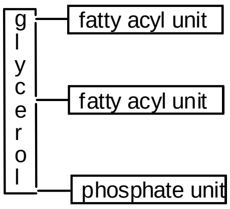
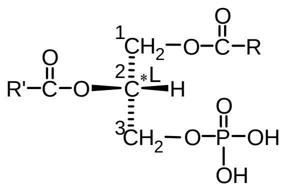
№ 45. COMPLEX LIPIDS. PHOSPHOGLYCERIDES, SPHINGOLIPIDS, AND GLYCOLIPIDS – TYPES, STRUCTURE, PROPERTIES, AND REPRESENTATIVES

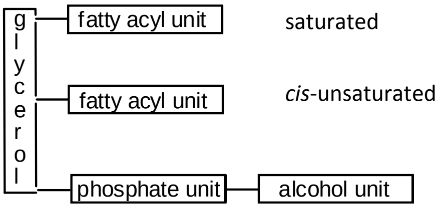
Compound (or complex) lipids are lipids that, upon hydrolysis, yield fatty acids (FA), an alcohol (either glycerol or sphingosine), and other compounds such as phosphoric acid, amino alcohol, sugar.

Phospholipids. When the lipid contains residues from FA, glycerol and phosphoric acid it is called glycerophospholipid. When besides FA and residue of phosphoric acid, the lipid contains long-chain unsaturated amino alcohol (instead of glycerol), the lipid is called sphingophospholipid.
There are two large groups of glycerophospholipids: **phosphatides** and **plasmalogens**. Both are esters of glycerol. Molecules of phosphatides have two ester bonds to fatty acids and one ester bond to phosphoric acid, resulting in phosphatidic acid. This acid has a chiral center (carbon atom 2) which in all natural lipids is with L-configuration related to L-glyceraldehyde in Fisher projection.



phosphatidic acid components


L-phosphatidic acid

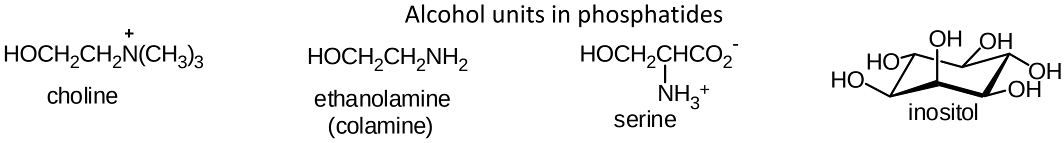


phosphatide components

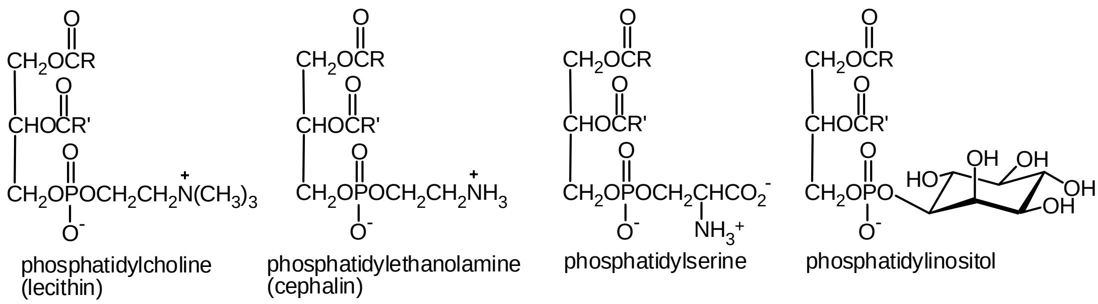
Phosphatidic acid exists in dianionic form at physiological pH. Phosphatidic acids are minor component of glycerophospholipids.

When the phosphoric acid group in a phosphatidic acid is joined via phosphate ester link to a small alcohol, the resulting molecules are called **phosphatides**. Often the C-1 glycerol hydroxyl group is esterified with saturated FA and C-2 hydroxyl group – with unsaturated FA. Three particularly important phosphatides are esters between phosphatidic acid and either choline, ethanolamine, or serine, forming, respectively, phosphatidylcholine (lecithin), phosphatidylethanolamine (cephalin), and phosphatidylserine. An important analog is phosphatidylinositol - a phospholipid, which is made up of glycerol, fatty acid and the base is replaced by a hexahydric alcohol namely inositol.

