Metabolism of Acylglycerols & Sphingolipids

BIOMEDICAL IMPORTANCE

Acylglycerols constitute the majority of lipids in the body. Triacylglycerols are the major lipids in fat deposits and in food. The amphipathic nature of phospholipids and sphingolipids makes them ideally suitable as the main lipid component of cell membranes.

Phospholipids also take part in the metabolism of many other lipids. Some phospholipids have specialized functions; eg, dipalmitoyl lecithin is a major component of **lung surfactant**, which is lacking in **respiratory distress syndrome** of the newborn. Inositol phospholipids in the cell membrane act as precursors of **hormone second messengers**, and **platelet activating factor** is an alkylphospholipid. Glycosphingolipids, containing sphingosine and sugar residues as well as fatty acid that are found in the outer leaflet of the plasma membrane with their oligosaccharide chains facing outward, form part of the **glycocalyx** of the cell surface and are important (1) in cell adhesion and cell recognition, (2) as receptors for bacterial toxins (eg, the toxin that causes cholera), and (3) as ABO blood group substances. A dozen or so **glycolipid storage diseases** have been described (eg, Gaucher's disease and Tay-Sachs disease), each due to a genetic defect in the pathway for glycolipid degradation in the lysosomes.

HYDROLYSIS INITIATES CATABOLISM OF TRIACYLGLYCEROLS

Triacylglycerols must be hydrolyzed by a **lipase** to their constituent fatty acids and glycerol before further catabolism can proceed. **Much of this hydrolysis** (lipolysis) occurs in adipose tissue with release of free fatty acids into the plasma, where they are found combined with serum albumin. This is followed by free fatty acid uptake into tissues (including liver, heart, kidney, muscle, lung, testis, and adipose tissue, but not readily by brain), where they are **oxidized to obtain energy or reesterified**. The utilization of glycerol depends upon whether such tissues have the enzyme **glycerol kinase**, which is found in significant amounts in liver, kidney, intestine, brown adipose tissue, and the lactating mammary gland.

TRIACYLGLYCEROLS & PHOSPHOGLYCEROLS ARE FORMED BY ACYLATION OF TRIOSE PHOSPHATES

The major pathways of triacylglycerol and phosphoglycerol biosynthesis are outlined in Figure 1. Important substances such as triacylglycerols, phosphatidylcholine,

phosphatidylethanolamine, phosphatidylinositol, and cardiolipin, a constituent of mitochondrial membranes, are formed from **glycerol-3-phosphate**. Significant branch points in the pathway occur at the **phosphatidate** and **diacylglycerol** steps. Phosphoglycerols containing an ether link (—C—O—C—), the best known of which are plasmalogens and platelet-activating factor (PAF), are derived from **dihydroxyacetone phosphate**. Glycerol 3-phosphate and dihydroxyacetone phosphate are intermediates in glycolysis, making a very important **connection** between carbohydrate and lipid metabolism.

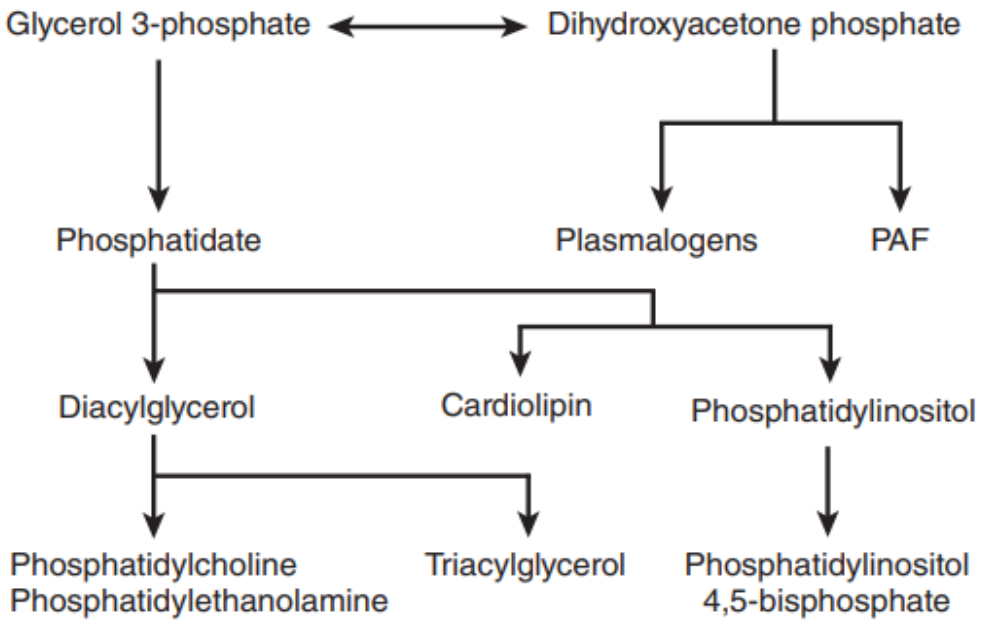

Figure 1 Overview of acylglycerol biosynthesis. (PAF, platelet-activating factor.)

