Lippincott® Illustrated Reviews: Biochemistry, 8e ›

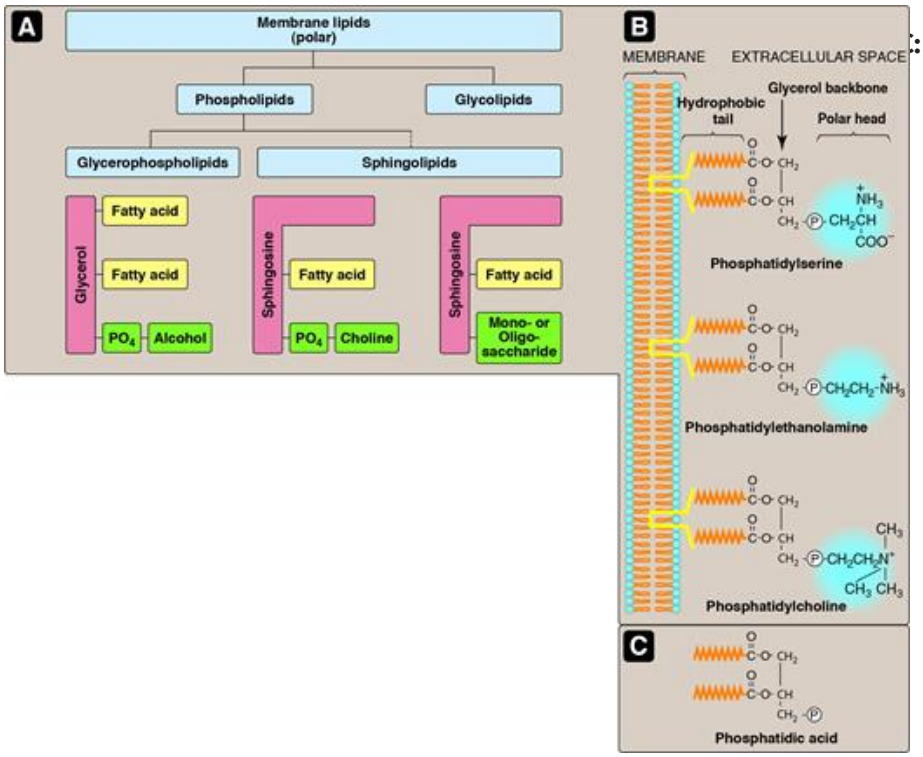
Chapter Contents

17: Phospholipid, Glycosphingolipid, and Eicosanoid Metabolism

Phospholipid Overview

Membrane lipids are composed of four major types: phospholipids, sphingolipids, glycolipids, and cholesterol. In this chapter, only the polar membrane lipids are discussed (Fig. 17.1A). Phospholipids are ionic compounds composed of an alcohol that is attached by a phosphodiester bond to either diacylglycerol (DAG) or sphingosine. Like fatty acids (FA), phospholipids are amphipathic in nature. That is, each has a hydrophilic head, which is the phosphate group plus whatever alcohol is attached to it (e.g., serine, ethanolamine, and choline; highlighted in blue in Fig. 17.1B), and a long, hydrophobic tail containing FA or FA-derived hydrocarbons (shown in orange in Fig. 17.1B). Phospholipids are the predominant lipids of cell membranes. In membranes, the hydrophobic portion of a phospholipid molecule is associated with the nonpolar portions of other membrane constituents, such as glycolipids, proteins, and cholesterol. The hydrophilic (polar) head of the phospholipid extends outward, interacting with the intracellular or extracellular aqueous environment (see Fig. 17.1B). Membrane phospholipids also function as a reservoir for intracellular messengers, and, for some proteins, phospholipids serve as anchors to cell membranes. Nonmembrane phospholipids serve additional functions in the body, for example, as components of lung surfactant and essential components of bile, where their detergent properties aid cholesterol solubilization.

FIGURE 17.1



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Phospholipid Structure

Listen

There are two classes of phospholipids: those that have glycerol (from glucose) as a backbone and those that have sphingosine (from serine and palmitate). Both classes are found as structural components of membranes, and both play a role in the generation of lipid-signaling molecules.

Glycerophospholipids

Phospholipids that contain glycerol are called glycerophospholipids (or phosphoglycerides). Glycerophospholipids constitute the major class of phospholipids and are the predominant lipids in membranes. All contain (or are derivatives of) phosphatidic acid (PA), which is DAG with a phosphate group on carbon 3 (Fig. 17.1C). Despite the apparent symmetry of the three-carbon glycerol backbone, phospholipids are directionally dependent, and C-1 is not interchangeable with C-3 of the glycerol backbone. PA is the simplest phosphoglyceride and is the precursor of the other members of this group.

Fromphosphatidic acid and an alcohol

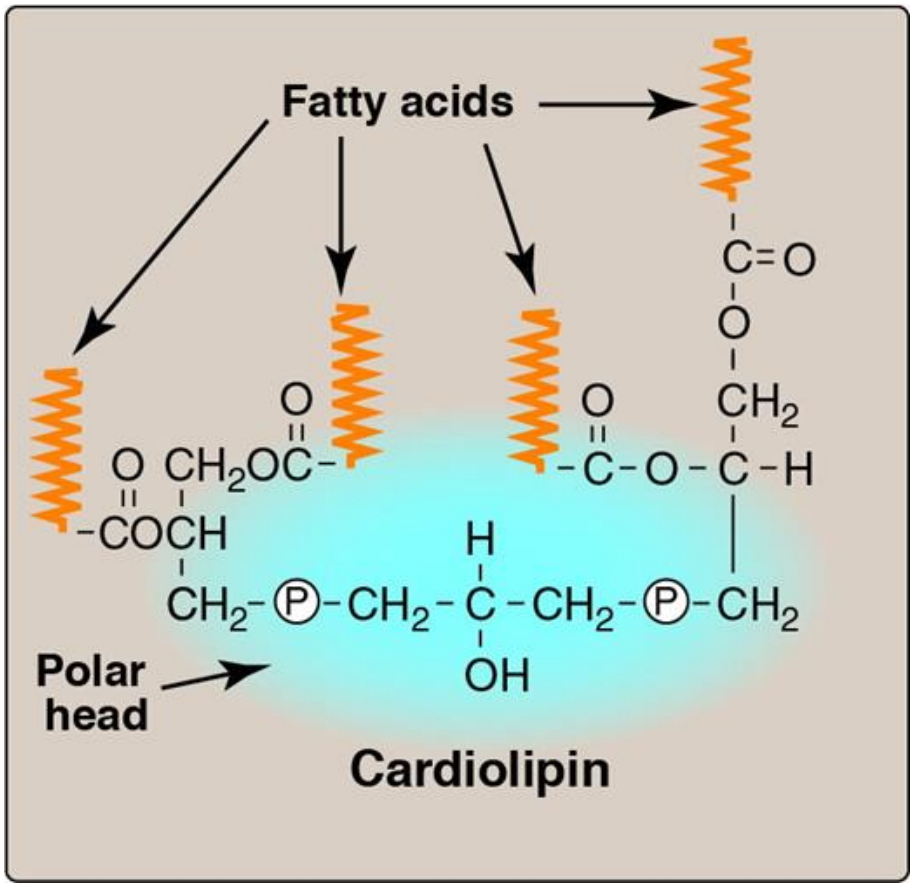
The phosphate group on PA can be esterified to a compound containing an alcohol group (see Fig. 17.1). For example:

Serine + PA → phosphatidylserine (PS)
Ethanolamine + PA → phosphatidylethanolamine (PE)
Choline + PA → phosphatidylcholine (PC) (lecithin)
Inositol + PA → phosphatidylinositol (PI)
Glycerol + PA → phosphatidylglycerol (PG)

Cardiolipin

Two molecules of PA esterified through their phosphate groups to an additional molecule of glycerol form cardiolipin, or diphosphatidylglycerol (Fig. 17.2). Cardiolipin is found in membranes in prokaryotes and eukaryotes. In eukaryotes, cardiolipin is virtually exclusive to the inner mitochondrial membrane, where it maintains the structure and function of certain respiratory complexes of the electron transport chain. (Note: Cardiolipin is antigenic. A patient infected with *Treponemapallidum [T. pallidum*], the bacterium that causes syphilis develops antibodies [Ab] against cardiolipin. The Wasserman test for syphilis detects Ab raised against *T. pallidum* by subjecting patient's serum to cardiolipin as an antigen. The source of antigenic response to cardiolipin is not well understood, that is, host cardiolipin due to tissue damage in the host or *T. pallidum* itself.)

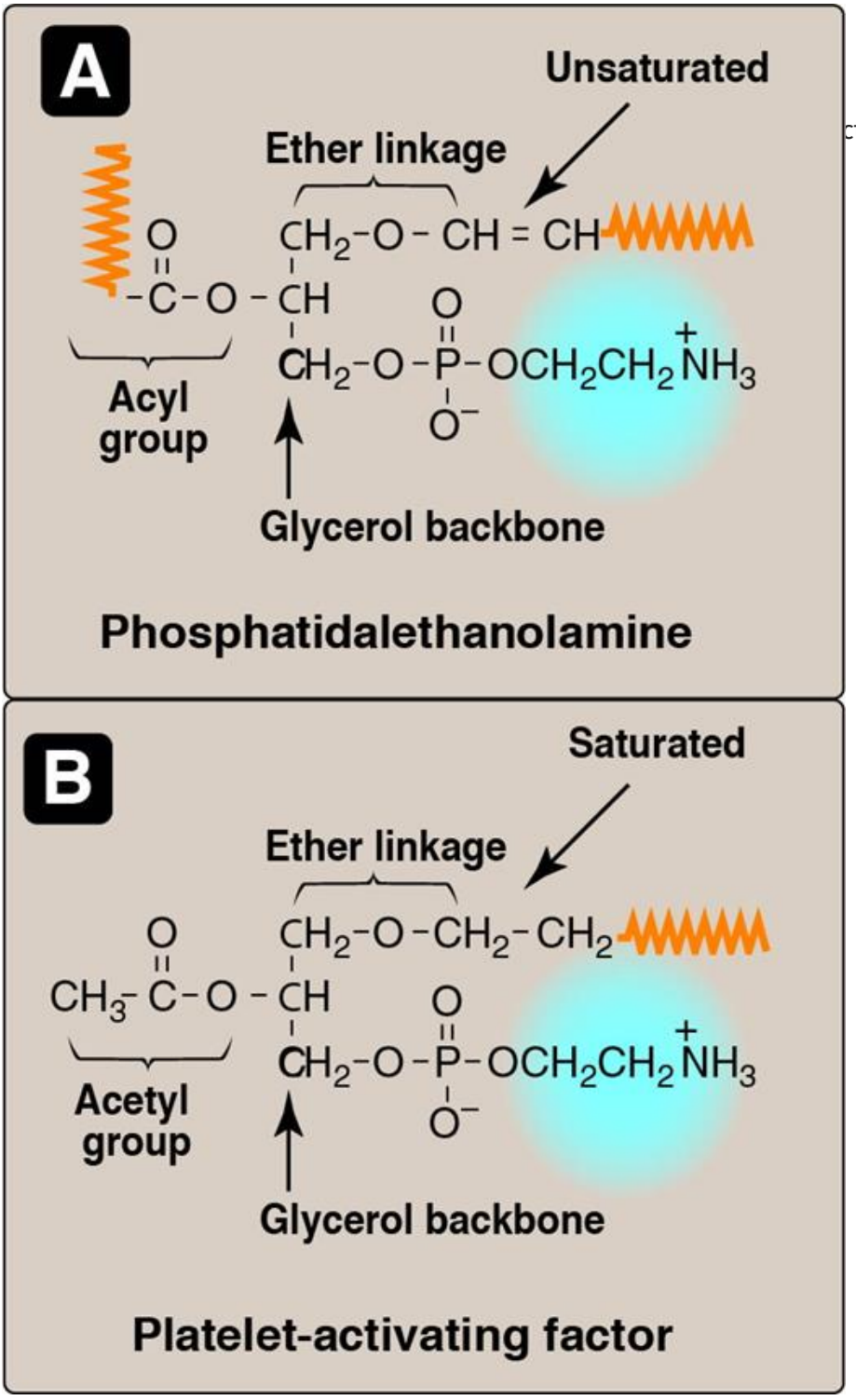
FIGURE 17.2



Plasmalogens

When the FA at carbon 1 of a glycerophospholipid is replaced by an unsaturated alkyl group attached by an ether (rather than by an ester) linkage to the core glycerol molecule, an ether phosphoglyceride known as a plasmalogen is produced. For example, phosphatidylethanolamine, which is abundant in nerve tissue (Fig. 17.3A), is the plasmalogen that is similar in structure to phosphatidylethanolamine. Phosphatidylcholine abundant in heart muscle is the other quantitatively significant ether lipid in mammals. (Note: Plasmalogens have “al” rather than “yl” in their names.)

FIGURE 17.3



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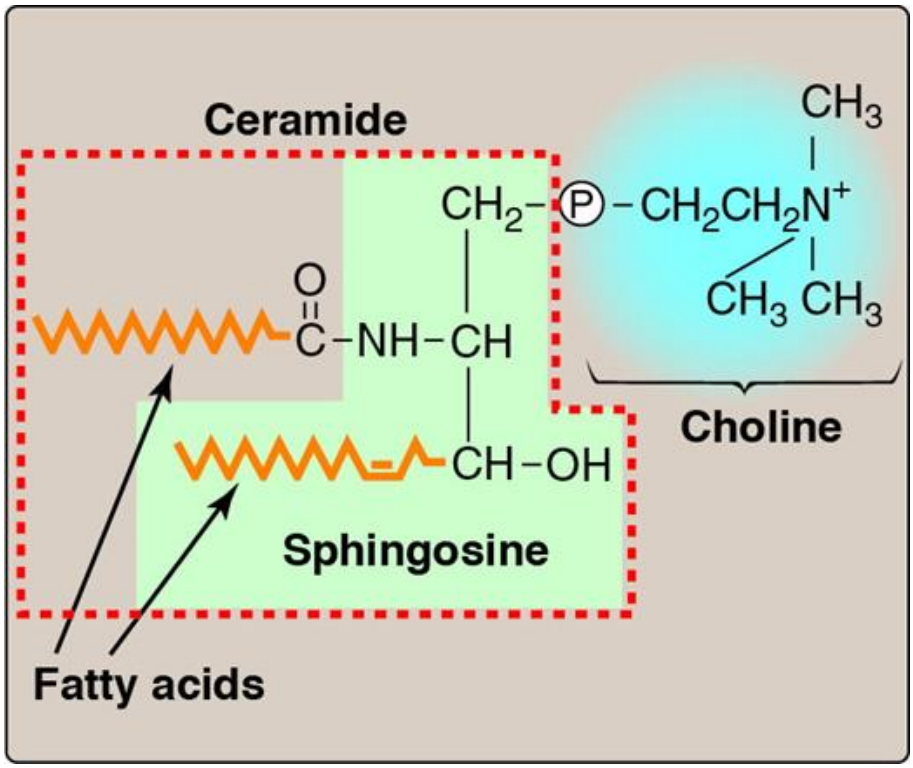
Platelet-activating factor

A second example of an ether glycerophospholipid is platelet-activating factor (PAF), which has a saturated alkyl group in an ether link to carbon 1 and an acetyl residue (rather than a FA) at carbon 2 of the glycerol backbone (Fig. 17.3B). PAF is synthesized and released by a variety of cell types. It binds to surface receptors, triggering potent thrombotic and acute inflammatory events. For example, PAF activates inflammatory cells and mediates hypersensitivity, acute inflammatory, and anaphylactic reactions. It causes platelets to aggregate and activate and neutrophils and alveolar macrophages to generate superoxide radicals to kill bacteria (see Chapter 13). It also lowers blood pressure. (Note: PAF is one of the most potent bioactive molecules known, causing effects at concentrations as low as 10^{-11} mol/l.)