Alcohol units in phosphatides

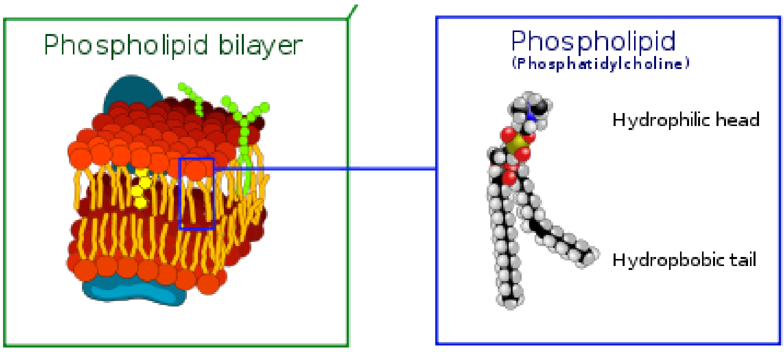


Important phosphatides from these alcohol units



As the structures above show, one part of each phosphatide is very polar because it carries full electrical charges. The dissociation of the proton of the phosphate oxygen in phosphatides at physiological pH is essentially complete. Phosphatidylcholine has a positive charge on the nitrogen atom since it is a quaternary ammonium ion. Phosphatidylethanolamine is protonated at the nitrogen atom at pH 7.0. As a result, both phosphaditylcholine and phosphatidylethanolamine are dipolar but have no net charge. The carboxyl group in phosphatidylserine is ionized as a carboxylate ion, and its amine group is protonated, thus the net negative charge of this molecule is due to dissociation of phosphoric acid residue, similarly to the charge origin in phosphatidylinositol. These electrical charges are partly responsible for the greater solubility in water of phosphatides compared to triacylglycerols. The remainder of a phosphatide molecule is nonpolar and hydrocarbon-like, so the phosphatides can be extracted from animal matter by relatively nonpolar solvents.

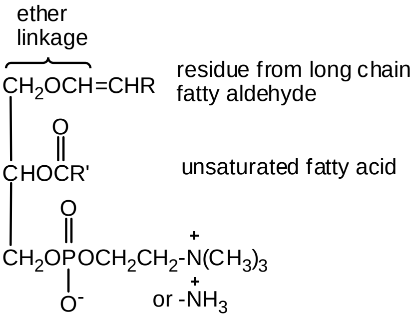
A characteristic feature of phospholipids is the presence of polar, hydrophilic (water-attracting) head and two nonpolar hydrophobic (water-repelling) tails. Such molecules are prone to aggregate in a specific manner studied in a modern branch of chemistry - supramolecular chemistry or chemistry beyond molecule. The nonpolar tails attract each other and form lipid bilayer when surrounded by aqueous environment. The phospholipids possess very good emulsifying and membrane forming properties. The cell membrane consists primarily of a thin layer of amphipathic phospholipids which spontaneously arrange so that the hydrophobic "tail" regions are shielded from the surrounding polar fluid, causing the more hydrophilic "head" regions to associate with the cytosolic and extracellular faces of the resulting bilayer. This aggregation may form a continuous, spherical lipid bilayer.



Membranes perform many specific functions in living organisms. The two mayor components of cell membranes are lipids and proteins, with the proportion of the two types of compounds varying among different kinds of membranes. For example, myelin sheath is about 70% lipids, whereas the nuclear membrane is only about 40% lipid. Membranes also contain small amount of carbohydrate found in glycolipids and glycoproteins. These carbohydrates serve as the biological markers for cellular recognition. Glycoproteins form the structure for receptor sites, which are areas on the membrane for attachment of specific molecules, e.g. hormones.

Phosphatidylcholine (PC, in older literature also called **lecithin**), R=$C_{17}H_{35}COOH$, R'= $C_{17}H_{33}COOH$, plays an important role in the metabolism of fats in the liver and in the transport of fats from one part of the body to another. It serves as a source of inorganic phosphate for tissue formation and is an excellent emulsifying agent. Egg yolks contain large amount PC and is used to emulsify salad oil and vinegar to make mayonnaise. The removal after selective hydrolysis of one FA from PC gives lysolecithin which is poisonous causing destruction of red blood cells and spasmodic muscle contractions. Poisonous snake venom contains enzymes catalyzing formation of lysolecithin from PC.

