channel (position 523) of COX1 and COX2 has been used to develop specific COX2 inhibitors. At position 523, COX1 has an isoleucine residue whereas COX2 has a valine residue which is smaller by a single CH2 group. The presence of the less bulky valine residue in the COX2 hydrophobic channel provides access for COX2 selective inhibitors. In COX1 the bulkier isoleucine residue prevents the entry of COX2 selective inhibitors.

In the treatment and management of pain and inflammation produced by arachidonic acid metabolites, COX inhibitors are widely used. These agents are known as **non-steroidal anti-inflammatory drugs** (NSAIDs). Acetylsalicylate (aspirin) is the classic anti-inflammatory and analgesic drug. Aspirin is an irreversible inhibitor of both COX1 and COX2 and it inhibits by acetylation of the hydroxyl group of the serine residue located at the active site of the enzymes. There are nonaspirin NSAIDs, the majority of which are organic acids (e.g., indomethacin, ibuprofen), that are reversible inhibitors of both COX1 and COX2. These inhibitors form a hydrogen bond with an arginine residue at position 120 of both COX1 and COX2 in the channel and block the entry of arachidonic acid.

Because of their non-selectivity, aspirin and nonaspirin NSAIDs cause undesirable side effects due to inhibition of the “housekeeping” COX1 enzyme. The side effects include gastrointestinal disorders, renal dysfunction and bleeding tendency. Thus, a COX2 selective or preferential inhibitor that spares COX1 activity is valuable in the treatment of pain and inflammation. Based on the biochemical differences between COX1 and COX2, drugs have been designed with COX2 inhibitor activity, which are associated with a markedly lower incidence of gastrointestinal injury. These drugs often possess sulfonyl, sulfone, or sulfonamide functional groups that bind with the COX2 side pocket in the hydrophobic channel. Examples of COX2 inhibitors are celecoxib, which is a 1,5-diarylpyrazole sulfonamide, and rofecoxib, which is a methylsulfonylphenyl derivative (Figure 18-21).

Since nitric oxide (NO) protects gastric mucosa (Chapter 17), a NO moiety linked to conventional NSAIDs may negate the gastric toxic effects due to prostaglandin deficiency. Such drugs of NO-NSAIDs are currently being tested.

Other potential uses for COX inhibitors (in particular for COX2 inhibitors) may include the treatment of Alzheimer’s disease and colon cancer. In Alzheimer’s disease it is thought that an inflammatory component may lead to deposition of β-amyloid protein in neuritic plaques in the hippocampus and cortex (Chapter 4). The potential use of COX2 inhibitors in colon cancer arises from studies with experimental animals in which COX2 activity is related to the promotion and survival of intestinal adenomas and colon tumors. The cyclooxygenase reaction is also inhibited by arachidonic acid analogues such as

![FIGURE 18-21 Structures of cyclooxygenase-2 (COX2) selective inhibitors. (A) Celecoxib and (B) Rofecoxib.](image)

PGH2 is converted to PGD2, PGE2, PGF2α, prostacyclin (PGl2), and thromboxane A2 (TXA2) by specific enzymes (Figure 18-22). PGA2 is obtained from PGE2 by dehydration. Since PGC2 and PGB2 are isomers of PGA2, they can be synthesized by isomerases. The formation of these compounds is shown in Figure 18-23. In some tissues, PGE2 and PGF2 undergo interconversion:

![Conversion of PGE2 to PGF2α](image)

The NAD(P)⁺ inhibits the conversion of PGE2 to PGF2α, while reducing agents favor the formation of PGF2α.
FIGURE 18-22
Synthesis of prostanoids from arachidonic acid. *Both activities reside in one enzyme.
SECTION 18.9 Metabolism of Eicosanoids

However, PGE\textsubscript{2} formation is favored by glutathione. In the initial catabolic reaction of both compounds by 15-hydroxy-PG-dehydrogenase (15-PGDH), the reduced NAD(P) formed in that reaction inhibits the first step. Thus, the ratio of reduced to oxidized NAD(P) may control the interconversion of PGE\textsubscript{2} and PGF\textsubscript{2\alpha} and also the first step in their catabolism. This finding is important because in many tissues PGE and PGF have opposing effects. PG biosynthesis can also be regulated by activation of latent forms of cyclooxygenase, promoted by catecholamines and serotonin. The PGs synthesized differ from tissue to tissue; within the same tissue, different cells may yield products with antagonistic actions. For example, the lung parenchymal cells may produce TXA\textsubscript{2}, while the lung vascular endothelial cells may produce PGI\textsubscript{2}.

