Fatty Acid and Triacylglycerol Metabolism

16

I. OVERVIEW

Fatty acids exist "free" in the body (that is, they are unesterified), and are also found as fatty acyl esters in more complex molecules, such as triacylglycerols. Low levels of free fatty acids occur in all tissues, but substantial amounts can sometimes be found in the plasma, particularly during fasting. Plasma free fatty acids (transported on serum albumin) are in route from their point of origin (triacylglycerol of adipose tissue or circulating lipoproteins) to their site of consumption (most tissues). Free fatty acids can be oxidized by many tissues—particularly liver and muscle—to provide energy. Fatty acids are also structural components of membrane lipids, such as phospholipids and glycolipids (see p. 201). Fatty acids are attached to certain intracellular proteins to enhance the ability of those proteins to associate with membranes (see p. 206). Fatty acids are also precursors of the hormone-like prostaglandins (see p. 213). Esterified fatty acids, in the form of triacylglycerols stored in adipose cells, serve as the major energy reserve of the body. Figure 16.1 illustrates the metabolic pathways of fatty acid synthesis and degradation, and their relationship to carbohydrate metabolism.

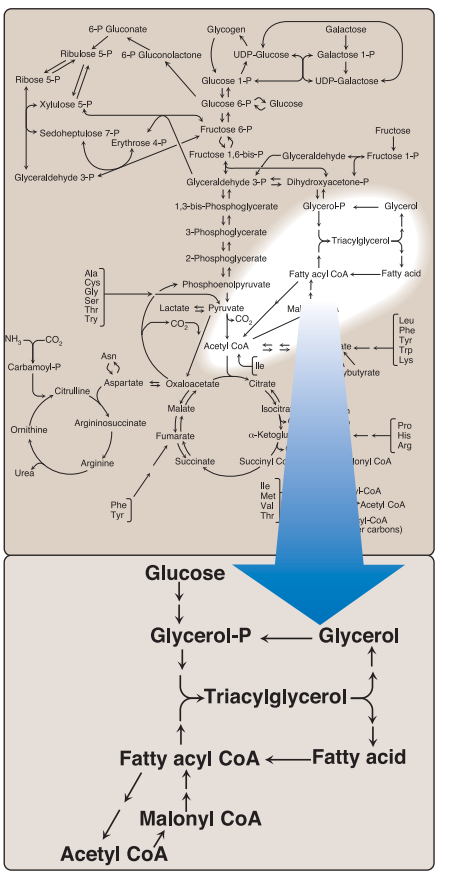


Figure 16.1
Triacylglycerol synthesis and degradation.

II. STRUCTURE OF FATTY ACIDS

A fatty acid consists of a hydrophobic hydrocarbon chain with a terminal carboxyl group that has a pK_a of about 4.8 (Figure 16.2). At physiologic pH, the terminal carboxyl group (–COOH) ionizes, becoming $–COO^-$. This anionic group has an affinity for water, giving the fatty acid its amphipathic nature (having both a hydrophilic and a hydrophobic region). However, for long-chain fatty acids (LCFAs), the hydrophobic portion is predominant. These molecules are highly water-insoluble, and must be transported in the circulation in association with protein. More than 90% of the fatty acids found in plasma are in the form of fatty acid esters (primarily triacylglycerol, cholesteryl esters, and phospholipids) contained in circulating lipoprotein particles (see p. 227). Unesterified (free) fatty acids are transported in the circulation in association with albumin.

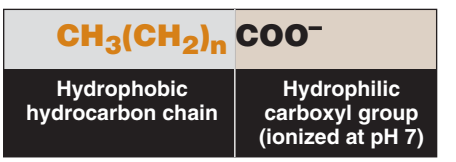


Figure 16.2
Structure of a fatty acid.

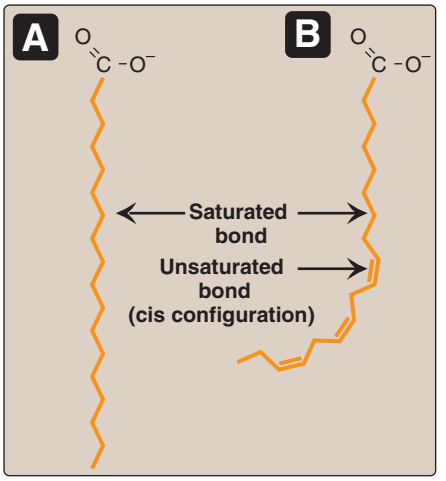
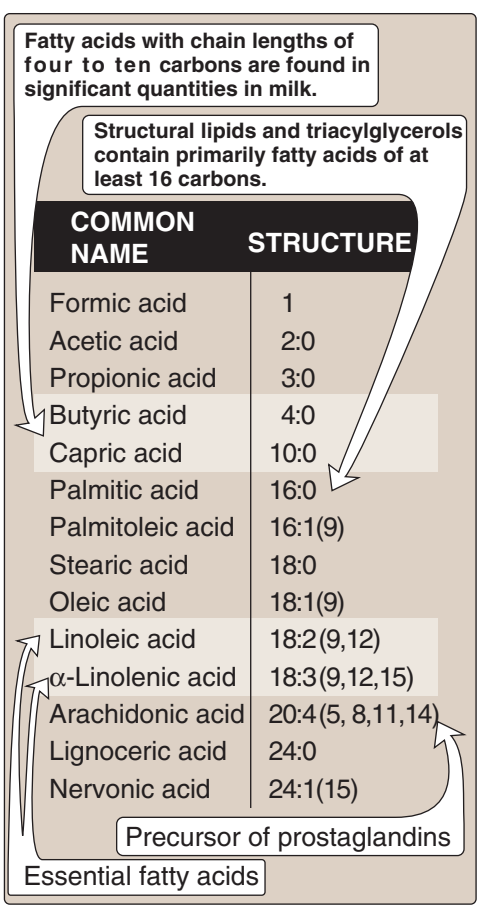


Figure 16.3
A saturated (A) and an unsaturated (B) fatty acid. Orange denotes hydrophobic portions of the molecules. [Note: Cis double bonds cause a fatty acid to "kink."]



COMMON NAME	STRUCTURE
Formic acid	1
Acetic acid	2:0
Propionic acid	3:0
Butyric acid	4:0
Capric acid	10:0
Palmitic acid	16:0
Palmitoleic acid	16:1(9)
Stearic acid	18:0
Oleic acid	18:1(9)
Linoleic acid	18:2(9,12)
α-Linolenic acid	18:3(9,12,15)
Arachidonic acid	20:4(5, 8,11,14)
Lignoceric acid	24:0
Nervonic acid	24:1(15)

Figure 16.4
Some fatty acids of physiologic importance.

A. Saturation of fatty acids

Fatty acid chains may contain no double bonds—that is, be saturated—or contain one or more double bonds—that is, be mono- or polyunsaturated. When double bonds are present, they are nearly always in the cis rather than in the trans configuration. (See p. 363 for a discussion of the dietary occurrence of cis and trans unsaturated fatty acids.) The introduction of a cis double bond causes the fatty acid to bend or "kink" at that position (Figure 16.3). If the fatty acid has two or more double bonds, they are always spaced at three-carbon intervals. [Note: In general, addition of double bonds decreases the melting temperature (T_m) of a fatty acid, whereas increasing the chain length increases the T_m. Because membrane lipids typically contain LCFA, the presence of double bonds in some fatty acids helps maintain the fluid nature of those lipids.]

B. Chain lengths of fatty acids

The common names and structures of some fatty acids of physiologic importance are listed in Figure 16.4. The carbon atoms are numbered, beginning with the carboxyl carbon as carbon 1. The number before the colon indicates the number of carbons in the chain, and those after the colon indicate the numbers and positions (relative to the carboxyl end) of double bonds. For example, as shown in Figure 16.5A, arachidonic acid, 20:4(5,8,11,14), is 20 carbons long and has 4 double bonds (between carbons 5–6, 8–9, 11–12, and 14–15). [Note: Carbon 2, the carbon to which the carboxyl group is attached, is also called the α-carbon, carbon 3 is the β-carbon, and carbon 4 is the γ-carbon. The carbon of the terminal methyl group is called the ω-carbon regardless of the chain length.] The double bonds in a fatty acid can also be denoted relative to the ω (or methyl-terminal) end of the chain. Arachidonic acid is referred to as an ω-6 fatty acid acid (also an n-6, Figure 16.5A) because the terminal double bond is six bonds in from the ω end (Figure 16.5B). Another ω-6 fatty acid is the essential linoleic acid, 18:2(9,12). In contrast, α-linolenic acid, 18:3(9,12,15), is an essential ω-3 fatty acid. (See p. 363 for a discussion of the nutritional significance of ω-3 and ω-6 fatty acids.)

C. Essential fatty acids

Two fatty acids are dietary essentials in humans because of our inability to synthesize them: linoleic acid, which is the precursor of ω-6 arachidonic acid, the substrate for prostaglandin synthesis (see p. 213), and α-linolenic acid, the precursor of other ω-3 fatty acids important for growth and development. Plants provide us with the essential fatty acids. [Note: Arachidonic acid becomes essential if linoleic acid is deficient in the diet.]

Essential fatty acid deficiency can result in a scaly dermatitis (ichthyosis), as well as visual and neurologic abnormalities. Essential fatty acid deficiency, however, is rare.

III. DE NOVO SYNTHESIS OF FATTY ACIDS

A large proportion of the fatty acids used by the body is supplied by the diet. Carbohydrates and protein obtained from the diet in excess of the body's needs for these compounds can be converted to fatty acids, which are stored as triacylglycerols. (See p. 321 for a discussion of the metabolism of dietary nutrients in the well-fed state.) In adult humans, fatty acid synthesis occurs primarily in the liver and lactating mammary glands and, to a lesser extent, in adipose tissue. This cytosolic process incorporates carbons from acetyl coenzyme A (CoA) into the growing fatty acid chain, using adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide phosphate (NADPH).

A. Production of cytosolic acetyl CoA

The first step in de novo fatty acid synthesis is the transfer of acetate units from mitochondrial acetyl CoA to the cytosol. Mitochondrial acetyl CoA is produced by the oxidation of pyruvate (see p. 109), and by the catabolism of fatty acids (see p. 190), ketone bodies (see p. 196), and certain amino acids (see p. 266). The CoA portion of acetyl CoA, however, cannot cross the inner mitochondrial membrane; only the acetyl portion enters the cytosol. It does so as part of citrate produced by the condensation of oxaloacetate (OAA) and acetyl CoA (Figure 16.6). [Note: This process of translocation of citrate from the mitochondrion to the cytosol, where it is cleaved by *ATP-citrate lyase* to produce cytosolic acetyl CoA and OAA, occurs when the mitochondrial citrate concentration is high. This is observed when *isocitrate dehydrogenase* is inhibited by the presence of large amounts of ATP, causing citrate and isocitrate to accumulate (see p. 112). Therefore, cytosolic citrate may be viewed as a high-energy signal.] Because a large amount of ATP is needed for fatty acid synthesis, the increase in both ATP and citrate enhances this pathway.

B. Carboxylation of acetyl CoA to form malonyl CoA

The energy for the carbon-to-carbon condensations in fatty acid synthesis is supplied by the process of carboxylation and then decarboxylation of acetyl groups in the cytosol. The carboxylation of acetyl CoA to form malonyl CoA is catalyzed by *acetyl CoA carboxylase* (Figure 16.7), and requires CO_2 and ATP. The coenzyme is the vitamin, biotin, which is covalently bound to a lysyl residue of the *carboxylase* (see Figure 28.16).