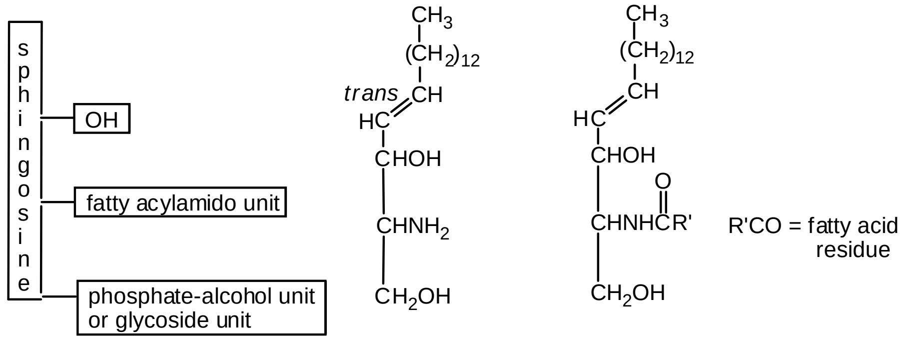
Phosphatidylethanolamines are also called **cephalins**. Like lecithin, cephalin consists of a combination of glycerol esterified with two fatty acids and phosphoric acid. Whereas the phosphate group is esterified with choline in lecithin, it is combined with ethanolamine in cephalin. Cephalin is found in all living cells, although in human physiology it is found particularly in nervous system tissue such as the white matter of brain, nerves, neural tissue, and in spinal cord. Whereas lecithin is the principal phospholipid in animals, cephalin is the principal one in bacteria.



plasmalogens

All considered above phospholipids are **ester phosphatides**. Their variety is due to different FA and differently esterified phosphoric acid at C-3 position (C-2 also possible). Another large group phospholipids are the so called **plasmalogens** (~10% of lipids in CNS). They are considered **acetal phosphatides**. They differ from the ester phosphatides by the presence of an unsaturated ether group instead of an acyl group at the glycerol carbon one. This double bond is a result from dehydration of an acetal formed between the glycerol OH and long-chain aliphatic aldehyde, hence the name acetal phosphatides. Plasmalogen molecules, similarly to phosphatides, carry electrically charged atoms, as well as long hydrocarbon chains. Plasmalogens occur widely in the membranes of both nerve and muscle cells.

Sphingophospholipids. Like phosphoglycerides, sphingophospholipids contain a phosphate group and chloline. Sphingophospholipids, however, contain residue of the alcohol **sphingosine** instead of glycerol. Sphingosine is a long-chain unsaturated 18 carbons dihydric amino alcohol. The configuration of sphingolipids is D-, D-.



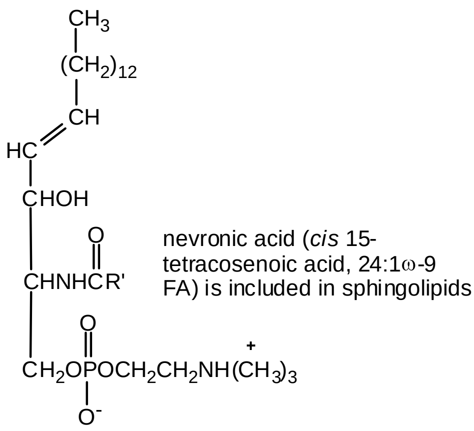
sphingolipid components · sphingosine · ceramide

Conversion of the amine group of sphingosine into an amide with a fatty acid yields a **ceramide**. Ceramides are not phospholipids. They are found in cell membranes as structural elements. Function as cellular signaling molecules for differentiation, proliferation, apoptosis.

Esterification of the primary alcohol of a ceramide with phosphoric acid and choline results in a **sphingophospholipid**.

Although the components of glycerophospholipids and sphingophospholipids are different, the overall structures are similar. Both classes of compounds consist of a polar head and two nonpolar tails. There are, however, chemical differences: the sphingophospholipids have a single amide group and are more stable towards hydrolysis than phosphoglycerolipids which have two ester groups.

Most abundant sphingolipids are **sphingomyelins** (~85% of all sphingolipids). Sphingomyelins contain sphingosine, fatty acid (both – a ceramide core), phosphoric acid and choline. They are found in large amounts in brain and the tissue of nervous system where they form part of the myelin sheath, the protective coating of nerve cell axons. In humans, sphingomyelin is believed to be the only cell membrane phospholipids not derived from glycerol.

