33 Synthesis of Fatty Acids, Triacylglycerols, and the Major Membrane Lipids

Fatty acids are synthesized mainly in the liver in humans, with dietary glucose serving as the major source of carbon. Glucose is converted through glycolysis to pyruvate, which enters the mitochondrion and forms both acetyl CoA and oxaloacetate (Fig. 33.1). These two compounds condense, forming citrate. Citrate is transported to the ***cytosol,*** *where it is cleaved to form acetyl CoA, the source of carbon for the reactions that occur on the* ***fatty acid synthase complex****. The key regulatory enzyme for the process,* ***acetyl CoA carboxylase****, produces* ***malonyl CoA*** *from acetyl CoA.*

The growing fatty acid chain, attached to the fatty acid synthase complex in the cytosol, is elongated by the sequential addition of 2-carbon units provided by malonyl CoA. ***NADPH****, produced by the* ***pentose phosphate pathway*** *and* ***the malic enzyme****, provides* ***reducing equivalents****. When the growing fatty acid chain is 16 carbons in length, it is released as* ***palmitate****. After activation to a CoA derivative, palmitate can be elongated and desaturated to produce a series of fatty acids.*

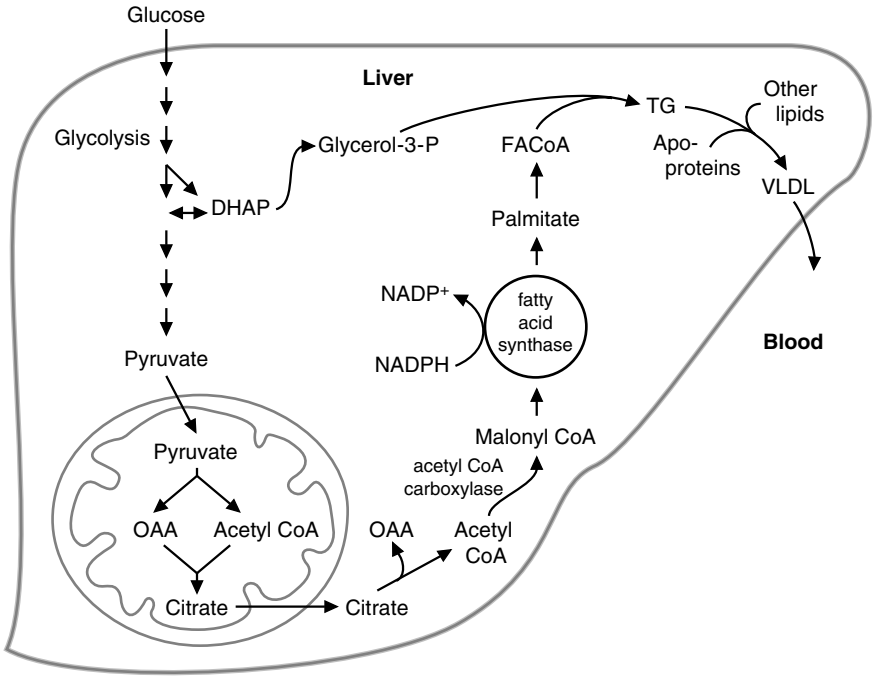


Fig. 33.1. Lipogenesis, the synthesis of triacylglycerols from glucose. In humans, the synthesis of fatty acids from glucose occurs mainly in the liver. Fatty acids (FA) are converted to triacylglycerols (TG), packaged in VLDL, and secreted into the blood. OAA = oxaloacetate.

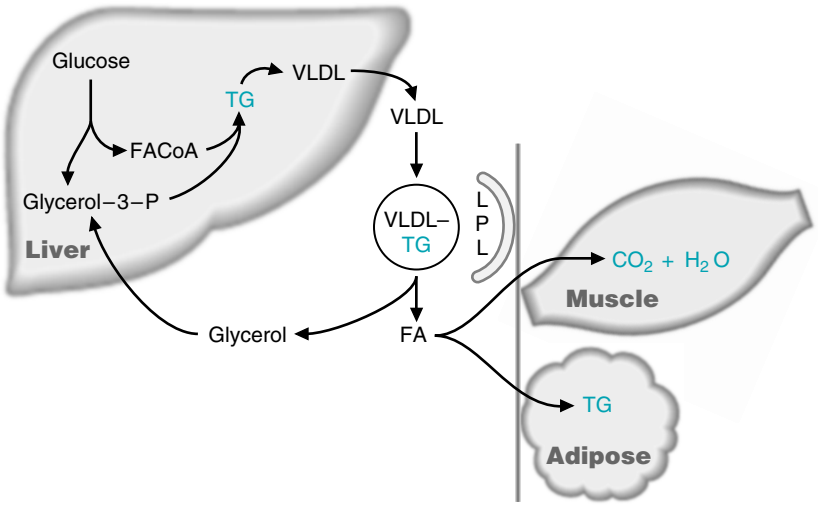


Fig. 33.2. Fate of VLDL triacylglycerol (TG). The TG of VLDL, produced in the liver, is digested by lipoprotein lipase (LPL) present on the lining cells of the capillaries in adipose and skeletal muscle tissue. Fatty acids are released and either oxidized or stored in tissues as TG. Glycerol is used by the liver and other tissues that contain glycerol kinase. FA = fatty acid (or fatty acyl group).

Fatty acids, produced in cells or obtained from the diet, are used by various tissues for the synthesis of ***triacylglycerols*** *(the major storage form of fuel) and the* ***glycerophospholipids*** *and* ***sphingolipids*** *(the major components of cell membranes).*

In the liver, triacylglycerols are produced from fatty acyl CoA and glycerol 3-phosphate. ***Phosphatidic acid*** *serves as an intermediate in this pathway. The triacylglycerols are not stored in the liver but rather packaged with apoproteins and other lipids in* ***very-low-density lipoprotein (VLDL)*** *and secreted into the blood (see Fig. 33.1).*

In the capillaries of various tissues (particularly adipose tissue, muscle, and the lactating mammary gland), ***lipoprotein lipase (LPL)*** *digests the triacylglycerols of VLDL, forming* ***fatty acids*** *and* ***glycerol*** *(Fig. 33.2). The glycerol travels to the liver and other tissues where it is used. Some of the fatty acids are oxidized by muscle and other tissues. After a meal, however, most of the fatty acids are converted to triacylglycerols in* ***adipose cells****, where they are* ***stored****. These fatty acids are released during fasting and serve as the predominant fuel for the body.*

Glycerophospholipids *are also synthesized from fatty acyl CoA, which forms esters with glycerol 3-phosphate, producing phosphatidic acid. Various head groups are added to carbon 3 of the glycerol 3-phosphate moiety of phosphatidic acid, generating amphipathic compounds such as* ***phosphatidylcholine****,* ***phosphatidylinositol****, and* ***cardiolipin*** *(Fig. 33.3). In the formation of* ***plasmalogens*** *and* ***platelet-activating factor (PAF)****, a long-chain fatty alcohol forms an* ***ether*** *with carbon 1, replacing the fatty acyl ester (Fig. 33.4). Cleavage of phospholipids is catalyzed by* ***phospholipases*** *found in cell membranes, lysosomes, and pancreatic juice.*

Sphingolipids*, which are prevalent in membranes and the myelin sheath of the central nervous system, are built on* ***serine*** *rather than glycerol. In the synthesis of sphingolipids, serine and palmityl CoA condense, forming a compound that is related to* ***sphingosine****. Reduction of this compound, followed by addition of a second fatty acid in amide linkage, produces* ***ceramide****. Carbohydrate groups attach to ceramide, forming* ***glycolipids*** *such as the* ***cerebrosides****,* ***globosides****, and* ***gangliosides*** *(Fig. 33.5). The addition of* ***phosphocholine*** *to ceramide produces* ***sphingomyelin****. These sphingolipids are degraded by lysosomal enzymes.*

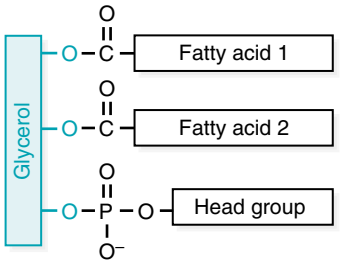


Fig. 33.3. General structure of a glycerophospholipid. The fatty acids are joined by ester bonds to the glycerol moiety. Various combinations of fatty acids may be present. The fatty acid at carbon 2 of the glycerol is usually unsaturated. The head group is the group attached to the phosphate on position 3 of the glycerol moiety. The most common head group is choline, but ethanolamine, serine, inositol, or phosphatidylglycerol also may be present. The phosphate group is negatively charged, and the head group may carry a positive charge (choline and ethanolamine), or both a positive and a negative charge (serine). The inositol may be phosphorylated and, thus, negatively charged.

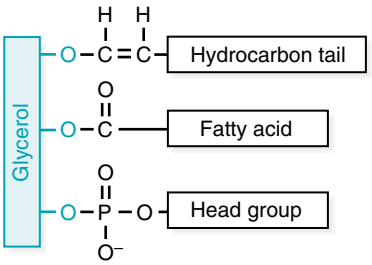


Fig. 33.4. General structure of a plasmalogen. Carbon 1 of glycerol is joined to a long-chain fatty alcohol by an ether linkage. The fatty alcohol group has a double bond between carbons 1 and 2. The head group is usually ethanolamine or choline.

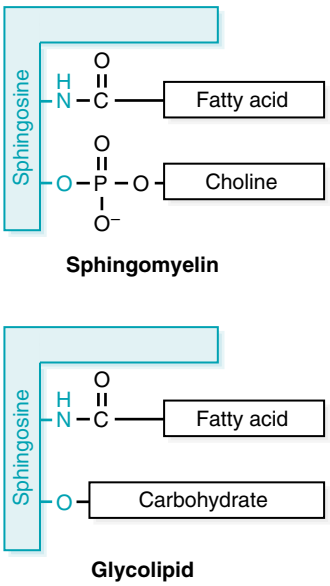


Fig. 33.5. General structures of the sphingolipids. The "backbone" is sphingosine rather than glycerol. Ceramide is sphingosine with a fatty acid joined to its amino group by an amide linkage. Sphingomyelin contains phosphocholine, whereas glycolipids contain carbohydrate groups.

The dietician did a careful analysis of **Percy Veere's** diet, which was indeed low in fat, adequate in protein, but excessive in carbohydrates, especially in refined sugars. Percy's total caloric intake averaged about 430 kilocalories (kcal) a day in excess of his isocaloric requirements. This excess carbohydrate was being converted to fats, accounting for Percy's weight gain. A new diet with a total caloric content that would prevent further gain in weight was prescribed.

THE WAITING ROOM

Percy Veere's mental depression slowly responded to antidepressant medication, to the therapy sessions with his psychiatrist, and to frequent visits from an old high school sweetheart whose husband had died several years earlier. While hospitalized for malnutrition, Mr. Veere's appetite returned. By the time of discharge, he had gained back 8 of the 22 lb he had lost and weighed 133 lb.

During the next few months, Mr. Veere developed a craving for "sweet foods" such as the candy he bought and shared with his new friend. After 6 months of this high-carbohydrate courtship, Percy had gained another 22 lb and now weighed 155 lb, just 8 lb more than he weighed when his depression began. He became concerned about the possibility that he would soon be overweight and consulted his dietitian, explaining that he had faithfully followed his low-fat diet but had "gone overboard" with carbohydrates. He asked whether it was possible to become fat without eating fat.

Cora Nari's hypertension and heart failure have been well controlled on medication, and she has lost 10 lb since she had her recent heart attack. Her fasting serum lipid profile on discharge from the hospital indicated significantly elevated serum low-density lipoprotein (LDL) cholesterol level of 175 mg/dL (recommended level for a patient with known coronary artery disease = 100 mg/dL or less), a serum triacylglycerol level of 280 mg/dL (reference range = 60–150), and a serum high-density lipoprotein (HDL) cholesterol level of 34 mg/dL (reference range > 50 for healthy women). While still in the hospital, she was asked to obtain the most recent serum lipid profiles of her older brother and her younger sister, both of whom were experiencing chest pain. Her brother's profile showed normal triacylglycerols, moderately elevated LDL cholesterol, and significantly suppressed HDL cholesterol levels. Her sister's profile showed only hypertriglyceridemia (high blood triacylglycerols).

Colleen Lakker was born 6 weeks prematurely. She appeared normal until about 30 minutes after delivery, when her respirations became rapid at 64 breaths/minute with audible respiratory grunting. The spaces between her ribs (intercostal spaces) retracted inward with each inspiration, and her lips and fingers became cyanotic from a lack of oxygen in her arterial blood. An arterial blood sample indicated a low partial pressure of oxygen (pO_2) and a slightly elevated partial pressure of carbon dioxide (pCO_2). The arterial pH was somewhat suppressed, in part from an accumulation of lactic acid secondary to the hypoxemia (a low level of oxygen in her blood). A chest x-ray showed a fine reticular granularity of the lung tissue, especially in the left lower lobe area. From these clinical data, a diagnosis of respiratory distress syndrome (RDS), also known as hyaline membrane disease, was made.

Colleen was immediately transferred to the neonatal intensive care unit, where, with intensive respiration therapy, she slowly improved.

I. FATTY ACID SYNTHESIS

Fatty acids are synthesized whenever an excess of calories is ingested. The major source of carbon for the synthesis of fatty acids is dietary carbohydrate. An excess of dietary protein also can result in an increase in fatty acid synthesis. In this case, the carbon source is amino acids that can be converted to acetyl CoA or tricarboxylic

acid (TCA) cycle intermediates (see Chapter 39). Fatty acid synthesis occurs mainly in the liver in humans, although the process also occurs in adipose tissue.