Phosphatidate Is the Common Precursor in the Biosynthesis of Triacylglycerols, Many Phosphoglycerols, & Cardiolipin

Both glycerol and fatty acids must be activated by ATP before they can be incorporated into acylglycerols. **Glycerol kinase** catalyzes the activation of glycerol to sn-glycerol 3-phosphate. If the activity of this enzyme is absent or low, as in muscle or adipose tissue, most of the glycerol-3-phosphate is formed from dihydroxyacetone phosphate by **glycerol-3-phosphate dehydrogenase** (Figure 2).

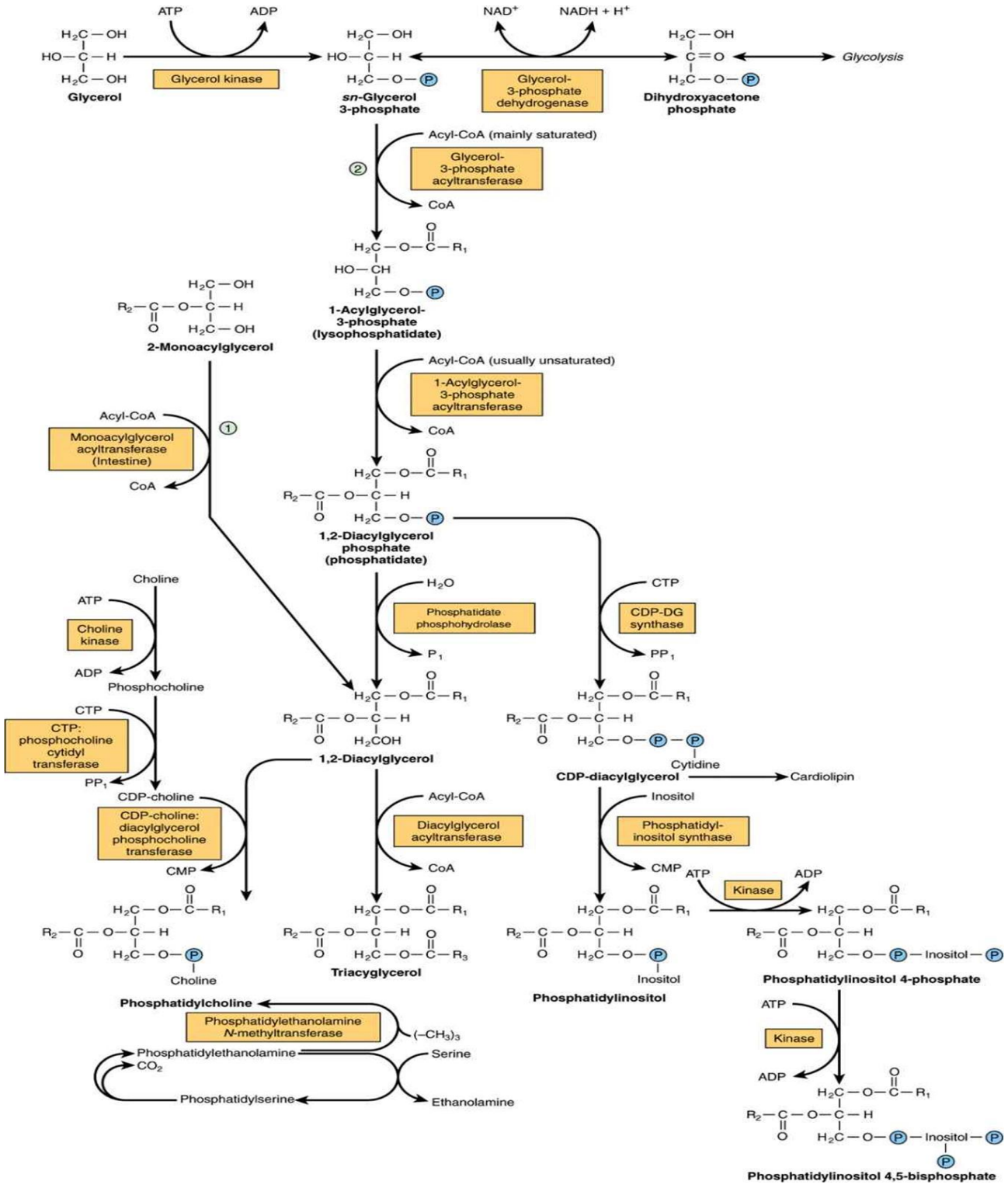

Figure 2 Biosynthesis of triacylglycerol and phospholipids. 1, Monoacylglycerol pathway; 2, glycerol phosphate pathway. Phosphatidylethanolamine may be formed from ethanolamine by a pathway similar to that shown for the formation of phosphatidylcholine from choline.