1. **Short-term regulation of acetyl CoA carboxylase (ACC):** This carboxylation is both the rate-limiting and the regulated step in fatty acid synthesis (see Figure 16.7). The inactive form of *ACC* is a protomer (dimer). The enzyme undergoes allosteric activation by citrate, which causes dimers to polymerize, and allosteric inactivation by long-chain fatty acyl CoA (the end product of the pathway), which causes its depolymerization. A second mechanism of short-term regulation is by reversible phosphorylation. *AMP-activated protein kinase* (*AMPK*) phosphorylates and inactivates *ACC*. *AMPK* itself is allosterically activated by AMP and covalently activated by phosphorylation via several *kinases*. At least one of these

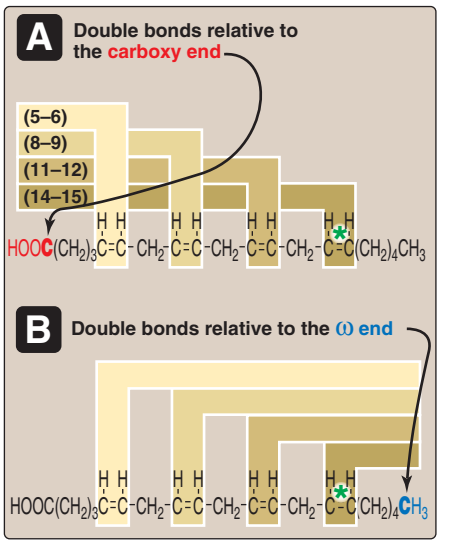


Figure 16.5
Arachidonic acid, illustrating the position of the double bonds. Arachidonic acid, 20:4(5,8,11,14) is an n-6 fatty acid because the double bond furthest from the carboxy end (carbon 1) is 14 carbons from that end: 20-14 = 6. It is also referred to as an ω-6 fatty acid because the terminal double bond is six bonds in from the ω end. Thus, the "ω" and "n" designations are equivalent (see *).

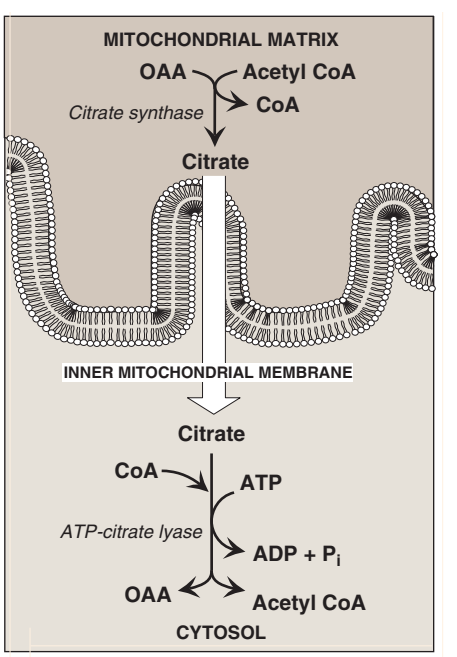


Figure 16.6
Production of cytosolic acetyl CoA.

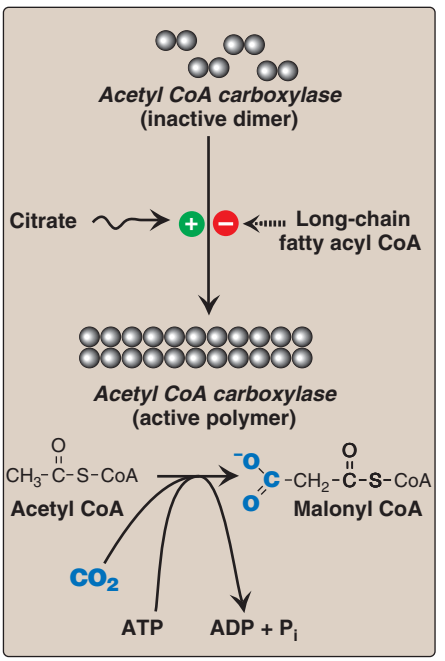


Figure 16.7
Allosteric regulation of malonyl CoA synthesis by *acetyl CoA carboxylase* (*ACC*).The carboxyl group contributed by dissolved CO_2 is shown in blue.

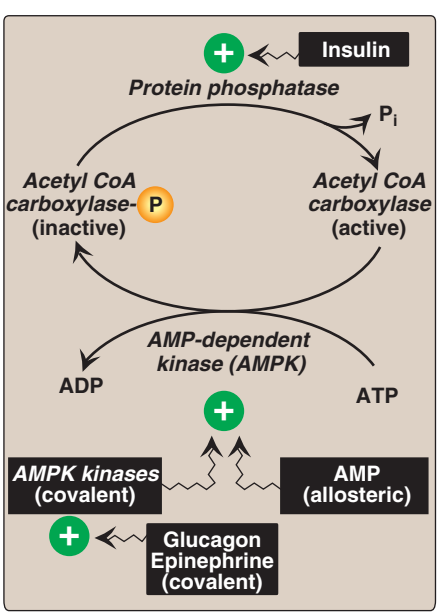


Figure 16.8
Covalent regulation (phosphorylation) of *acetyl CoA carboxylase* (*ACC*) by *AMP-dependent kinase* (*AMPK*), which itself is regulated both covalently and allosterically.

AMPK kinases is activated by *cAMP-dependent protein kinase A* (*PKA*). Thus, in the presence of counterregulatory hormones, such as epinephrine and glucagon, *ACC* is phosphorylated and, thereby, inactivated (Figure 16.8). In the presence of insulin, *ACC* is dephosphorylated and, thereby, activated. [Note: This is analogous to the regulation of *glycogen synthase*, see p. 131.]

2. **Long-term regulation of acetyl CoA carboxylase:** Prolonged consumption of a diet containing excess calories (particularly high-calorie, high-carbohydrate diets) causes an increase in *ACC* synthesis, thus increasing fatty acid synthesis. Conversely, a low-calorie or a high-fat diet causes a reduction in fatty acid synthesis by decreasing the synthesis of *ACC*. [Note: Synthesis of the *carboxylase* is upregulated by insulin via a sterol response element binding protein, SREBP-1. The function and regulation of SREBPs are described on p. 222. *Fatty acid synthase* (see below) is similarly regulated by diet and SREBP-1.] Metformin, used in the treatment of type 2 diabetes, lowers serum TAG through activation of *AMPK* resulting in inhibition of *ACC* activity (by phosphorylation) and inhibition of *ACC* and *fatty acid synthase* expression (by decreasing SREBP-1). Metformin also lowers blood glucose by increasing *AMPK*-mediated uptake of glucose by muscle.

C. Fatty acid synthase: a multifunctional enzyme in eukaryotes

The remaining series of reactions of fatty acid synthesis in eukaryotes is catalyzed by the multifunctional, dimeric enzyme, *fatty acid synthase* (*FAS*). Each *FAS* monomer is a multicatalytic polypeptide with seven different enzymic activities plus a domain that covalently binds a molecule of 4'-phosphopantetheine. [Note: 4'-Phosphopantetheine, a derivative of the vitamin pantothenic acid (see p. 381), carries acyl units on its terminal thiol (–SH) group during fatty acid synthesis. It also is a component of CoA.] In prokaryotes, *FAS* is a multienzyme complex, and the 4'-phosphopantetheine domain is a separate protein, referred to as the acyl carrier protein (ACP). ACP is used below to refer to the phosphopantetheine-containing domain of eukaryotic *FAS*. The reaction numbers in brackets below refer to Figure 16.9. [Note: The enzyme activities listed are separate catalytic domains present in each multicatalytic *FAS* monomer.]

[1] A molecule of acetate is transferred from acetyl CoA to the –SH group of the ACP. Domain: *Acetyl CoA-ACP acetyltransacylase.*

[2] Next, this two-carbon fragment is transferred to a temporary holding site, the thiol group of a cysteine residue on the enzyme.

[3] The now-vacant ACP accepts a three-carbon malonate unit from malonyl CoA. Domain: *Malonyl CoA-ACP transacylase.*

[4] The acetyl group on the cysteine residue condenses with the malonyl group on ACP as the CO_2 originally added by *acetyl CoA carboxylase* is released. The result is a four-carbon unit attached to the ACP domain. The loss of free energy from the decarboxylation drives the reaction. Domain: *3-Ketoacyl-ACP synthase.*

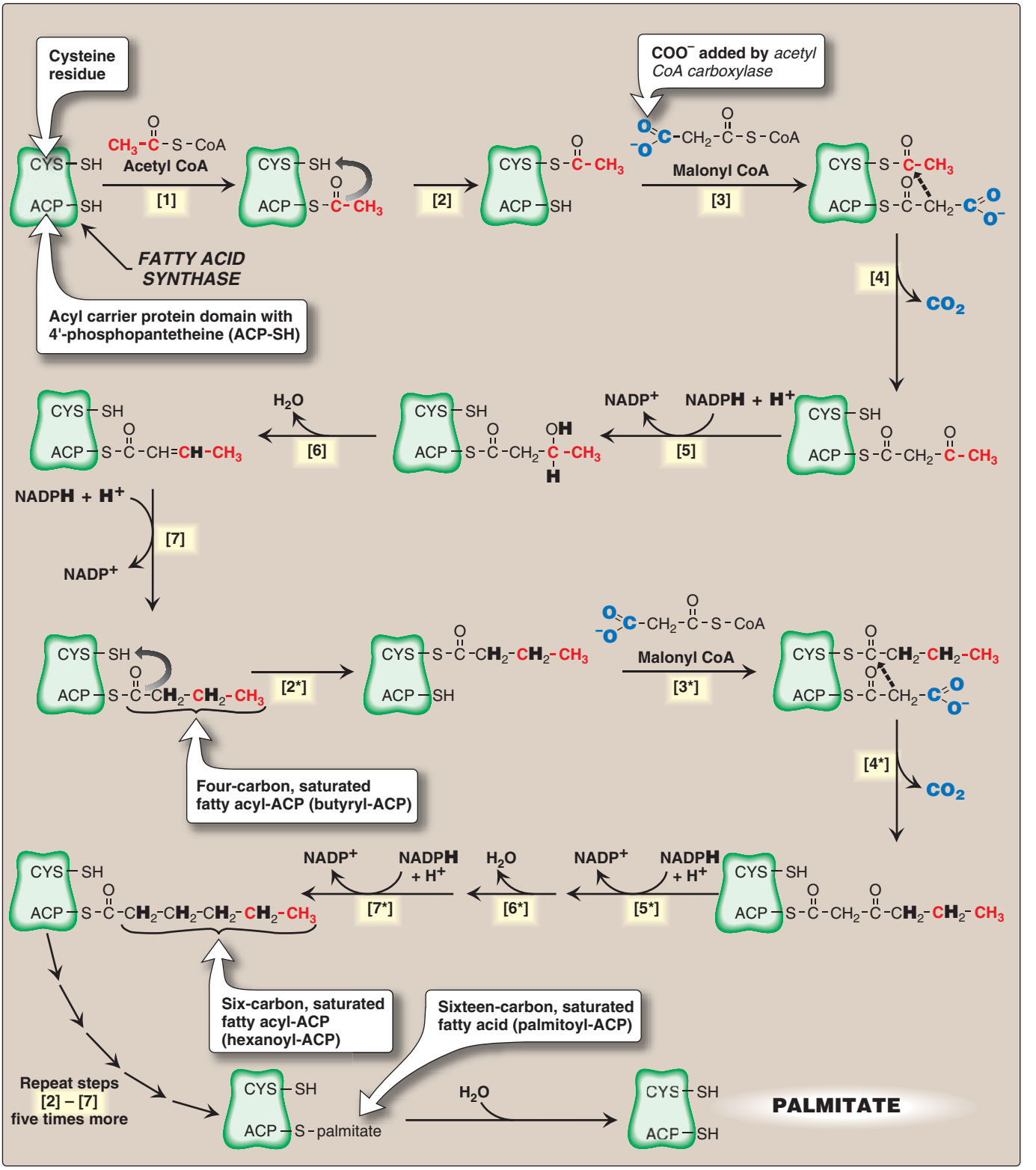


Figure 16.9
Synthesis of palmitate (16:0) by multifunctional *fatty acid synthase* (*FAS*). [Note: Numbers in brackets correspond to bracketed numbers in the text. A second repetition of the steps is indicated by numbers with an asterisk (*). Carbons provided directly by acetyl CoA are shown in red.]