When an excess of dietary carbohydrate is consumed, glucose is converted to acetyl CoA, which provides the 2-carbon units that condense in a series of reactions on the fatty acid synthase complex, producing palmitate (see Fig. 33.1). Palmitate is then converted to other fatty acids. The fatty acid synthase complex is located in the cytosol, and, therefore, it uses cytosolic acetyl CoA.

A. Conversion of Glucose to Cytosolic Acetyl CoA

The pathway for the synthesis of cytosolic acetyl CoA from glucose begins with glycolysis, which converts glucose to pyruvate in the cytosol (Fig. 33.6). Pyruvate enters mitochondria, where it is converted to acetyl CoA by pyruvate dehydrogenase and to oxaloacetate by pyruvate carboxylase. The pathway pyruvate follows is dictated by the acetyl CoA levels in the mitochondria. When acetyl CoA levels are high, pyruvate dehydrogenase is inhibited, and pyruvate carboxylase activity is stimulated. As oxaloacetate levels increase because of the activity of pyruvate carboxylase, oxaloacetate condenses with acetyl CoA to form citrate. This condensation reduces the acetyl CoA levels, which leads to the activation of pyruvate dehydrogenase and inhibition of pyruvate carboxylase. Through such reciprocal regulation, citrate can be continuously synthesized and transported across the inner mitochondrial membrane. In the cytosol, citrate is cleaved by citrate lyase to re-form acetyl CoA and oxaloacetate. This circuitous route is required because pyruvate dehydrogenase, the enzyme that converts pyruvate to acetyl CoA, is found only in mitochondria and because acetyl CoA cannot directly cross the mitochondrial membrane.

The NADPH required for fatty acid synthesis is generated by the pentose phosphate pathway (see Chapter 29) and from recycling of the oxaloacetate produced by citrate lyase (Fig. 33.7). Oxaloacetate is converted back to pyruvate in two steps: the reduction of oxaloacetate to malate by NAD^+-dependent malate dehydrogenase and the oxidative decarboxylation of malate to pyruvate by an $NADP^+$-dependent malate dehydrogenase (malic enzyme) (Fig. 33.8). The pyruvate formed by malic enzyme is reconverted to citrate. The NADPH that is generated by malic enzyme, along with the NADPH generated by glucose 6-phosphate and gluconate 6-phosphate dehydrogenases in the pentose phosphate pathway, is used for the reduction reactions that occur on the fatty acid synthase complex (Fig. 33.9).

The generation of cytosolic acetyl CoA from pyruvate is stimulated by elevation of the insulin/glucagon ratio after a carbohydrate meal. Insulin activates pyruvate dehydrogenase by stimulating the phosphatase that dephosphorylates the enzyme to

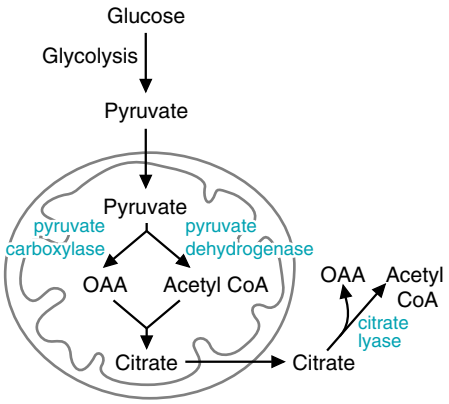


Fig. 33.6. Conversion of glucose to cytosolic acetyl CoA. OAA = oxaloacetate.

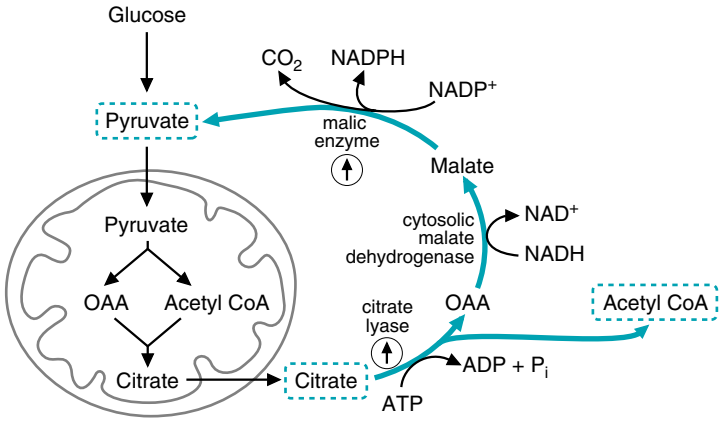


Fig. 33.7. Fate of citrate in the cytosol. Citrate lyase is also called citrate cleavage enzyme. OAA = oxaloacetate; circled ↑ = inducible enzyme.

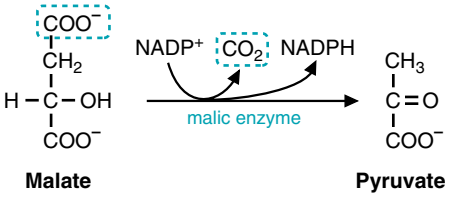


Fig. 33.8. Reaction catalyzed by malic enzyme. This enzyme is also called the decarboxylating or NADP-dependent malate dehydrogenase.

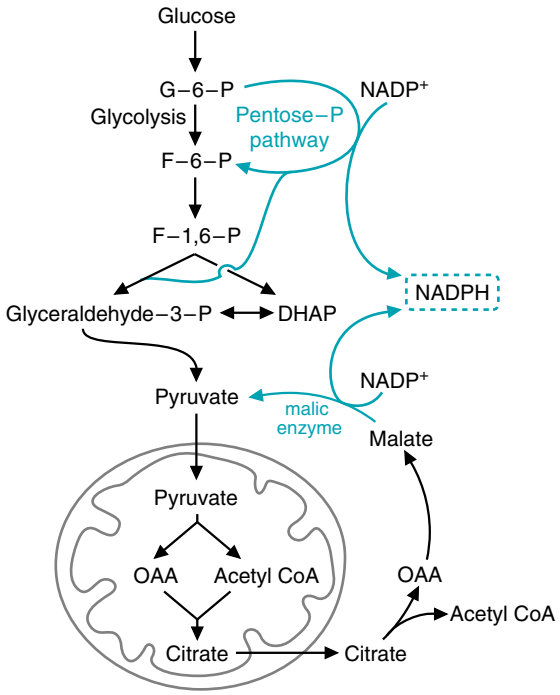


Fig. 33.9. Sources of NADPH for fatty acid synthesis. NADPH is produced by the pentose phosphate pathway and by malic enzyme. OAA = oxaloacetate.

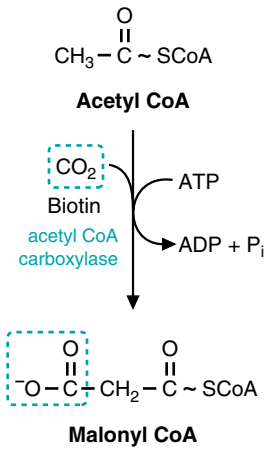


Fig. 33.10. Reaction catalyzed by acetyl CoA carboxylase. CO_2 is covalently attached to biotin, which is linked by an amide bond to the ε-amino group of a lysine residue of the enzyme. Hydrolysis of ATP is required for the attachment of CO_2 to biotin.

AMP is a much more sensitive indicator of low energy levels because of the adenylate kinase reaction. The [AMP] to [ATP] ratio is proportional to the square of the [ADP] to [ATP] ratio, so a fivefold change in ADP levels corresponds to a 25-fold change in AMP levels.

an active form (see Chapter 20). The synthesis of malic enzyme, glucose 6-phosphate dehydrogenase, and citrate lyase is induced by the high insulin/glucagon ratio. The ability of citrate to accumulate, and leave the mitochondrial matrix for the synthesis of fatty acids, is attributable to the allosteric inhibition of isocitrate dehydrogenase by high energy levels within the matrix under these conditions. The concerted regulation of glycolysis and fatty acid synthesis is described in Chapter 36.

B. Conversion of Acetyl CoA to Malonyl CoA

Cytosolic acetyl CoA is converted to malonyl CoA, which serves as the immediate donor of the 2-carbon units that are added to the growing fatty acid chain on the fatty acid synthase complex. To synthesize malonyl CoA, acetyl CoA carboxylase adds a carboxyl group to acetyl CoA in a reaction requiring biotin and adenosine triphosphate (ATP) (Fig. 33.10).

Acetyl CoA carboxylase is the rate-limiting enzyme of fatty acid synthesis. Its activity is regulated by phosphorylation, allosteric modification, and induction/repression of its synthesis (Fig. 33.11). Citrate allosterically activates acetyl CoA carboxylase by causing the individual enzyme molecules (each composed of 4 subunits) to polymerize. Palmityl CoA, produced from palmitate (the endproduct of fatty acid synthase activity), inhibits acetyl CoA carboxylase. Phosphorylation by an AMP-dependent protein kinase inhibits the enzyme in the fasting state when energy levels are low. The enzyme is activated by dephosphorylation in the fed state when energy and insulin levels are high. A high insulin/glucagon ratio also results in induction of the synthesis of both acetyl CoA carboxylase and the next enzyme in the pathway, fatty acid synthase.

C. Fatty Acid Synthase Complex

As an overview, fatty acid synthase sequentially adds 2-carbon units from malonyl CoA to the growing fatty acyl chain to form palmitate. After the addition of each 2-carbon unit, the growing chain undergoes two reduction reactions that require NADPH.

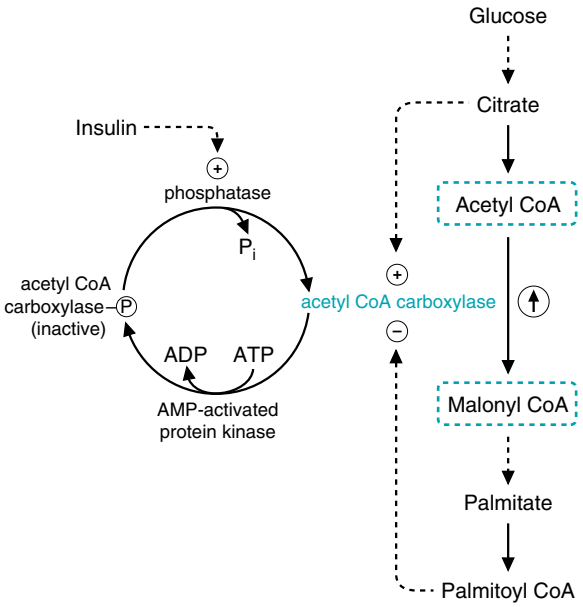


Fig. 33.11. Regulation of acetyl CoA carboxylase. This enzyme is regulated allosterically, both positively and negatively, by phosphorylation (circled P) and dephosphorylation, and by diet-induced induction (circled ↑). It is active in the dephosphorylated state when citrate causes it to polymerize. Dephosphorylation is catalyzed by an insulin-stimulated phosphatase. Low energy levels, via activation of an AMP-dependent protein kinase, cause the enzyme to be phosphorylated and inactivated. The ultimate product of fatty acid synthesis, palmitate, is converted to its CoA derivative palmityl CoA, which inhibits the enzyme. A high-calorie diet increases the rate of transcription of the gene for acetyl CoA carboxylase, whereas a low-calorie diet reduces transcription of this gene.

Fatty acid synthase is a large enzyme composed of two identical dimers, which each have seven catalytic activities and an acyl carrier protein (ACP) segment in a continuous polypeptide chain. The ACP segment contains a phosphopantetheine residue that is derived from the cleavage of coenzyme A (Fig. 33.12). The two dimers associate in a head-to-tail arrangement, so that the phosphopantetheinyl sulfhydryl group on one subunit and a cysteinyl sulfhydryl group on another subunit are closely aligned.

In the initial step of fatty acid synthesis, an acetyl moiety is transferred from acetyl CoA to the ACP phosphopantetheinyl sulfhydryl group of one subunit, and then to the cysteinyl sulfhydryl group of the other subunit. The malonyl moiety from malonyl CoA then attaches to the ACP phosphopantetheinyl sulfhydryl group of the first subunit. The acetyl and malonyl moieties condense, with the release of the malonyl carboxyl group as CO_2. A 4-carbon α-keto acyl chain is now attached to the ACP phosphopantetheinyl sulfhydryl group (Fig. 33.13).

A series of three reactions reduces the 4-carbon keto group to an alcohol, removes water to form a double bond, and reduces the double bond (Fig. 33.14). NADPH provides the reducing equivalents for these reactions. The net result is that the original acetyl group is elongated by two carbons.

The 4-carbon fatty acyl chain is then transferred to the cysteinyl sulfhydryl group and subsequently condenses with a malonyl group. This sequence of reactions is repeated until the chain is 16 carbons in length. At this point, hydrolysis occurs, and palmitate is released (Fig. 33.15).

Palmitate is elongated and desaturated to produce a series of fatty acids. In the liver, palmitate and other newly synthesized fatty acids are converted to triacylglycerols that are packaged into VLDL for secretion.

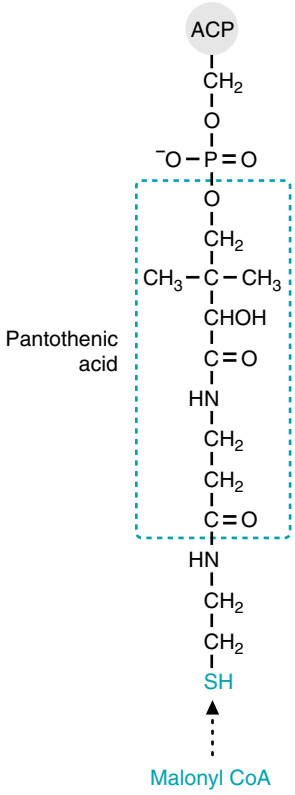


Fig. 33.12. Phosphopantetheinyl residue of the fatty acid synthase complex. The portion derived from the vitamin, pantothenic acid, is indicated. Phosphopantetheine is covalently linked to a serine residue of the acyl carrier protein (ACP) segment of the enzyme. The sulfhydryl group reacts with malonyl CoA to form a thioester.