Biosynthesis of Triacylglycerols

Two molecules of acyl-CoA, formed by the activation of fatty acids by **acyl-CoA synthetase**, combine with glycerol-3-phosphate to form **phosphatidate** (1,2-diacylglycerol phosphate). This takes place in two stages, catalyzed by **glycerol-3-phosphate acyltransferase** and **1-acylglycerol-3-phosphate acyltransferase**. Phosphatidate is converted by **phosphatidate phosphohydrolase** (also called **phosphatidate phosphatase** (PAP)) and **diacylglycerol acyltransferase (DGAT)** to 1,2-diacylglycerol and then triacylglycerol. **Lipins**, a family of three proteins, have PAP activity and they also act as transcription factors which regulate the expression of genes involved in lipid metabolism. DGAT catalyzes the **only step specific** for triacylglycerol synthesis and is thought to be **rate limiting** in most circumstances. In intestinal mucosa, **monoacylglycerol acyltransferase** converts **monoacylglycerol** to 1,2-diacylglycerol in the **monoacylglycerol pathway**. Most of the activity of these enzymes resides in the endoplasmic reticulum, but some is found in mitochondria. Although phosphatidate phosphohydrolase protein is found mainly in the cytosol, the active form of the enzyme is membrane bound.

Biosynthesis of Phospholipids

In the biosynthesis of **phosphatidylcholine** and **phosphatidylethanolamine** (Figure 2), choline or ethanolamine must first be activated by phosphorylation by ATP followed by linkage to CDP. The resulting CDP-choline or CDP-ethanolamine reacts with 1,2-diacylglycerol to form either phosphatidylcholine or phosphatidylethanolamine, respectively. **Phosphatidylserine** is formed from phosphatidylethanolamine directly by reaction with serine (Figure 2).

Phosphatidylserine may re-form phosphatidylethanolamine by **decarboxylation**. An alternative pathway in **liver** enables phosphatidylethanolamine to give rise directly to phosphatidylcholine by **progressive methylation** of the ethanolamine residue. In spite of these sources of choline, it is considered to be an essential nutrient in many mammalian species, although this has not been established in humans.

The regulation of triacylglycerol, phosphatidylcholine, and phosphatidylethanolamine biosynthesis is driven by the availability of free fatty acids. Those that escape oxidation are preferentially converted to phospholipids, and when this requirement is satisfied, they are used for triacylglycerol synthesis.

Cardiolipin (diphosphatidylglycerol) is a phospholipid present in mitochondria. It is formed from **phosphatidylglycerol**, which in turn is synthesized from CDP-diacylglycerol (Figure 2) and glycerol 3-phosphate according to the scheme shown in Figure 3.

Cardiolipin, found in the inner membrane of mitochondria, has a key role in mitochondrial structure and function, and is also thought to be involved in programmed cell death (**apoptosis**).

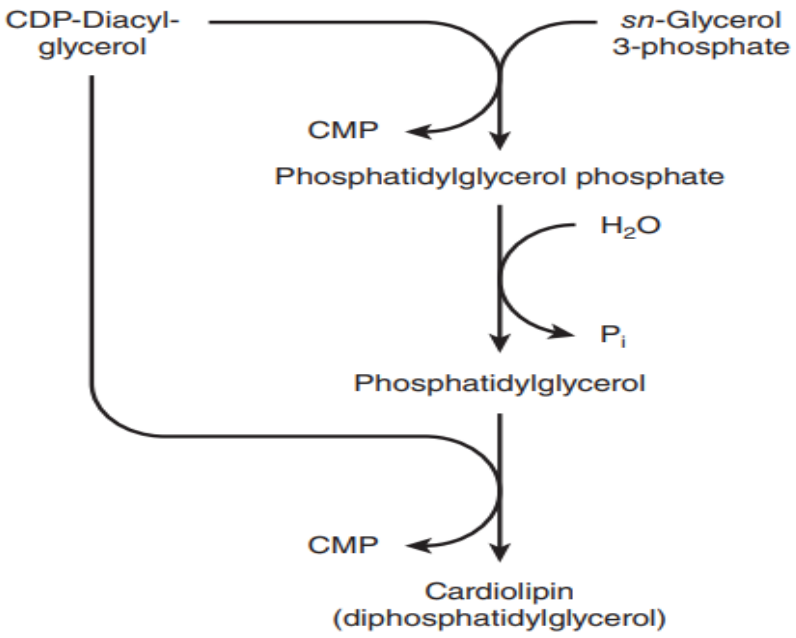

Figure 3 Biosynthesis of cardiolipin.

Biosynthesis of Glycerol Ether Phospholipids

In **glycerol ether phospholipids**, one or more of the glycerol carbons is attached to a hydrocarbon chain by an ether linkage rather than an ester bond. **Plasmalogens and platelet activating factor** are important examples of this type of lipid. The biosynthetic pathway is located in **peroxisomes**. Dihydroxyacetone phosphate is the precursor of the glycerol moiety (Figure 4). It combines with acyl-CoA to give 1-acyldihydroxyacetone phosphate, and the ether link is formed in the next reaction, producing 1-alkyldihydroxyacetone phosphate, which is then converted to 1-alkylglycerol 3-phosphate. After further acylation in the 2 position, the resulting 1-alkyl-2-acylglycerol 3-phosphate (analogous to phosphatidate in Figure 2) is hydrolyzed to give the free glycerol derivative. Plasmalogens, which comprise much of the phospholipid in mitochondria, are formed by desaturation of the **analogous 3-phosphoethanolamine** derivative (Figure 4). Platelet-activating factor (PAF) (1-alkyl-2-acetyl-sn-glycerol-3-phosphocholine) is synthesized from the **corresponding 3-phosphocholine derivative**. It is formed by many blood cells and other tissues and aggregates platelets at concentrations as low as 10^{-11} mol/L. It also has hypotensive and ulcerogenic properties

and is involved in a variety of biologic responses, including inflammation, chemotaxis, and protein phosphorylation.