Sphingophospholipids: sphingomyelin

The backbone of sphingomyelin is the amino alcohol sphingosine, rather than glycerol (Fig. 17.4). A long-chain-length FA (LCFA) is attached to the amino group of sphingosine through an amide linkage, producing a ceramide, which can also serve as a precursor of glycolipids. The alcohol group at carbon 1 of sphingosine is esterified to phosphorylcholine, producing sphingomyelin, the only significant sphingophospholipid in humans. Sphingomyelin is an important constituent of the myelin sheath of nerve fibers and it is essential for myelin integrity and function. (Note: The myelin sheath is a layered, membranous structure that insulates and protects neuronal axons of the central nervous system [CNS]. It also allows rapid neuronal conduction along axons.)

FIGURE 17.4



and ceramide components (in

Phospholipid Synthesis

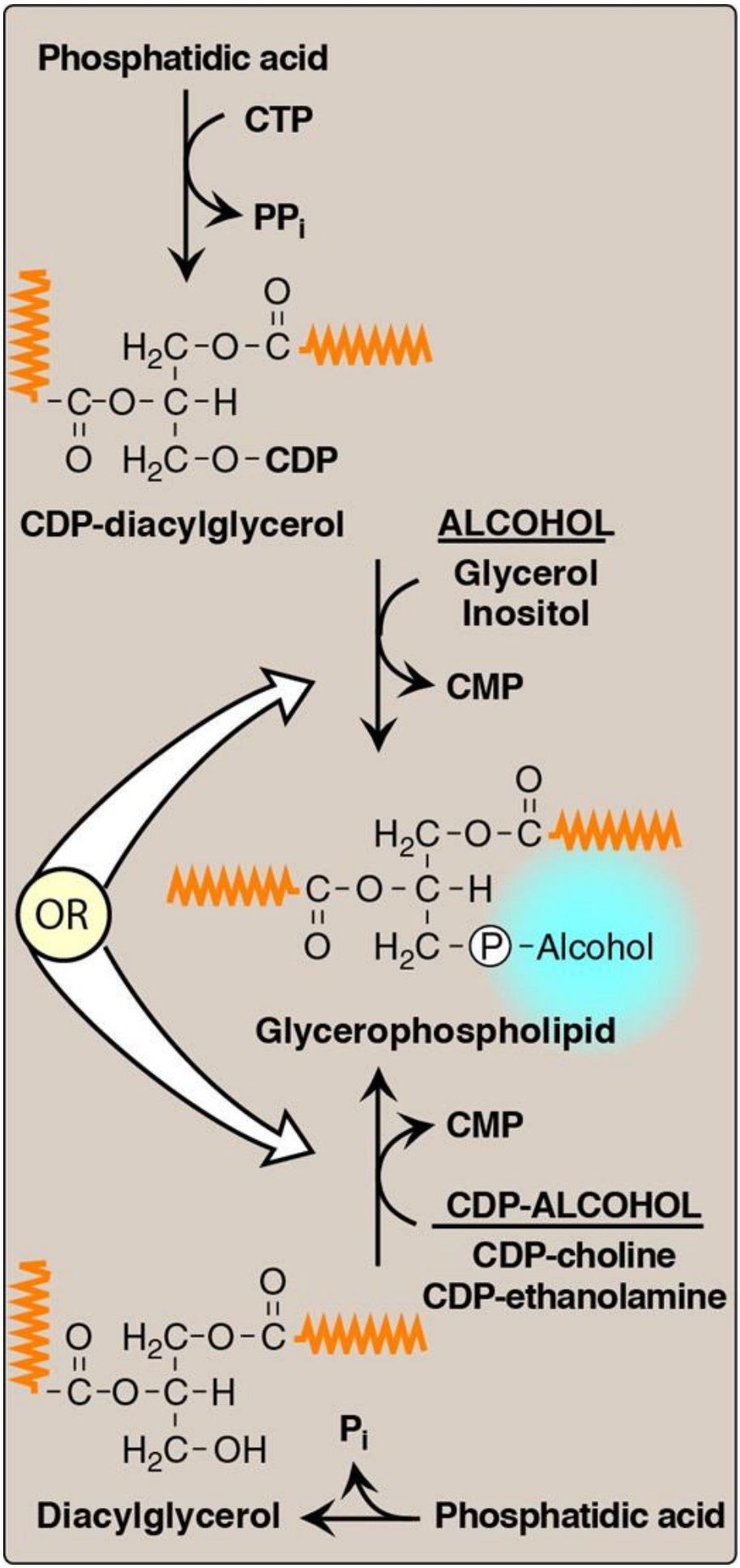
Listen

Glycerophospholipid synthesis involves either the donation of PA from cytidinediphosphate (CDP)-DAG to an alcohol or the donation of the phosphomonoester of the alcohol from CDP-alcohol to DAG (Fig. 17.5). In both cases, the CDP-bound structure is considered an activated intermediate, and cytidine monophosphate (CMP) is released as a side product. Therefore, a key concept in glycerophospholipid synthesis is activation, of either DAG or the alcohol to be added, by linkage with CDP. (Note: This is similar in principle to the activation of sugars by their attachment to uridinediphosphate [UDP] [see Chapter 11].) The FA esterified to the glycerol alcohol groups can vary widely, contributing to the heterogeneity of this group of compounds, with saturated FA typically found at carbon 1 and unsaturated ones at carbon 2. Most phospholipids are synthesized in the smooth endoplasmic reticulum (SER). From there, they are transported to the Golgi and then to membranes of organelles or the plasma membrane or are secreted from the cell by exocytosis. (Note: Ether lipid synthesis from dihydroxyacetone phosphate begins in peroxisomes.)

FIGURE 17.5

Glycerophospholipid synthesis requires activation of either diacylglycerol or an alcohol by linkage to cytidinediphosphate (CDP).

CMP and CTP = cytidine mono- and triphosphates; P_i = inorganic phosphate; PP_i = pyrophosphate. ( is a fatty acid hydrocarbon chain.)


Phosphatidic acid
CTP
PPi
CDP-diacylglycerol
ALCOHOL
Glycerol
Inositol
CMP
OR
Alcohol
Glycerophospholipid
CMP
CDP-ALCOHOL
CDP-choline
CDP-ethanolamine
Pi
Diacylglycerol
Phosphatidic acid

Phosphatidic acid

PA is the precursor of other glycerophospholipids. The steps in its synthesis from glycerol 3-phosphate and two fatty acyl coenzyme A (CoA) molecules were illustrated in Figure 16.14, in which PA is shown as a precursor of triacylglycerol (TAG).

Essentially all cells except mature erythrocytes can synthesize phospholipids, whereas TAG synthesis occurs essentially only in the liver, adipose tissue, lactating mammary glands, and intestinal mucosal cells.

Phosphatidylcholine and phosphatidylethanolamine

The neutral phospholipids PC and PE are the most abundant phospholipids in most eukaryotic cells. The primary route of their synthesis uses choline and ethanolamine obtained either from the diet or from the turnover of the body's phospholipids. (Note: In the liver, PC also can be synthesized from PS and PE [see 2. below].)

Synthesis from pre-existing choline and ethanolamine

These synthetic pathways involve the phosphorylation of choline or ethanolamine by kinases, followed by conversion to the activated form, CDP-choline or CDP-ethanolamine. Finally, choline phosphate or ethanolamine phosphate is transferred from the nucleotide (leaving CMP) to a molecule of DAG (see Fig. 17.5).

Significance of choline reutilization

The reutilization of choline is important because, although humans can synthesize choline *de novo*, the amount made is insufficient for our needs. Thus, choline is an essential dietary nutrient with an adequate intake (see p. 402) of 550 mg for men and 425 mg for women. (Note: Choline is also used for the synthesis of acetylcholine, a neurotransmitter.) Although choline deficiency is rare, it may lead to muscle damage and nonalcoholic fatty liver disease.

Phosphatidylcholine in lung surfactant

The pathway described above is the principal pathway for the synthesis of dipalmitoylphosphatidylcholine (DPPC or, dipalmitoyl lecithin). In DPPC, positions 1 and 2 on the glycerol are occupied by palmitate, a saturated LCFA. DPPC, made and secreted by type II pneumocytes, is a major lipid component of lung surfactant, which is the extracellular fluid layer lining the alveoli. Surfactant serves to decrease the surface tension of this fluid layer, reducing the pressure needed to reinflate alveoli, thereby preventing alveolar collapse (atelectasis). (Note: Surfactant is a complex mixture of lipids [90%] and proteins [10%], with DPPC being the major component for reducing surface tension.)

Fetal lung maturity can be gauged by determining the lecithin/sphingomyelin (L/S) ratio in amniotic fluid. A value ≥2 is evidence of maturity, because it reflects the shift from sphingomyelin to DPPC synthesis that occurs in pneumocytes at ~32 weeks' gestation.

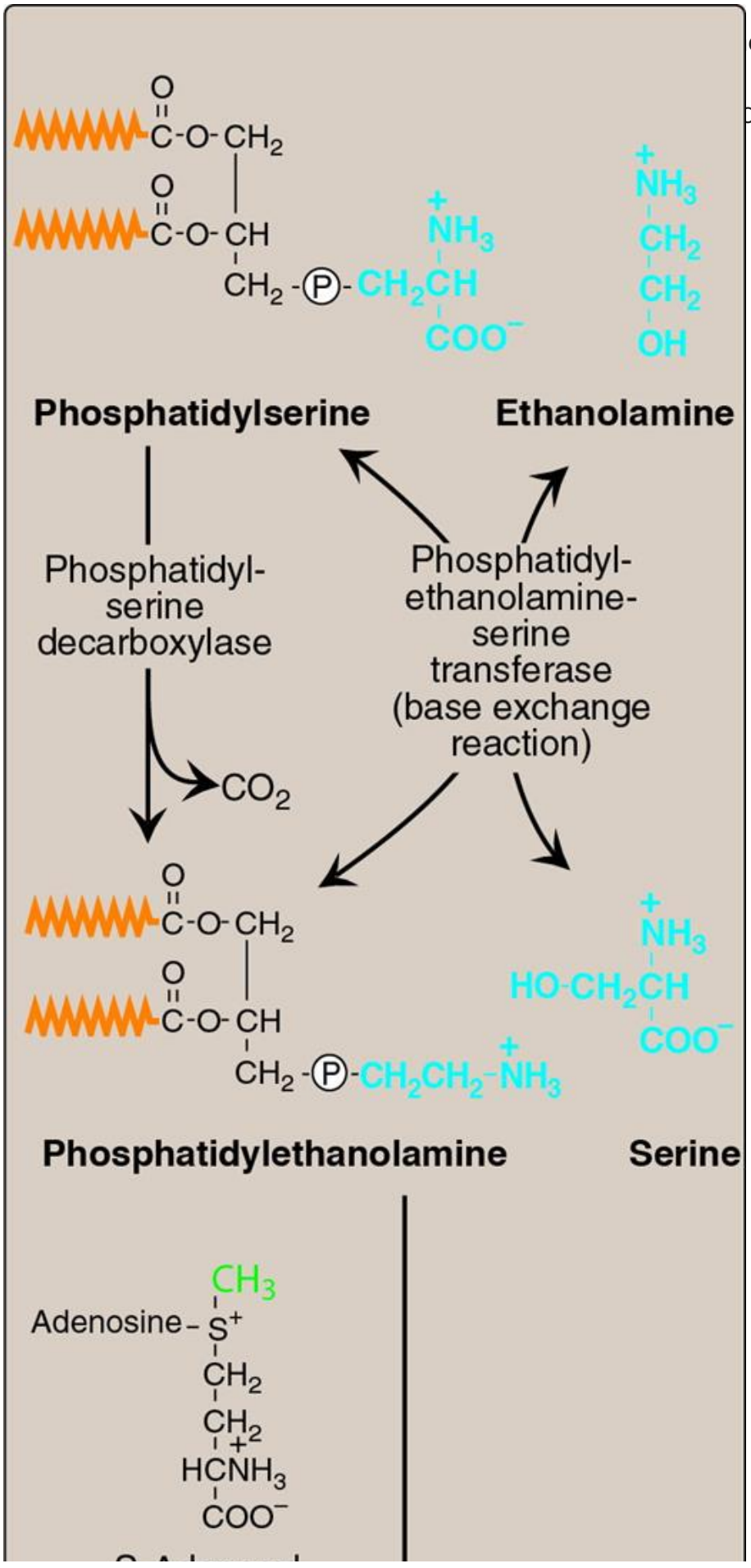
Lung maturity

Respiratory distress syndrome (RDS) in preterm infants is associated with insufficient surfactant production and/or secretion and is a significant cause of all neonatal deaths in Western countries. Lung maturation can be accelerated by giving the mother glucocorticoids shortly before delivery to induce expression of specific genes. Postnatal administration of natural or synthetic surfactant (by intratracheal instillation) is also used. (Note: Acute RDS, seen in all age groups, is the result of alveolar damage [due to infection, injury, or aspiration] that causes fluid to accumulate in the alveoli, impeding the exchange of oxygen [O_2] and carbon dioxide [CO_2].)