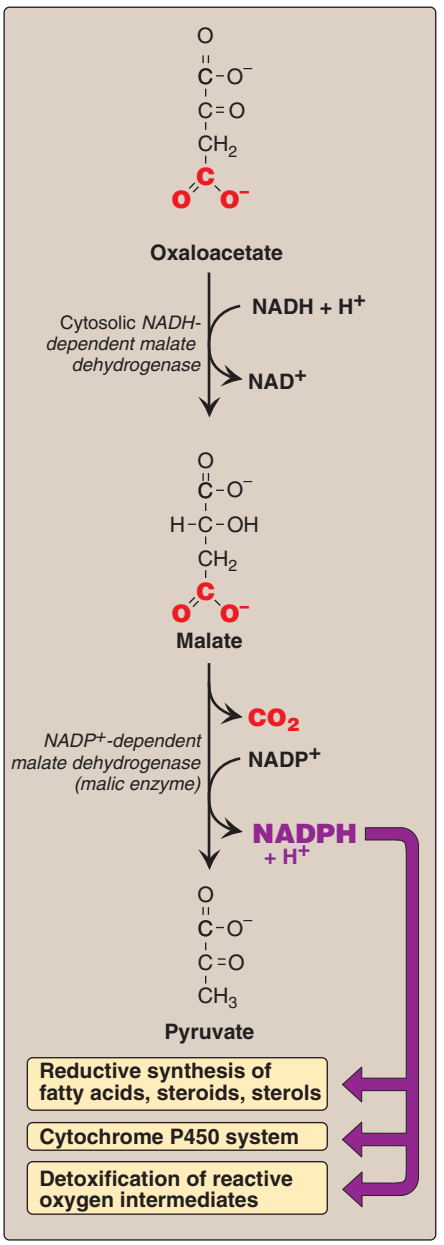


Figure 16.10
Cytosolic conversion of oxaloacetate to pyruvate with the generation of NADPH. [Note: The pentose phosphate pathway is the primary source of the NADPH.]

The next three reactions convert the 3-ketoacyl group to the corresponding saturated acyl group by a pair of reductions requiring NADPH and a dehydration step.

[5] The keto group is reduced to an alcohol. Domain: *3-Ketoacyl-ACP reductase.*

[6] A molecule of water is removed to introduce a double bond between carbons 2 and 3 (the α- and β-carbons). Domain: *3-Hydroxyacyl-ACP dehydratase.*

[7] The double bond is reduced. Domain: *Enoyl-ACP reductase.*

The result of these seven steps is production of a four-carbon compound (butyryl) whose three terminal carbons are fully saturated, and which remains attached to the ACP. These seven steps are repeated, beginning with the transfer of the butyryl chain from the ACP to the Cys residue [2*], the attachment of a molecule of malonate to the ACP [3*], and the condensation of the two molecules liberating CO_2 [4*]. The carbonyl group at the β-carbon (carbon 3—the third carbon from the sulfur) is then reduced [5*], dehydrated [6*], and reduced [7*], generating hexanoyl-ACP. This cycle of reactions is repeated five more times, each time incorporating a two-carbon unit (derived from malonyl CoA) into the growing fatty acid chain at the carboxyl end. When the fatty acid reaches a length of 16 carbons, the synthetic process is terminated with palmitoyl-S-ACP. [Note: Shorter-length fatty acids are important end-products in the lactating mammary gland.] *Palmitoyl thioesterase* cleaves the thioester bond, releasing a fully saturated molecule of palmitate (16:0). [Note: All the carbons in palmitic acid have passed through malonyl CoA except the two donated by the original acetyl CoA, which are found at the methyl-group (ω) end of the fatty acid. This underscores the rate-limiting nature of the *acetyl CoA carboxylase* reaction.]

D. Major sources of the NADPH required for fatty acid synthesis

The hexose monophosphate pathway (see p. 145) is the major supplier of NADPH for fatty acid synthesis. Two NADPH are produced for each molecule of glucose that enters this pathway. The cytosolic conversion of malate to pyruvate, in which malate is oxidized and decarboxylated by cytosolic *malic enzyme* (*$NADP^+$-dependent malate dehydrogenase*), also produces cytosolic NADPH (and CO_2, Figure 16.10). [Note: Malate can arise from the reduction of OAA by cytosolic *NADH-dependent malate dehydrogenase* (see Figure 16.10). One source of the cytosolic NADH required for this reaction is that produced during glycolysis (see p. 101). OAA, in turn, can arise from citrate. Recall from Figure 16.6 that citrate was shown to move from the mitochondria into the cytosol, where it is cleaved into acetyl CoA and OAA by *ATP-citrate lyase.*] A summary of the interrelationship between glucose metabolism and palmitate synthesis is shown in Figure 16.11.

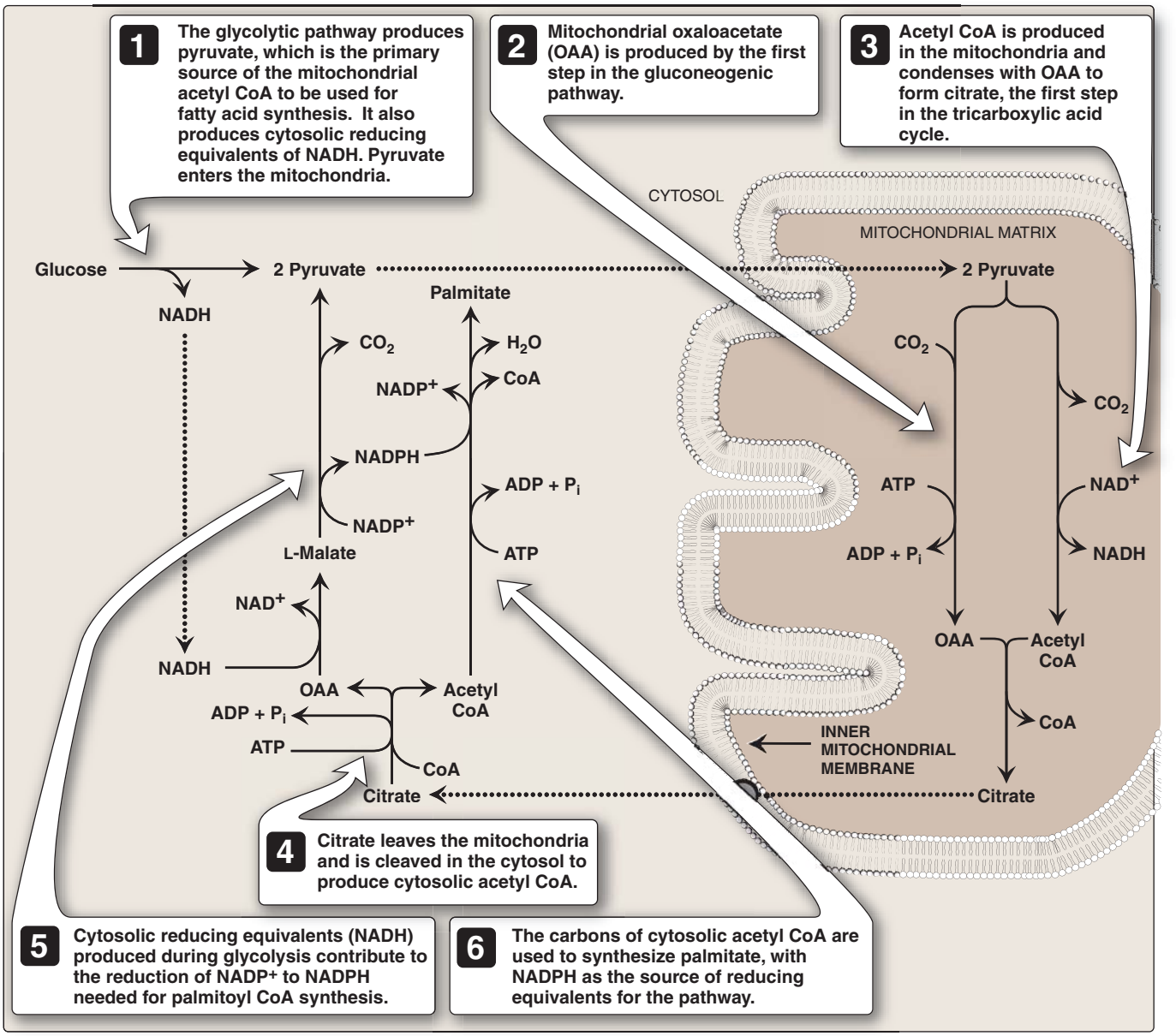


Figure 16.11
Interrelationship between glucose metabolism and palmitate synthesis.

E. Further elongation of fatty acid chains

Although palmitate, a 16-carbon, fully saturated long-chain length fatty acid (16:0), is the primary endproduct of *fatty acid synthase* activity, it can be further elongated by the addition of two-carbon units in the smooth endoplasmic reticulum (SER). Elongation requires a system of separate enzymes rather than a multifunctional enzyme. Malonyl CoA is the two-carbon donor and NADPH supplies the electrons. The brain has additional elongation capabilities, allowing it to produce the very-long-chain fatty acids (over 22 carbons) that are required for synthesis of brain lipids.

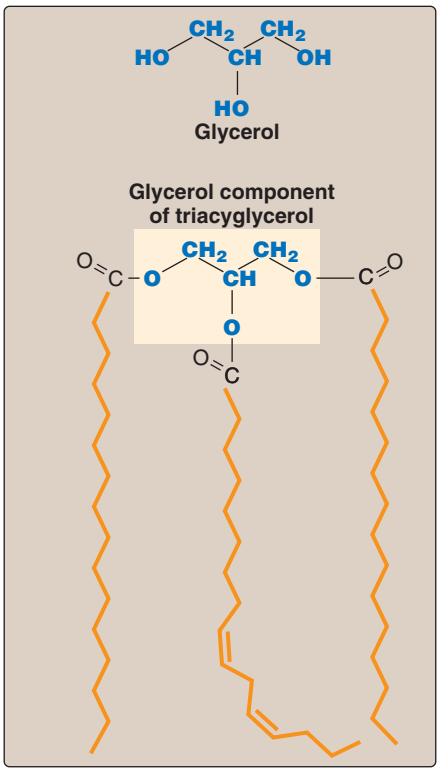


Figure 16.12
A triacylglycerol with an unsaturated fatty acid on carbon 2.