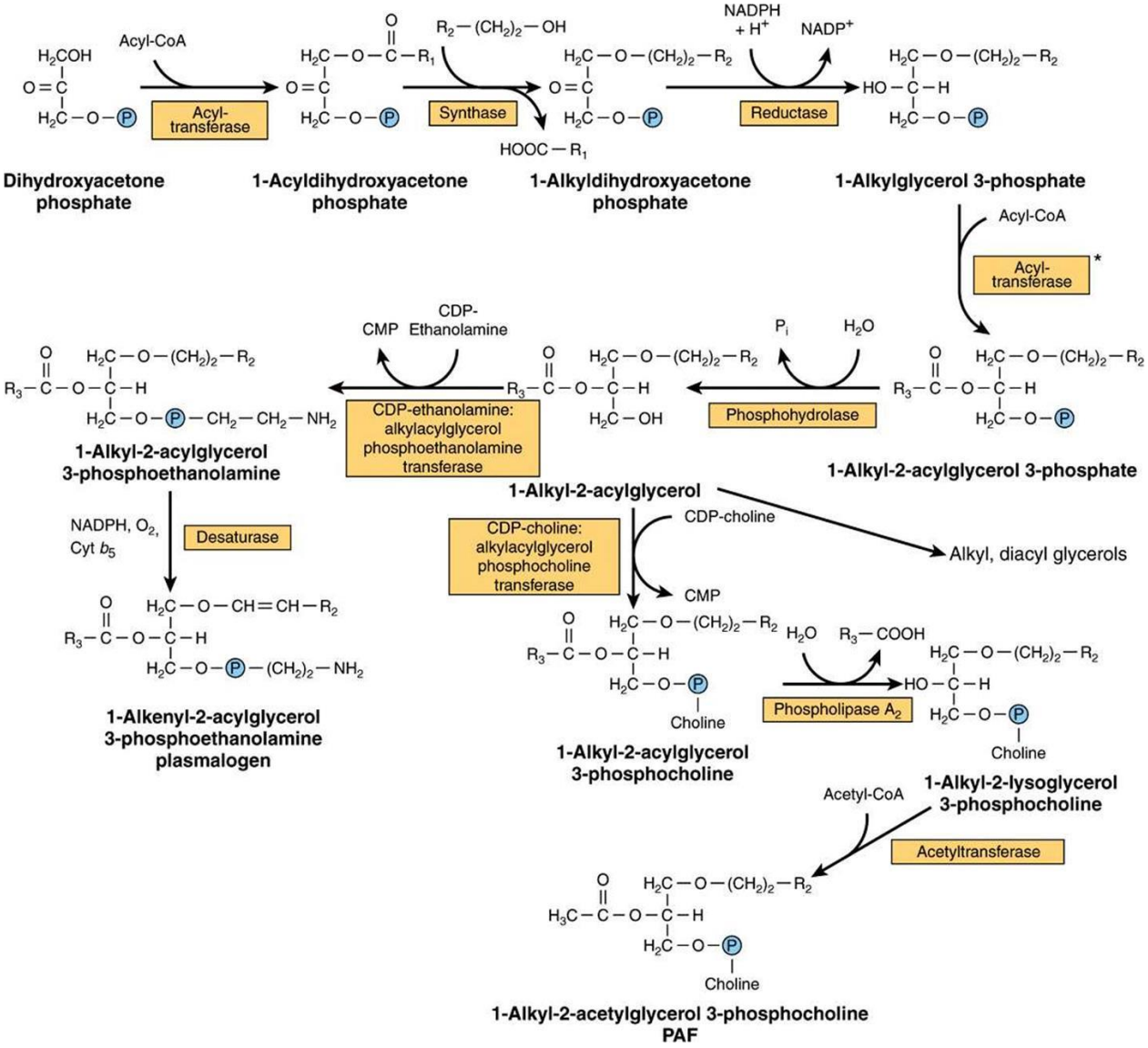

FIGURE 4 Biosynthesis of ether lipids, including plasmalogens, and platelet-activating factor (PAF). In the de novo pathway for PAF synthesis, acetyl-CoA is incorporated at stage∗ , avoiding the last two steps in the pathway shown here.