Catabolism of prostanoids occurs throughout the body, but the lungs can remove most of the plasma PGs during a single circulatory cycle. Despite this rapid removal, the PGs have adequate access to target organs. Catabolism starts with the reactions of 15-PGDH (oxidation of allylic –OH group at C\textsubscript{15}) and of PG reductase (reduction of the Δ\textsubscript{13} double bond). 15-PGDH is found in the cytoplasm (lungs), requires NAD\textsuperscript{+}, and is specific for the C\textsubscript{15(S)} alcohol group. These reactions are followed by β-oxidation, ω-oxidation of the alkyl side chains, and elimination of the products. The catabolism of PGE\textsubscript{2} and PGF\textsubscript{2\alpha} is shown in Figure 18-24. The thromboxanes (TX), first isolated from human and equine thrombocytes (platelets), contain an oxane ring. TXA\textsubscript{2} is synthesized from PGH\textsubscript{2} by microsomal thromboxane synthase. Thromboxane synthase is inhibited by imidazole derivatives. TXA\textsubscript{2} has a very short half-life (t\textsubscript{1/2} = 30 seconds at 37°C and pH 7.5) and undergoes rapid, nonenzymatic hydrolysis to the inactive TXB\textsubscript{2} (Figure 18-22).

Prostacyclin (PG\textsubscript{I\beta}) is an active and unstable metabolite (t\textsubscript{1/2} = 3 minutes at 37°C and pH 7.5) formed from PGH\textsubscript{2} by prostacyclin synthase. PG\textsubscript{I\beta} has a double-ring structure and is converted by nonenzymatic hydrolysis to 6-keto-PGF\textsubscript{1\alpha} (Figure 18-22).

**Biological Properties of Prostanoids**

Many effects of prostanoids are mediated through adenylyl cyclase or mobilization of Ca\textsuperscript{2+} from intracellular stores. PGs increase cAMP in adenohypophysis, corpus luteum, fetal bone, lung platelets, and thyroid but decrease it in adipose tissue. Thromboxanes block the production of cAMP by PGs and mobilize intracellular Ca\textsuperscript{2+}. Thus, many endocrine glands (e.g., adrenal cortex, ovary, pancreatic islets, parathyroids) secrete hormones in response to PGs. Some of these effects are stimulation of steroid hormone production in the adrenal cortex, insulin release, thyroid hormone production, and progesterone secretion from the corpus luteum. *In vitro* PGs, notably PGE\textsubscript{1}, inhibit adipocyte lipolysis—the basal rate as well as that stimulated by catecholamine and other lipolytic hormones. Low doses of PGE\textsubscript{1} in humans tend to stimulate lipolysis through stimulation of release of catecholamines. PGs stimulate the activity of osteoclasts with the mobilization of Ca\textsuperscript{2+} from bone, an effect independent of that of parathyroid hormone (Chapter 37).

Problems in delineating the primary actions of PGs arise from their frequently opposing effects and from the difficulty of distinguishing between physiological and pharmacological actions. In general, PGE\textsubscript{2} and PGF\textsubscript{2\alpha} have opposing effects on smooth muscle tone, release of mediators of immediate hypersensitivity, and cyclic nucleotide
levels. Thus, the ratio between E and F compounds (due to changes in the \([\text{NAD}^+]/[\text{NADH}]\) ratio) may be a crucial factor in control of a given physiological response. The relative proportions of TXs and leukotrienes, as opposed to PGI, also appear to exert an important influence on physiological response.

In most animal species, PGI2, PGEs, and PGAs are vasodilators, while TXA2 is a vasoconstrictor. PGF2α and 15-methyl PGF2α are used for induction of mid-trimester abortions because they stimulate uterine muscle. Several PGs suppress gastric HCl production, which has therapeutic potential in the treatment of gastric ulceration and may explain the effect of aspirin to increase HCl secretion by inhibition of PG synthesis. PGE2 elevation causes fever by increasing firing rates of neurons that control thermoregulation in the hypothalamus.