F. Desaturation of fatty acid chains

Enzymes (*desaturases*) also present in the SER are responsible for desaturating long-chain fatty acids (that is, adding cis double bonds). The desaturation reactions require NADH, cytochrome b_5 and its FAD-linked *reductase*. The first double bond is typically inserted between carbons 9 and 10, producing primarily 18:1(9) and small amounts of 16:1(9). A variety of polyunsaturated fatty acids can be made through additional desaturation combined with elongation.

> Humans have carbon 9, 6, 5 and 4 *desaturases*, but lack the ability to introduce double bonds from carbon 10 to the ω end of the chain. This is the basis for the nutritional essentiality of the polyunsaturated linoleic and linolenic acids.

G. Storage of fatty acids as components of triacylglycerols

Mono-, di-, and triacylglycerols consist of one, two, or three molecules of fatty acid esterified to a molecule of glycerol. Fatty acids are esterified through their carboxyl groups, resulting in a loss of negative charge and formation of "neutral fat." [Note: If a species of acylglycerol is solid at room temperature, it is called a "fat"; if liquid, it is called an "oil."]

1. **Structure of triacylglycerol (TAG):** The three fatty acids esterified to a glycerol molecule are usually not of the same type. The fatty acid on carbon 1 is typically saturated, that on carbon 2 is typically unsaturated, and that on carbon 3 can be either. Recall that the presence of the unsaturated fatty acid(s) decrease(s) the melting temperature (T_m) of the lipid. An example of a TAG molecule is shown in Figure 16.12.

2. **Storage of TAG:** Because TAGs are only slightly soluble in water and cannot form stable micelles by themselves, they coalesce within adipocytes to form oily droplets that are nearly anhydrous. These cytosolic lipid droplets are the major energy reserve of the body.

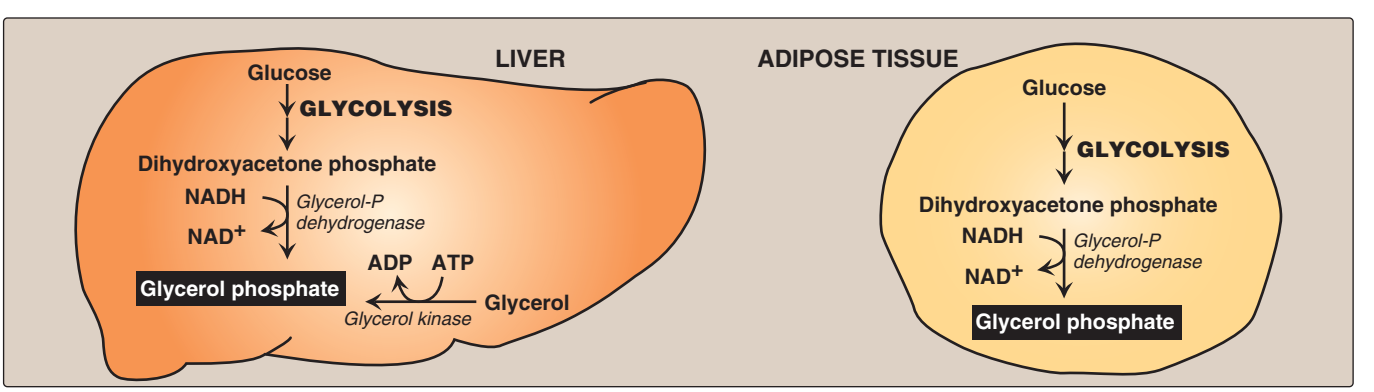


Figure 16.13
Pathways for production of glycerol phosphate in liver and adipose tissue.

3. **Synthesis of glycerol phosphate:** Glycerol phosphate is the initial acceptor of fatty acids during TAG synthesis. There are two pathways for glycerol phosphate production (Figure 16.13). In both liver (the primary site of TAG synthesis) and adipose tissue, glycerol phosphate can be produced from glucose, using first the reactions of the glycolytic pathway to produce dihydroxyacetone phosphate (DHAP, see p. 101). Next, DHAP is reduced by *glycerol phosphate dehydrogenase* to glycerol phosphate. A second pathway found in the liver, but not in adipose tissue, uses *glycerol kinase* to convert free glycerol to glycerol phosphate (see Figure 16.13). [Note: The glucose transporter in adipocytes (GLUT-4) is insulin-dependent (see p. 312). Thus, when plasma glucose—and, therefore, plasma insulin—levels are low, adipocytes have only a limited ability to synthesize glycerol phosphate, and cannot produce TAG.]

4. **Conversion of a free fatty acid to its activated form:** A fatty acid must be converted to its activated form (attached to CoA) before it can participate in metabolic processes such as TAG synthesis. This reaction, illustrated in Figure 15.6, is catalyzed by a family of *fatty acyl CoA synthetases* (*thiokinases*).

5. **Synthesis of a molecule of TAG from glycerol phosphate and fatty acyl CoA:** This pathway involves four reactions, shown in Figure 16.14. These include the sequential addition of two fatty acids from fatty acyl CoA, the removal of phosphate, and the addition of the third fatty acid.

H. Different fates of TAG in the liver and adipose tissue

In white adipose tissue, TAG is stored in a nearly anhydrous form as fat droplets in the cytosol of the cells. It serves as "depot fat," ready for mobilization when the body requires it for fuel. Little TAG is stored in the liver. Instead, most is exported, packaged with other lipids and apoproteins to form lipoprotein particles called very-low-density lipoproteins (VLDL). Nascent VLDL are secreted directly into the blood where they mature and function to deliver the endogenously derived lipids to the peripheral tissues. [Note: Recall that chylomicrons deliver primarily dietary (exogenously derived) lipids.] Plasma lipoproteins are discussed in Chapter 18.

IV. MOBILIZATION OF STORED FATS AND OXIDATION OF FATTY ACIDS

Fatty acids stored in adipose tissue, in the form of neutral TAG, serve as the body's major fuel storage reserve. TAGs provide concentrated stores of metabolic energy because they are highly reduced and largely anhydrous. The yield from the complete oxidation of fatty acids to CO_2 and H_2O is 9 kcal/g fat (as compared to 4 kcal/g protein or carbohydrate, see Figure 27.5). [Note: Fatty acids are also supplied to tissues by lipoproteins (see p. 228).]

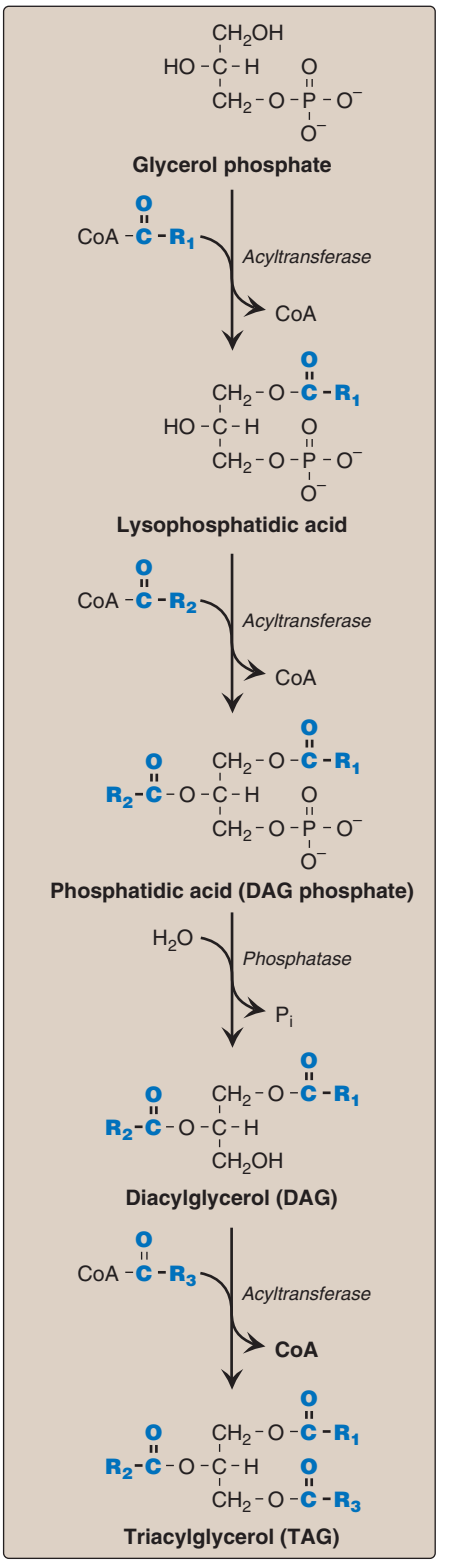


Figure 16.14
Synthesis of triacylglycerol.

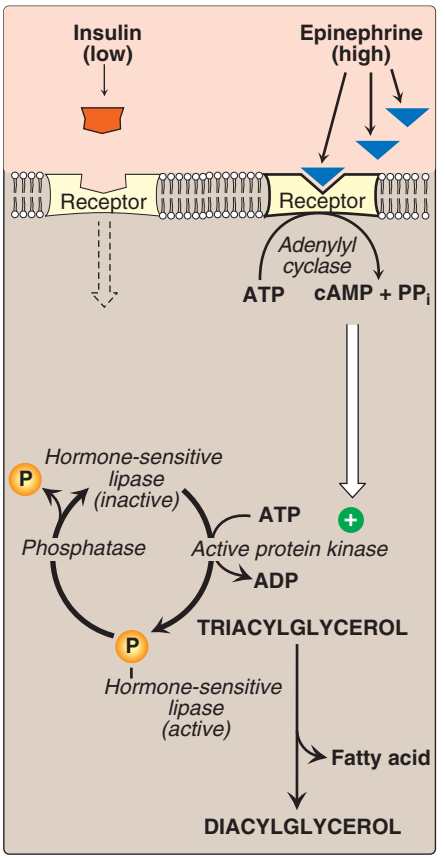


Figure 16.15
Hormonal regulation of triacylglycerol degradation in the adipocyte.

A. Release of fatty acids from TAG

The mobilization of stored fat requires the hydrolytic release of fatty acids and glycerol from their TAG form. This process is initiated by *hormone-sensitive lipase*, which removes a fatty acid from carbon 1 and/or carbon 3 of the TAG. Additional *lipases* specific for diacylglycerol or monoacylglycerol remove the remaining fatty acid(s).

1. **Activation of hormone-sensitive lipase (HSL):** This enzyme is activated when phosphorylated by a *3',5'-cyclic AMP(cAMP)–dependent protein kinase*. 3',5'-Cyclic AMP is produced in the adipocyte when one of several hormones (such as epinephrine or glucagon) binds to receptors on the cell membrane, and activates *adenylyl cyclase* (Figure 16.15). The process is similar to that of the activation of *glycogen phosphorylase* (see Figure 11.10). [Note: Because *acetyl CoA carboxylase* is inhibited by hormone-directed phosphorylation when the cAMP-mediated cascade is activated (see Figure 16.8), fatty acid synthesis is turned off when TAG degradation is turned on.] In the presence of high plasma levels of insulin and glucose, *HSL* is dephosphorylated, and becomes inactive.

2. **Fate of glycerol:** The glycerol released during TAG degradation cannot be metabolized by adipocytes because they apparently lack *glycerol kinase*. Rather, glycerol is transported through the blood to the liver, where it can be phosphorylated. The resulting glycerol phosphate can be used to form TAG in the liver, or can be converted to DHAP by reversal of the *glycerol phosphate dehydrogenase* reaction illustrated in Figure 16.13. DHAP can participate in glycolysis or gluconeogenesis.