Phospholipases Allow Degradation & Remodeling of Phosphoglycerols

Although phospholipids are actively degraded, each portion of the molecule turns over at a different rate—eg, the turnover time of the phosphate group is different from that of the 1-acyl group. This is due to the presence of enzymes that allow partial degradation followed by resynthesis (Figure 5). **Phospholipase A_2** catalyzes the

hydrolysis of glycerophospholipids to form a free fatty acid and lysophospholipid, which in turn may be reacylated by acyl-CoA in the presence of an acyltransferase. Alternatively, lysophospholipid (eg, lysolecithin) is attacked by **lysophospholipase**, forming the corresponding glyceryl phosphoryl base, which may then be split by a **hydrolase** liberating glycerol 3-phosphate plus base. **Phospholipases A_1 , A_2 , B, C, and D** attack the bonds indicated in Figure 6. **Phospholipase A_2** is found in pancreatic fluid and snake venom as well as in many types of cells; **phospholipase C** is one of the major toxins secreted by bacteria; and **phospholipase D** is known to be involved in mammalian signal transduction.

Lysolecithin (lysophosphatidylcholine) may be formed by an alternative route that involves **lecithin: cholesterol acyltransferase (LCAT)**. This enzyme, found in plasma, catalyzes the transfer of a fatty acid residue from the 2 position of lecithin to cholesterol to form cholesteryl ester and lysolecithin, and is considered to be responsible for much of the cholesteryl ester in plasma lipoproteins.

Long-chain saturated fatty acids are found predominantly in the 1 position of phospholipids, whereas the polyunsaturated fatty acids (eg, the precursors of prostaglandins) are incorporated more frequently into the 2 position. The incorporation of fatty acids into lecithin occurs in **three ways**; by complete synthesis of the phospholipid; by transacylation between cholesteryl ester and lysolecithin; and by direct acylation of lysolecithin by acyl-CoA. Thus, a continuous exchange of the fatty acids is possible, particularly with regard to introducing essential fatty acids into phospholipid molecules.

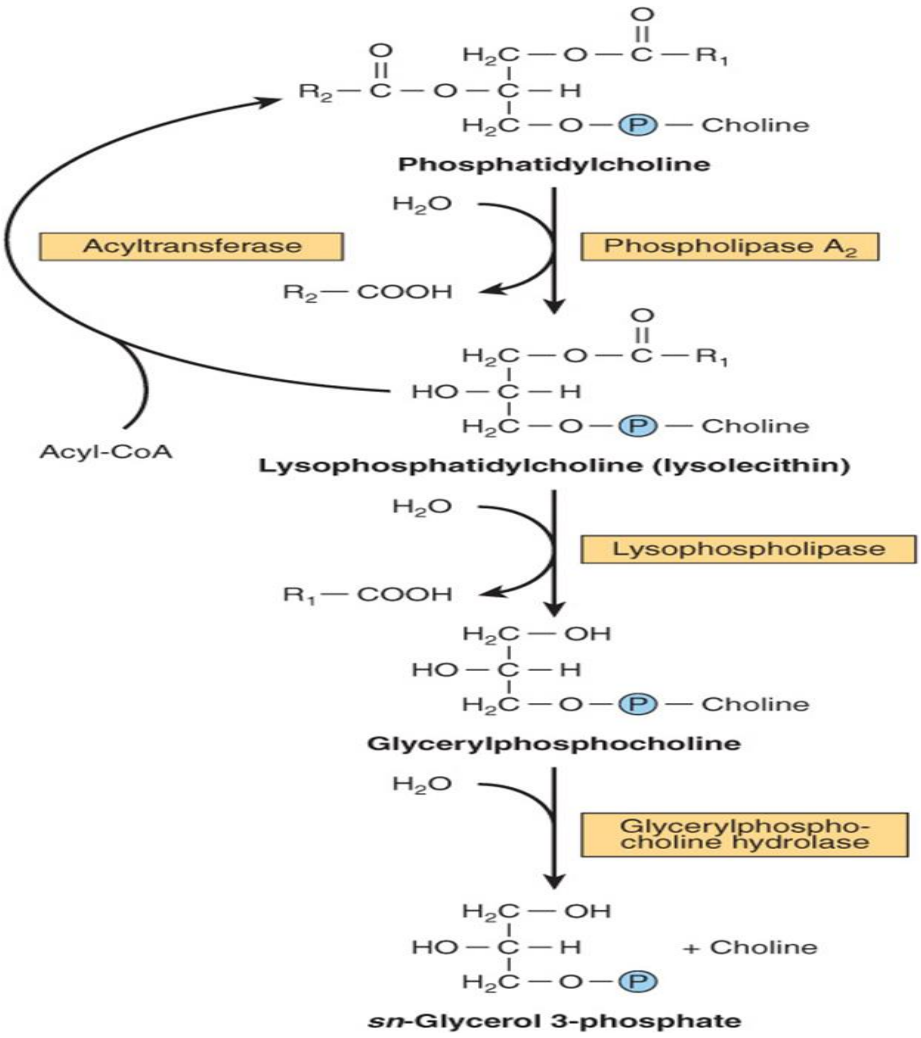

Figure 5 Metabolism of phosphatidylcholine (lecithin).