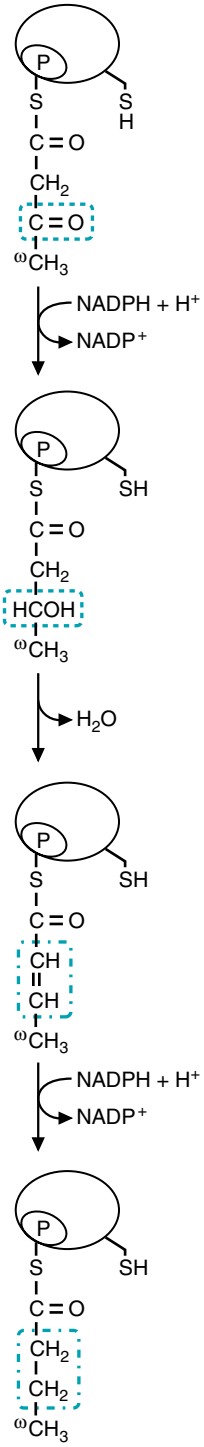


Fig. 33.14. Reduction of a β-ketoacyl group on the fatty acid synthase complex. NADPH is the reducing agent.

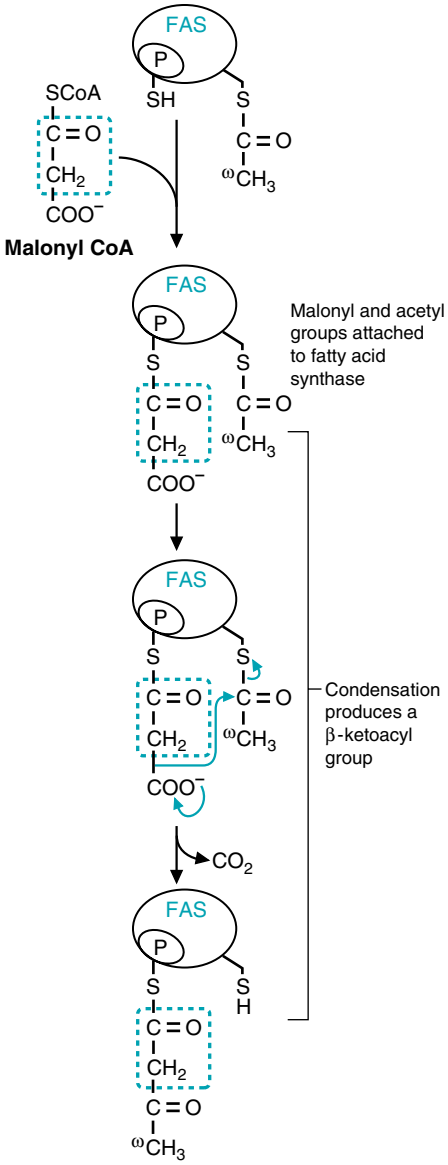


Fig. 33.13. Addition of a 2-carbon unit to an acetyl group on fatty acid synthase. The malonyl group attaches to the phosphopantetheinyl residue (P) of the ACP of the fatty acid synthase. The acetyl group, which is attached to a cysteinyl sulfhydryl group, condenses with the malonyl group. CO_2 is released, and a 3-ketoacyl group is formed. The carbon that eventually forms the ω-methyl group of palmitate is labeled ω.

In the liver, the oxidation of newly synthesized fatty acids back to acetyl CoA via the mitochondrial β-oxidation pathway is prevented by malonyl CoA. Carnitine:palmitoyltransferase I, the enzyme involved in the transport of long-chain fatty acids into mitochondria (see Chapter 23), is inhibited by malonyl CoA (Fig. 33.16). Malonyl CoA levels are elevated when acetyl CoA carboxylase is activated, and, thus, fatty acid oxidation is inhibited while fatty acid synthesis is proceeding. This inhibition prevents the occurrence of a futile cycle.

Q: Where does the methyl group of the first acetyl CoA that binds to fatty acid synthase appear in palmitate, the final product?

D. Elongation of Fatty Acids

After synthesis on the fatty acid synthase complex, palmitate is activated, forming palmityl CoA. Palmityl CoA and other activated long-chain fatty acids can be

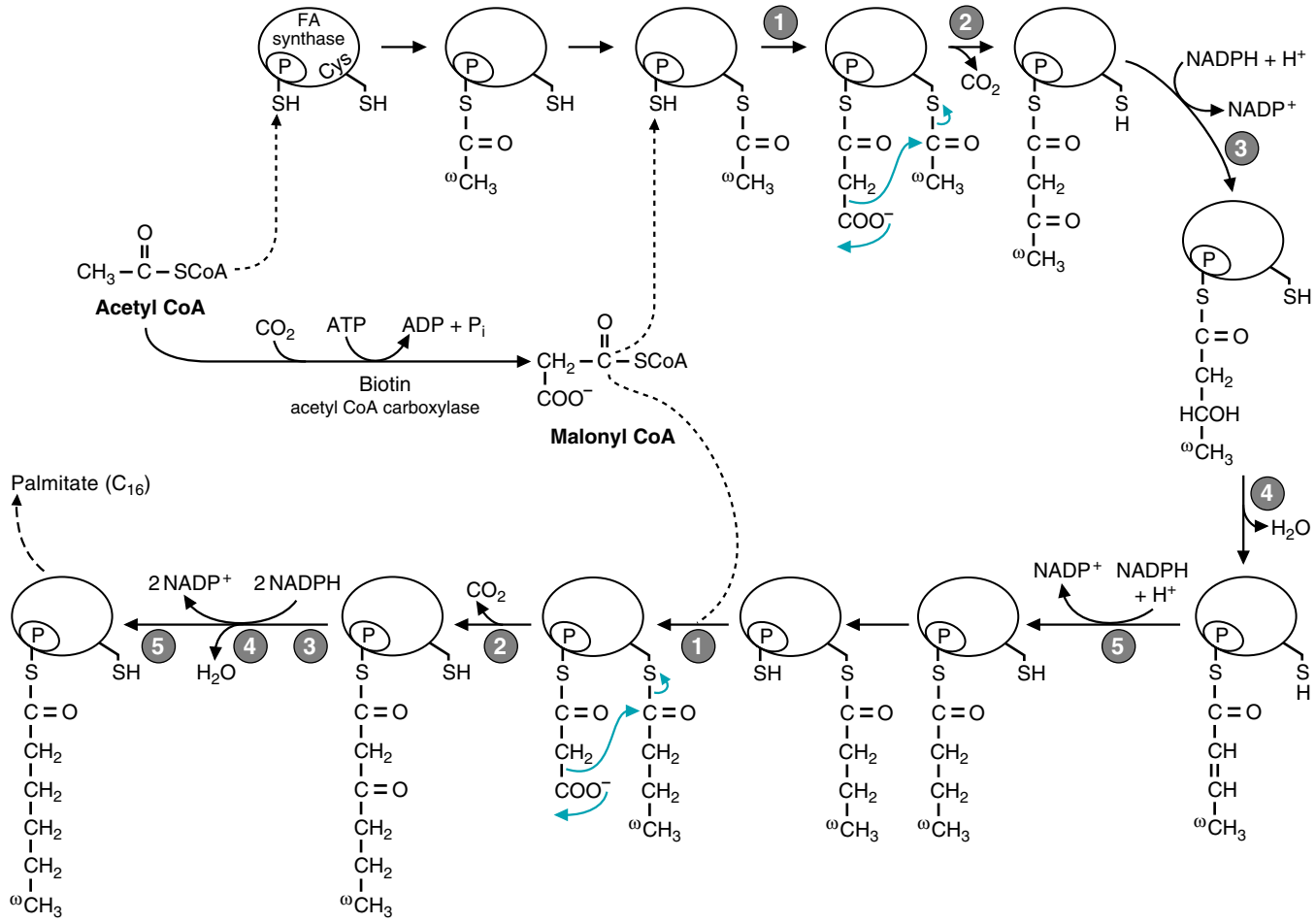


Fig. 33.15. Synthesis of palmitate on the fatty acid synthase complex. Initially, acetyl CoA adds to the synthase. It provides the ω-methyl group of palmitate. Malonyl CoA provides the 2-carbon units that are added to the growing fatty acyl chain. The addition and reduction steps are repeated until palmitate is produced. 1. Transfer of the malonyl group to the phosphopantetheinyl residue. 2. Condensation of the malonyl and fatty acyl groups. 3. Reduction of the β-ketoacyl group. 4. Dehydration. 5. Reduction of the double bond. P = a phosphopantetheinyl group attached to the fatty acid synthase complex; Cys-SH = a cysteinyl residue.

elongated, two carbons at a time, by a series of reactions that occur in the endoplasmic reticulum (Fig. 33.17). Malonyl CoA serves as the donor of the 2-carbon units, and NADPH provides the reducing equivalents. The series of elongation reactions resemble those of fatty acid synthesis except that the fatty acyl chain is attached to coenzyme A rather than to the phosphopantetheinyl residue of an ACP. The major elongation reaction that occurs in the body involves the conversion of palmityl CoA (C16) to stearyl CoA (C18). Very-long-chain fatty acids (C22 to C24) are also produced, particularly in the brain.

E. Desaturation of Fatty Acids

Desaturation of fatty acids involves a process that requires molecular oxygen (O_2), NADH, and cytochrome b_5. The reaction, which occurs in the endoplasmic reticulum, results in the oxidation of both the fatty acid and NADH (Fig. 33.18). The most common desaturation reactions involve the placement of a double bond between carbons 9 and 10 in the conversion of palmitic acid to palmitoleic acid (16:1, Δ^9) and the conversion of stearic acid to oleic acid (18:1, Δ^9). Other positions that can be desaturated in humans include carbons 4, 5, and 6.

A: The methyl group of acetyl CoA becomes the ω-carbon (the terminal methyl group) of palmitate. Each new 2-carbon unit is added to the carboxyl end of the growing fatty acyl chain (see Fig. 33.13).

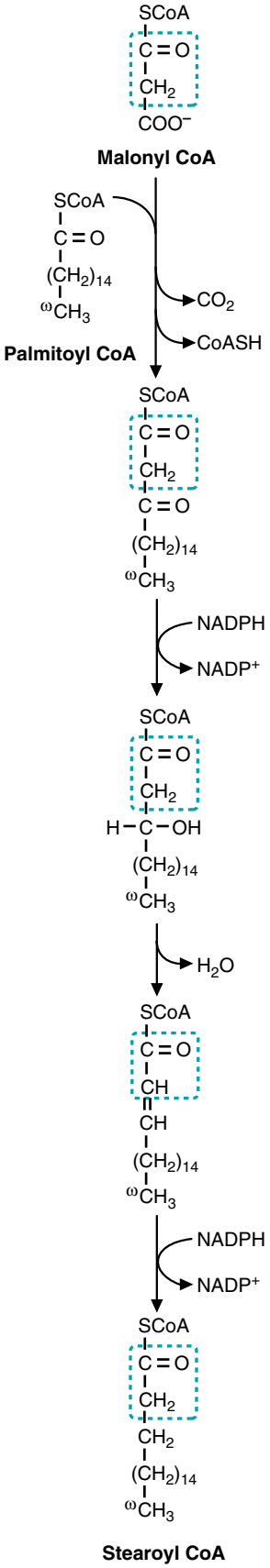


Fig. 33.17. Elongation of long-chain fatty acids in the endoplasmic reticulum.

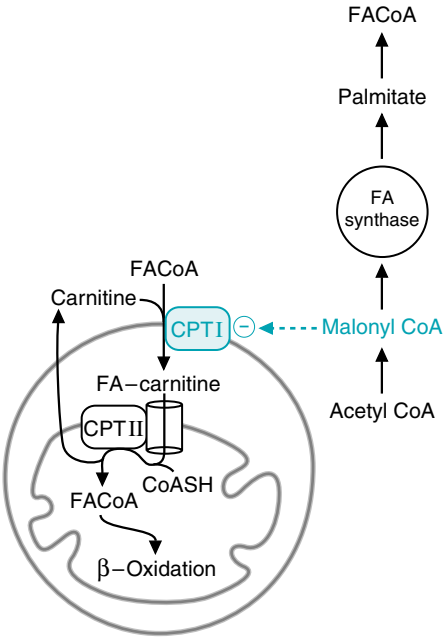


Fig. 33.16. Inhibition of carnitine:palmitoyltransferase (CPTI, also called carnitine:acyltransferase I) by malonyl CoA. During fatty acid synthesis, malonyl CoA levels are high. This compound inhibits CPTI, which is involved in the transport of long-chain fatty acids into mitochondria for β-oxidation. This mechanism prevents newly synthesized fatty acids from undergoing immediate oxidation.

Polyunsaturated fatty acids with double bonds three carbons from the methyl end (ω3 fatty acids) and six carbons from the methyl end (ω6 fatty acids) are required for the synthesis of eicosanoids (see Chapter 35). Because humans cannot synthesize these fatty acids de novo (i.e., from glucose via palmitate), they must be present in the diet or the diet must contain other fatty acids that can be converted to these fatty acids. We obtain ω6 and ω3 polyunsaturated fatty acids mainly from dietary plant oils that contain the ω6 fatty acid linoleic acid (18:2, $\Delta^{9,12}$) and the ω3 fatty acid α-linolenic acid (18:3, $\Delta^{9,12,15}$). In the body, linoleic acid can be converted by elongation and desaturation reactions to arachidonic acid (20:4, $\Delta^{5,8,11,14}$), which is used for the synthesis of the major class of human prostaglandins and other eicosanoids (Fig. 33.19). Elongation and desaturation of α-linolenic acid produces eicosapentaenoic acid (EPA; 20:5, $\Delta^{5,8,11,14,17}$), which is the precursor of a different class of eicosanoids (see Chapter 35).