Phosphatidylcholine synthesis from phosphatidylserine

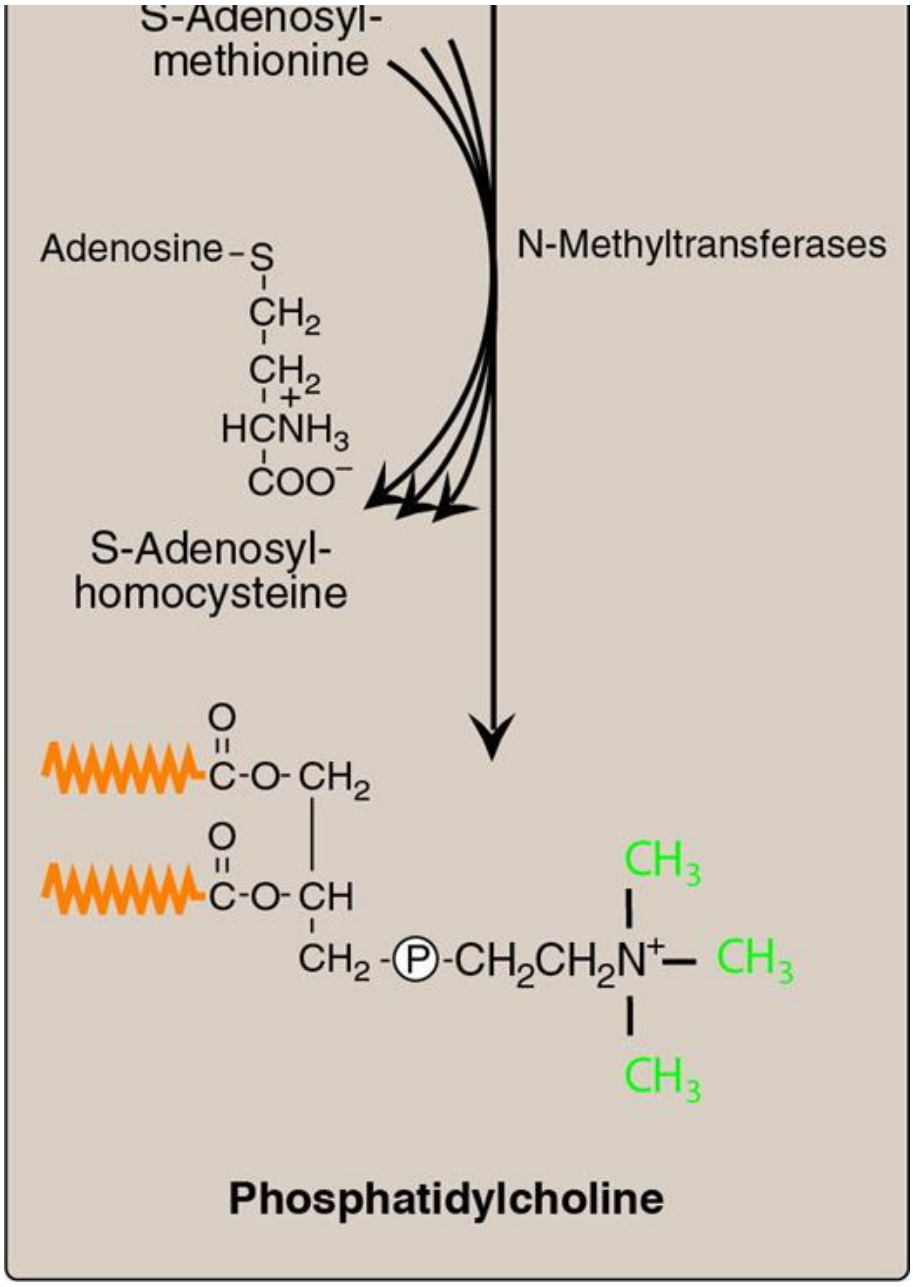
The liver requires a mechanism for producing PC, even when free choline levels are low, because it exports significant amounts of PC in the bile and as a component of plasma lipoproteins. To provide the needed PC, PS is decarboxylated to PE by PS decarboxylase. PE then undergoes three methylation steps to produce PC, as illustrated in Figure 17.6. S-adenosylmethionine is the methyl group donor (see Chapter 20).

FIGURE 17.6



e liver.

CO_2 = carbon dioxide.



Phosphatidylserine

PS synthesis in mammalian tissues is provided by the base exchange reaction, in which the ethanolamine of PE is exchanged for free serine (see Fig. 17.6). This reaction, although reversible, is used primarily to produce the PS required for membrane synthesis. PS has a net negative charge. (See Chapter 35 for the role of PS in clotting.)

Phosphatidylinositol

Phosphatidylinositol (PI) is synthesized from free inositol and CDP-DAG, as shown in Figure 17.5. PI is an unusual phospholipid in that it most frequently contains stearic acid on carbon 1 and arachidonic acid on carbon 2 of the glycerol. Therefore, PI serves as a reservoir of arachidonic acid in membranes and, thus, provides the substrate for prostaglandin (PG) synthesis when required. Like PS, PI has a net negative charge. (Note: There is asymmetry in the phospholipid composition of the cell membrane. PS and PI, for example, are found primarily on the inner leaflet. Asymmetry is achieved by ATP-dependent enzymes known as "flippases" and "floppases.")

Role in signal transduction across membranes

The phosphorylation of membrane-bound PI produces polyphosphoinositides such as phosphatidylinositol 4,5-bisphosphate ([PIP_2]; Fig. 17.7). The cleavage of PIP_2 by phospholipase C occurs in response to the binding of various neurotransmitters, hormones, and growth factors to G protein–coupled receptors (GPCRs), such as the α_1-adrenergic receptor, on the cell membrane and activation of the G_q α-subunit (Fig. 17.8). The products of this cleavage, inositol 1,4,5-trisphosphate (IP_3) and DAG, mediate the mobilization of intracellular calcium and the activation of protein kinase C, which act synergistically to evoke specific cellular responses. Signal transduction across the membrane is, thus, accomplished.

FIGURE 17.7

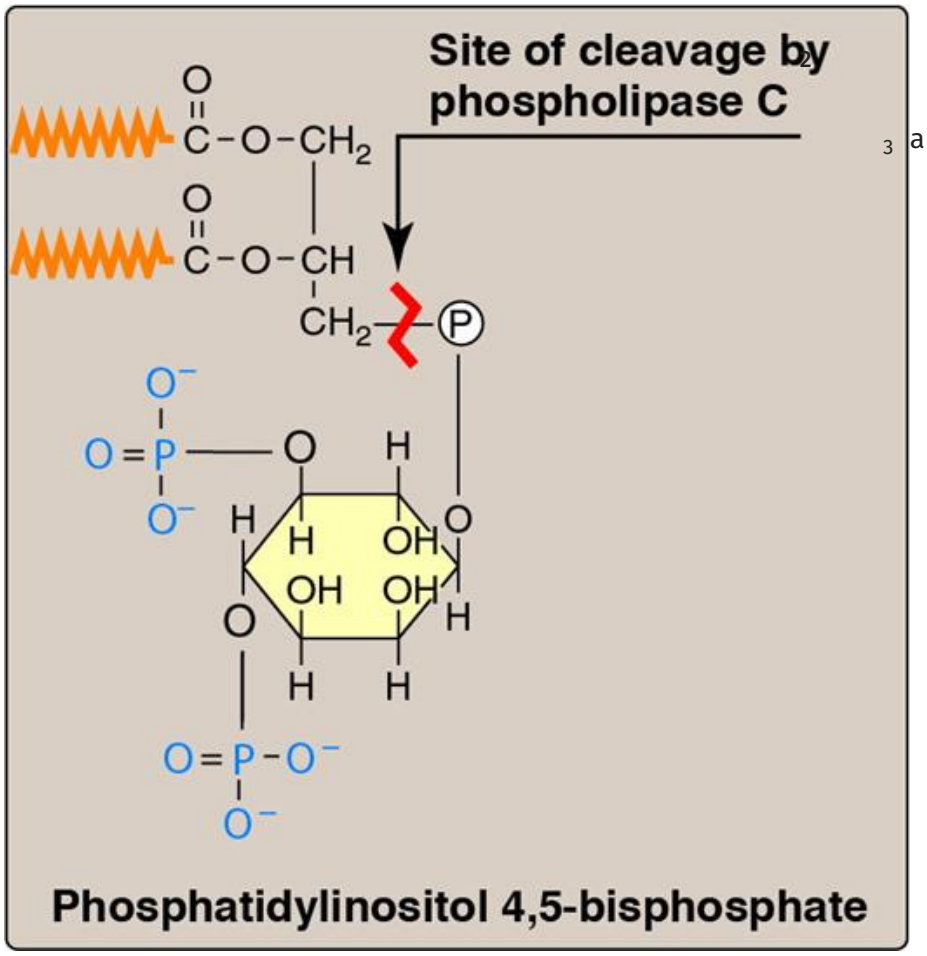


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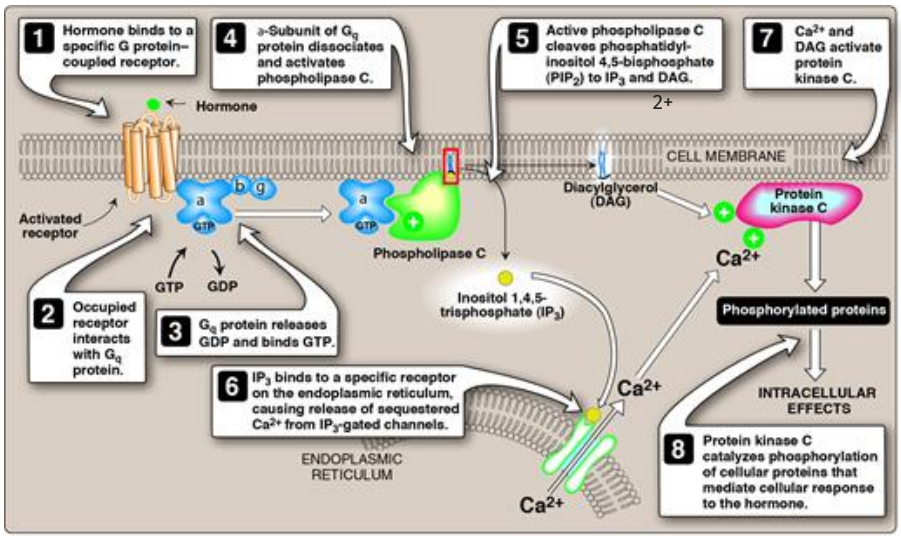
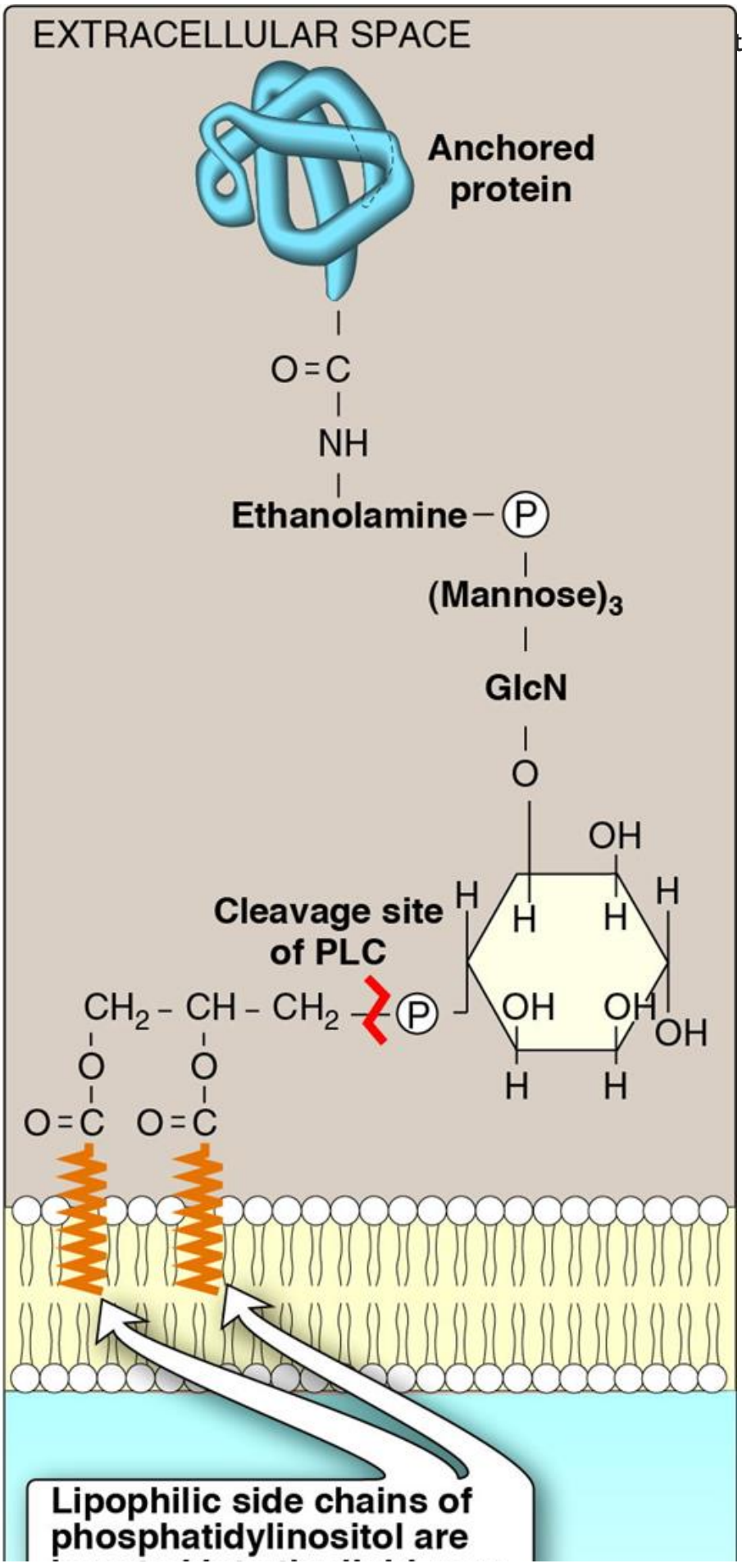
FIGURE 17.8



Role in membrane protein anchoring

Specific proteins can be covalently attached through a carbohydrate bridge to membrane-bound PI (Fig. 17.9). For example, lipoprotein lipase, an enzyme that degrades TAG in lipoprotein particles (see p. 254), is attached to capillary endothelial cells by a glycosyl phosphatidylinositol (GPI) anchor. (Note: GPI-linked proteins are also found in a variety of parasitic protozoans, such as trypanosomes and leishmania.) Being attached to a membrane lipid (rather than being an integral part of the membrane) allows GPI-anchored proteins increased lateral mobility on the extracellular surface of the plasma membrane. The protein can be cleaved from its anchor by the action of phospholipase C (see Fig. 17.9). (Note: A deficiency in the synthesis of GPI in hematopoietic cells results in the hemolytic disease paroxysmal nocturnal hemoglobinuria. Some of the GPI-anchored proteins protect blood cells from the immune system which recognizes foreign substances such as viruses and bacteria in the body. The lack of GPI-anchored proteins on the red blood cells are no longer recognized as “self” and are susceptible to destruction by complement-mediated lysis.)