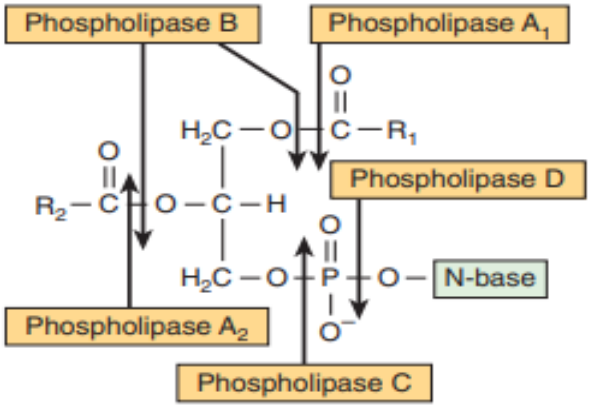

Figure 6 Sites of the hydrolytic activity of phospholipases on a phospholipid substrate.

ALL SPHINGOLIPIDS ARE FORMED FROM CERAMIDE

Ceramide is synthesized in the endoplasmic reticulum from the amino acid serine as shown in Figure 7. Ceramide is an important **signaling molecule (second messenger)** regulating pathways including programmed cell death **(apoptosis)**, the **cell cycle**, and **cell differentiation and senescence**.

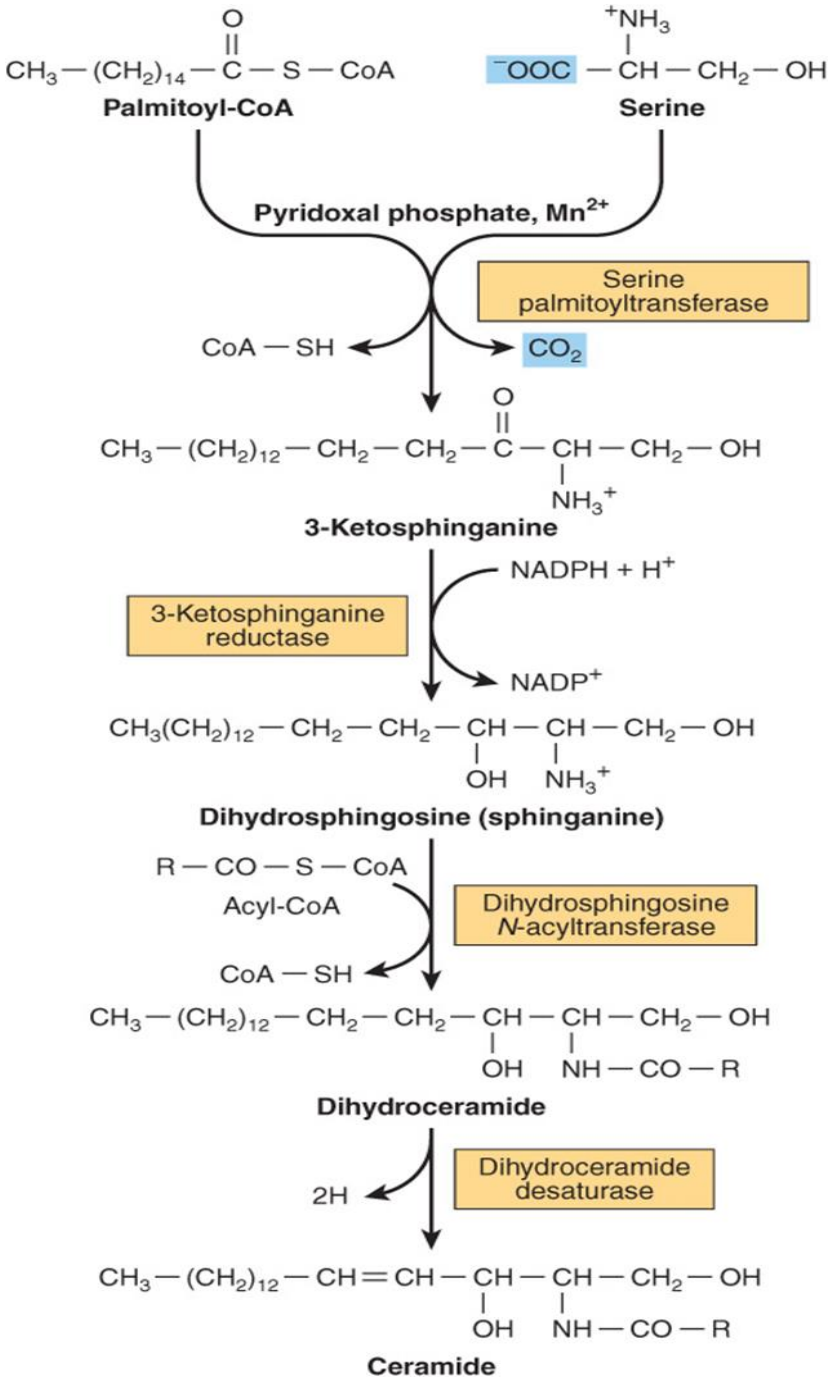

Figure 7 Biosynthesis of ceramide.

Sphingomyelins (Figure 8) are phospholipids and are formed when ceramide reacts with phosphatidylcholine to form sphingomyelin plus diacylglycerol (Figure 9A). This occurs mainly in the Golgi apparatus and to a lesser extent in the plasma membrane.