Plants are able to introduce double bonds into fatty acids in the region between C10 and the ω-end and therefore can synthesize ω3 and ω6 polyunsaturated fatty acids. Fish oils also contain ω3 and ω6 fatty acids, particularly eicosapentaenoic acid (EPA; ω3, 20:5, Δ5, 8, 11, 14, 17) and docosahexaenoic acid (DHA; ω3,22:6, Δ4,7,10,13,16,19). The fish obtain these fatty acids by eating phytoplankton (plants that float in water).

Arachidonic acid is listed in some textbooks as an essential fatty acid. Although it is an ω6 fatty acid, it is not essential in the diet if linoleic acid is present because arachidonic acid can be synthesized from dietary linoleic acid (see Fig. 33.19).

The essential fatty acid linoleic acid is required in the diet for at least three reasons: (*a*) It serves as a precursor of arachidonic acid from which eicosanoids are produced. (*b*) It covalently binds another fatty acid attached to cerebrosides in the skin, forming an unusual lipid (acylglucosylceramide) that helps to make the skin impermeable to water. This function of linoleic acid may help to explain the red, scaly dermatitis and other skin problems associated with a dietary deficiency of essential fatty acids. *(c)* It is the precursor of C22:6ω3, an important neuronal fatty acid.

The other essential fatty acid, α-linolenic acid (18:3, Δ9, 12, 15), also forms eicosanoids.

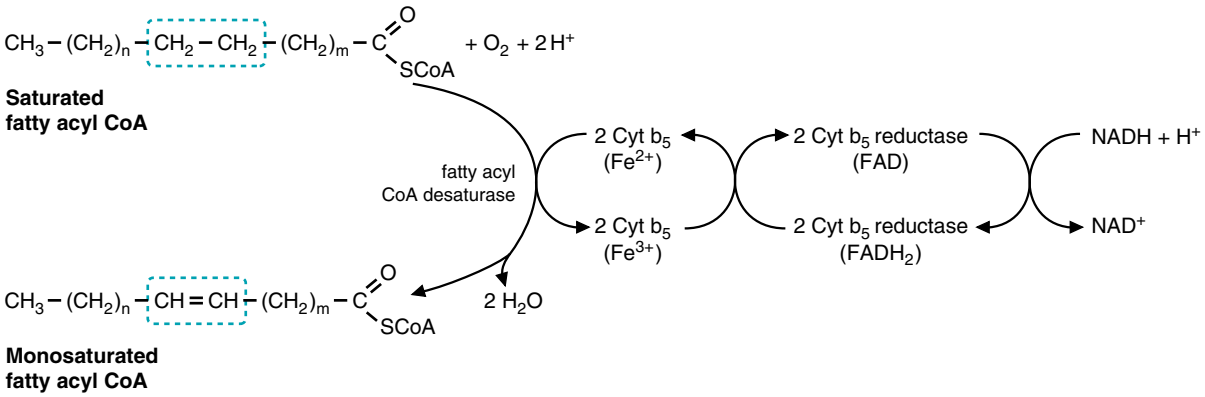


Fig. 33.18. Desaturation of fatty acids. The process occurs in the endoplasmic reticulum and uses molecular oxygen. Both the fatty acid and NADH are oxidized. Human desaturases cannot introduce double bonds between carbon 9 and the methyl end. Therefore, m is equal to or less than 7.

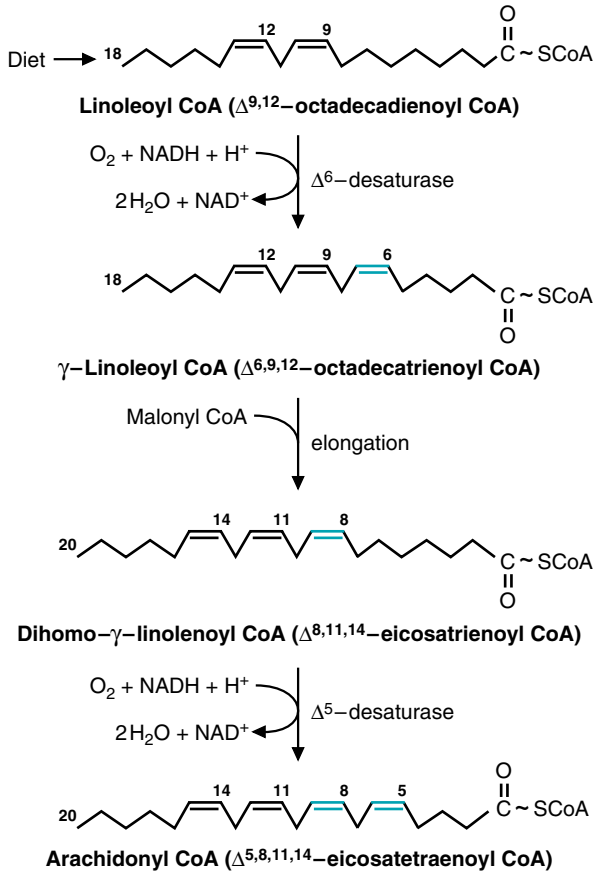


Fig. 33.19. Conversion of linoleic acid to arachidonic acid. Dietary linoleic acid (as linoleoyl CoA) is desaturated at carbon 6, elongated by 2 carbons, and then desaturated at carbon 5 to produce arachidonyl CoA.

II. SYNTHESIS OF TRIACYLGLYCEROLS AND VLDL PARTICLES

In liver and adipose tissue, triacylglycerols are produced by a pathway containing a phosphatidic acid intermediate (Fig. 33.20). Phosphatidic acid is also the precursor of the glycerolipids found in cell membranes and the blood lipoproteins.

The sources of glycerol 3-phosphate, which provides the glycerol moiety for triacylglycerol synthesis, differ in liver and adipose tissue. In liver, glycerol 3-phosphate

Recent experiments have shown functional glycerol kinase activity in muscle cells. The significance of this finding is under investigation, but it may indicate that muscle has a greater capacity for fatty acid synthesis than previously believed.

is produced from the phosphorylation of glycerol by glycerol kinase or from the reduction of dihydroxyacetone phosphate derived from glycolysis. Adipose tissue lacks glycerol kinase and can produce glycerol 3-phosphate only from glucose via dihydroxyacetone phosphate. Thus, adipose tissue can store fatty acids only when glycolysis is activated, i.e., in the fed state.

In both adipose tissue and liver, triacylglycerols are produced by a pathway in which glycerol 3-phosphate reacts with fatty acyl CoA to form phosphatidic acid. Dephosphorylation of phosphatidic acid produces diacylglycerol. Another fatty acyl CoA reacts with the diacylglycerol to form a triacylglycerol (see Fig. 33.20).

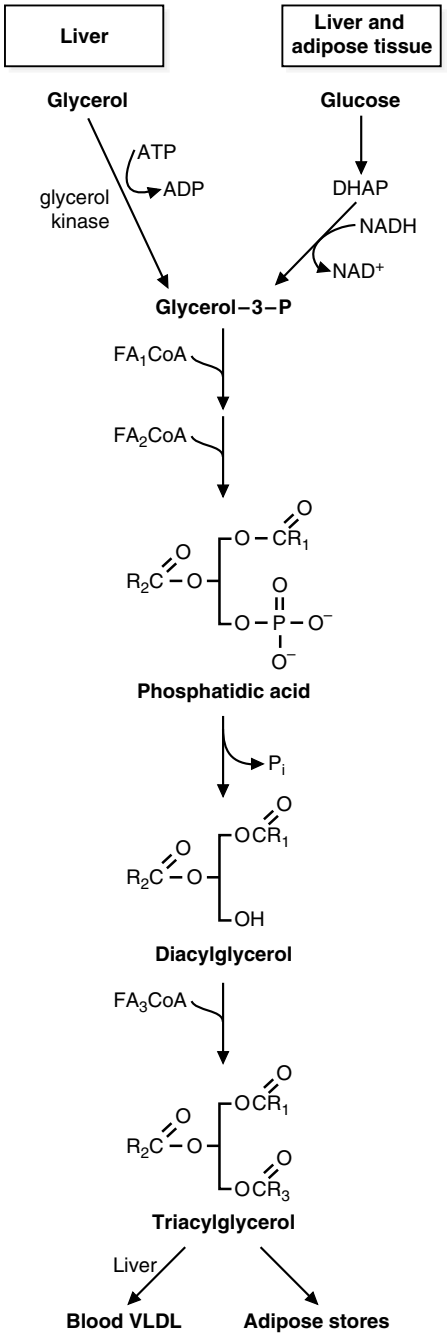
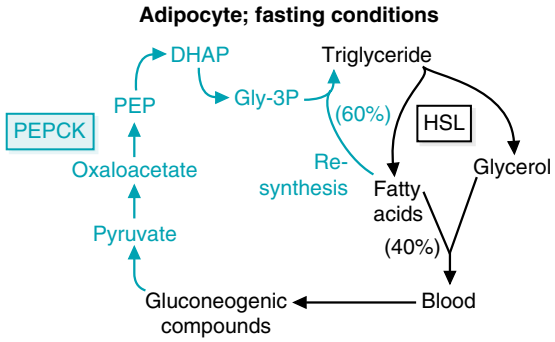


Fig. 33.20. Synthesis of triacylglycerol in liver and adipose tissue. Glycerol 3-phosphate is produced from glucose in both tissues. It is also produced from glycerol in liver, but not in adipose tissue, which lacks glycerol kinase. The steps from glycerol 3-phosphate are the same in the two tissues. FA = fatty acyl group.

Adipose tissue also undergoes glyceroneogenesis, the process of synthesizing glycerol from gluconeogenic precursors in the blood, such as alanine, aspartate, and malate. Glyceroneogenesis occurs primarily in the fasting state and is dependent on the induction of cytoplasmic PEPCK in the adipocyte. The re-synthesis of triglycerides by adipose tissue during fasting modulates the release of fatty acids in the circulation. Mice that have been engineered to not express PEPCK in adipose tissue display reduced levels of triglyceride in their adipocytes; mice that overproduce adipocyte PEPCK were obese. Thus, although activation of hormone-sensitive lipase during fasting results in the release of fatty acids from adipocytes, the release is carefully modulated through glyceroneogenesis and re-synthesis of triglycerides.



The triacylglycerol, which is produced in the smooth endoplasmic reticulum of the liver, is packaged with cholesterol, phospholipids, and proteins (synthesized in the rough endoplasmic reticulum) to form VLDL (Fig. 33.21). The microsomal triglyceride transfer protein (MTP), which is required for chylomicron assembly, is also required for VLDL assembly. The major protein of VLDL is apoB-100. There is one long apoB-100 molecule wound through the surface of each VLDL particle. ApoB-100 is encoded by the same gene as the apoB-48 of chylomicrons, but is a longer protein (see Fig. 32.11). In intestinal cells, RNA editing produces a smaller mRNA and, thus, a shorter protein, apoB-48.

VLDL is processed in the Golgi complex and secreted into the blood by the liver (Figs. 33.22 and 33.23). The fatty acid residues of the triacylglycerols ultimately are stored in the triacylglycerols of adipose cells. Note that, in comparison to chylomicrons (see Chapter 32), VLDL particles are more dense, as they contain a lower percentage of triglyceride than do the chylomicrons. Similar to chylomicrons, VLDL particles are first synthesized in a nascent form, and on entering the circulation they acquire apoproteins CII and E from HDL particles to become mature VLDL particles.

Abetalipoproteinemia, which is due to a lack of MTP (microsomal triglyceride transfer protein; see Chapter 32) activity, results in an inability to assemble both chylomicrons in the intestine and VLDL particles in the liver.

Why do some alcoholics have high VLDL levels?

The fact that a number of different abnormal lipoprotein profiles were found in **Cora Nari** and her siblings, and that each had evidence of coronary artery disease, suggests that Cora has familial combined hyperlipidemia (FCH). This diagnostic impression is further supported by the finding that Cora's profile of lipid abnormalities appeared to change somewhat from one determination to the next, a characteristic of FCH. This hereditary disorder of lipid metabolism is believed to be quite common, with an estimated prevalence of about 1 per 100 population.

The mechanisms for FCH are incompletely understood but may involve a genetically determined increase in the production of apoprotein B-100. As a result, packaging of VLDL is increased, and blood VLDL levels may be elevated. Depending on the efficiency of lipolysis of VLDL by LPL, VLDL levels may be normal and LDL levels may be elevated, or both VLDL and LDL levels may be high. In addition, the phenotypic expression of FCH in any given family member may be determined by the degree of associated obesity, the diet, the use of specific drugs, or other factors that change over time.

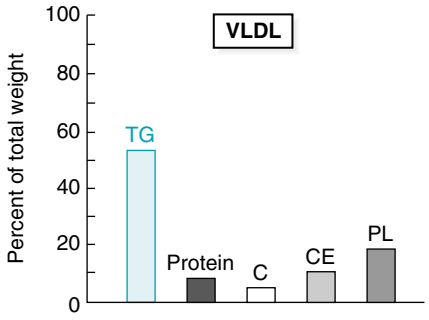


Fig. 33.21. Composition of a typical VLDL particle. The major component is triacylglycerol (TG). C = cholesterol; CE = cholesterol ester; PL = phospholipid.