3. **Fate of fatty acids:** The free (unesterified) fatty acids move through the cell membrane of the adipocyte, and bind to plasma albumin. They are transported to the tissues, enter cells, get activated to their CoA derivatives, and are oxidized for energy. Regardless of their levels, plasma free fatty acids (FFA) cannot be used for fuel by erythrocytes, which have no mitochondria. Brain, too, does not use fatty acids for energy, but the reasons are less clear. [Note: Over 50% of the fatty acids released from adipose TAG are reesterified to glycerol 3-phosphate. White adipose does not express *glycerol kinase*, and the phosphorylated glycerol is produced by glyceroneogenesis, an incomplete version of gluconeogenesis: pyruvate to PEP to OAA to DHAP to glycerol 3-phosphate. The process reduces plasma FFA, molecules associated with insulin resistance in type 2 diabetes and obesity (see p. 343).]

B. β-Oxidation of fatty acids

The major pathway for catabolism of fatty acids is a mitochondrial pathway called β-oxidation, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and $FADH_2$.

1. **Transport of long-chain fatty acids (LCFA) into the mitochondria:** After a LCFA enters a cell, it is converted in the cytosol to its CoA derivative by *long-chain fatty acyl CoA synthetase* (*thiokinase*), an enzyme of the outer mitochondrial membrane. Because β-oxida-

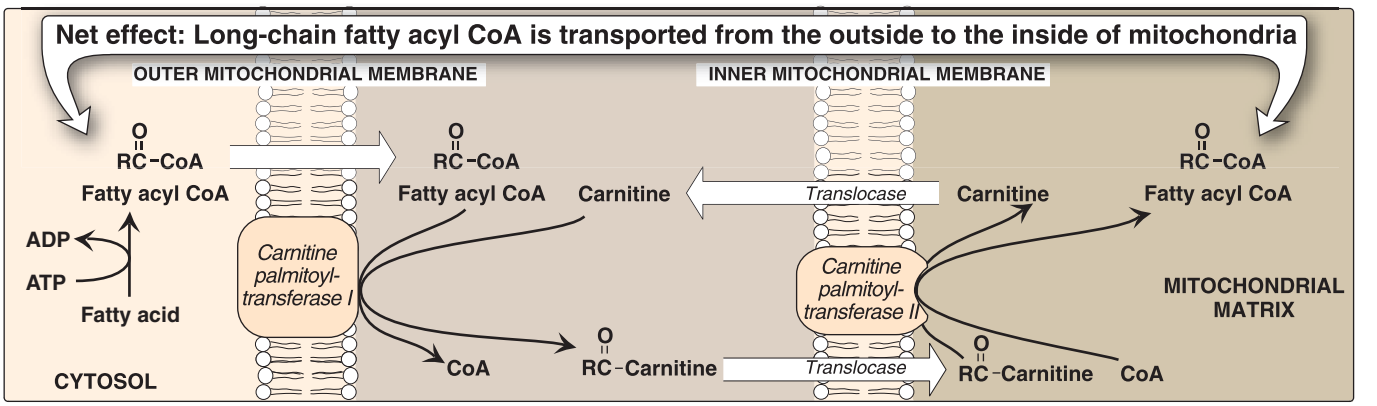


Figure 16.16
Carnitine shuttle. [Note: *Long-chain fatty acyl CoA synthetase* is in the outer mitochondrial membrane; active site faces the cytosol.]

tion occurs in the mitochondrial matrix, the fatty acid must be transported across the inner mitochondrial membrane that is impermeable to CoA. Therefore, a specialized carrier transports the long-chain acyl group from the cytosol into the mitochondrial matrix. This carrier is carnitine, and this rate-limiting transport process is called the carnitine shuttle (Figure 16.16).

a. Steps in LCFA translocation: First, the acyl group is transferred from CoA to carnitine by *carnitine palmitoyltransferase I* (*CPT-I*)—an enzyme of the outer mitochondrial membrane. [Note: *CPT-I* is also known as *CAT-I* for *carnitine acyltransferase I*.] This reaction forms acylcarnitine, and regenerates free CoA. Second, the acylcarnitine is transported into the mitochondrial matrix in exchange for free carnitine by *carnitine–acylcarnitine translocase*. *Carnitine palmitoyltransferase II* (*CPT-II*, or *CAT-II*)—an enzyme of the inner mitochondrial membrane—catalyzes the transfer of the acyl group from carnitine to CoA in the mitochondrial matrix, thus regenerating free carnitine.

b. Inhibitor of the carnitine shuttle: Malonyl CoA inhibits *CPT-I*, thus preventing the entry of long-chain acyl groups into the mitochondrial matrix. Therefore, when fatty acid synthesis is occurring in the cytosol (as indicated by the presence of malonyl CoA), the newly made palmitate cannot be transferred into the mitochondria and degraded. [Note: Muscle, though it does not synthesize fatty acids, contains the mitochondrial isoform of *acetyl CoA carboxylase* (*ACC2*), allowing muscle to regulate β-oxidation.] Fatty acid oxidation is also regulated by the acetyl CoA to CoA ratio: as the ratio increases, the CoA-requiring *thiolase* reaction decreases (Figure 16.17).

c. Sources of carnitine: Carnitine can be obtained from the diet, where it is found primarily in meat products. Carnitine can also be synthesized from the amino acids lysine and methionine by an enzymatic pathway found in the liver and kidney but not in skeletal or heart muscle. Therefore, these latter tissues are totally dependent on uptake of carnitine provided by endogenous synthesis or the diet, and distributed by the blood. [Note: Skeletal muscle contains about 97% of all carnitine in the body.]

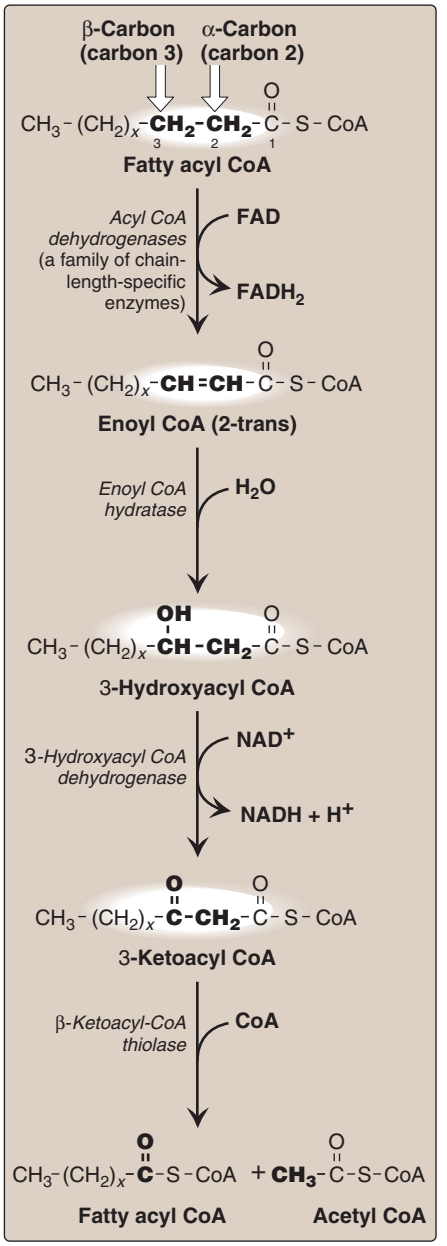


Figure 16.17
Enzymes involved in the β-oxidation of fatty acyl CoA. [Note: *Enoyl CoA hydratase* requires a trans double bond between carbon 2 and carbon 3.]

d. Carnitine deficiencies: Such deficiencies result in a decreased ability of tissues to use LCFA as a metabolic fuel. Secondary carnitine deficiency occurs in many situations, including: 1) in patients with liver disease causing decreased synthesis of carnitine; 2) in individuals suffering from malnutrition or those on strictly vegetarian diets; 3) in those with an increased requirement for carnitine as a result of, for example, pregnancy, severe infections, burns, or trauma; or 4) in those undergoing hemodialysis, which removes carnitine from the blood. Congenital deficiencies in one of the components of the *carnitine palmitoyltransferase* system, in renal tubular reabsorption of carnitine, or in carnitine uptake by cells cause primary carnitine deficiency. Genetic *CPT-I* deficiency affects the liver, where an inability to use LCFA for fuel greatly impairs that tissue's ability to synthesize glucose during a fast. This can lead to severe hypoglycemia, coma, and death. *CPT-II* deficiency occurs primarily in cardiac and skeletal muscle, where symptoms of carnitine deficiency range from cardiomyopathy to muscle weakness with myoglobinemia following prolonged exercise. [Note: This is an example of how the impaired flow of a metabolite from one cell compartment to another results in pathology.] Treatment includes avoidance of prolonged fasts, adopting a diet high in carbohydrate and low in LCFA, but supplemented with medium-chain fatty acids and carnitine.

2. **Entry of short- and medium-chain fatty acids into the mitochondria:** Fatty acids shorter than 12 carbons can cross the inner mitochondrial membrane without the aid of carnitine or the *CPT* system. Once inside the mitochondria, they are activated to their CoA derivatives by matrix enzymes, and are oxidized. [Note: Medium-chain fatty acids are plentiful in human milk. Because their oxidation is not dependent on *CPT-I*, it is not subject to inhibition by malonyl CoA.]

3. **Reactions of β-oxidation:** The first cycle of β-oxidation is shown in Figure 16.17. It consists of a sequence of four reactions involving the β-carbon (carbon 3) that results in shortening the fatty acid chain by two carbons. The steps include an oxidation that produces $FADH_2$, a hydration step, a second oxidation that produces NADH, and a thiolytic cleavage that releases a molecule of acetyl CoA. Each step is catalyzed by enzymes with chain-length specificity. These four steps are repeated for saturated fatty acids of even-numbered carbon chains (n/2) – 1 times (where n is the number of carbons), each cycle producing an acetyl group plus one NADH and one $FADH_2$. The final thiolytic cleavage produces two acetyl groups. [Note: Acetyl CoA is a positive allosteric effector of *pyruvate carboxylase* (see p. 119), thus linking fatty acid oxidation and gluconeogenesis.]

4. **Energy yield from fatty acid oxidation:** The energy yield from the β-oxidation pathway is high. For example, the oxidation of a molecule of palmitoyl CoA to CO_2 and H_2O produces 8 acetyl CoA, 7 NADH, and 7 $FADH_2$, from which 131 ATP can be generated; however, activation of the fatty acid requires 2 ATP. Thus, the net yield from palmitate is 129 ATP (Figure 16.18). A comparison of the processes of synthesis and degradation of long-chain saturated fatty acids with an even number of carbon atoms is provided in Figure 16.19.