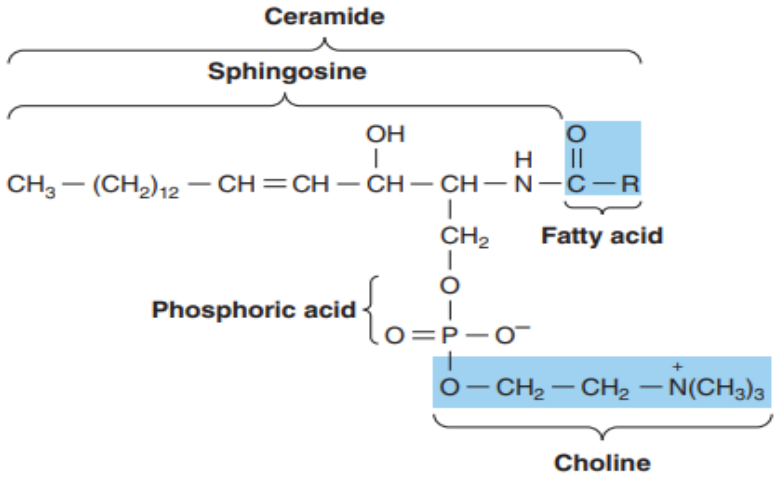

Figure 8 A sphingomyelin.

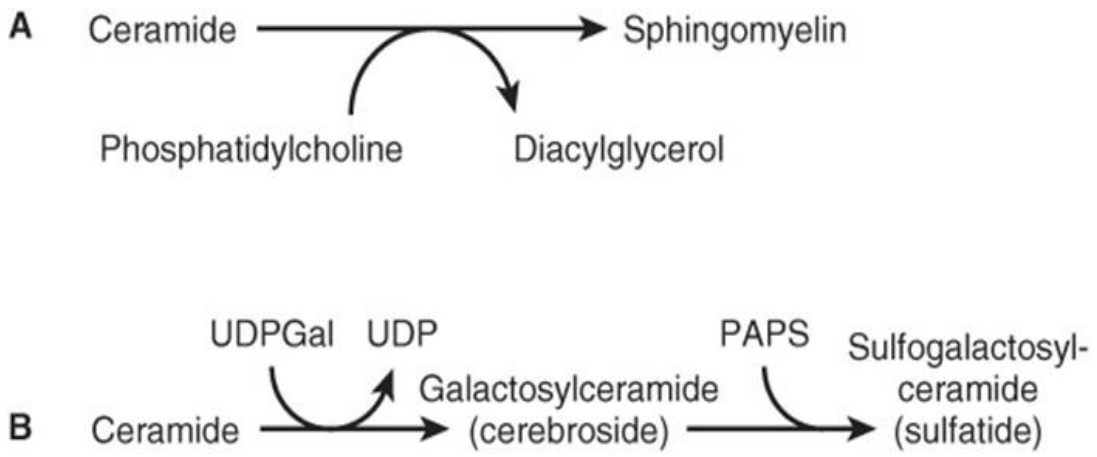

Figure 9 Biosynthesis of (A) sphingomyelin, (B) galactosylceramide and its sulfo derivative. (PAPS, "active sulfate," adenosine 3′-phosphate-5′-phosphosulfate.)

Glycosphingolipids Are a Combination of Ceramide With One or More Sugar Residues

The simplest glycosphingolipids **(cerebrosides)** are **galactosylceramide (GalCer)** (Figure 10) and **glucosylceramide (GlcCer)**. GalCer is a major lipid of **myelin**, whereas GlcCer is the major glycosphingolipid of **extraneural tissues** and a precursor of most of the more

complex glycosphingolipids. GalCer (Figure 9B) is formed in a reaction between ceramide and UDPGal (formed by epimerization from UDPGlc).

Sulfogalactosylceramide and other sulfolipids such as the **sulfo(galacto)-glycerolipids** and the **steroid sulfates** are formed after further reactions involving 3′-phosphoadenosine 5′-phosphosulfate (PAPS; "active sulfate"). **Gangliosides** are synthesized from ceramide by the stepwise addition of activated sugars (eg, UDPGlc and UDPGal) and a **sialic acid**, usually N-acetylneuraminic acid (Figure 11). A large number of gangliosides of increasing molecular weight may be formed. Most of the enzymes transferring sugars from nucleotide sugars (glycosyl transferases) are found in the Golgi apparatus.

Glycosphingolipids are constituents of the outer leaflet of plasma membranes and are important in **cell adhesion** and **cell recognition**. Some are antigens, for example, ABO blood group substances. Certain gangliosides function as receptors for bacterial toxins (eg, for **cholera toxin**, which subsequently activates adenylyl cyclase).