FIGURE 17.9



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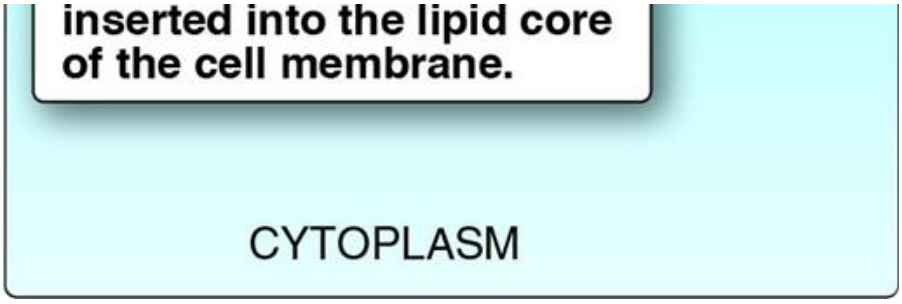


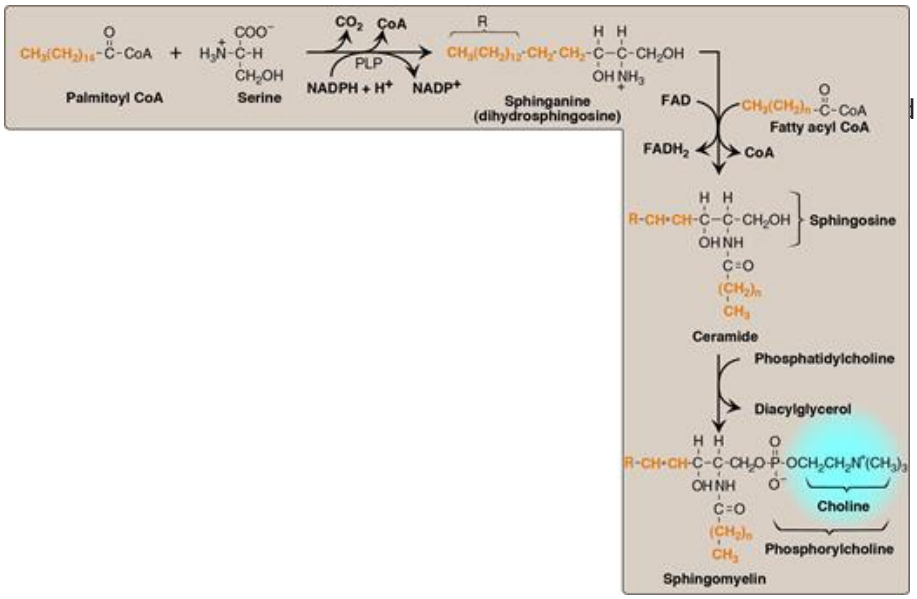
Phosphatidylglycerol and cardiolipin

Phosphatidylglycerol is found in relatively large concentrations in mitochondrial membranes and is a precursor of cardiolipin (diphosphatidylglycerol). It is synthesized from CDP-DAG and glycerol 3-phosphate. Cardiolipin (see Fig. 17.2) is synthesized by the transfer of DAG 3-phosphate from CDP-DAG to a pre-existing molecule of phosphatidylglycerol.

Sphingomyelin

Sphingomyelin, a sphingosine-based phospholipid, is found in cell membranes and in the myelin sheath. The synthesis of sphingomyelin is shown in Figure 17.10. Briefly, palmitoyl CoA condenses with serine, as CoA and the carboxyl group (as CO_2) of serine are lost. (Note: This reaction, like the decarboxylation reactions involved in the synthesis of PE from PS and of regulators from amino acids [e.g., the catecholamines from tyrosine; see Chapter 21], requires pyridoxal phosphate [a derivative of vitamin B_6] as a coenzyme.) The product is reduced in a nicotinamide adenine dinucleotide phosphate (NADPH)-requiring reaction to sphinganine (dihydrosphingosine). The sphinganine is acylated at the amino group with one of a variety of LCFA and then desaturated to produce a ceramide, the immediate precursor of sphingomyelin (and other sphingolipids, as described in section V.).

FIGURE 17.10



…le phosphate; FAD(H_2) = flavin adenine

Ceramides play a key role in maintaining the skin's water-permeability barrier. Decreased ceramide levels are associated with a number of skin diseases.

Phosphorylcholine from PC is transferred to the ceramide, producing sphingomyelin and DAG. (Note: Sphingomyelin of the myelin sheath contains predominantly longer-chain FA such as lignoceric acid and nervonic acid, whereas gray matter of the brain has sphingomyelin that contains primarily stearic acid.)

Phospholipid Degradation

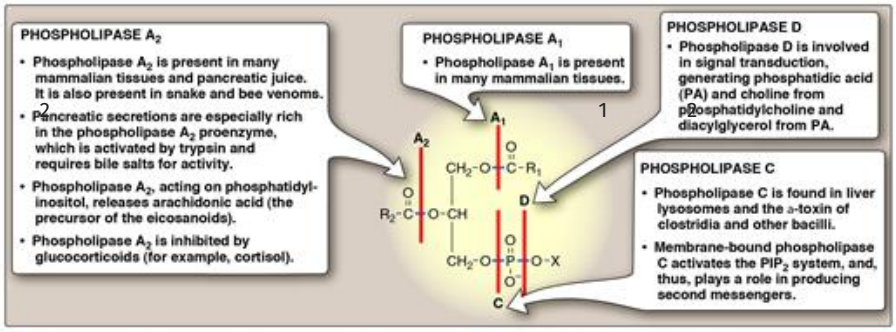
Listen

The degradation of phosphoglycerides is performed by phospholipases found in all tissues and pancreatic juice. (Note: For a discussion of phospholipid digestion, see Chapter 15. Section D.3.) A number of toxins and venoms have phospholipase activity, and several pathogenic bacteria produce phospholipases that dissolve cell membranes and allow the spread of infection. Sphingomyelin is degraded by the lysosomal phospholipase, sphingomyelinase (see B. below).

Phosphoglycerides

Phospholipases hydrolyze the phosphodiester bonds of phosphoglycerides, with each enzyme cleaving the phospholipid at a specific site. The major phospholipases are shown in Figure 17.11. (Note: Removal of the FA from carbon 1 or 2 of a phosphoglyceride produces a lysophosphoglyceride, which is the substrate for lysophospholipases.) Phospholipases release molecules that can serve as second messengers (e.g., DAG and IP_3) or that are the substrates for synthesis of messengers (e.g., arachidonic acid). Phospholipases are responsible not only for degrading phospholipids but also for remodeling them. For example, phospholipases A_1 and A_2 remove specific FA from membrane-bound phospholipids, which can be replaced with different FA using fatty acyl CoA transferase. This mechanism is used as one way to create the unique lung surfactant DPCC and to ensure that carbon 2 of PI (and sometimes of PC) is bound to arachidonic acid. (Note: Barth syndrome, a rare X-linked disorder characterized by cardiomyopathy, muscle weakness, and neutropenia, is the result of defects in cardiolipin remodeling.)

FIGURE 17.11

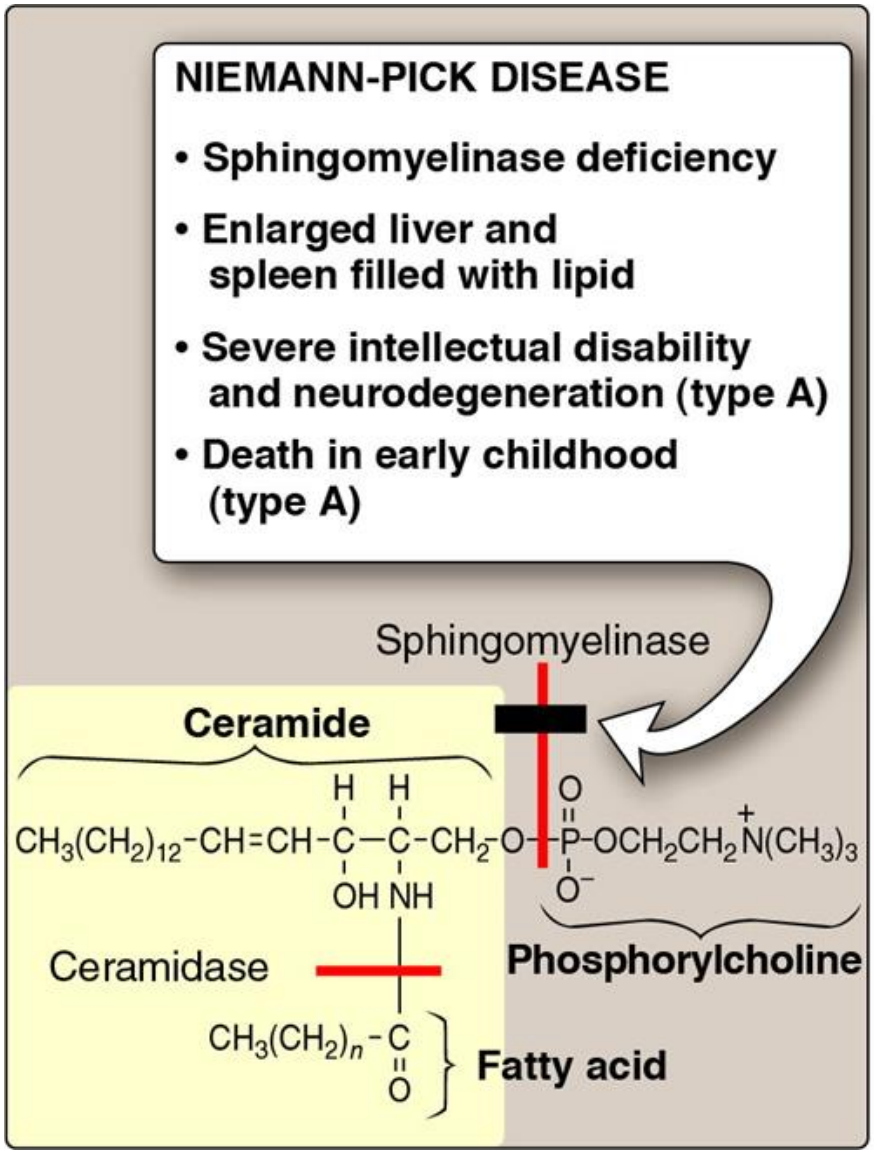


an alcohol.

Sphingomyelin

Sphingomyelin is degraded by sphingomyelinase, a lysosomal enzyme that removes phosphorylcholine, leaving a ceramide. The ceramide is, in turn, cleaved by ceramidase into sphingosine and a free FA (Fig. 17.12). (Note: The released ceramide and sphingosine regulate signal transduction pathways, in part by influencing the activity of protein kinase C and, thus, the phosphorylation of its protein substrates. They also promote apoptosis.) Niemann–Pick disease (types A and B) is an autosomal-recessive disorder caused by the inability to degrade sphingomyelin due to a deficiency of sphingomyelinase, a type of phospholipase C.

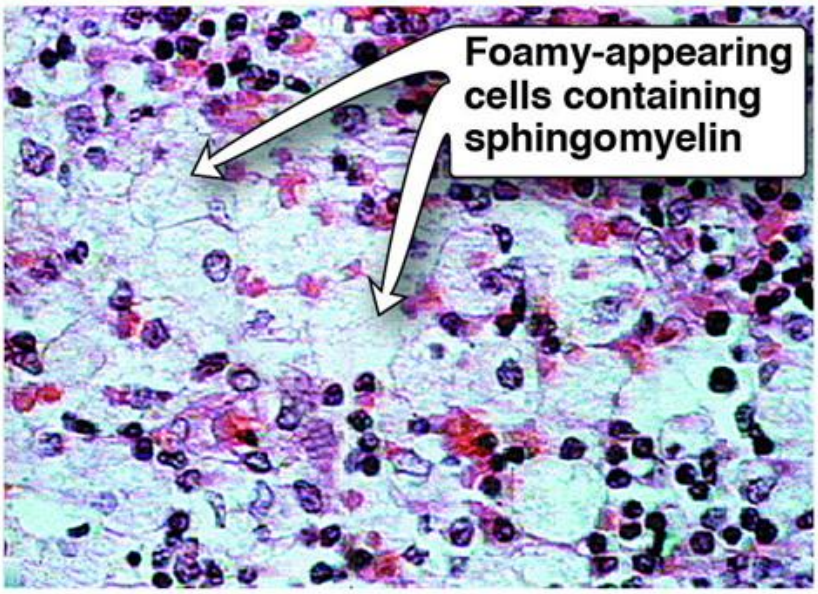
FIGURE 17.12



l a longer survival time than type A.)

In the severe infantile form (type A, which shows <1% of normal enzymic activity), the liver and spleen are the primary sites of lipid deposits and therefore, hepatosplenomegaly develops. The lipid consists primarily of the sphingomyelin that cannot be degraded (Fig. 17.13). Macrophages of the reticuloendothelial system become engorged with sphingomyelin, which gives them a foamy histologic appearance. Infants with this lysosomal storage disease experience rapid and progressive neurodegeneration as a result of deposition of sphingomyelin in the CNS. As a result, a cherry-red spot in the macula of the eye develops due to lipid deposition and edema in the retinal ganglion cells. These infants die in early childhood. A less severe variant (type B, which shows up to 10% of normal activity) with a later age of onset and a longer survival time causes little to no damage to neural tissue, but lungs, spleen, liver, and bone marrow are affected, resulting in a chronic form of the disease. Although Niemann–Pick disease occurs in all ethnic groups, type A occurs with greater frequency in the Ashkenazi Jewish population. (Note: Niemann–Pick disease Type C [NPC] results from mutations in either the NPC1 or NPC2, genes important in processing endocytosed cholesterol, and leads to both cholesterol and sphingomyelin accumulation.)

FIGURE 17.13



nn–Pick disease.

rbana-Champaign. Image number 26.

Glycolipid Overview

Listen

Glycolipids are molecules that contain both carbohydrate and lipid components. Like the phospholipid sphingomyelin, glycolipids are derivatives of ceramides in which a LCFA is attached to the amino alcohol sphingosine. Therefore, they are more precisely called glycosphingolipids. (Note: Thus, ceramides are the precursors of both phosphorylated and glycosylated sphingolipids.) Like the phospholipids, glycosphingolipids are essential components of all membranes in the body, but they are found in greatest amounts in nerve tissue. They are located in the outer leaflet of the plasma membrane, where they interact with the extracellular environment. As such, they play a role in the regulation of cellular interactions (e.g., adhesion and recognition), growth, and development.

Membrane glycosphingolipids associate with cholesterol and GPI-anchored proteins to form lipid rafts, laterally mobile microdomains of the plasma membrane that function to organize and regulate membrane signaling and trafficking functions.