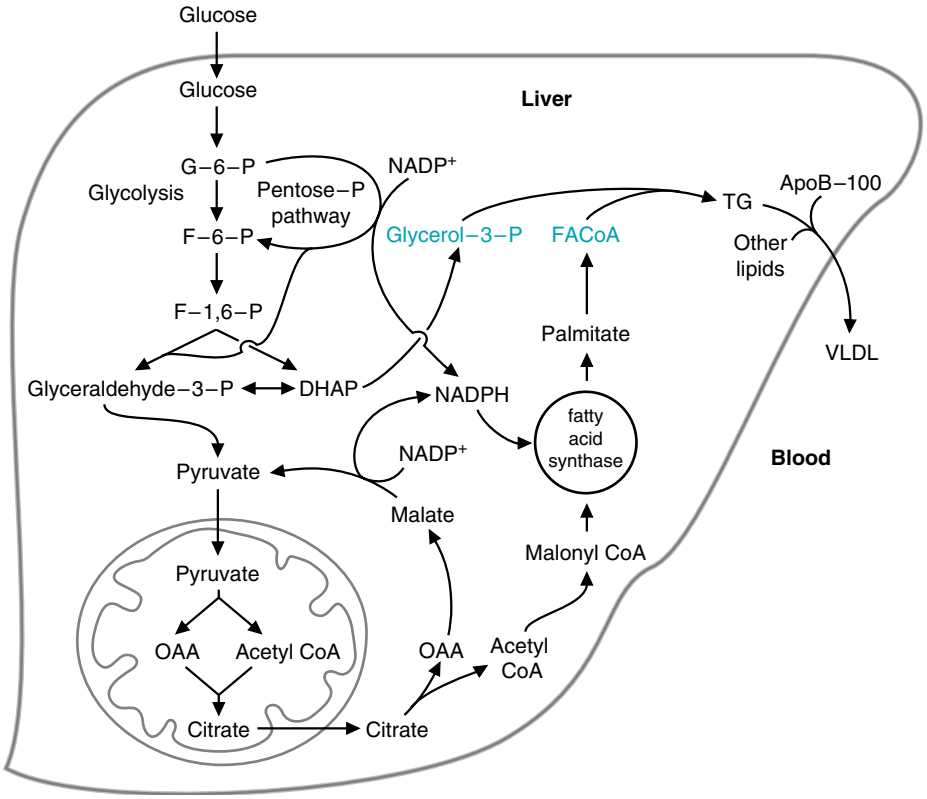


Fig. 33.22. Synthesis of VLDL from glucose in the liver. G-6-P = glucose 6-phosphate; F-6-P = fructose 6-phosphate; F-1,6-BP = fructose 1,6-bisphosphate; FA = fatty acyl group; TG = triacylglycerol.

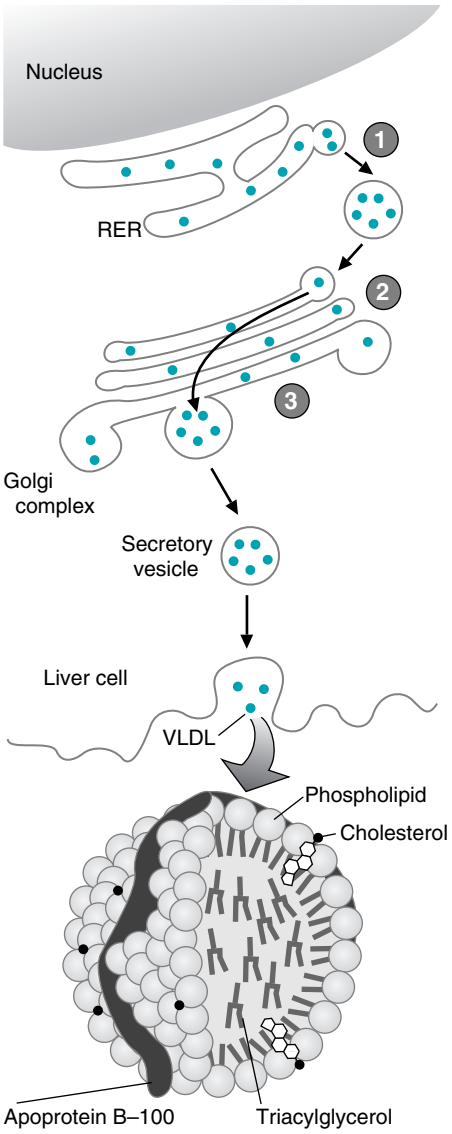


Fig. 33.23. Synthesis, processing, and secretion of VLDL. Proteins synthesized on the rough endoplasmic reticulum (RER) are packaged with triacylglycerols in the ER and Golgi complex to form VLDL. VLDL are transported to the cell membrane in secretory vesicles and secreted by endocytosis. Blue dots represent VLDL particles. An enlarged VLDL particle is depicted at the bottom of the figure.

III. FATE OF VLDL TRIACYLGLYCEROL

Lipoprotein lipase (LPL), which is attached to the basement membrane proteoglycans of capillary endothelial cells, cleaves the triacylglycerols in both VLDL and chylomicrons, forming fatty acids and glycerol. The C-II apoprotein, which these lipoproteins obtain from HDL, activates LPL. The low K_m of the muscle LPL isozyme permits muscle to use the fatty acids of chylomicrons and VLDL as a source of fuel even when the blood concentration of these lipoproteins is very low. The isozyme in adipose tissue has a high K_m and is most active after a meal, when blood levels of chylomicrons and VLDL are elevated. The fate of the VLDL particle after triglyceride has been removed by LPL is the generation of an IDL particle (intermediate-density lipoprotein), which can further lose triglyceride to become an LDL particle (low-density lipoprotein). The fate of the IDL and LDL particles is discussed in Chapter 34.

Fatty acids for VLDL synthesis in the liver may be obtained from the blood or they may be synthesized from glucose. In a healthy individual, the major source of the fatty acids of VLDL triacylglycerol is excess dietary glucose. In individuals with diabetes mellitus, fatty acids mobilized from adipose triacylglycerols in excess of the oxidative capacity of tissues are a major source of the fatty acids re-esterified in liver to VLDL triacylglycerol. These individuals frequently have elevated levels of blood triacylglycerols.

A: In alcoholism, NADH levels in the liver are elevated (see Chapter 25). High levels of NADH inhibit the oxidation of fatty acids. Therefore, fatty acids, mobilized from adipose tissue, are re-esterified to glycerol in the liver, forming triacylglycerols, which are packaged into VLDL and secreted into the blood. Elevated VLDL is frequently associated with chronic alcoholism. As alcohol-induced liver disease progresses, the ability to secrete the triacylglycerols is diminished, resulting in a fatty liver.

IV. STORAGE OF TRIACYLGLYCEROLS IN ADIPOSE TISSUE

After a meal, the triacylglycerol stores of adipose tissue increase (Fig. 33.24). Adipose cells synthesize LPL and secrete it into the capillaries of adipose tissue when the insulin/glucagon ratio is elevated. This enzyme digests the triacylglycerols of both chylomicrons and VLDL. The fatty acids enter adipose cells and are activated, forming fatty acyl CoA, which reacts with glycerol 3-phosphate to form triacylglycerol by the same pathway used in the liver (see Fig. 33.20). Because adipose tissue lacks glycerol kinase and cannot use the glycerol produced by LPL, the glycerol travels through the blood to the liver, which uses it for the synthesis of triacylglycerol. In adipose cells, glycerol 3-phosphate is derived from glucose.

In addition to stimulating the synthesis and release of LPL, insulin stimulates glucose metabolism in adipose cells. Insulin leads to the activation of the glycolytic enzyme phosphofructokinase-1 by an activation of PFK-2, which increases fructose 2,6-bisphosphate levels. Insulin also stimulates the dephosphorylation of pyruvate dehydrogenase, so that the pyruvate produced by glycolysis can be oxidized in the TCA cycle. Furthermore, insulin stimulates the conversion of glucose to fatty acids in adipose cells, although the liver is the major site of fatty acid synthesis in humans.

V. RELEASE OF FATTY ACIDS FROM ADIPOSE TRIACYLGLYCEROLS

During fasting, the decrease of insulin and the increase of glucagon cause cAMP levels to rise in adipose cells, stimulating lipolysis (Fig. 33.25). Protein kinase A phosphorylates hormone-sensitive lipase to produce a more active form of the enzyme. Hormone-sensitive lipase, also known as adipose triacylglycerol lipase, cleaves a fatty acid from a triacylglycerol. Subsequently, other lipases complete the process of lipolysis, and fatty acids and glycerol are released into the blood. Simultaneously, to regulate the amount of fatty acids released into circulation, triglyceride synthesis occurs along with glyceroneogenesis.

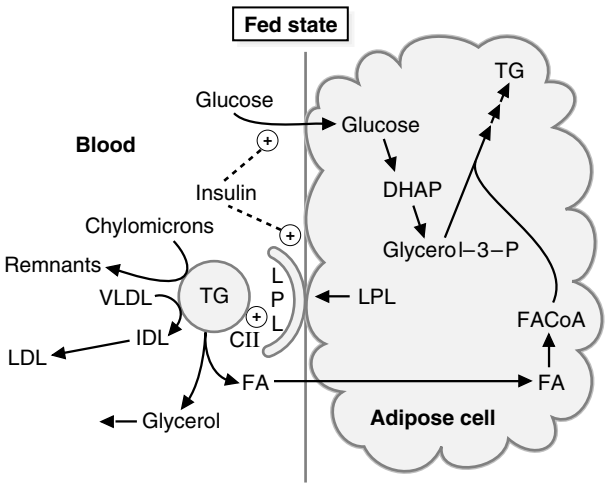


Fig. 33.24. Conversion of the fatty acid (FA) from the triacylglycerols (TG) of chylomicrons and VLDL to the TG stored in adipose cells. Note that insulin stimulates both the transport of glucose into adipose cells and the secretion of LPL from the cells. Glucose provides the glycerol 3-phosphate for TG synthesis. Insulin also stimulates the synthesis and secretion of lipoprotein lipase (LPL). Apoprotein C-II activates LPL.

In some cases of hyperlipidemia, LPL is defective. If a blood lipid profile is performed on patients with an LPL deficiency, which lipids would be elevated?

Because the fatty acids of adipose triacylglycerols come both from chylomicrons and VLDL, we produce our major fat stores both from dietary fat (which produces chylomicrons) and dietary sugar (which produces VLDL). An excess of dietary protein also can be used to produce the fatty acids for VLDL synthesis.

The dietician carefully explained to **Percy Veere** that we can become fat from eating excess fat, excess sugar, or excess protein.

A: Individuals with a defective LPL have high blood triacylglycerol levels. Their levels of chylomicrons and VLDL (which contain large amounts of triacylglycerols) are elevated because they are not digested at the normal rate by LPL.

LPL can be dissociated from capillary walls by treatment with heparin (a glycosaminoglycan). Measurements can be made on blood after heparin treatment to determine whether LPL levels are abnormal.

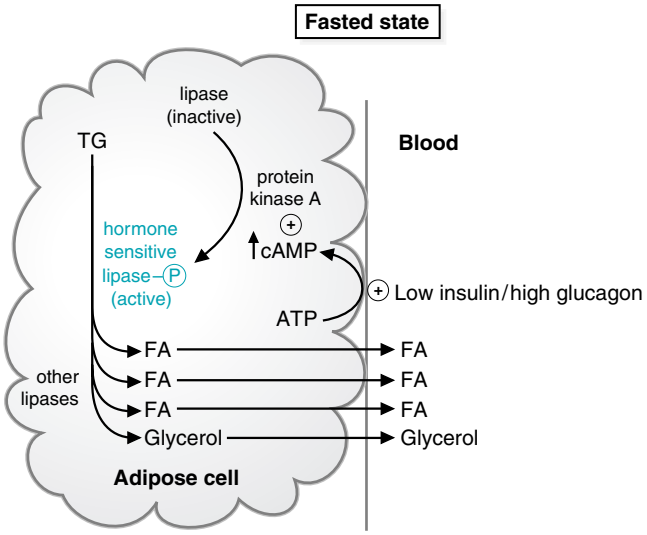


Fig. 33.25. Mobilization of adipose triacylglycerol (TG). In the fasted state, when insulin levels are low and glucagon is elevated, intracellular cAMP increases and activates protein kinase A, which phosphorylates hormone-sensitive lipase (HSL). Phosphorylated HSL is active and initiates the breakdown of adipose TG. Recall, however, that re-esterification of fatty acids does occur, along with glyceroneogenesis, in the fasted state. HSL is also called triacylglycerol lipase. FA = fatty acid.

The fatty acids, which travel in the blood complexed with albumin, enter cells of muscle and other tissues, where they are oxidized to CO_2 and water to produce energy. During prolonged fasting, acetyl CoA produced by β-oxidation of fatty acids in the liver is converted to ketone bodies, which are released into the blood. The glycerol derived from lipolysis in adipose cells is used by the liver during fasting as a source of carbon for gluconeogenesis.

VI. METABOLISM OF GLYCEROPHOSPHOLIPIDS AND SPHINGOLIPIDS

Fatty acids, obtained from the diet or synthesized from glucose, are the precursors of glycerophospholipids and of sphingolipids (Fig. 33.26). These lipids are major components of cellular membranes. Glycerophospholipids are also components of blood lipoproteins, bile, and lung surfactant. They are the source of the polyunsaturated fatty acids, particularly arachidonic acid, that serve as precursors of the eicosanoids (e.g., prostaglandins, thromboxanes, leukotrienes; see Chapter 35). Ether glycerophospholipids differ from other glycerophospholipids in that the alkyl or alkenyl chain (an alkyl chain with a double bond) is joined to carbon 1 of the glycerol moiety by an ether rather than an ester bond. Examples of ether lipids are the plasmalogens and platelet activating factor. Sphingolipids are particularly important in forming the myelin sheath surrounding nerves in the central nervous system, and in signal transduction.