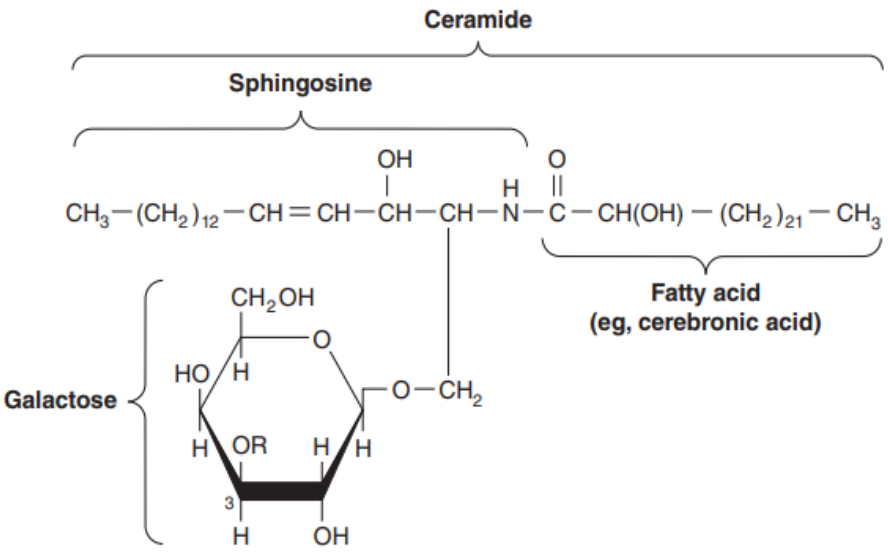

Figure 10 Structure of galactosylceramide.

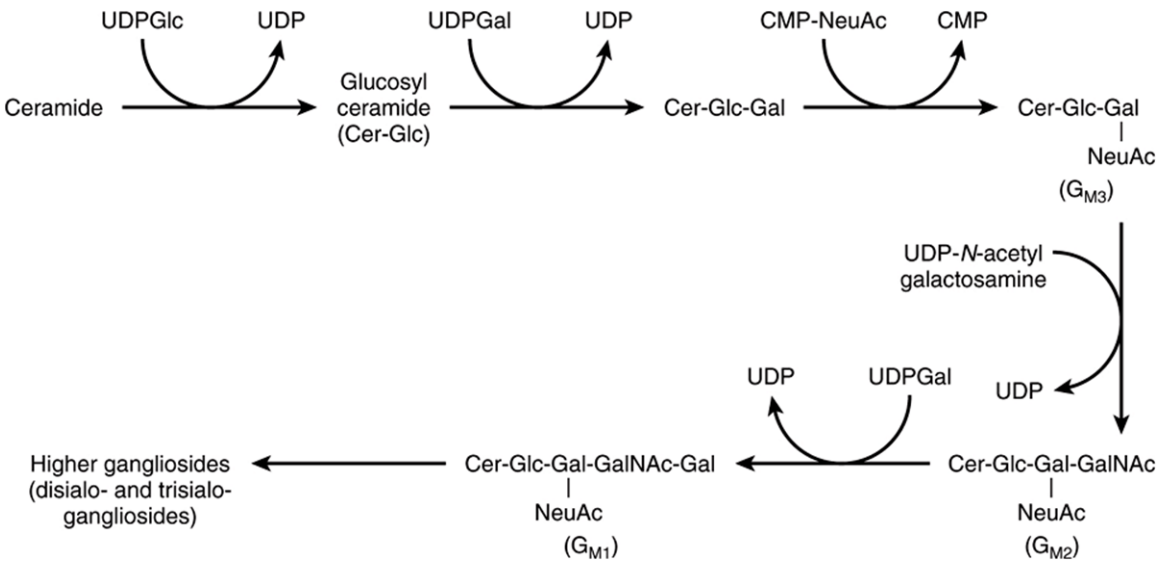

Figure 11 Biosynthesis of gangliosides. (NeuAc, N-acetylneuraminic acid.)

SUMMARY

■ Triacylglycerols are the major energy-storing lipids, whereas phosphoglycerols, sphingomyelin, and glycosphingolipids are amphipathic and have structural functions in cell membranes as well as other specialized roles.

■ Triacylglycerols and some phosphoglycerols are synthesized by progressive acylation of glycerol-3-phosphate. The pathway bifurcates at phosphatidate, forming inositol phospholipids and cardiolipin on the one hand and triacylglycerol and choline and ethanolamine phospholipids on the other.

■ Plasmalogens and platelet-activating factor (PAF) are ether phospholipids formed from dihydroxyacetone phosphate.

■ Sphingolipids are formed from ceramide (N-acylsphingosine). Sphingomyelin is present in membranes of organelles involved in secretory processes (eg, Golgi apparatus). The simplest glycosphingolipids are a combination of ceramide plus a sugar residue (eg, GalCer in myelin). Gangliosides are more complex glycosphingolipids containing more sugar residues plus sialic acid. They are present in the outer layer of the plasma membrane, where they contribute to the glycocalyx and are important as antigens and cell receptors.

■ Phospholipids and sphingolipids are involved in several disease processes, including infant respiratory distress syndrome (lack of lung surfactant), multiple sclerosis (demyelination), and sphingolipidoses (inability to break down sphingolipids in lysosomes due to inherited defects in hydrolase enzymes).