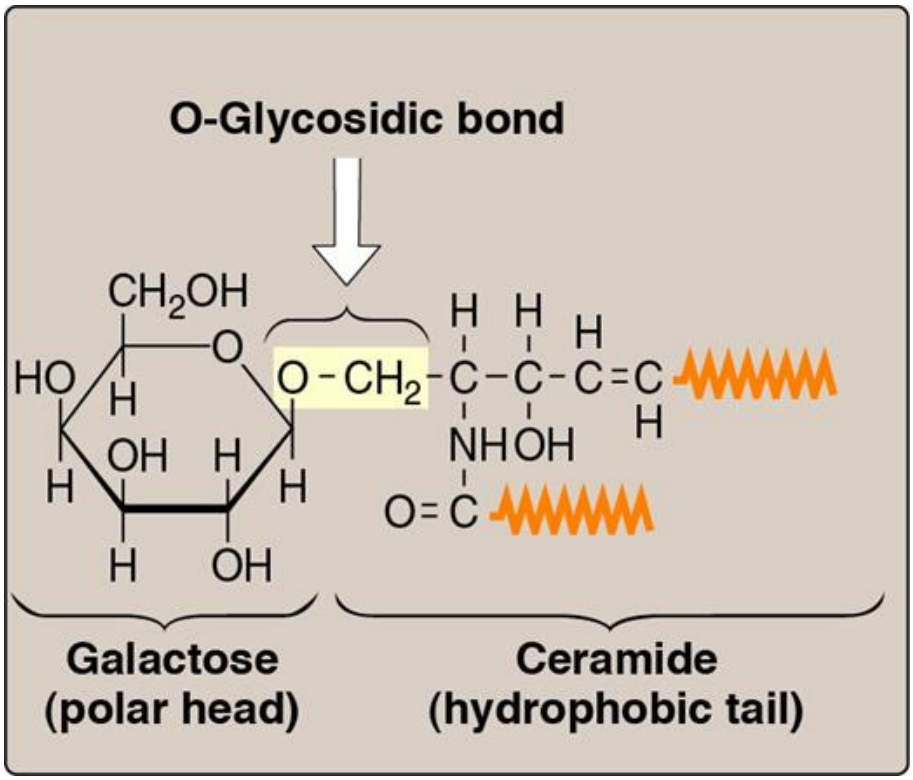
Glycosphingolipids are antigenic and are the source of ABO blood group antigens (Chapter 4, Section VII. B), various embryonic antigens specific for particular stages of fetal development, and some tumor antigens. (Note: The carbohydrate portion of a glycolipid is the antigenic determinant and the lipid portion serves as the membrane anchor.) They have been co-opted for use as cell surface receptors for cholera and tetanus toxins as well as for certain viruses and microbes. Genetic disorders associated with an inability to properly degrade the glycosphingolipids result in lysosomal accumulation of these compounds. (Note: Changes in the carbohydrate portion of glycosphingolipids [and glycoproteins] are characteristic of transformed cells [cells with dysregulated growth].)

Glycosphingolipid Structure

Listen

The glycosphingolipids differ from sphingomyelin in that they do not contain phosphate, and the polar head function is provided by a monosaccharide or oligosaccharide attached directly to the ceramide by an O-glycosidic bond (Fig. 17.14). The number and type of carbohydrate moieties present determine the type of glycosphingolipid.

FIGURE 17.14



Neutral glycosphingolipids

The simplest neutral glycosphingolipids are the cerebrosides. These are ceramide monosaccharides that contain either a molecule of galactose (forming ceramide-galactose or galactocerebroside, the most common cerebroside found in myelin, as shown in Fig. 17.14) or glucose (forming ceramide-glucose or glucocerebroside, an intermediate in the synthesis and degradation of the more complex glycosphingolipids). (Note: Members of a group of galacto- or glucocerebrosides may also differ from each other in the type of FA attached to the sphingosine.) As their name implies, cerebrosides are found predominantly in the brain and peripheral nerves, with high concentrations in the myelin sheath. Ceramide oligosaccharides (or globosides) are produced by attaching additional monosaccharides to a glucocerebroside, for example, ceramide-glucose-galactose (also known as lactosylceramide). The additional monosaccharides can include substituted sugars such as *N*-acetylgalactosamine.

Acidic glycosphingolipids

Acidic glycosphingolipids are negatively charged at physiologic pH. The negative charge is provided by N-acetylneuraminic acid ([NANA], a sialic acid, as shown in Fig. 17.15) in gangliosides or by sulfate groups in sulfatides.

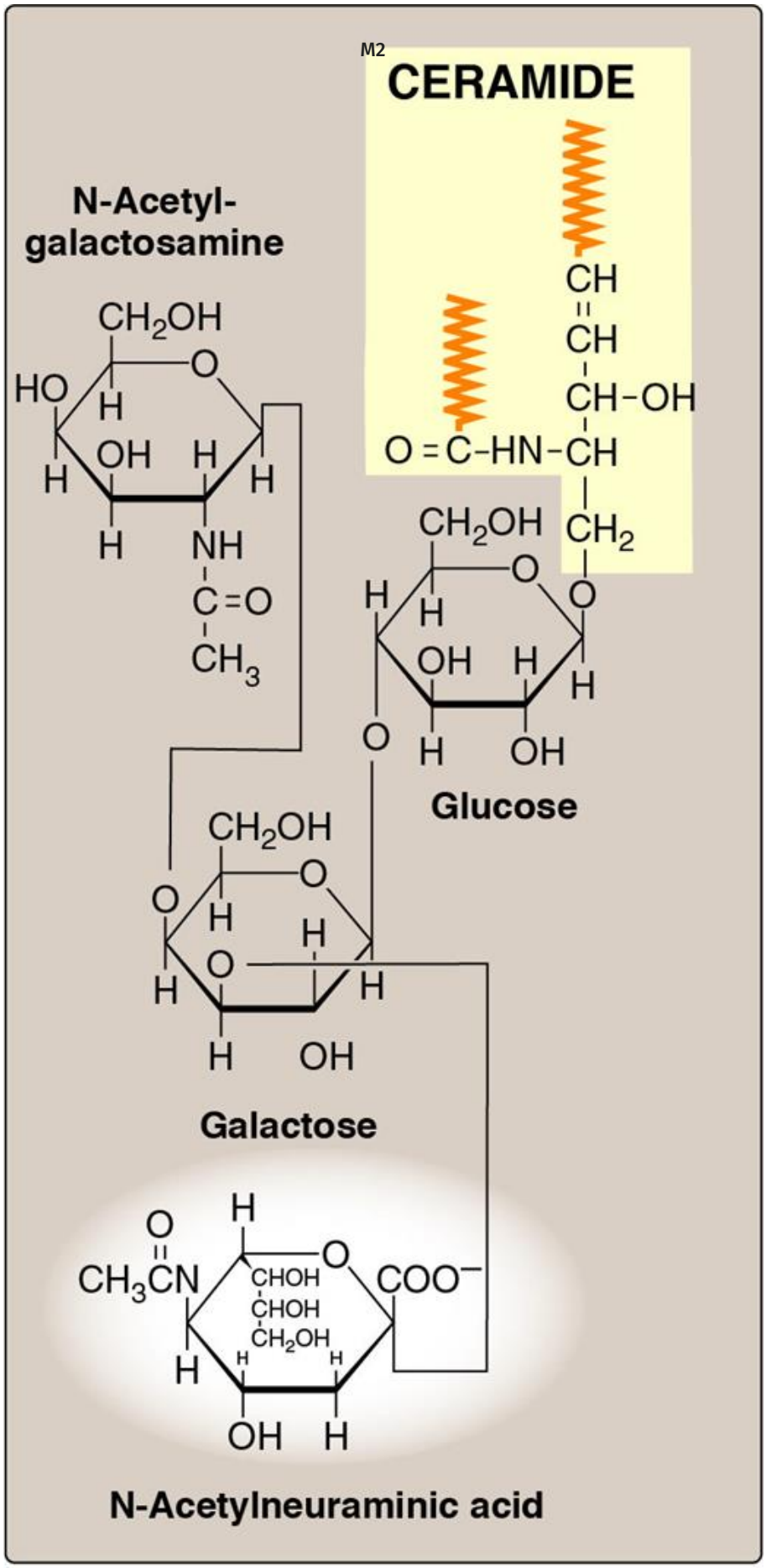
Gangliosides

These are the most complex glycosphingolipids and are found primarily in the ganglion cells of the CNS, particularly at the nerve endings. They are derivatives of ceramide oligosaccharides and contain one or more molecules of NANA (from CMP-NANA). The notation for these compounds is G (for ganglioside) plus a subscript M, D, T, or Q to indicate whether there is one (mono), two (di), three (tri), or four (quatro) molecules of NANA in the ganglioside, respectively. Additional numbers and letters in the subscript designate the monomeric sequence of the carbohydrate attached to the ceramide. (See Fig. 17.15 for the structure of G_{M2}.) Gangliosides are of medical interest because several lipid storage disorders involve the accumulation of NANA-containing glycosphingolipids in cells (see Fig. 17.19).

Sulfatides

These sulfoglycosphingolipids are sulfated galactocerebrosides that are negatively charged at physiologic pH. Sulfatides are found predominantly in the brain and kidneys.

FIGURE 17.15


M2
CERAMIDE
N-Acetyl-
galactosamine
Glucose
Galactose
N-Acetylneuraminic acid

Glycosphingolipid Synthesis and Degradation

Listen

Synthesis of glycosphingolipids occurs primarily in the Golgi by sequential addition of glycosyl monomers transferred from UDP-sugar donors to the acceptor molecule. The mechanism is similar to that used in glycoprotein synthesis (see Chapter 14).

Enzymes involved in synthesis

The enzymes involved in the synthesis of glycosphingolipids are glycosyltransferases that are specific for the type and location of the glycosidic bond formed. (Note: These enzymes can recognize both glycosphingolipids and glycoproteins as substrates.)

Sulfate group addition

A sulfate group from the sulfate carrier 3′-phosphoadenosine-5′-phosphosulfate ([PAPS], Fig. 17.16) is added by a sulfotransferase to the 3′-hydroxyl group of the galactose in a galactocerebroside, forming the sulfatidegalactocerebroside 3-sulfate (Fig. 17.17). (Note: PAPS is also the sulfur donor in glycosaminoglycan synthesis [see p. 178] and steroid hormone catabolism [see Chapter 18].) An overview of the synthesis of sphingolipids is shown in Figure 17.18.

FIGURE 17.16

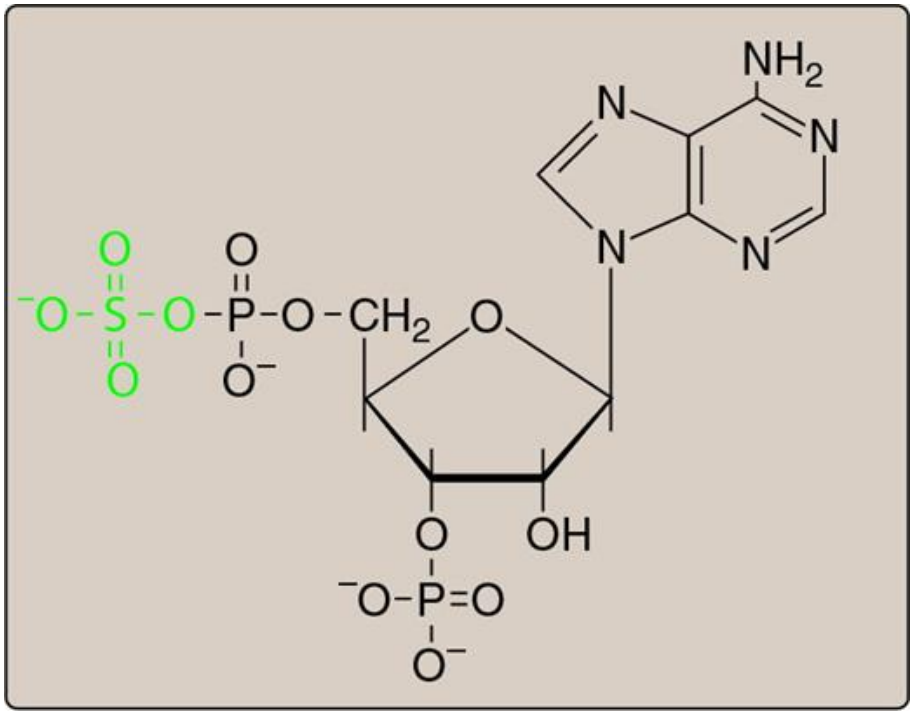


FIGURE 17.17

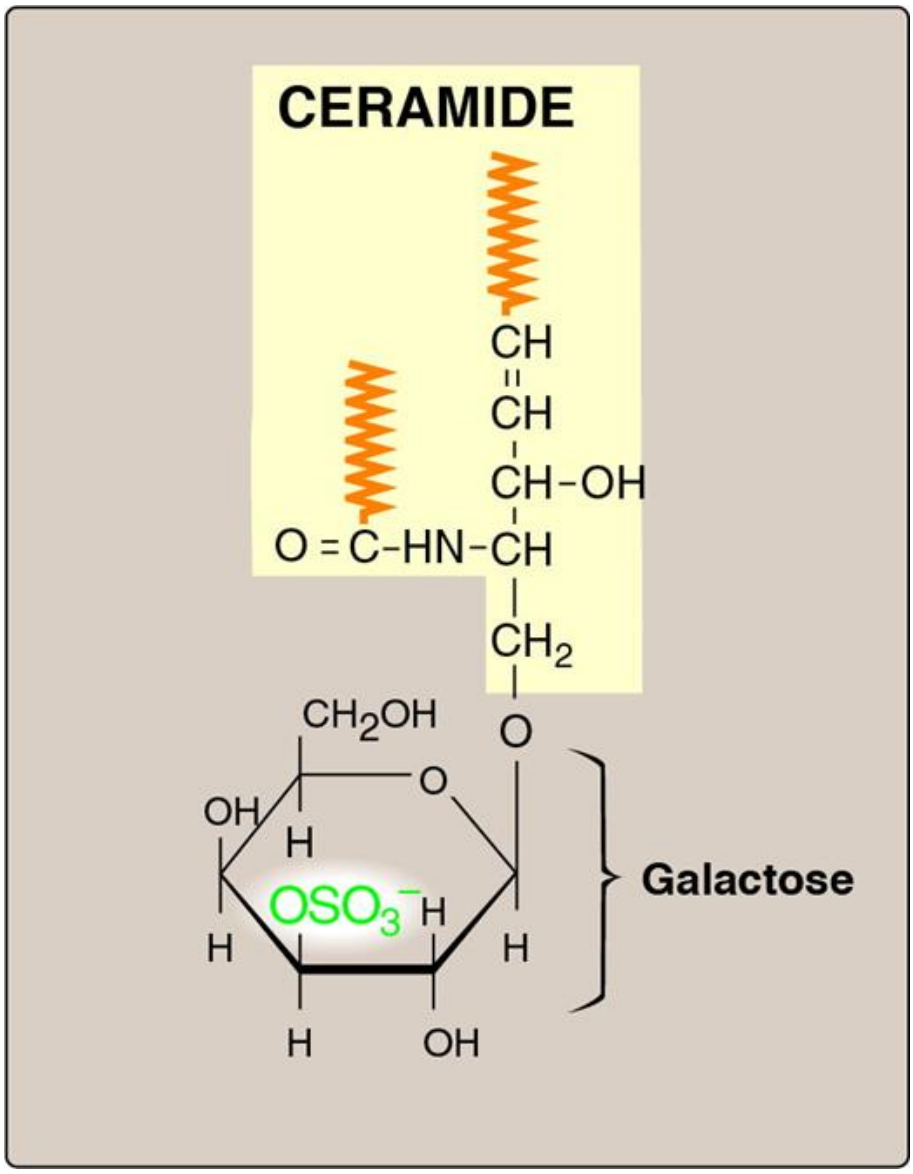
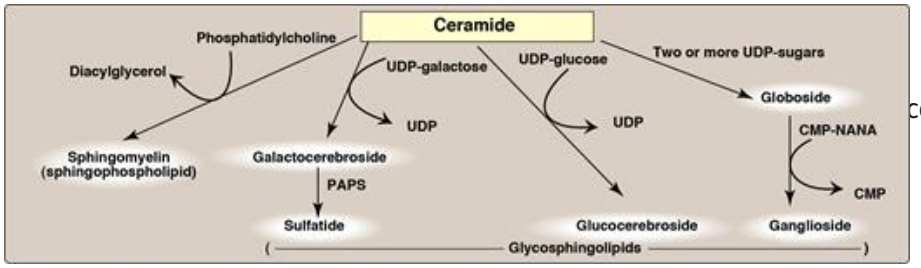


FIGURE 17.18



cetylneuraminic acid; PAPS = 3′-

Glycosphingolipid degradation

Glycosphingolipids are internalized by phagocytosis as described for the glycosaminoglycans (see Chapter 14). All of the enzymes required for the degradative process are present in lysosomes, which fuse with the phagosomes. The lysosomal enzymes hydrolytically and irreversibly cleave specific bonds in the glycosphingolipid. As seen with the glycosaminoglycans and glycoproteins, degradation is a sequential process following the rule "last on, first off," in which the last group added during synthesis is the first group removed in degradation. Therefore, defects in the degradation of the polysaccharide chains in these three glycoconjugates result in lysosomal storage diseases.