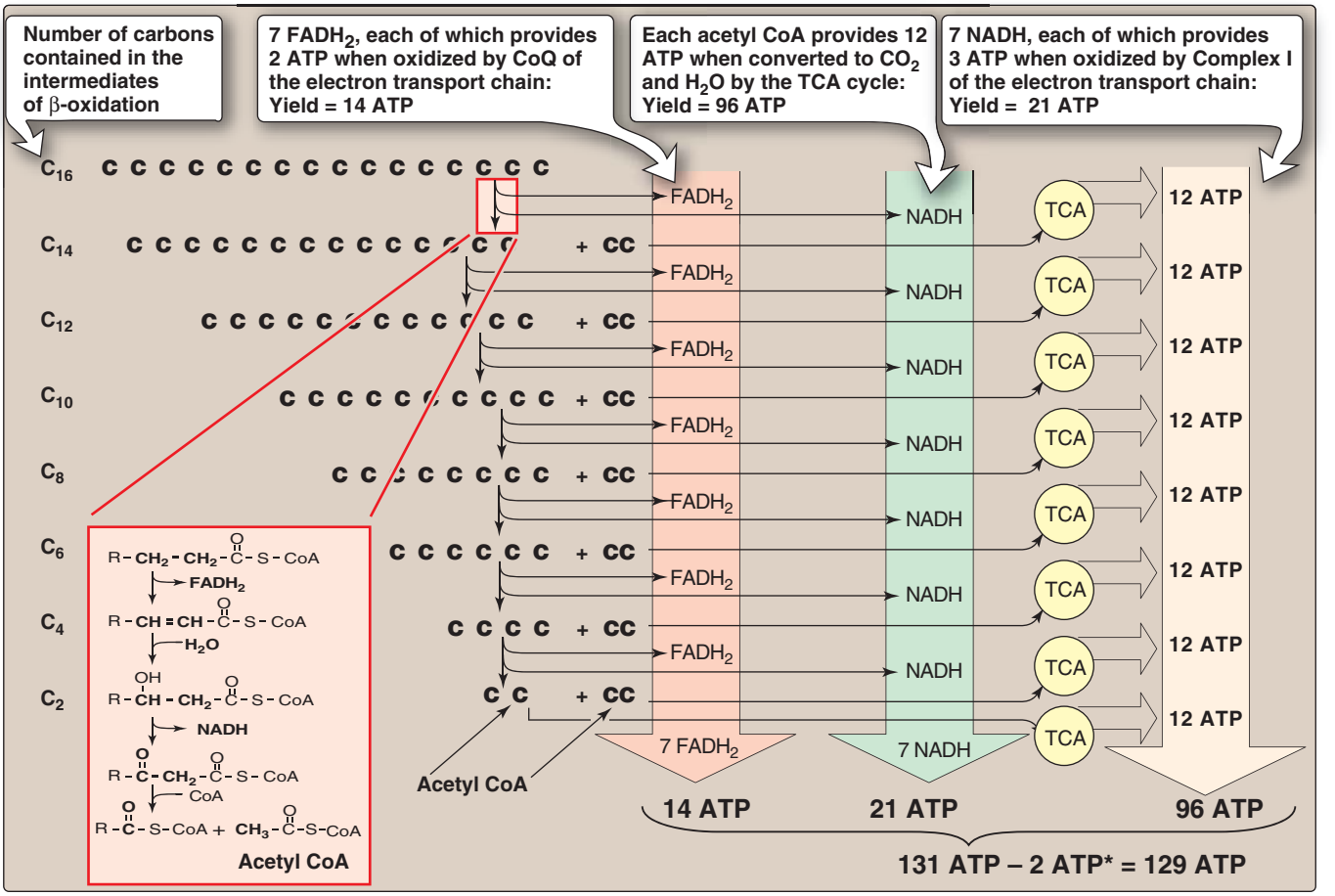


Figure 16.18
Summary of the energy yield from the oxidation of palmitoyl CoA (16 carbons). CC = acetyl CoA. *Activation of palmitate to palmitoyl CoA requires the equivalent of 2 ATP.

5. **Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency:** In mitochondria, there are four *fatty acyl CoA dehydrogenase* species, each with a specificity for either short-, medium-, long-, or very-long-chain fatty acids. *MCAD* deficiency, an autosomal recessive disorder, is one of the most common inborn errors of metabolism, and the most common inborn error of fatty acid oxidation, being found in 1:14,000 births worldwide, with a higher incidence in Northern Europeans. It results in decreased ability to oxidize fatty acids with six to ten carbons (these accumulate and can be measured in urine), and severe hypoglycemia (because the tissues must increase their reliance on glucose). Treatment includes avoidance of fasting. *MCAD* deficiency has been identified as the cause of some cases originally reported as sudden infant death syndrome (SIDS) or Reye syndrome.

6. **Oxidation of fatty acids with an odd number of carbons:** The β-oxidation of a saturated fatty acid with an odd number of carbon atoms proceeds by the same reaction steps as that of fatty acids with an even number, until the final three carbons are reached. This compound, propionyl CoA, is metabolized by a three-step pathway (Figure 16.20). [Note: Propionyl CoA is also produced during the metabolism of certain amino acids (see Figure 20.10).]

	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Primarily cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymers	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	
Inhibitor	Long-chain fatty acyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis

Figure 16.19
Comparison of the synthesis and degradation of long-chain, even-numbered, saturated fatty acids.

a. Synthesis of D-methylmalonyl CoA: First, propionyl CoA is carboxylated, forming D-methylmalonyl CoA. The enzyme *propionyl CoA carboxylase* has an absolute requirement for the coenzyme biotin, as do most other *carboxylases* (see p. 381).

b. Formation of L-methylmalonyl CoA: Next, the D-isomer is converted to the L-form by the enzyme, *methylmalonyl CoA racemase*.

c. Synthesis of succinyl CoA: Finally, the carbons of L-methylmalonyl CoA are rearranged, forming succinyl CoA, which can enter the tricarboxylic acid (TCA) cycle (see p. 109). [Note: This is the only example of a glucogenic precursor generated from fatty acid oxidation.] The enzyme, *methylmalonyl CoA mutase*, requires a coenzyme form of vitamin B_{12} (deoxyadenosylcobalamin) for its action. The *mutase* reaction is one of only two reactions in the body that require vitamin B_{12} (see p. 375). [Note: In patients with vitamin B_{12} deficiency, both propionate and methylmalonate are excreted in the urine. Two types of heritable methylmalonic acidemia and aciduria have been described: one in which the *mutase* is missing or deficient (or has reduced affinity for the coenzyme), and one in which the patient is unable to convert vitamin B_{12} into its coenzyme form. Either type results in metabolic acidosis, with developmental retardation seen in some patients.]

7. Oxidation of unsaturated fatty acids: The oxidation of unsaturated fatty acids provides less energy than that of saturated fatty acids because unsaturated fatty acids are less highly reduced and, therefore, fewer reducing equivalents can be produced from these structures. Oxidation of monounsaturated fatty acids, such as 18:1(9) (oleic acid) requires one additional enzyme, *3,2-enoyl CoA isomerase*, which converts the 3-trans derivative obtained after three rounds of β-oxidation to the 2-trans derivative required as a substrate by the *enoyl CoA hydratase*. Oxidation of polyunsaturated fatty acids, such as 18:2(9,12) (linoleic acid), requires an *NADPH-dependent 2,4-dienoyl CoA reductase* in addition to the *isomerase*.

8. β-Oxidation in the peroxisome: Very-long-chain fatty acids (VLCFA), or those 22 carbons long or longer, undergo a preliminary β-oxidation in peroxisomes. The shortened fatty acid (linked to carnitine) diffuses to a mitochondrion for further oxidation. In contrast to mitochondrial β-oxidation, the initial dehydrogenation in peroxisomes is catalyzed by an FAD-containing *acyl CoA oxidase*. The $FADH_2$ produced is oxidized by molecular oxygen, which is reduced to H_2O_2; thus, no ATP is generated by this step. The H_2O_2 is reduced to H_2O by *catalase* (see p. 148). [Note: Genetic defects either in the ability to target matrix proteins to peroxisomes (resulting in Zellweger syndrome—a peroxisomal biogenesis disorder) or in the ability to transport VLCFA across the peroxisomal membrane (resulting in X-linked adrenoleukodystrophy), lead to accumulation of VLCFA in the blood and tissues.]

C. α-Oxidation of fatty acids

Branched-chain, 20 carbon fatty acid, phytanic acid: This is not a substrate for *acyl CoA dehydrogenase* because of the methyl group on its β carbon (Figure 16.21). Instead, it is hydroxylated at the α-carbon by *phytanoyl CoA α-hydroxylase* (*PhyH*), carbon 1 is released as CO_2, and the product, 19 carbon pristanic acid, is activated to its CoA derivative and undergoes β-oxidation. Refsum disease is a rare, autosomal recessive disorder caused by a deficiency of peroxisomal *PhyH*. This results in the accumulation of phytanic acid in the plasma and tissues. The symptoms are primarily neurologic, and the treatment involves dietary restriction to halt disease progression. [Note: ω-Oxidation (at the methyl terminus) also is known, and generates dicarboxylic acids. Normally a minor pathway of the ER, its up-regulation is seen with conditions such as MCAD deficiency that limit fatty acid β-oxidation.]

V. KETONE BODIES: AN ALTERNATE FUEL FOR CELLS

Liver mitochondria have the capacity to convert acetyl CoA derived from fatty acid oxidation into ketone bodies. The compounds categorized as ketone bodies are acetoacetate, 3-hydroxybutyrate (also called β-hydroxybutyrate), and acetone (a nonmetabolized side product, Figure 16.22). [Note: The two functional ketone bodies are actually organic acids.] Acetoacetate and 3-hydroxybutyrate are transported in the blood to the peripheral tissues. There they can be reconverted to acetyl CoA, which can be oxidized by the TCA cycle. Ketone bodies

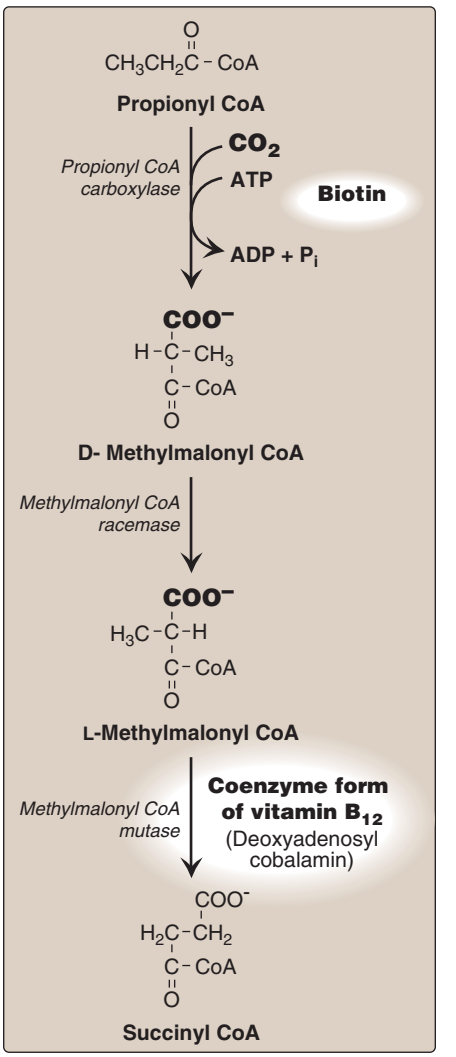


Figure 16.20
Metabolism of propionyl CoA.

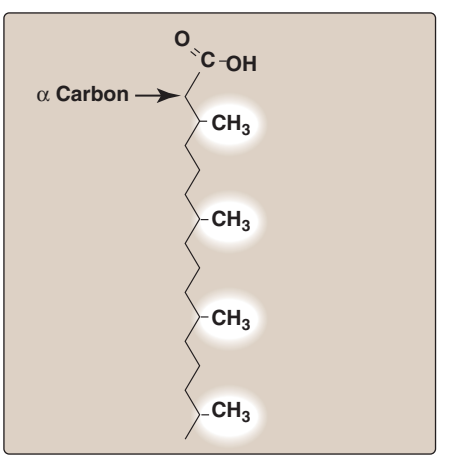


Figure 16.21
Phytanic acid—a branched-chain fatty acid.