The effect of prostanoids on platelets has received considerable interest. TXA2 synthesized in platelets induces platelet aggregation, whereas PGI2 generated in the vessel wall inhibits platelet aggregation. PGI3 (Figure 18-17), a product of eicosapentaenoic acid (an \(\omega-3\) fatty acid), inhibits TXA2 synthesis by inhibiting release of arachidonate from phospholipids and by competing for thromboxane synthase. TXA3 is a much weaker aggregator of platelets than is TXA2, while PGI3 is a stronger antiaggregator than is PGI2. The net effect is an antiplatelet effect, which may be beneficial in patients with thrombotic complications (e.g., myocardial infarction). The low incidence of coronary thrombosis in Greenland Eskimos, whose diet is almost completely derived from marine sources rich in \(\omega-3\) fatty acids, has been attributed to antiplatelet effects. This diet is also associated with lower levels of serum cholesterol and triacylglycerol than typical Western diets.

**Leukotrienes**

Leukotrienes (LTs) are most commonly found in leukocytes, mast cells, platelets, and vascular tissues of the lung and heart. They are formed chiefly from arachidonic acid,
but they may be derived from eicosatrienoic and eicosapentaenoic acids. The name “leukotrienes” derives from their discovery in leukocytes and from the conjugated triene structure they contain. In the most active LTs, the conjugated triene is in a trans, trans, cis arrangement. They are distinguished by letters A–E and by a subscript that indicates the number of double bonds present.

LTs are produced in the 5-lipoxygenase pathway (Figure 18-25). Their synthesis begins with arachidonic acid obtained from cleavage of the membrane phospholipid pool due to the action of phospholipase A2. Arachidonic acid is converted in a catalytic sequence by 5-lipoxygenase complex and its activating protein to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and
then to leukotriene A₄ (5,6-oxido-7,9-trans-11,14-cis-eicosatetraenoic acid). Leukotriene A₄ (LTA₄) is transformed by LTA₄ hydrolase into 5,12-dihydroxy-eicosatetraenoic acid (leukotriene B₄, LTB₄) or into a glutathione adduct with the formation of a thioether linkage at C₆, (leukotriene C₄, LTC₄) by leukotriene C₄ synthase (also known as glutathione S-transferase). Leukotriene D₄ (LTD₄) and LTE₄ are synthesized in the extracellular space from LTC₄. A specific transmembrane transporter exports LTC₄ to the extracellular space. In the extracellular space, removal of the glutamyl residue from LTC₄ by γ-glutamyltransferase yields LTD₄ and the removal of the glycyl residue from LTD₄ by a variety of dipeptidases results in the formation LTE₄ (Figure 18-25).

The three cysteinyl linked leukotrienes, namely LTC₄, LTD₄, and LTE₄ are known collectively as cysteinyl leukotrienes. All three cysteinyl leukotrienes are potent mediators of inflammation and cause microvascular permeability, chemotaxis (particularly eosinophils), mucus hypersecretion, and neuronal stimulation. The potential role of LTC₄ as a neuromessenger or modulator has been implicated in an infant with LTC₄ synthase deficiency. The clinical features include muscular hypotonia, psychomotor retardation, failure to thrive, microcephaly, and a fatal outcome. In lung tissue mast cells, eosinophils and alveolar macrophages possess the enzyme activities to synthesize cysteinyl leukotrienes and cause, in addition to above mentioned biological actions, bronchial smooth muscle constriction and proliferation. Thus, cysteinyl leukotrienes are important mediators of immune-mediated inflammatory reactions of anaphylaxis and are constituents of substances originally called "slow reacting substances of anaphylaxis" (SRS-A). They are several times more potent than histamine in constricting airways and promoting tissue edema formation. The proinflammatory effect of LTE₄ is less than that of LTC₄ and LTD₄; it is excreted in the urine and is used as a marker of leukotriene production.

Antileukotriene agents, which can be used in treatment of allergen and exercise-induced asthma and allergic rhinitis, inhibit 5-lipoxygenase or the binding of the activator protein with 5-lipoxygenase or antagonists of leukotriene receptors at the target cell (e.g., airway epithelial cell). The traditional drugs used for treatment of asthma include inhaled corticosteroids, β₂-agonists, and theophyllines. Leukotriene receptor antagonists are orally active and are a new class of antiasthmatic therapeutic agents (Figure 18-26).

Supplemental Readings and References