Sphingolipidoses

In a normal individual, synthesis and degradation of glycosphingolipids are balanced, so that the amount of these compounds present in membranes is constant. If a specific lysosomal acid hydrolase required for degradation is partially or totally missing, a sphingolipid accumulates. Lysosomal lipid storage diseases caused by these deficiencies are called sphingolipidoses. The result of a specific acid hydrolase deficiency may be seen dramatically in nerve tissue, where neurologic deterioration can lead to early death. Figure 17.19 provides an outline of the pathway of sphingolipid degradation and descriptions of some sphingolipidoses. (Note: Some sphingolipidoses can also result from defects in lysosomal activator proteins [e.g., the saposins] that facilitate access of the hydrolases to short carbohydrate chains as degradation proceeds.)

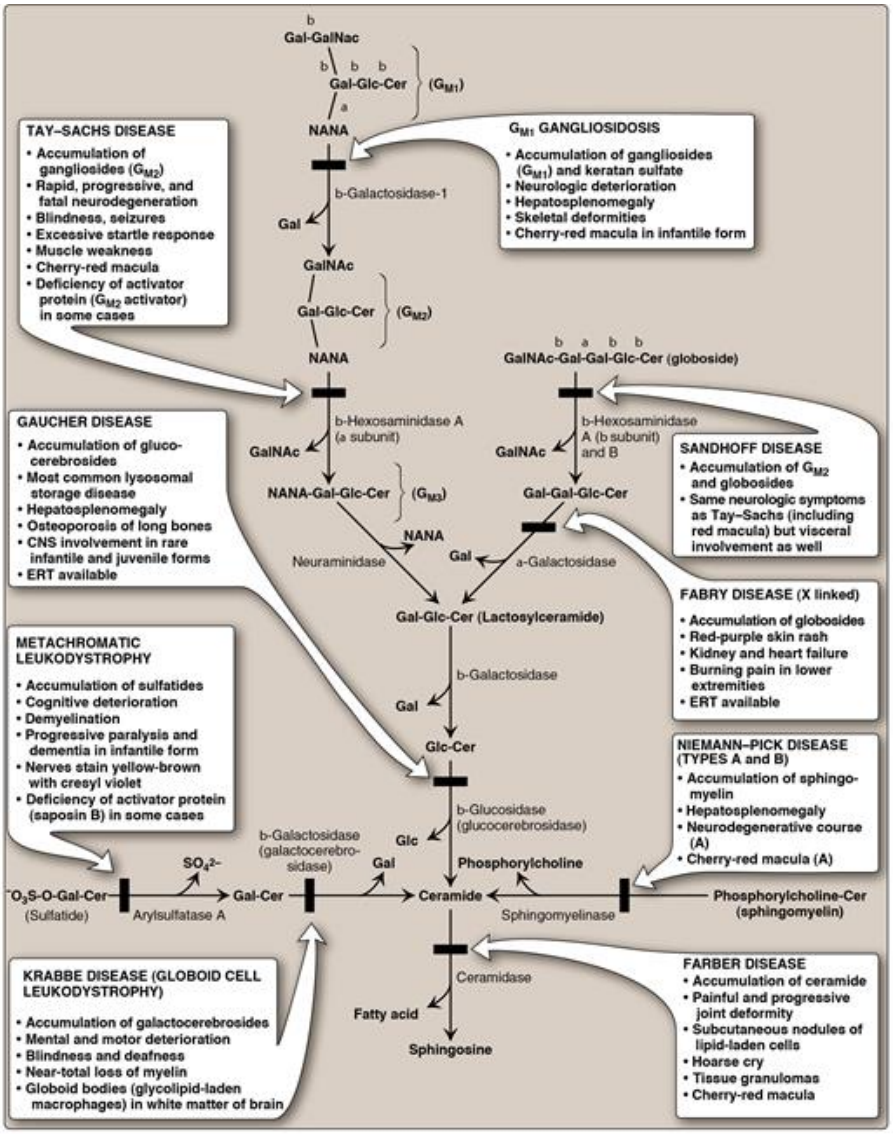
Common properties

A specific lysosomal hydrolytic enzyme is deficient in the classic form of each disorder. Therefore, usually, only a single sphingolipid (the substrate for the deficient enzyme) accumulates in the involved organs in each disease. (Note: The rate of biosynthesis of the accumulating lipid is normal.) The disorders are progressive and, although many are fatal in childhood, extensive phenotypic variability is seen leading to the designation of different clinical types, such as types A and B in Niemann–Pick disease. Genetic variability is also seen because a given disorder can be caused by any one of a variety of mutations within a single gene. The sphingolipidoses are autosomal-recessive disorders, except for Fabry disease, which is X linked. The incidence of the sphingolipidoses is low in most populations, except for Gaucher and Tay–Sachs diseases, which, like Niemann–Pick disease, show a high frequency in the Ashkenazi Jewish population. (Note: Tay–Sachs also has a high frequency in Irish American, French Canadian, and Louisiana Cajun populations.)

Diagnosis and treatment

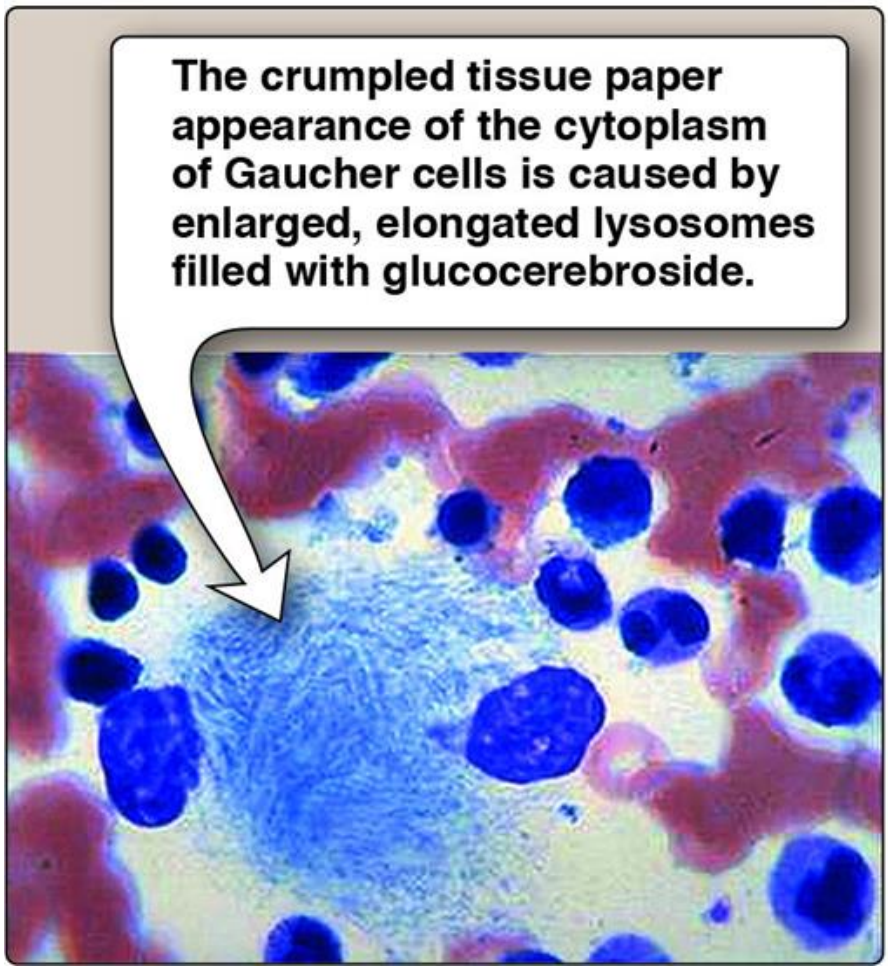
A specific sphingolipidosis can be diagnosed by measuring enzyme activity in patient cultured fibroblasts or peripheral leukocytes or by analyzing patient DNA (see Chapter 34). Histologic examination of the affected tissue is also useful. (Note: Shell-like inclusion bodies are seen in Tay–Sachs, and a crumpled tissue paper appearance of the cytosol is seen in Gaucher disease [Fig. 17.20].) Prenatal diagnosis, using cultured amniocytes or chorionic villi, is available. Gaucher disease, in which macrophages become engorged with glucocerebroside, and Fabry disease, in which globosides accumulate in the vascular endothelial lysosomes of the brain, heart, kidneys, and skin, are treated by recombinant human enzyme replacement therapy, but the monetary cost is extremely high. Gaucher has also been treated by bone marrow transplantation (because macrophages are derived from hematopoietic stem cells). It is also treated pharmacologically using miglustat, which reduces the substrate (glucosylceramide) for the deficient enzyme. This strategy is known as substrate reduction therapy.

FIGURE 17.19



ffected in related genetic diseases, pt Fabry, which is X linked, and all ucose; GalNAc = N- ntral nervous system. SO_4^{2-} =

FIGURE 17.20

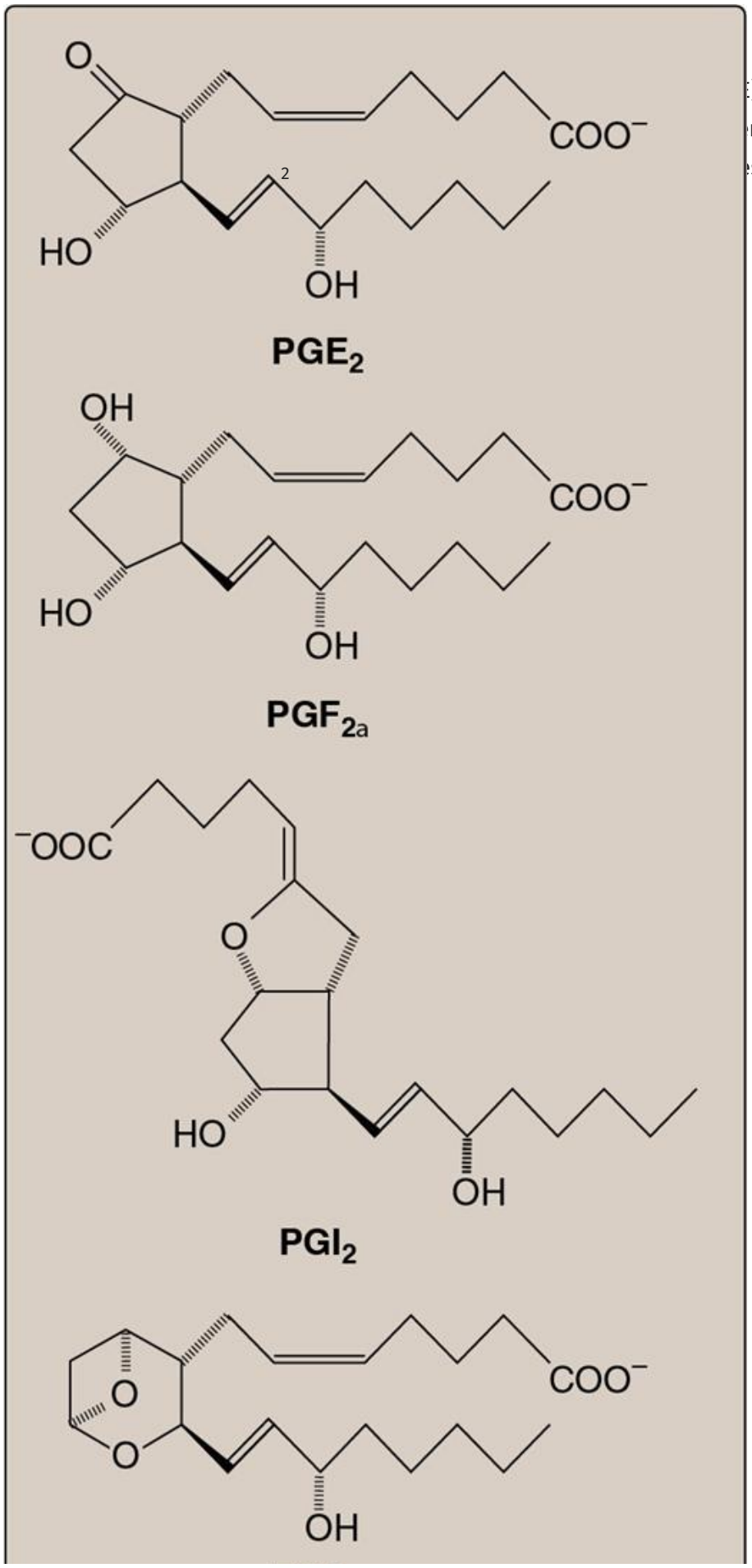


Eicosanoids: Prostaglandins, Thromboxanes, and Leukotrienes

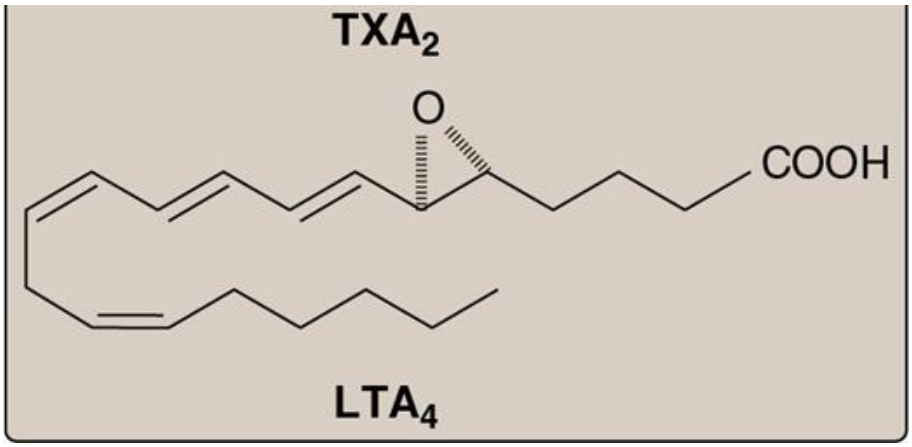
Listen

PGs, thromboxanes (TXs), and leukotrienes (LTs) are collectively known as eicosanoids to reflect their origin from ω-3 and ω-6 polyunsaturated FA with 20 carbons (eicosa = 20). They are extremely potent compounds that elicit a wide range of responses, both physiologic (inflammatory response) and pathologic (hypersensitivity). They ensure gastric integrity and renal function, regulate smooth muscle contraction (the intestine and uterus are key sites) and blood vessel diameter, and maintain platelet homeostasis. Although they have been compared to hormones in terms of their actions, eicosanoids differ from endocrine hormones in that they are produced in very small amounts in almost all tissues rather than in specialized glands and act locally rather than after transport in the blood to distant sites. Eicosanoids are not stored, and they have an extremely short half-life, being rapidly metabolized to inactive products. Their biologic actions are mediated by plasma membrane GPCRs (see p. 103), which are different in different organ systems and typically result in changes in cyclic adenosine monophosphate production. Examples of eicosanoid structures are shown in Figure 17.21.