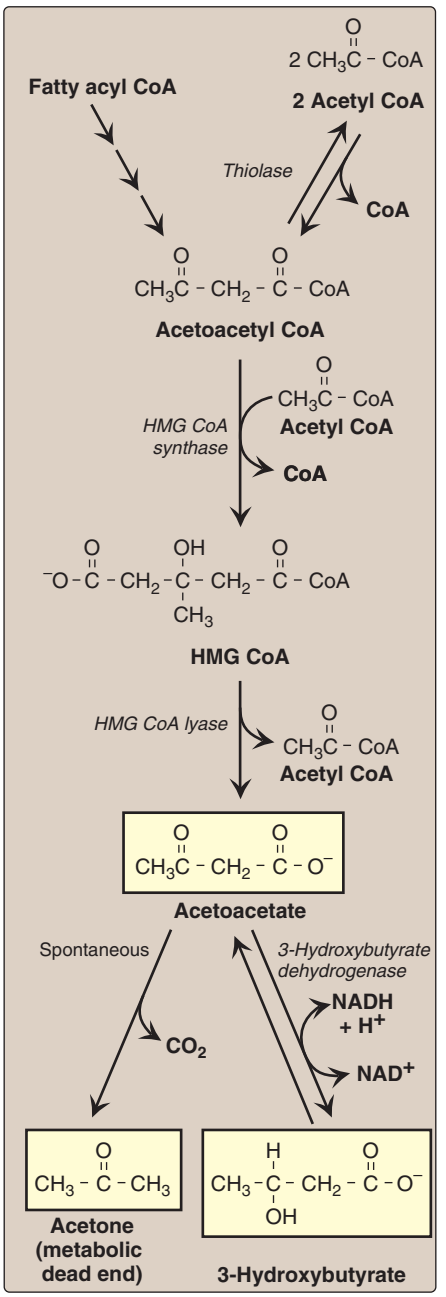


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.

are important sources of energy for the peripheral tissues because 1) they are soluble in aqueous solution and, therefore, do not need to be incorporated into lipoproteins or carried by albumin as do the other lipids; 2) they are produced in the liver during periods when the amount of acetyl CoA present exceeds the oxidative capacity of the liver; and 3) they are used in proportion to their concentration in the blood by extrahepatic tissues, such as the skeletal and cardiac muscle and renal cortex. Even the brain can use ketone bodies to help meet its energy needs if the blood levels rise sufficiently; thus, ketone bodies spare glucose.This is particularly important during prolonged periods of fasting (see p. 332). [Note: Disorders of fatty acid oxidation present with the general picture of hypoketosis (due to decreased availability of acetyl CoA) and hypoglycemia (due to increased reliance on glucose for energy.]

A. Synthesis of ketone bodies by the liver: ketogenesis

During a fast, the liver is flooded with fatty acids mobilized from adipose tissue. The resulting elevated hepatic acetyl CoA produced primarily by fatty acid degradation inhibits *pyruvate dehydrogenase* (see p. 111), and activates *pyruvate carboxylase* (see p. 119). The OAA thus produced is used by the liver for gluconeogenesis rather than for the TCA cycle. Therefore, acetyl CoA is channeled into ketone body synthesis. [Note: Fatty acid oxidation decreases the NAD^+ to NADH ratio, and the rise in NADH shifts OAA to malate (see p. 113). This pushes acetyl CoA away from gluconeogenesis and into ketogenesis (Figure 16.24).]

1. **Synthesis of 3-hydroxy-3-methylglutaryl (HMG) CoA:** The first synthetic step, formation of acetoacetyl CoA, occurs by reversal of the *thiolase* reaction of fatty acid oxidation (see Figure 16.17). Mitochondrial *HMG CoA synthase* combines a third molecule of acetyl CoA with acetoacetyl CoA to produce HMG CoA. [Note: HMG CoA is also a precursor of cholesterol (see p. 220). These pathways are separated by location in, and conditions of, the cell.] *HMG CoA synthase* is the rate-limiting step in the synthesis of ketone bodies, and is present in significant quantities only in the liver.

2. **Synthesis of the ketone bodies:** HMG CoA is cleaved to produce acetoacetate and acetyl CoA, as shown in Figure 16.22. Acetoacetate can be reduced to form 3-hydroxybutyrate with NADH as the hydrogen donor. Acetoacetate can also spontaneously decarboxylate in the blood to form acetone—a volatile, biologically nonmetabolized compound that can be released in the breath. The equilibrium between acetoacetate and 3-hydroxybutyrate is determined by the NAD^+/NADH ratio. Because this ratio is low during fatty acid oxidation, 3-hydroxybutyrate synthesis is favored. [Note: The generation of free CoA during ketogenesis allows fatty acid oxidation to continue.]

B. Use of ketone bodies by the peripheral tissues: ketolysis

Although the liver constantly synthesizes low levels of ketone bodies, their production becomes much more significant during fasting

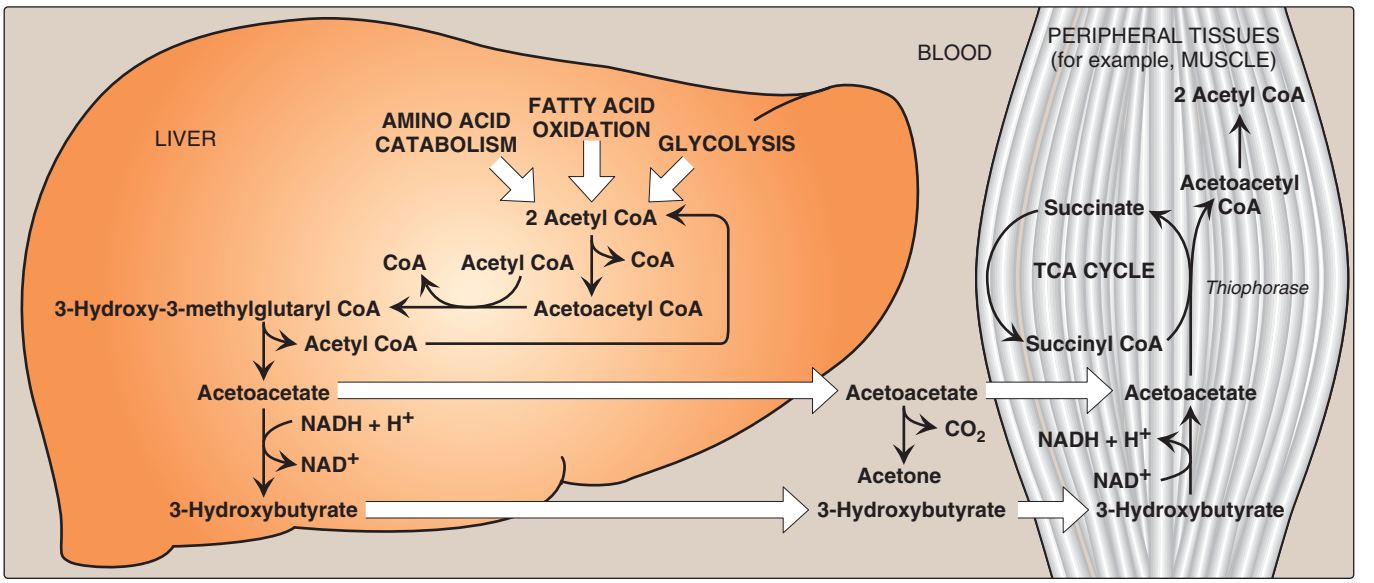


Figure 16.23
Ketone body synthesis in the liver and use in peripheral tissues. [Note: *Thiophorase* is also known as *succinyl CoA: acetoacetate CoA transferase*.]

when ketone bodies are needed to provide energy to the peripheral tissues. 3-Hydroxybutyrate is oxidized to acetoacetate by *3-hydroxybutyrate dehydrogenase*, producing NADH (Figure 16.23). Acetoacetate is then provided with a CoA molecule taken from succinyl CoA by *succinyl CoA:acetoacetate CoA transferase* (*thiophorase*). This reaction is reversible, but the product, acetoacetyl CoA, is actively removed by its conversion to two acetyl CoA. Extrahepatic tissues, including the brain but excluding cells lacking mitochondria (for example, red blood cells), efficiently oxidize acetoacetate and 3-hydroxybutyrate in this manner. In contrast, although the liver actively produces ketone bodies, it lacks *thiophorase* and, therefore, is unable to use ketone bodies as fuel.

C. Excessive production of ketone bodies in diabetes mellitus

When the rate of formation of ketone bodies is greater than the rate of their use, their levels begin to rise in the blood (ketonemia) and, eventually, in the urine (ketonuria). This is seen most often in cases of uncontrolled, type 1 diabetes mellitus. In diabetic individuals with severe ketosis, urinary excretion of the ketone bodies may be as high as 5,000 mg/24 hr, and the blood concentration may reach 90 mg/dl (versus less than 3 mg/dl in normal individuals). A frequent symptom of diabetic ketoacidosis is a fruity odor on the breath, which results from increased production of acetone. An elevation of the ketone body concentration in the blood results in acidemia. [Note: The carboxyl group of a ketone body has a pK_a of about 4. Therefore, each ketone body loses a proton (H^+) as it circulates in the blood, which lowers the pH of the body. Also, excretion of glucose and ketone bodies in the urine results in dehydration of the body. Therefore, the increased number of H^+, circulating in a decreased volume of plasma, can cause severe acidosis (ketoacidosis).] Ketoacidosis may also be seen in cases of fasting (see p. 330).

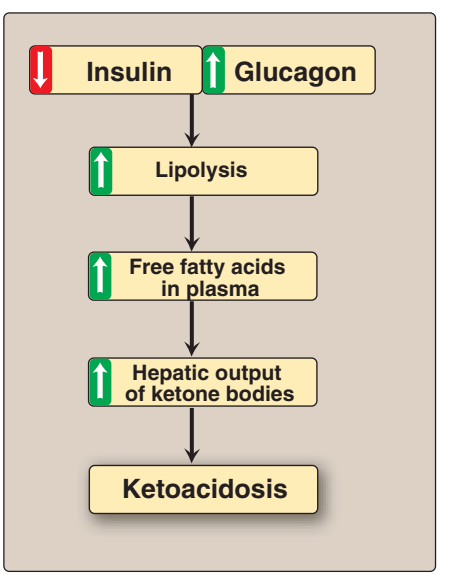


Figure 16.24
Mechanism of diabetic ketoacidosis seen in type 1 diabetes.