In glycerolipids and ether glycerolipids, glycerol serves as the backbone to which fatty acids and other substituents are attached. Sphingosine, derived from serine, provides the backbone for sphingolipids.

A. Synthesis of Phospholipids Containing Glycerol

1. GLYCEROPHOSPHOLIPIDS

The initial steps in the synthesis of glycerophospholipids are similar to those of triacylglycerol synthesis. Glycerol 3-phosphate reacts with fatty acyl CoA to form

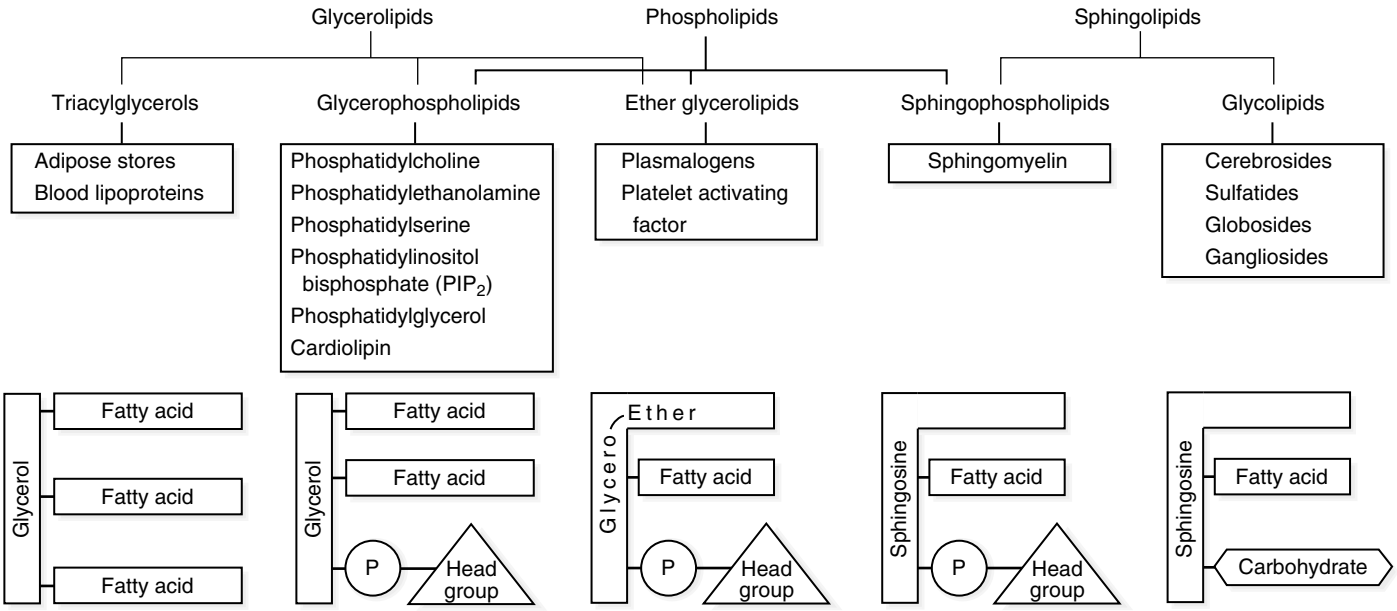


Fig. 33.26. Types of glycerolipids and sphingolipids. Glycerolipids contain glycerol, and sphingolipids contain sphingosine. The category of phospholipids overlaps both glycerolipids and sphingolipids. The head groups include choline, ethanolamine, serine, inositol, glycerol, and phosphatidylglycerol. The carbohydrates are monosaccharides (which may be sulfated), oligosaccharides, and oligosaccharides with branches of *N*-acetylneuraminic acid. P = phosphate.

phosphatidic acid. Two different mechanisms are then used to add a head group to the molecule (Fig. 33.27). A head group is a chemical group, such as choline or serine, attached to carbon 3 of a glycerol moiety that contains hydrophobic groups, usually fatty acids, at positions 1 and 2. Head groups are hydrophilic, either charged or polar.

In the first mechanism, phosphatidic acid is cleaved by a phosphatase to form diacylglycerol (DAG). DAG then reacts with an activated head group. In the synthesis of phosphatidylcholine, the head group choline is activated by combining with CTP to form CDP-choline (Fig. 33.28). Phosphocholine is then transferred to carbon 3 of DAG, and CMP is released. Phosphatidylethanolamine is produced by a similar reaction involving CDP-ethanolamine.

Various types of interconversions occur among these phospholipids (see Fig. 33.28). Phosphatidylserine is produced by a reaction in which the ethanolamine moiety of

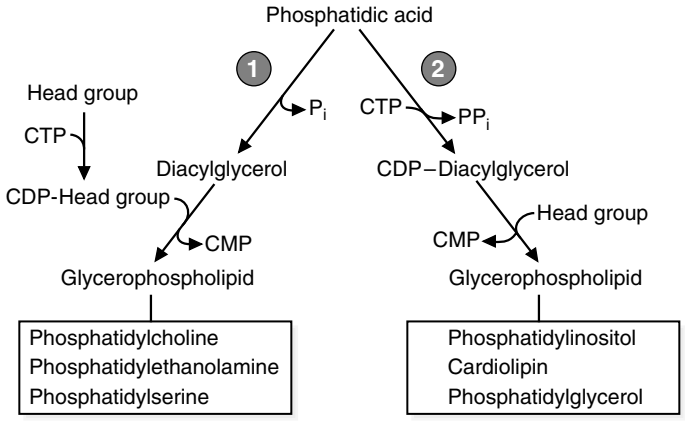


Fig. 33.27. Strategies for addition of the head group to form glycerophospholipids. In both cases, CTP is used to drive the reaction.

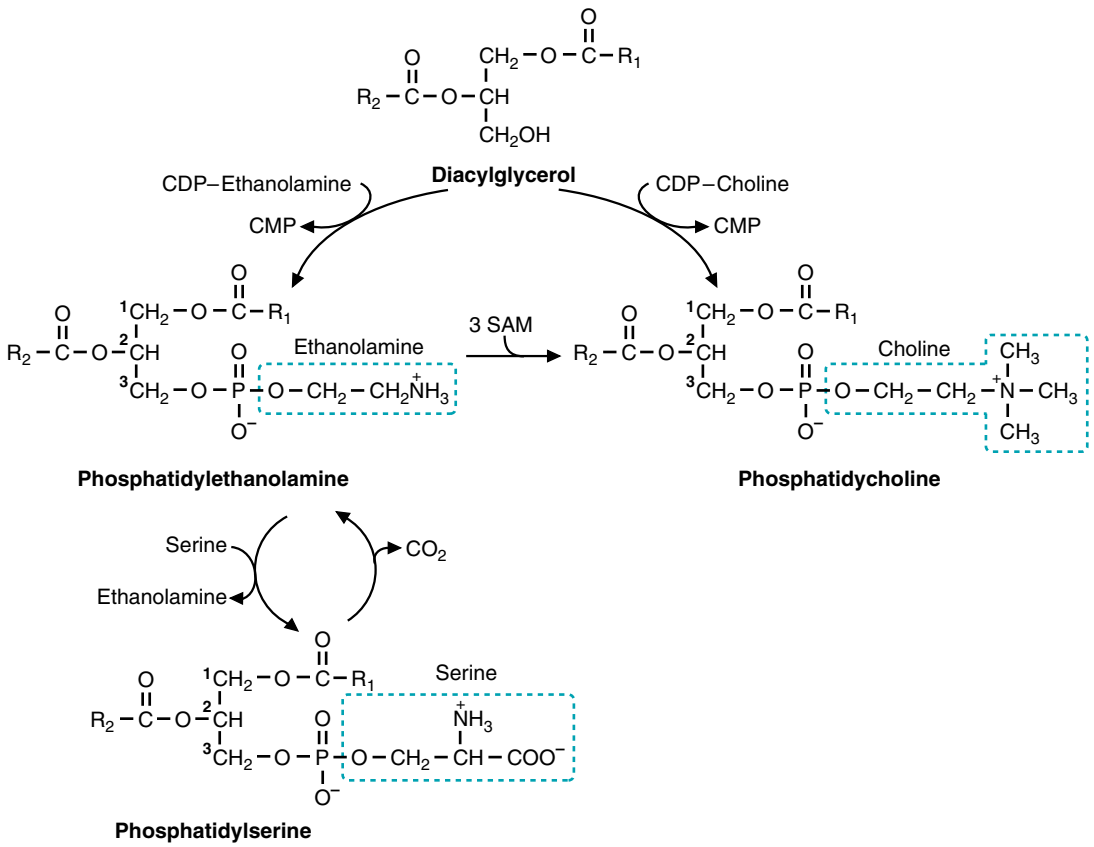


Fig. 33.28. Synthesis of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. The multiple pathways reflect the importance of phospholipids in membrane structure. For example, phosphatidylcholine (PC) can be synthesized from dietary choline when it is available. If choline is not available, PC can be made from dietary carbohydrate, although the amount synthesized is inadequate to prevent choline deficiency. SAM is S-adenosylmethionine, a methyl group donor for many biochemical reactions (see Chapter 40).

Phosphatidylcholine (lecithin) is not required in the diet because it can be synthesized in the body. The components of phosphatidylcholine (including choline) all can be produced, as shown in Figure 33.28. A pathway for de novo choline synthesis from glucose exists, but the rate of synthesis is inadequate to provide for the necessary amounts of choline. Thus, choline has been classified as an essential nutrient, with an AI (adequate intake) of 425 mg/day in females and 550 mg/day in males.

Because choline is widely distributed in the food supply, primarily in phosphatidylcholine (lecithin), deficiencies have not been observed in humans on a normal diet. Deficiencies may occur, however, in patients on total parental nutrition (TPN), i.e., supported solely by intravenous feeding. The fatty livers that have been observed in these patients probably result from a decreased ability to synthesize phospholipids for VLDL formation.

phosphatidylethanolamine is exchanged for serine. Phosphatidylserine can be converted back to phosphatidylethanolamine by a decarboxylation reaction. Phosphatidylethanolamine can be methylated to form phosphatidylcholine (see Chapter 40).

In the second mechanism for the synthesis of glycerolipids, phosphatidic acid reacts with CTP to form CDP-diacylglycerol (Fig. 33.29). This compound can react with phosphatidylglycerol (which itself is formed from the condensation of CDP-diacylglycerol and glycerol 3-phosphate) to produce cardiolipin or with inositol to produce phosphatidylinositol. Cardiolipin is a component of the inner mitochondrial membrane. Phosphatidylinositol can be phosphorylated to form phosphatidylinositol 4,5-bisphosphate (PIP_2), which is a component of cell membranes. In response to signals such as the binding of hormones to membrane receptors, PIP_2 can be cleaved to form the second messengers diacylglycerol and inositol triphosphate (see Chapter 11).

2. ETHER GLYCEROLIPIDS

The ether glycerolipids are synthesized from the glycolytic intermediate dihydroxyacetone phosphate (DHAP). A fatty acyl CoA reacts with carbon 1 of DHAP, forming an ester (Fig. 33.30). This fatty acyl group is exchanged for a fatty alcohol, produced by reduction of a fatty acid. Thus, the ether linkage is formed. Then the keto group on carbon 2 of the DHAP moiety is reduced and esterified to a fatty acid. Addition of the head group proceeds by a series of reactions analogous to those for synthesis of phosphatidylcholine. Formation of a double bond between carbons 1 and 2 of the alkyl group produces a plasmalogen. Ethanolamine plasmalogen is found in

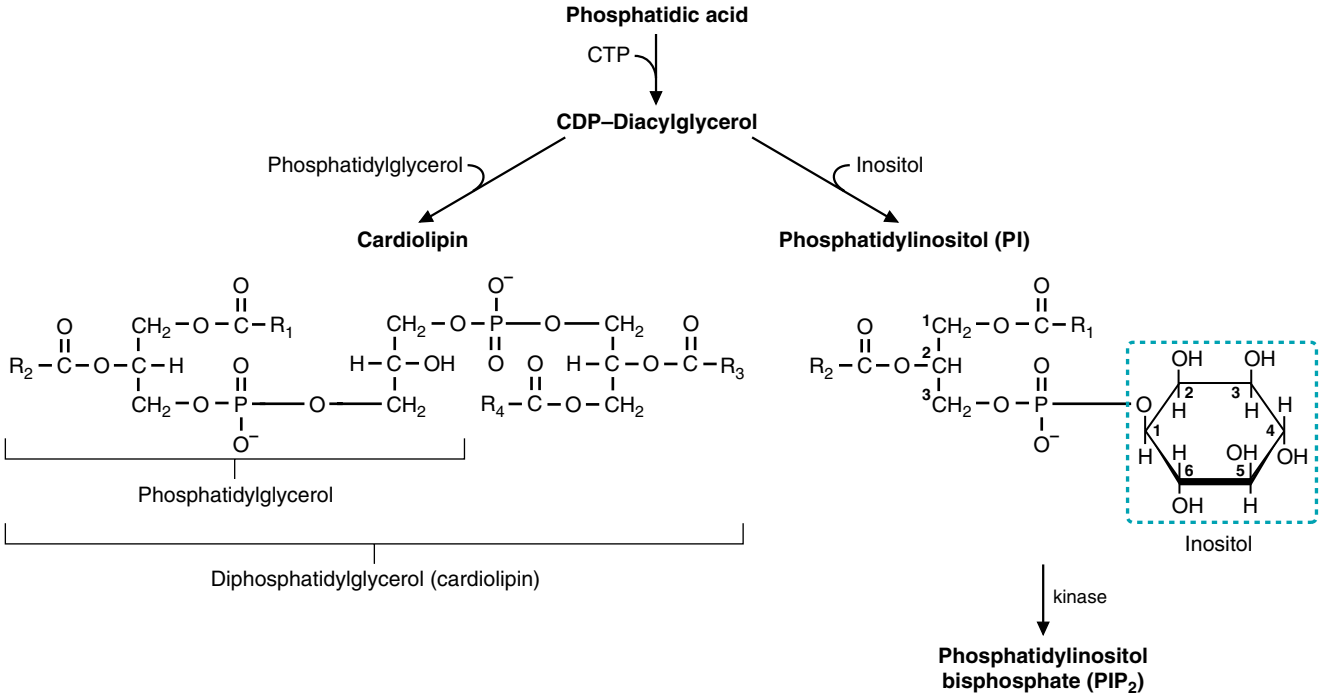
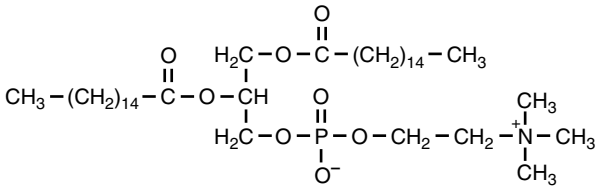