FIGURE 17.21



), which designates the type and
r indicates the number of double
s are designated by TXs and



Prostaglandin and thromboxane synthesis

Arachidonic acid, an ω-6 FA containing 20 carbons and four double bonds (an eicosatetraenoic FA), is the immediate precursor of the predominant type of human PG (series 2 or those with two double bonds, as shown in Fig. 17.22). It is derived by the elongation and desaturation of the essential FA linoleic acid, also an ω-6 FA. Arachidonic acid is incorporated into membrane phospholipids (typically PI) at carbon 2, from which it is released by phospholipase A_2 (Fig. 17.23) in response to a variety of signals, such as a rise in calcium. (Note: Series 1 PGs contain one double bond and are derived from an ω-6 eicosatrienoic FA, dihomo-γ-linolenic acid, whereas series 3 PGs contain three double bonds and are derived from eicosapentaenoic acid [EPA], an ω-3 FA. See p. 292.)

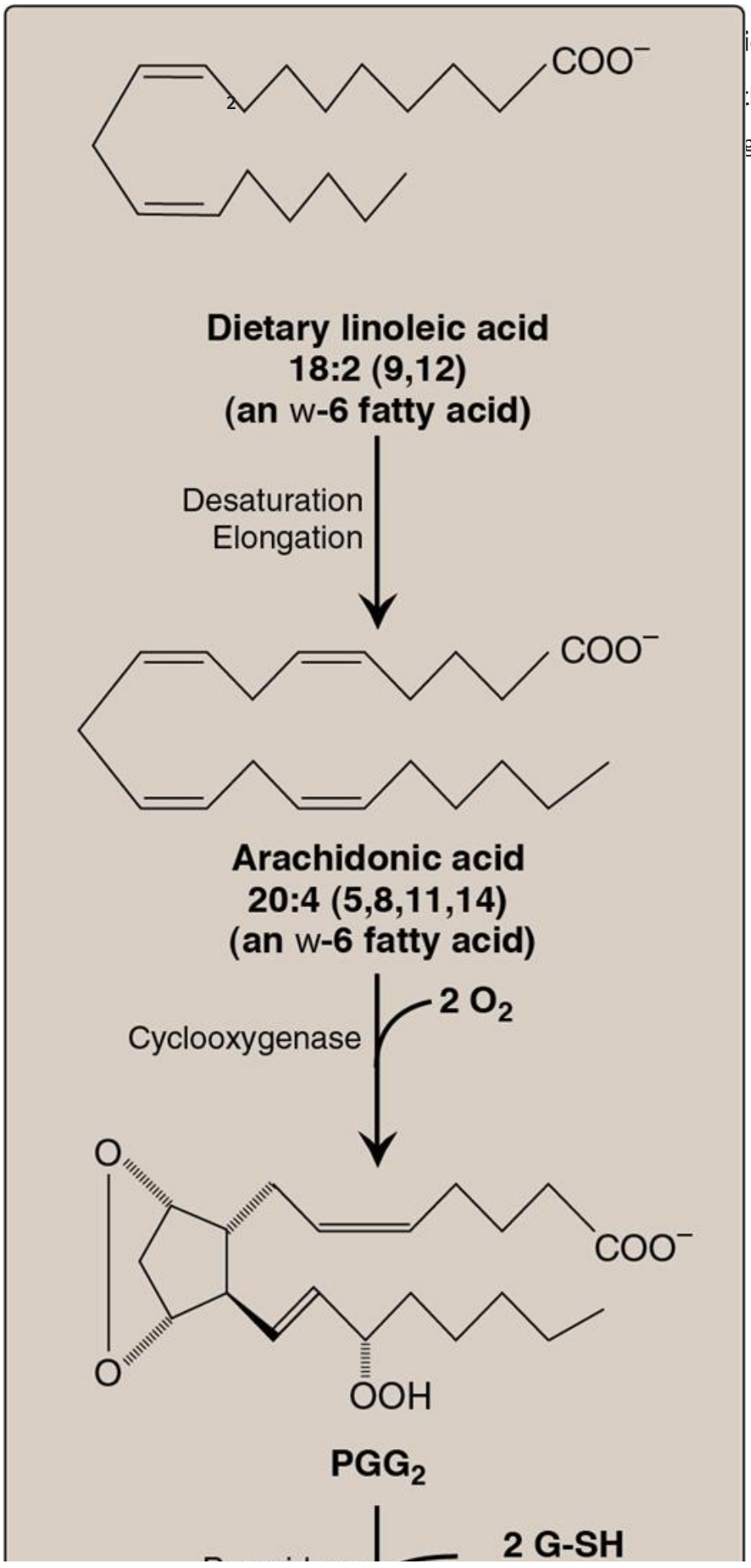
Prostaglandin H2 synthase

The first step in PG and TX synthesis is the oxidative cyclization of free arachidonic acid to yield PGH_2 by PGH_2 synthase (or, prostaglandin endoperoxide synthase). This enzyme is an ER membrane-bound protein that has two catalytic activities: fatty acid cyclooxygenase (COX), which requires two molecules of O_2, and peroxidase, which requires reduced glutathione (see Chapter 13). PGH_2 is converted to a variety of PGs and TXs, as shown in Figure 17.23, by cell-specific synthases. (Note: PGs contain a five-carbon ring, whereas TXs contain a heterocyclic six-membered oxane ring [see Fig. 17.21].) Two isozymes of PGH_2 synthase, usually denoted as COX-1 and COX-2, are known. COX-1 is made constitutively in most tissues and is required for maintenance of healthy gastric tissue, renal homeostasis, and platelet aggregation. COX-2 is inducible in a limited number of tissues in response to products of activated immune and inflammatory cells. (Note: The increase in PG synthesis subsequent to the induction of COX-2 mediates the pain, heat, redness, and swelling of inflammation and the fever of infection.)

Synthesis inhibition

The synthesis of PG and TX can be inhibited by unrelated compounds. For example, cortisol (a steroidal anti-inflammatory agent) inhibits phospholipase A_2 activity (see Fig. 17.23) and, therefore, arachidonic acid, the substrate for PG and TX synthesis, is not released from membrane phospholipids. Aspirin, indomethacin, and phenylbutazone (all nonsteroidal anti-inflammatory drugs [NSAIDs]) inhibit both COX-1 and COX-2 and, thus, prevent the synthesis of the parent molecule, PGH_2. (Note: Systemic inhibition of COX-1, with subsequent damage to the stomach and the kidneys and impaired clotting of blood, is the basis of aspirin's toxicity.) Aspirin (but not other NSAIDs) also induces synthesis of lipoxins (anti-inflammatory mediators made from arachidonic acid) and resolvins and protectins (inflammation-resolving mediators made from EPA). Inhibitors specific for COX-2 (the coxibs) are designed to reduce the pathologic inflammatory processes mediated by COX-2 while maintaining the physiologic functions of COX-1. Currently, celecoxib is the only FDA-approved coxib.

FIGURE 17.22



ic activities (cyclooxygenase and

hase).

glandin.

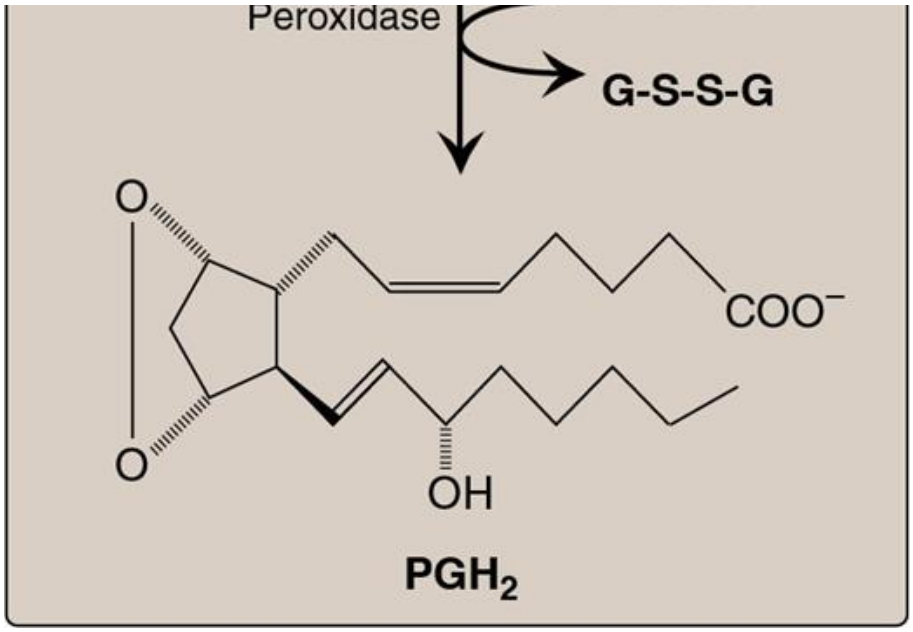
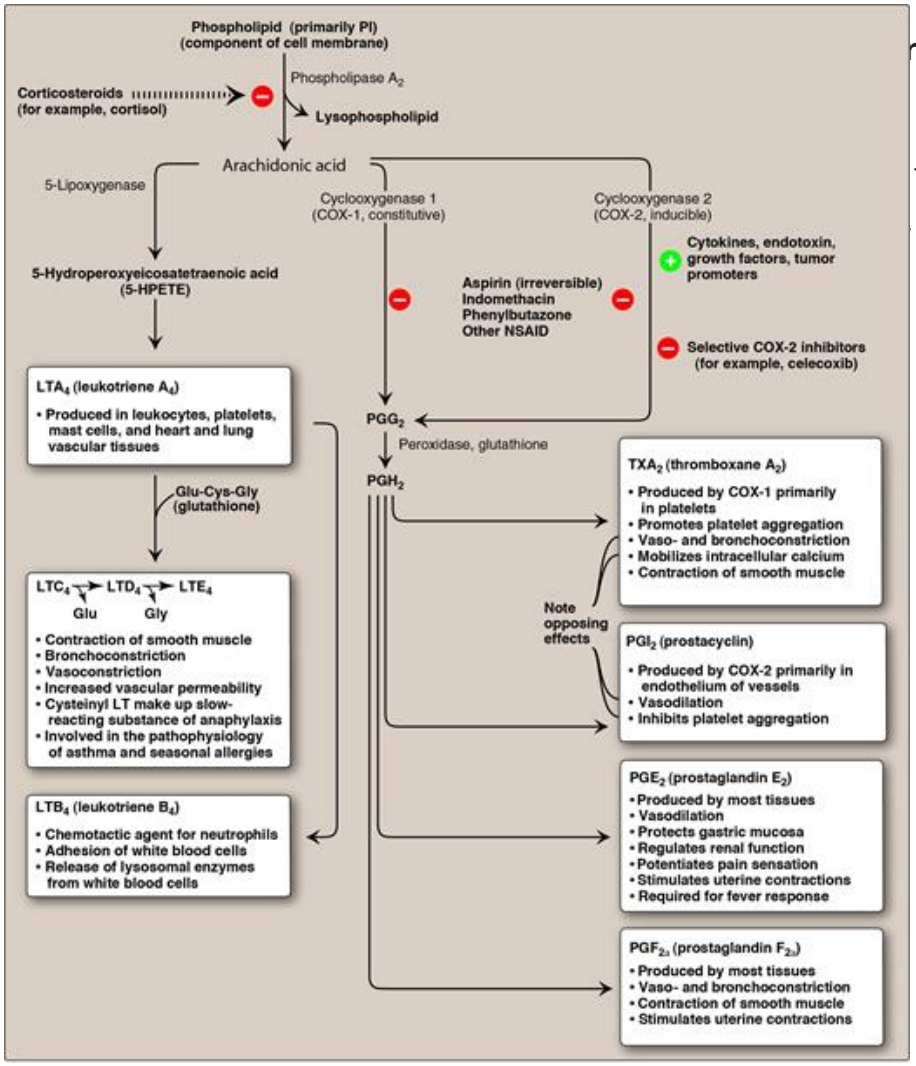