VI. CHAPTER SUMMARY

Generally a linear hydrocarbon chain with a terminal carboxyl group, a fatty acid can be **saturated** or **unsaturated**. Two fatty acids are essential (must be obtained from the diet): **linoleic** and **α-linolenic acids**. Fatty acids are synthesized in the cytosol of **liver** following a meal containing excess carbohydrate and protein. Carbons used to synthesize fatty acids are provided by **acetyl CoA**, energy by **ATP**, and reducing equivalents by **NADPH** (Figure 16.25). **Citrate** carries two-carbon acetyl units from the mitochondrial matrix to the cytosol. The regulated step in fatty acid synthesis is catalyzed by **acetyl CoA carboxylase**, which requires **biotin**. **Citrate** is the allosteric **activator** and **long-chain fatty acyl CoA** is the **inhibitor**. The enzyme can also be activated in the presence of **insulin** and inactivated by **AMPK** in response to **epinephrine**, **glucagon**, or a **rise in AMP**. The rest of the steps in fatty acid synthesis are catalyzed by the multifunctional enzyme, **fatty acid synthase**, which produces **palmitoyl CoA** from acetyl CoA and malonyl CoA, with NADPH (from the pentose phosphate pathway) as the source of reducing equivalents. Fatty acids can be elongated and desaturated in the ER. When fatty acids are required by the body for energy, adipose cell **hormone-sensitive lipase** (**activated** by **epinephrine** or **glucagon**, and **inhibited** by **insulin**) initiates degradation of stored triacylglycerol. Fatty acids are carried by **serum albumin** to the liver and peripheral tissues, where oxidation of the fatty acids provides energy. The **glycerol** backbone of the degraded triacylglycerol is carried by the blood to the **liver**, where it serves as an important **gluconeogenic precursor**. Fatty acid degradation (**β-oxidation**) occurs in **mitochondria**. The **carnitine shuttle** is required to transport LCFA from the cytosol to the mitochondrial matrix. A translocase and the enzymes **carnitine palmitoyltransferases I** and **II** are required. Carnitine palmitoyltransferase I is **inhibited** by **malonyl CoA**. This prevents fatty acids being synthesized in the cytosol from malonyl CoA from being transported into the mitochondria where they would be degraded. Once in the mitochondria, fatty acids are oxidized, producing acetyl CoA, NADH, and $FADH_2$. The first step in the β-oxidation pathway is catalyzed by one of a family of four acyl CoA dehydrogenases, each of which has a specificity for either short-, medium-, long-, or very-long-chain fatty acids. **Medium-chain fatty acyl CoA dehydrogenase** (**MCAD**) **deficiency** is one of the most common inborn errors of metabolism. It causes a decrease in fatty acid oxidation (process stops once a medium chain fatty acid is produced), resulting in hypoketonemia and severe hypoglycemia. Oxidation of fatty acids with an odd number of carbons proceeds two carbons at a time (producing acetyl CoA) until three carbons remain (**propionyl CoA**). This compound is converted to **methylmalonyl CoA** (a reaction requiring **biotin**), which is then converted to **succinyl CoA** (a gluconeogenic precursor) by methylmalonyl CoA mutase (requiring **vitamin B_{12}**). A genetic error in the mutase or vitamin B_{12} deficiency causes **methylmalonic acidemia** and **aciduria**. β-Oxidation of VLCFA and α-oxidation of branched-chain fatty acids occur in the peroxisome. ω-Oxidation occurs in the ER. Liver mitochondria can convert acetyl CoA derived from fatty acid oxidation into the ketone bodies, **acetoacetate** and **3-hydroxybutyrate**. Peripheral tissues possessing mitochondria can oxidize 3-hydroxybutyrate to acetoacetate, which can be reconverted to acetyl CoA, thus producing energy for the cell. Unlike fatty acids, ketone bodies are utilized by the **brain** and, therefore, are important fuels during a fast. The liver lacks the ability to degrade ketone bodies, and so synthesizes them specifically for the peripheral tissues. **Ketoacidosis** occurs when the rate of formation of ketone bodies is greater than their rate of use, as is seen in cases of uncontrolled, **type 1 diabetes mellitus**.

Study Questions

Choose the ONE correct answer.

16.1 Triacylglycerol molecules stored in adipose tissue represent the major reserve of substrate providing energy during a prolonged fast. During such a fast:

A. the stored fatty acids are released from adipose tissue into the plasma as components of the serum lipoprotein particle, VLDL.

B. free fatty acids are produced at a high rate in the plasma by the action of lipoprotein lipase on chylomicrons.

C. glycerol produced by the degradation of triacylglycerol is an important direct source of energy for adipocytes and fibroblasts.

D. hormone-sensitive lipase is phosphorylated and activated by a cAMP-activated protein kinase.

Correct answer = D. Hormone-sensitive lipase is phosphorylated by cAMP-activated protein kinase, which is itself activated by epinephrine or glucagon. Fatty acids released from adipose tissue are carried in the plasma by serum albumin, not VLDL. During a fast, the amount of circulating triacylglycerol (found in chylomicrons and VLDL) will be low. Therefore, there is little substrate for lipoprotein lipase. The glycerol produced during triacylglycerol degradation cannot be metabolized by adipocytes or fibroblasts, but rather must go to the liver where it can be phosphorylated (by glycerol kinase).

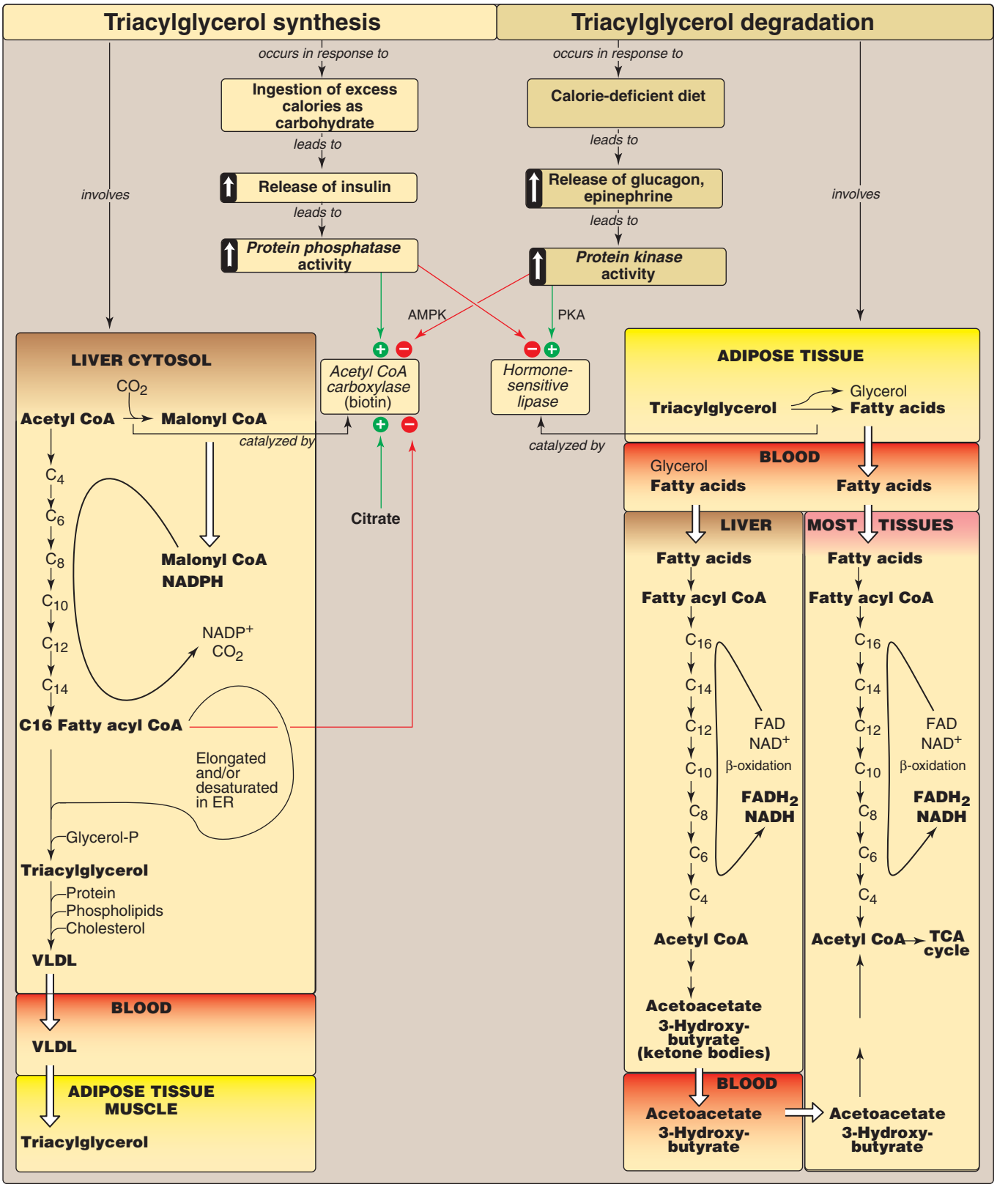


Figure 16.25
Key concept map for fatty acid and triacylglycerol metabolism.

16.2 A low level of carbon dioxide labeled with ^{14}C is accidentally released into the atmosphere surrounding industrial workers as they resume work following the lunch hour. Unknowingly, they breathe the contaminated air for 1 hour. Which of the following compounds will be radioactively labeled?

A. All of the carbon atoms of newly synthesized fatty acid.
B. About one half of the carbon atoms of newly synthesized fatty acids.
C. The carboxyl atom of newly synthesized fatty acids.
D. About one third of the carbons of newly synthesized malonyl CoA.
E. One half of the carbon atoms of newly synthesized acetyl CoA.

Correct answer = D. Malonyl CoA (three carbons) is synthesized from acetyl CoA (two carbons) by the addition of CO_2, using the enzyme acetyl CoA carboxylase. Because CO_2 is subsequently removed during fatty acid synthesis, the radioactive label will not appear at any position in newly synthesized fatty acids.

16.3 A teenager, concerned about his weight, attempts to maintain a fat-free diet for a period of several weeks. If his ability to synthesize various lipids were examined, he would be found to be most deficient in his ability to synthesize:

A. triacylglycerol.
B. phospholipids.
C. cholesterol.
D. sphingolipids.
E. prostaglandins.

Correct answer = E. Prostaglandins are synthesized from arachidonic acid. Arachidonic acid is synthesized from linoleic acid, an essential fatty acid obtained by humans from dietary lipids. The teenager would be able to synthesize all other compounds, but presumably in somewhat depressed amounts.

16.4 A 6-month-old boy was hospitalized following a seizure. History revealed that for several days prior, his appetite was decreased due to a "stomach virus". At admission, his blood glucose was 24 mg/dl (age-referenced normal is 60-100). His urine was negative for ketone bodies, but positive for a variety of dicarboxylic acids. A tentative diagnosis of medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency is made. In patients with MCAD deficiency, the fasting hypoglycemia is a consequence of:

A. decreased acetyl CoA production.
B. decreased ability to convert acetyl CoA to glucose.
C. increased conversion of acetyl CoA to acetoacetate.
D. increased production of ATP and NADH.

Correct answer = A. Impaired oxidation of fatty acids less than 12 carbons in length results in decreased production of acetyl CoA, the allosteric activator of pyruvate carboxylase, a gluconeogenic enzyme; thus, glucose levels fall. Acetyl CoA cannot be used for the net synthesis of glucose. Acetoacetate is a ketone body, and with MCAD deficiency ketogenesis is decreased. Impaired fatty acid oxidation means that less ATP and NADH are made, and both are needed for gluconeogenesis.

16.5 Explain why with Zellweger syndrome both very long chain fatty acids (VLCFA) and phytanic acid accumulate, whereas with X-linked adrenoleukodystrophy (X-ALD) only VLCFA accumulate.

Zellweger syndrome is caused by an inability to target matrix proteins to the peroxisome; thus, all peroxisomal activities are affected because functional peroxisomes are not able to be formed. In X-ALD, the defect is an inability to transport VLCFA into the peroxisome—other peroxisomal functions such as α oxidation are normal.