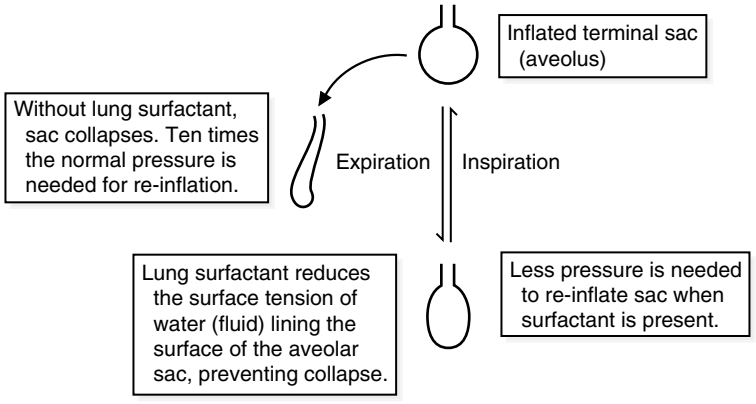
Fig. 33.29. Synthesis of cardiolipin and phosphatidylinositol.

The respiratory distress syndrome (RDS) of a premature infant such as **Colleen Lakker** is, in part, related to a deficiency in the synthesis of a substance known as lung surfactant. The major constituents of surfactant are dipalmitoylphosphatidylcholine, phosphatidylglycerol, apoproteins (surfactant proteins: Sp-A,B,C), and cholesterol.



Dipalmitoylphosphatidycholine, the major component of lung surfactant

These components of lung surfactant normally contribute to a reduction in the surface tension within the air spaces (alveoli) of the lung, preventing their collapse. The premature infant has not yet begun to produce adequate amounts of lung surfactant.



The effect of lung surfactant

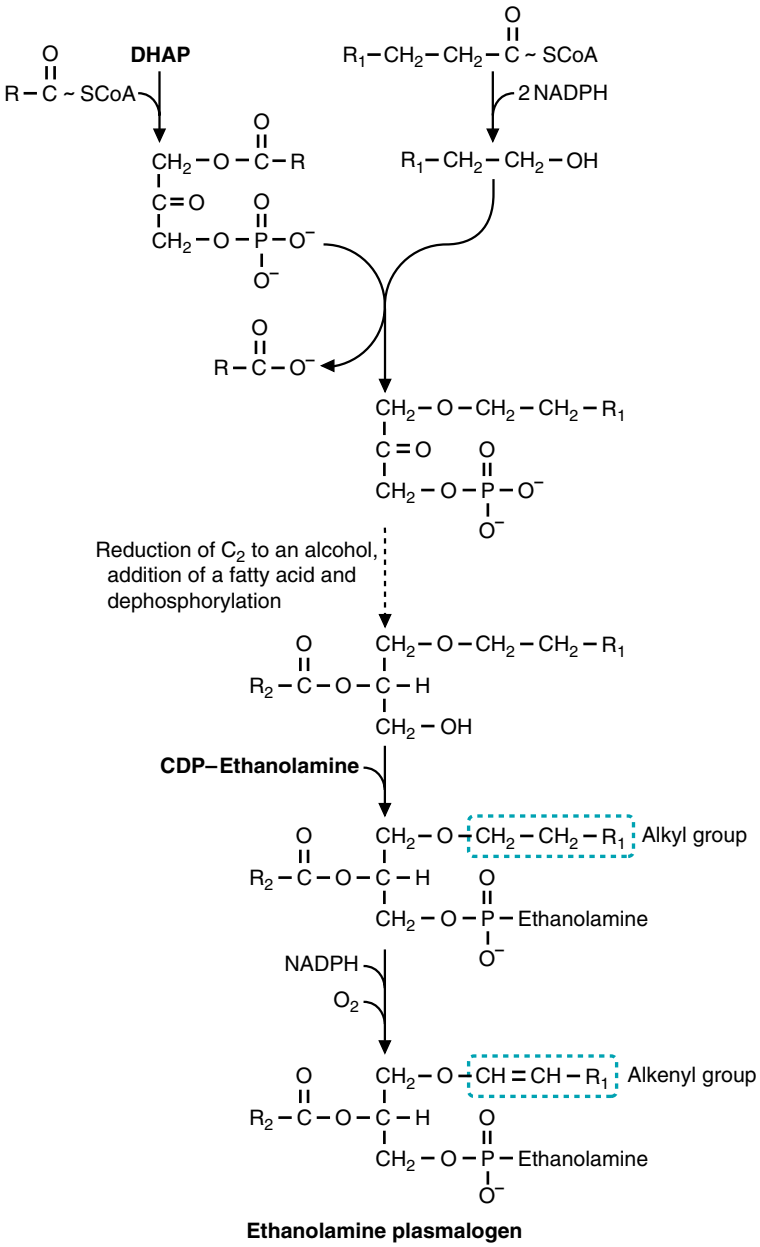


Fig. 33.30. Synthesis of a plasmalogen.

myelin and choline plasmalogen in heart muscle. Platelet-activating factor (PAF) is similar to choline plasmalogen except that an acetyl group replaces the fatty acyl group at carbon 2 of the glycerol moiety, and the alkyl group on carbon 1 is saturated. PAF is released from phagocytic blood cells in response to various stimuli. It causes platelet aggregation, edema, and hypotension, and it is involved in the allergic response. Plasmalogen synthesis occurs within peroxisomes, and, in individuals with Zellweger's syndrome (a defect in peroxisome biogenesis), plasmalogen synthesis is compromised. If severe enough, this syndrome leads to death at an early age.

Phospholipase A2 provides the major repair mechanism for membrane lipids damaged by oxidative free radical reactions. Arachidonic acid, which is a polyunsaturated fatty acid, can be peroxidatively cleaved in free radical reactions to malondialdehyde and other products. Phospholipase A_2 recognizes the distortion of membrane structure caused by the partially degraded fatty acid and removes it. Acyltransferases then add back a new arachidonic acid molecule.

B. Degradation of Glycerophospholipids

Phospholipases located in cell membranes or in lysosomes degrade glycerophospholipids. Phospholipase A1 removes the fatty acyl group on carbon 1 of the glycerol moiety, and phospholipase A2 removes the fatty acid on carbon 2 (Fig. 33.31). The C2 fatty acid in cell membrane phospholipids is usually an unsaturated fatty acid,

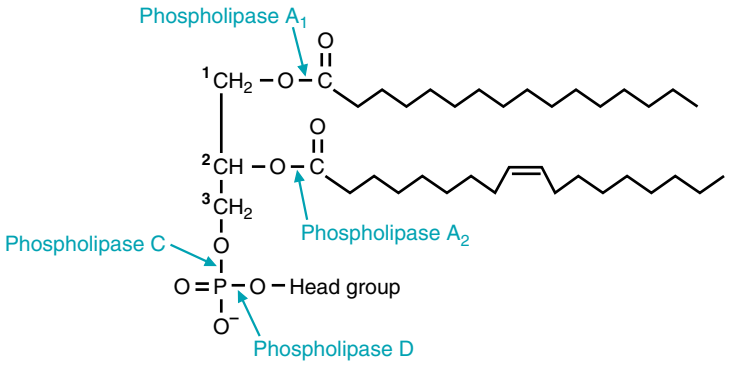


Fig. 33.31. Bonds cleaved by phospholipases.

which is frequently arachidonic acid. It is removed in response to signals for the synthesis of eicosanoids. The bond joining carbon 3 of the glycerol moiety to phosphate is cleaved by phospholipase C. Hormonal stimuli activate phospholipase C, which hydrolyzes PIP_2 to produce the second messengers DAG and inositol triphosphate (IP_3). The bond between the phosphate and the head group is cleaved by phospholipase D, producing phosphatidic acid and the free alcohol of the head group.

C. Sphingolipids

Sphingolipids serve in intercellular communication and as the antigenic determinants of the ABO blood group. Some are used as receptors by viruses and bacterial toxins, although it is unlikely that this was the purpose for which they originally evolved. Before the functions of the sphingolipids were elucidated, these compounds appeared to be inscrutable riddles. They were, therefore, named for the Sphinx of Thebes, who killed passersby that could not solve her riddle.

The synthesis of sphingolipids begins with the formation of ceramide (Fig. 33.32). Serine and palmityl CoA condense to form a product that is reduced. A very-long-chain fatty acid (usually containing 22 carbons) forms an amide with the amino group, a double bond is generated, and ceramide is formed.

Ceramide reacts with phosphatidylcholine to form sphingomyelin, a component of the myelin sheath (Fig. 33.33). Ceramide also reacts with UDP-sugars to form cerebrosides (which contain a single monosaccharide, usually galactose or glucose). Galactocerebroside may react with 3′-phosphoadenosine 5′-phosphosulfate (PAPS, an active sulfate donor; Figure 33.34) to form sulfatides, the major sulfolipids of the brain.

Additional sugars may be added to ceramide to form globosides, and gangliosides are produced by the addition of *N*-acetylneuraminic acid (NANA) as branches from the oligosaccharide chains (see Fig. 33.33 and Chapter 30).

Sphingolipids are degraded by lysosomal enzymes (see Chapter 30). Deficiencies of these enzymes result in a group of lysosomal storage diseases known as the sphingolipidoses.

CLINICAL COMMENTS

If **Percy Veere** had continued to eat a hypercaloric diet rich in carbohydrates, he would have become obese. In an effort to define obesity, it has been agreed internationally that the ratio of the patient's body weight in kilograms and their height in meters squared (W/H^2) is the most useful and reproducible measure. This ratio is referred to as the body mass index or BMI. Normal men and women fall into the range of 20 to 25. Percy's current value is 21.3 and rising.

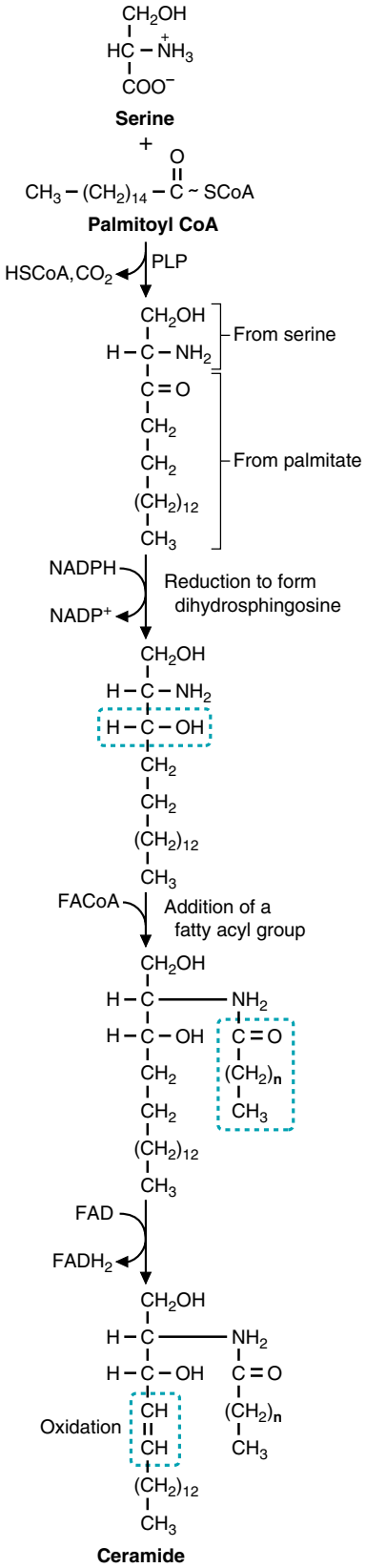


Fig. 33.32. Synthesis of ceramide. The changes that occur in each reaction are highlighted. PLP = pyridoxal phosphate.