FIGURE 17.23



rostaglandins (PGs), leukotrienes

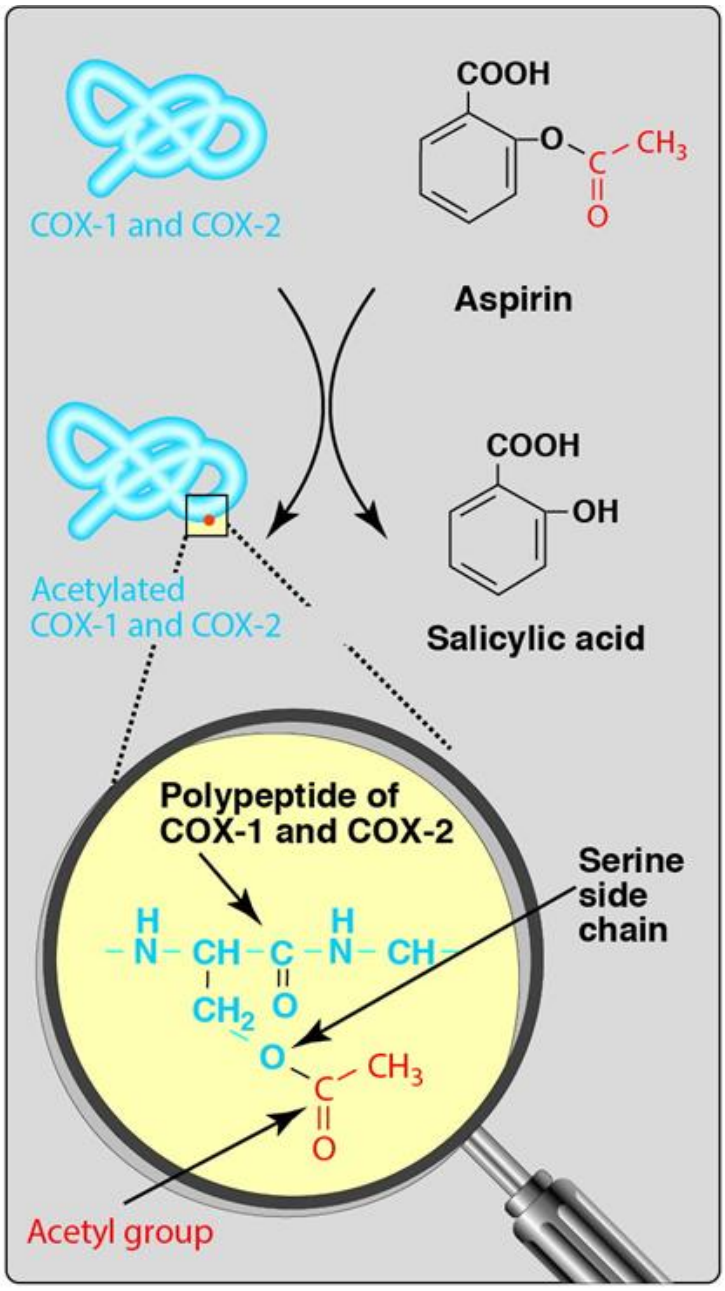
from the ω-6 essential fatty acid [FA],

anti-inflammatory drugs; Glu =

Thromboxanes and prostaglandins in platelet homeostasis

Thromboxane A_2 (TXA_2) is produced by COX-1 in activated platelets. It promotes platelet adhesion and aggregation and contraction of vascular smooth muscle, thereby promoting formation of blood clots (thrombi). (See online Chapter 35.) Prostacyclin (PGI_2), produced by COX-2 in vascular endothelial cells, inhibits platelet aggregation and stimulates vasodilation and, so, impedes thrombogenesis. The opposing effects of TXA_2 and PGI_2 limit thrombi formation to sites of vascular injury. (Note: Aspirin has an antithrombogenic effect. It inhibits TXA_2 synthesis by COX-1 in platelets and PGI_2 synthesis by COX-2 in endothelial cells through irreversible acetylation of these isozymes [Fig. 17.24]. COX-1 inhibition cannot be overcome in platelets, which lack nuclei. However, COX-2 inhibition can be overcome in endothelial cells because they have a nucleus and, therefore, can generate more of the enzyme. This difference is the basis of low-dose aspirin therapy used to lower the risk of stroke and heart attacks by decreasing formation of thrombi.)

FIGURE 17.24



aspirin.

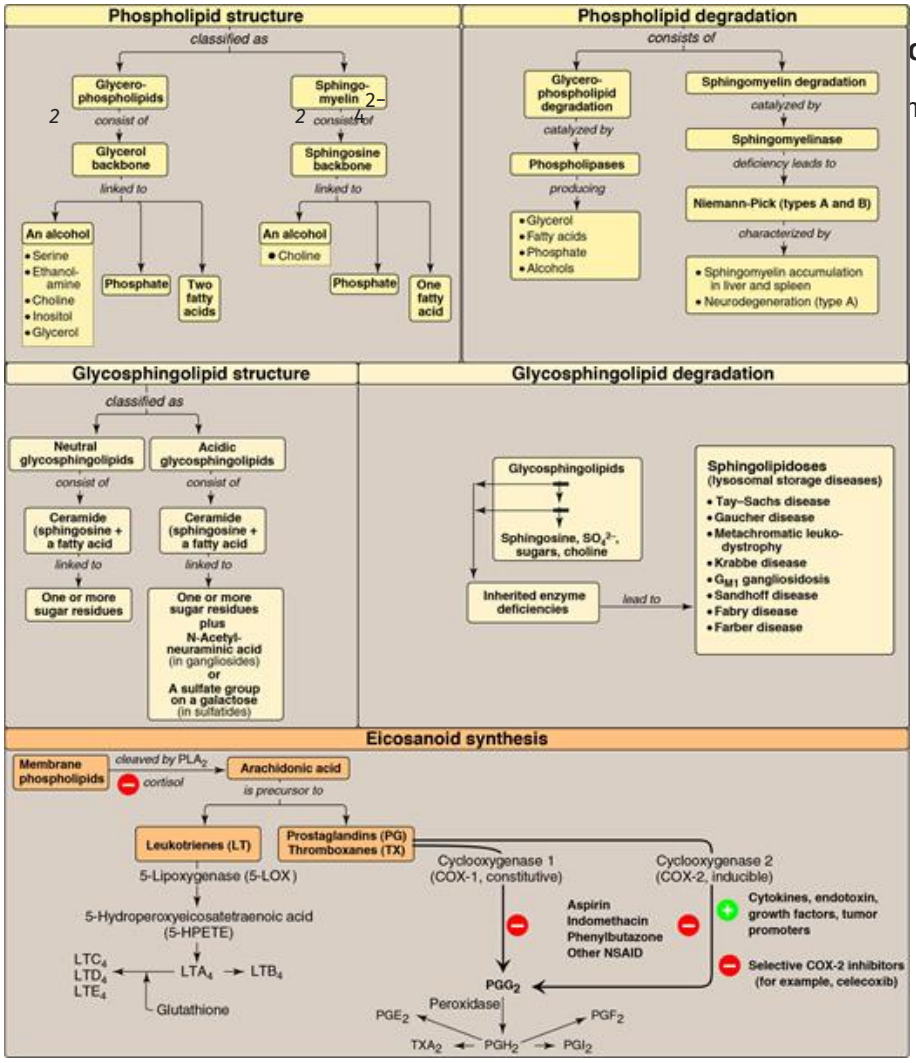
Leukotriene synthesis

Arachidonic acid is converted to a variety of linear hydroperoxy (–OOH) acids by a separate pathway involving a family of lipoxygenases (LOXs). For example, 5-LOX converts arachidonic acid to 5-hydroperoxy-6,8,11,14 eicosatetraenoic acid ([5-HPETE]; see Fig. 17.23). 5-HPETE is converted to a series of LTs containing four double bonds, the nature of the final products varying according to the tissue. LTs are mediators of allergic response and inflammation. Inhibitors of 5-LOX and LT-receptor antagonists are used in the treatment of asthma. (Note: LT synthesis is inhibited by cortisol and not by NSAIDs. Aspirin-exacerbated respiratory disease is a response to LT overproduction with NSAID use in ~10% of individuals with asthma.)

Chapter Summary

- **Phospholipids** are polar, ionic compounds composed of an **alcohol** (e.g., **choline** or **ethanolamine**) attached by a phosphodiester bond either to **DAG**, producing **phosphatidylcholine** or **phosphatidylethanolamine**, or to the amino alcohol **sphingosine** (Fig. 17.25).

FIGURE 17.25



osanoids.

nflammatory drugs.

- Addition of a long-chain fatty acid to sphingosine produces a **ceramide**.
- Addition of **phosphorylcholine** produces the phospholipid **sphingomyelin**.
- Phospholipids are the predominant lipids of **cell membranes**.
- Nonmembrane phospholipids serve as components of **lung surfactant** and **bile**.
- **Dipalmitoylphosphatidylcholine**, also called **dipalmitoyl lecithin**, is the major lipid component of **lung surfactant**.
- Insufficient surfactant production causes **RDS**.
- **PI** serves as a reservoir for **arachidonic acid** in membranes.
- The phosphorylation of membrane-bound PI produces **PIP_2**. This compound is degraded by **phospholipase C** in response to the binding of various neurotransmitters, hormones, and growth factors to membrane **GPCRs**.

- The products of **phospholipase C**, **IP_3,** and **DAG,** mediate the mobilization of intracellular **calcium** and the activation of **protein kinase C**, which act synergistically to evoke cellular responses.
- Specific proteins can be covalently attached via a carbohydrate bridge to membrane-bound PI, forming a **GPIanchor**. A deficiency in GPI synthesis in hematopoietic cells results in the hemolytic disease **paroxysmal nocturnal hemoglobinuria**.
- The degradation of phosphoglycerides is performed by **phospholipases** found in all tissues and pancreatic juice.
- **Sphingomyelin** is degraded to a ceramide plus phosphorylcholine by the lysosomal enzyme **sphingomyelinase**, a deficiency of which causes **Niemann–Pick** (**A and B**) **disease**.
- **Glycosphingolipids** are derivatives of **ceramides** to which carbohydrates have been attached. Adding one sugar molecule to the ceramide produces a **cerebroside**, adding an oligosaccharide produces a **globoside**, and adding an acidic **NANA** molecule produces a **ganglioside**.
- Glycosphingolipids are found predominantly in cell membranes of the **brain** and **peripheral nervous tissue**, with high concentrations in the **myelin sheath**. They are **antigenic**. Glycolipids are degraded in the **lysosomes** by **acid hydrolases**. A deficiency of any one of these enzymes causes a **sphingolipidosis**, in which a characteristic sphingolipid accumulates.
- **PGs**, **TXs**, and **LTs**, the **eicosanoids**, are produced in very small amounts in almost all tissues, act locally, and have an extremely short half-life.
- **Eicosanoids** serve as mediators of the **inflammatory response**. **Arachidonic acid** is the immediate precursor of the predominant class of human PGs (those with two double bonds). It is derived by the elongation and desaturation of the essential fatty acid **linoleic acid** and is stored in the membrane as a component of a phospholipid, generally PI.
- Arachidonic acid is released from the phospholipid by **phospholipase A_2** (inhibited by **cortisol**).
- Synthesis of the **PG** and **TX** begins with the oxidative cyclization of free arachidonic acid to yield PGH_2 by **PGH_2 synthase** (or, **prostaglandin endoperoxide synthase**), an endoplasmic reticular membrane protein that has two catalytic activities: **fatty acid COX** and **peroxidase**.
- There are two isozymes of PGH_2 synthase: **COX-1** (constitutive) and **COX-2** (inducible).
- **Aspirin** irreversibly inhibits both **COX-1** and **COX-2**. Opposing effects of PGI_2 and TXA_2 limit clot formation.
- **LTs** are linear molecules produced from arachidonic acid by the **5-LOX** pathway. They mediate allergic response. Their synthesis is inhibited by cortisol and not by aspirin.

Study Questions

Listen

Choose the ONE best answer.

17.1. Aspirin-exacerbated respiratory disease (AERD) is a severe reaction to nonsteroidal anti-inflammatory drugs (NSAIDs) characterized by bronchoconstriction 30 minutes to several hours after ingestion. Which of the following statements about NSAIDs best explains the symptoms seen in patients with AERD?

A. Inhibition of the activity of the cystic fibrosis transmembrane conductance regulator protein, resulting in thickened mucus that block airways.

B. Inhibition of cyclooxygenase but not lipoxygenase, resulting in the flow of arachidonic acid to leukotriene synthesis.

C. Activation of the cyclooxygenase activity of prostaglandin H_2 synthase, resulting in increased synthesis of prostaglandins that promote vasodilation.

D. Activation phospholipases, resulting in decreased amounts of dipalmitoylphosphatidylcholine and alveolar collapse (atelectasis).

Correct answer = B. NSAIDs inhibit cyclooxygenase but not lipoxygenase, so any arachidonic acid available is used for the synthesis of bronchoconstricting leukotrienes. NSAIDs have no effect on the cystic fibrosis (CF) transmembrane conductance regulator protein, defects in which are the cause of CF. Steroids, not NSAIDs, inhibit phospholipase A_2. Cyclooxygenase is inhibited by NSAIDs, not activated. NSAIDs have no effect on phospholipases.

17.2. An infant, born at 28 weeks' gestation, rapidly gave evidence of respiratory distress. Clinical laboratory and imaging results supported the diagnosis of infant respiratory distress syndrome. Which of the following is the most accurate statement about this syndrome?

A. It is unrelated to the baby's premature birth.

B. It is a consequence of too few type II pneumocytes.

C. The lecithin/sphingomyelin ratio in the amniotic fluid is likely to be high (>2).

D. The concentration of dipalmitoylphosphatidylcholine in the amniotic fluid would be expected to be lower than that of a full-term baby.

E. It is an easily treated disorder with low mortality.

F. It is treated by administering surfactant to the mother just before she gives birth.

Correct answer = D. Dipalmitoylphosphatidylcholine (DPPC or, dipalmitoyl lecithin) is the lung surfactant found in mature, healthy lungs. Respiratory distress syndrome (RDS) can occur in lungs that make too little of this compound. If the lecithin/sphingomyelin (L/S) ratio in amniotic fluid is ≥2, a newborn's lungs are considered to be sufficiently mature (premature lungs would be expected to have a ratio <2). The RDS would not be due to too few type II pneumocytes, which would simply be secreting sphingomyelin rather than DPPC at 28 weeks' gestation. The mother is given a glucocorticoid, not surfactant, prior to giving birth (antenatally). Surfactant would be administered to the baby postnatally to reduce surface tension.

17.3. A 10-year-old male was evaluated for burning sensations in his feet and clusters of small, red-purple spots on his skin. Laboratory studies revealed protein in his urine. Enzymatic analysis revealed a deficiency of α-galactosidase, and enzyme replacement therapy was recommended. Which of the following is the most likely working diagnosis?

A. Fabry disease

B. Farber disease

C. Gaucher disease

D. Krabbe disease

E. Niemann–Pick disease

Correct answer = A. Fabry disease, a deficiency of α-galactosidase, is the only X-linked sphingolipidosis. It is characterized by pain in the extremities, a red-purple skin rash (generalized angiokeratomas), and kidney and cardiac complications. Protein in his urine indicates kidney damage. Enzyme replacement therapy is available.

17.4. A 5-year-old child is brought to the pediatrician by his mother due to abdominal distention and pain in his leg. The mother states that her son started having difficulty walking and began to fall repeatedly. Physical examination shows developmental delay and hepatosplenomegaly. Fundoscopic examination shows cherry-red spots in the macula. Which of the following histologic finding of the affected tissue is most likely to confirm the diagnosis?

A. Shell-like inclusion bodies in neuronal cells

B. Crumpled tissue paper appearance of the cytosol

C. Foamy macrophages in the bone marrow

D. Globoid bodies in macrophages

Correct answer = C. Niemann–Pick disease type B is the most likely diagnosis due to the presence of hepatomegaly, neurologic defects leading to falls and cherry-red areas in the macula. The histologic finding is the foamy appearance of macrophages of the reticuloendothelial system because of sphingomyelin accumulation.

17.5. Current medical advice for individuals experiencing chest pain is to call emergency medical services and chew a regular strength, noncoated aspirin. What is the basis for recommending aspirin?

Aspirin has an antithrombogenic effect: It prevents formation of blood clots that could occlude heart vessels. Aspirin inhibits thromboxane A_2 synthesis by cyclooxygenase-1 in platelets through irreversible acetylation, thereby inhibiting platelet activation and vasoconstriction. Chewing a noncoated aspirin increases the rate of its absorption.