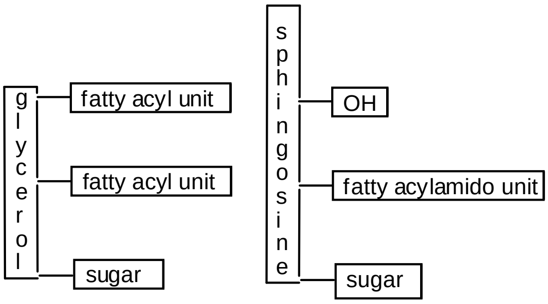


sphingomyelins

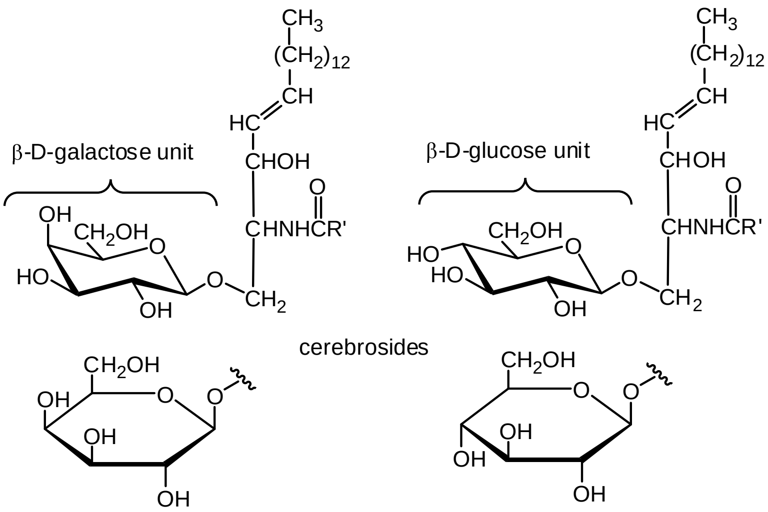
Glycolipids. The main difference between glycolipids and phospholipids is that a glycolipid contains a sugar group rather then a phosphate group. The sugar group is usually **galactose** but may also be **glucose**, connected via a **β-glycoside bond**. The alcohol is either glycerol or sphingosine.

Glycosphingolipids are similar to sphingophospholipids since they contain sphingosine and a fatty acid residue bonded as an amide in ceramide. However, glycosphingolipids do not contain phosphate. A carbohydrate is connected via β-glycoside bond to the primary alcohol group of ceramide. The two main groups of glycolipids are: **cerebrosides** and **gangliosides**. Cerebrosides usually contain one monosaccharide whereas gangliosides contain an oligosaccharide.

Cerebrosides are sphingolipids (without phosphate group). They contain sphingosine, fatty acid (often lingoceric acid $C_{23}H_{47}COOH$), monosaccharide (β-D-galactose – in galactocerebrosides or β-D-glucose – in glucocerebrosides). The sugar unit, with its four OH groups, provides strongly polar (uncharged) hydrophilic site. Cerebrosides are less polar than sphingomyelins which carry charged atoms. Cerebrosides, as the name suggests, are formed in high concentrations in the brain and nerve cells, especially in the myelin sheath. Several hereditary fat metabolism diseases have been linked to errors in the enzymes that hydrolyze glycolipids.

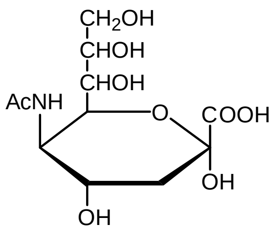


glycolipids



cerebrosides

Ganglioside is a compound composed of a glycosphingolipid (ceramide) and oligosacharide with one or more attached sialic acid residues. Gangliosides are more complex glycosphingolipids in which oligosaccharide chains containing N-acetylneuraminic acid (NeuNAc) are attached to a ceramide, thus providing an anionic head from the ionized carboxylic acid group. Their structural diversity results from variation in the composition and sequence of the sugar residues. In all gangliosides, the ceramide is linked through its C-1 to a β-glucosyl residue, which, in turn, is bound to a β-galactosyl residue. Gangliosides occur in the grey matter of the brain, in ganglion cells.



N-acetylneuraminic acid
sialic acid