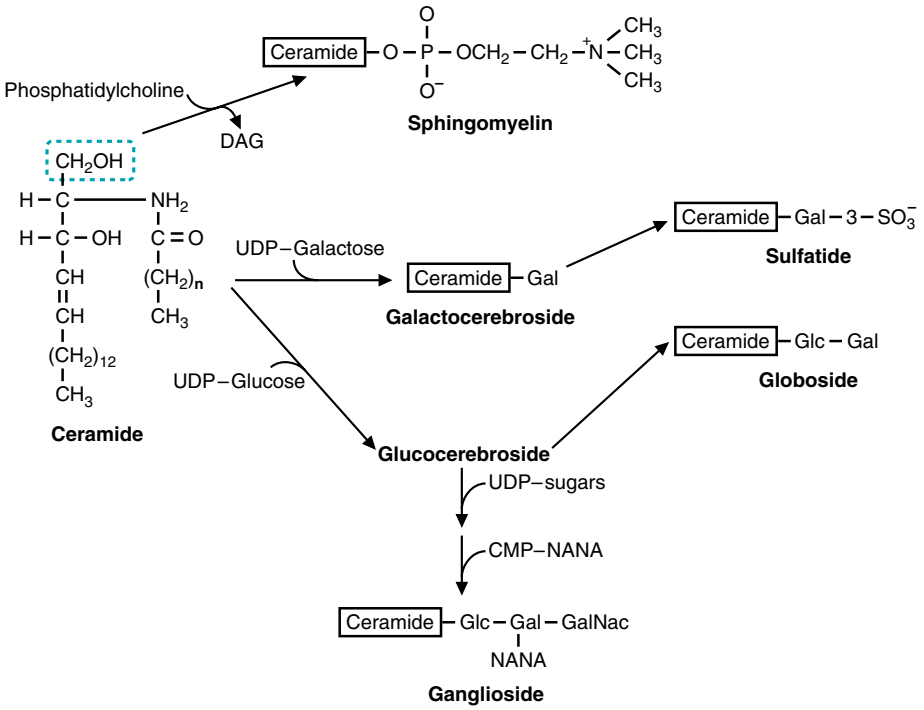


Fig. 33.33. Synthesis of sphingolipids from ceramide. Phosphocholine or sugars add to the hydroxymethyl group of ceramide (in blue) to form sphingomyelins, cerebrosides, sulfatides, globosides, and gangliosides. Gal = galactose; Glc = gucose; GalNAc = *N*-acetylgalactosamine; NANA = *N*-acetylneuraminic acid.

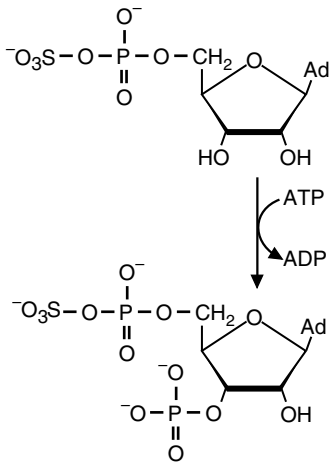


Fig. 33.34. The synthesis of 3′-phosphoadenosine 5′-phosphosulfate (PAPS), an active sulfate donor. PAPS donates sulfate groups to cerebrosides to form sulfatides and is also involved in glycosaminoglycan biosynthesis (see Chapter 49). Ad = adenosine.

Approximately 36 million people in the United States have a BMI greater than 27.8 (for men) or 27.3 (for women). At this level of obesity, which is quite close to a 20% weight increase above the "ideal" or desirable weight, an attempt at weight loss should be strongly advised. The idea that obesity is a benign condition unless accompanied by other risk factors for cardiovascular disease is disputed by several long-term, properly controlled prospective studies. These studies show that obesity

is an independent risk factor not only for heart attacks and strokes, but for the development of insulin resistance, type 2 diabetes mellitus, hypertension, and gallbladder disease.

Percy did not want to become overweight and decided to follow his new diet faithfully.

Because **Cora Nari's** lipid profile indicated an elevation in both serum triacylglycerols and LDL cholesterol, she was classified as having a combined hyperlipidemia. The dissimilarities in the lipid profiles of Cora and her two siblings, both of whom were experiencing anginal chest pain, is characteristic of the multigenic syndrome referred to as familial combined hyperlipidemia (FCH).

Approximately 1% of the North American population has FCH. It is the most common cause of coronary artery disease in the United States. In contrast to patients with familial hypercholesterolemia (FH), patients with FCH do not have fatty deposits within the skin or tendons (xanthomas) (see Chapter 34). In FCH, coronary artery disease usually appears by the fifth decade of life.

Treatment of FCH includes restriction of dietary fat. Patients who do not respond adequately to dietary therapy are treated with antilipidemic drugs. Selection of the appropriate antilipidemic drugs depends on the specific phenotypic expression of the patient's multigenic disease as manifest by their particular serum lipid profile. In Cora's case, a decrease in both serum triacylglycerols and LDL cholesterol must be achieved. If possible, her serum HDL cholesterol level should also be raised to a level above 40 mg/dL.

To accomplish these therapeutic goals, her physician initially prescribed fast-release nicotinic acid (niacin), because this agent has the potential to lower serum triacylglycerol levels and cause a reciprocal rise in serum HDL cholesterol levels, as well as to lower serum total and LDL cholesterol levels. The mechanisms suggested for niacin's triacylglycerol-lowering action include enhancement of the action of LPL, inhibition of lipolysis in adipose tissue, and a decrease in esterification of triacylglycerols in the liver (see Table 34.5). The mechanism by which niacin lowers the serum total and LDL cholesterol levels is related to the decrease in hepatic production of VLDL. When the level of VLDL in the circulation decreases, the production of its daughter particles, IDL and LDL, also decreases. Cora found niacin's side effects of flushing and itching to be intolerable, and the drug was discontinued.

Pravastatin was given instead. Pravastatin inhibits cholesterol synthesis by inhibiting hydroxymethylglutaryl CoA (HMG-CoA) reductase, the rate-limiting enzyme in the pathway (see Chapter 34). After 3 months of therapy, pravastatin decreased Cora's LDL cholesterol from a pretreatment level of 175 to 122 mg/dL (still higher than the recommended treatment goal of 100 mg/dL or less in a patient with established coronary artery disease). Her fasting serum triacylglycerol concentration was decreased from a pretreatment level of 280 to 178 mg/dL (a treatment goal for serum triacylglycerol when the pretreatment level is less than 500 mg/dL has not been established).

Colleen Lakker suffered from respiratory distress syndrome (RDS), which is a major cause of death in the newborn. RDS is preventable if prematurity can be avoided by appropriate management of high-risk pregnancy and labor. Before delivery, the obstetrician must attempt to predict and possibly treat pulmonary prematurity in utero. For example, estimation of fetal head circumference by ultrasonography, monitoring for fetal arterial oxygen saturation, and determination of the ratio of the concentrations of phosphatidylcholine (lecithin) and that of sphingomyelin in the amniotic fluid may help to identify premature infants who are predisposed to RDS (Fig. 33.35).

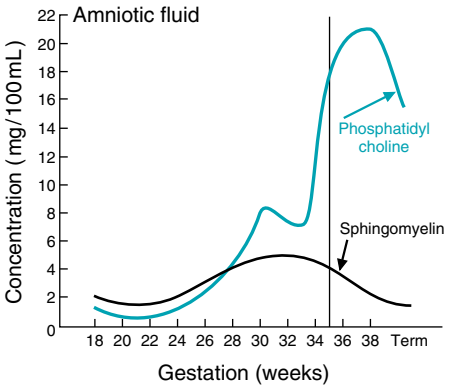


Fig. 33.35. Comparison of phosphatidylcholine and sphingomyelin in amniotic fluid. Phosphatidylcholine is the major lipid in lung surfactant. The concentration of phosphatidylcholine relative to sphingomyelin rises at 35 weeks of gestation, indicating pulmonary maturity.

The administration of synthetic corticosteroids 48 to 72 hours before delivery of a fetus of less than 33 weeks of gestation in women who have toxemia of pregnancy, diabetes mellitus, or chronic renal disease may reduce the incidence or mortality of RDS by stimulating fetal synthesis of lung surfactant.

The administration of one dose of surfactant into the trachea of the premature infant immediately after birth may transiently improve respiratory function but does not improve overall mortality. In Colleen's case, intensive therapy allowed her to survive this acute respiratory complication of prematurity.

BIOCHEMICAL COMMENTS

Biochemically, what makes people become obese? Obviously, the amount of fat an individual can store depends on the number of fat cells in the body and the amount of triacylglycerol each cell can accommodate. In obese individuals, both the number of fat cells and the size of the cells (i.e., the total storage capacity) is greater than in individuals with no history of obesity. To fill these stores, however, an individual must eat more than required to support the basal metabolic rate and physical activity.

Fat cells begin to proliferate early in life, starting in the third trimester of gestation. Proliferation essentially ceases before puberty, and thereafter fat cells change mainly in size. However, some increase in the number of fat cells can occur in adulthood if preadipocytes are induced to proliferate by growth factors and changes in the nutritional state. Weight reduction results in a decrease in the size of fat cells rather than a decrease in number. After weight loss, the amount of LPL, an enzyme involved in the transfer of fatty acids from blood triacylglycerols to the triacylglycerol stores of adipocytes, increases. In addition, the amount of mRNA for LPL also increases. All of these factors suggest that individuals who become obese, particularly those who do so early in life, will have difficulty losing weight and maintaining a lower body adipose mass.

Signals that initiate or inhibit feeding are extremely complex and include psychological and hormonal factors as well as neurotransmitter activity. These signals are integrated and relayed through the hypothalamus. Destruction of specific regions of the hypothalamus can lead to overeating and obesity or to anorexia and weight loss. Overeating and obesity are associated with damage to the ventromedial or the paraventricular nucleus, whereas weight loss and anorexia are related to damage to more lateral hypothalamic regions. Compounds that act as satiety signals have been identified in brain tissue and include leptin and glucagon-like peptide-1 (GLP-1). Appetite suppressors developed from compounds such as these may be used in the future for the treatment of obesity.

Recently it has become apparent that the adipocyte, in addition to storing triacylglycerol, secretes hormones that regulate both glucose and fat metabolism. The hormones leptin, resistin (resists insulin action), and adiponectin (also known as Acrp30) are all secreted from adipocytes under different conditions. The role of these hormones has been best understood in mouse models; unfortunately, extrapolation to the human condition has been difficult. In mice, leptin is released from adipocytes as triglyceride levels increase and signals the hypothalamus to reduce eating and to increase physical activity. Mice lacking the ability to secrete leptin (the ob mouse), or respond to leptin (the db mouse) are obese. Injecting leptin into ob mice allows them to lose weight.

The adipocytes in mice have been shown to release a hormone known as resistin. This hormone may contribute to insulin resistance in these animals. The mechanism by which resistin causes an insensitivity of cells to the actions of insulin is unknown. It is of great interest, however, that the class of drugs known as thiazolidinediones, which are given to individuals with type 2 diabetes, suppress resistin transcription, reduce resistin levels, and increase sensitivity to insulin in these patients. Addition-

ally, thiazolidinediones may upregulate adipose PEPCK, resulting in a reduced fatty acid output from the adipocyte because of increased glyceroneogenesis.

In humans, adiponectin is secreted from adipocytes in inverse proportion to their adipose mass, lean individuals secreting more adiponectin than obese individuals. This is the exact opposite of leptin secretion. The effects of adiponectin, and how it interacts with resistin and leptin, are active areas of current research.

Further complicating the issue of glucose and lipid homeostasis is the effect of nuclear receptors known as peroxisome proliferator activated receptors (PPAR). These nuclear receptors (see Chapter 10) exist in three forms; α, β/δ, and γ. PPARγ is found in highest levels in adipocytes, and activation of the receptor leads to gene transcription, which is necessary for adipocyte differentiation and regulation of lipid metabolism. The thiazolidinediones activate PPARγ, which leads to a decrease in circulating resistin levels. Understanding more about the physiologic regulators of PPARγ is also an active area of research. The role of PPAR in liver is discussed in Chapter 46.

Although an increase in food intake beyond the daily requirements results in an increase in body weight and in fat stores, there is a large variation among individuals in the amount of weight gained for a given number of excess calories consumed. Both genetic and environmental factors influence the development of obesity. Studies of identical twins who were purposely overfed showed that the amount of weight gained was more similar within sets than between sets. Other studies of identical and fraternal twins, in which the members of a set were reared apart, support the conclusion that heredity plays a major role in determining body weight.

Suggested Readings

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REVIEW QUESTIONS—CHAPTER 33

1. Which of the following is involved in the synthesis of triacylgycerols in adipose tissue?

   (A) Fatty acids obtained from chylomicrons and VLDL
   (B) Glycerol 3-phosphate derived from blood glycerol
   (C) 2-Monoacylglycerol as an obligatory intermediate
   (D) Lipoprotein lipase to catalyze the formation of ester bonds
   (E) Acetoacetyl CoA as an obligatory intermediate

2. A molecule of palmitic acid, attached to carbon 1 of the glycerol moiety of a triacylglycerol, is ingested and digested. It passes into the blood, is stored in a fat cell, and ultimately is oxidized to carbon dioxide and water in a muscle cell. Choose the molecular complex in the blood in which the palmitate residue is carried from the lumen of the gut to the surface of the gut epithelial cell.

   (A) VLDL
   (B) Chylomicron
   (C) Fatty acid-albumin complex
   (D) Bile salt micelle
   (E) LDL

3. A patient with hyperlipoproteinemia would be most likely to benefit from a low-carbohydrate diet if the lipoproteins that are elevated in blood are which of the following?

   (A) Chylomicrons
   (B) VLDL
   (C) HDL
   (D) LDL
   (E) IDL

4. Which of the following is a characteristic of sphingosine?

   (A) It is converted to ceramide by reacting with a UDP-sugar.
   (B) It contains a glycerol moiety.
   (C) It is synthesized from palmitoyl CoA and serine.
   (D) It is a precursor of cardiolipin.
   (E) It is only synthesized in neuronal cells.

5. Newly synthesized fatty acids are not immediately degraded because of which of the following?

   (A) Tissues that synthesize fatty acids do not contain the enzymes that degrade fatty acids.
   (B) High NADPH levels inhibit β-oxidation.
   (C) In the presence of insulin, the key fatty acid degrading enzyme is not induced.
   (D) Newly synthesized fatty acids cannot be converted to their CoA derivatives.
   (E) Transport of fatty acids into mitochondria is inhibited under conditions in which fatty acids are being synthesized.