

1.2: Lipid Headgroup Types

Lipid headgroups comprise part of the hydrophilic backbone of membrane phospholipids. There are a number of headgroups, each of which correlates with a particular type of backbone. Membrane lipids are split into three categories: phospholipids and glycolipids (Figure 1.2.1). Sterols are the third type of membrane lipid (not pictured) that will be discussed.

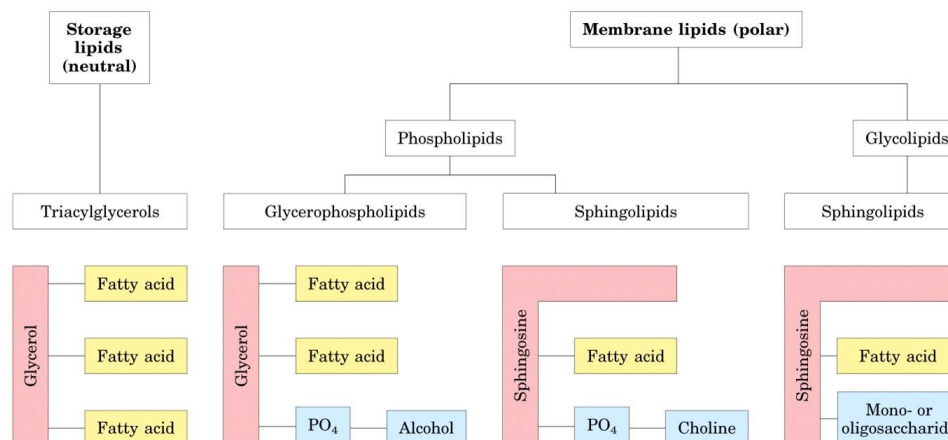


Figure 1.2.1: Membrane lipids are polar and can be separated into phospholipids and glycolipids, for which the basic structures are shown. Note the difference in the third binding site. Phospholipids have a phosphate bound to an alcohol (glycerol-) or choline (sphingo-), while glycolipids have a sugar group. Source: Lafer, Eileen. "Membrane Lipids I and II: Glycerophospholipids and Sphingolipids." Lecture. San Antonio, Texas. December 6, 2011

Lipid headgroups are substituents that attach to the glycerol, sphingosine, or cholesterol backbones of polar membrane lipids. Phospho- and glycolipids have headgroups linked to the backbone through a phosphodiester bond (Figure 1.2.2).

Understanding head group behavior is necessary for the study of membrane biology. The high structural diversity allows for a large range of functions, including effects on membrane curvature [1] cell signaling, substrate transport [2], and more. Consequently, their crucial role in membrane biology also ties them in with a broad range of diseases, from cardiovascular defects to cancer.

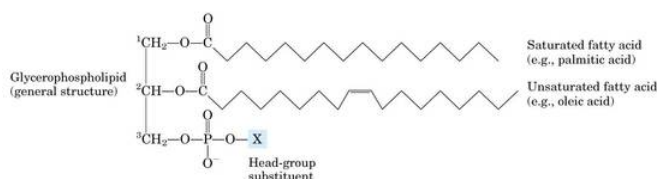


Figure 1.2.2: headgroups are the substituent bound to the phosphate group of a hydrophilic lipid backbone. Source: Lafer, Eileen. "Membrane Lipids I and II: Glycerophospholipids and Sphingolipids." Lecture. San Antonio, Texas. December 6, 2011

II. PHOSPHOLIPIDS

A. GLYCEROPHOSPHOLIPIDS

Glycerophospholipids are classified by the alcohol that is bound to the phosphate group on the glycerol backbone. The backbone always consists of a glycerol esterified to fatty acids in positions *Csn*-1 and *Csn*-2, with the head group substituent bound to the phosphate in position *Csn*-3 [2]. Interestingly, archaeobacteria have the headgroup at the *Csn*-1 position [3]. The headgroup classes are differentiated by the *Csn*-1 and *Csn*-2 substituents. If the *Csn*-1 and *Csn*-3 substituents are unique, the *Csn*-2 carbon becomes a chiral center [4].

Phosphatidic acid has the simplest substituent: hydrogen. This parent compound, phosphomonoester, is then built upon by naming the derivatives for the head-group alcohol (X, Figure 1.2.2) with "phosphatidyl-" as a prefix. For example, phosphatidyl-choline, phosphatidyl-ethanolamine, and phosphatidyl-serine are other common membrane lipids [4].

Some of the common glycerophospholipid head groups are shown in Table 1:

Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	— H	−1
Phosphatidylethanolamine	Ethanolamine	— CH ₂ —CH ₂ —NH ₃ ⁺	0
Phosphatidylcholine	Choline	— CH ₂ —CH ₂ —N ⁺ (CH ₃) ₃	0
Phosphatidylserine	Serine	— CH ₂ —CH(NH ₃ ⁺)—COO [−]	−1
Phosphatidylglycerol	Glycerol	— CH ₂ —CH(OH)—CH ₂ —OH	−1
Phosphatidylinositol 4,5-bisphosphate	<i>myo</i> -Inositol 4,5-bisphosphate		−4
Cardiolipin	Phosphatidyl-glycerol		−2

Table 1: common head groups found in glycerophospholipids and their basic characteristics. Source: Lafer, Eileen. “Membrane Lipids I and II: Glycerophospholipids and Sphingolipids.” Lecture. San Antonio, Texas. December 6, 2011

Phosphatidylinositol (PI) is interesting in that it can be phosphorylated to make PI phosphate (PIP), PI bisphosphate (PIP₂), and PI trisphosphate (PIP₃). These compounds are found on the cytoplasmic leaflet of membranes and therefore heavily influence the membrane-cytosol interface. This makes them particularly relevant to membrane trafficking, regulating cell growth, proliferation, and apoptosis [2].

B. SPHINGOLIPIDS

Sphingolipids have a base made of a long (carbon) chain called sphingosine, which is bound with fatty acids using amide linkages to make ceramides (Figure 1.2.3). The sphingoid base backbone is synthesized from a long-chain fatty acyl-CoA and serine. Ceramide is the most basic sphingolipid, with only a hydrogen in the Csp-3 position and an amide-linked fatty acid [4] (Table 2). More complex (phosphor)sphingolipids have headgroups attached via phosphodiester linkages [4]. The Sphingosine backbone, fatty acid, and headgroup of a sphingolipid are also highlighted in Table 2.

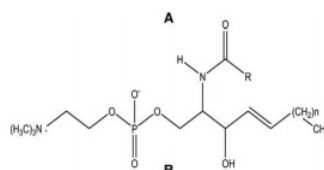


Figure 1.2.3: Structure of sphingolipids in which R represents a fatty acid. Source: Montealegre, C., et al., Analysis of glycerophospho- and sphingolipids by CE. Electrophoresis, 2014. 35(6): p. 779-92.

Some common sphingolipids headgroups are depicted in Table 2:

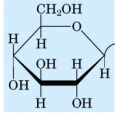
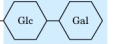
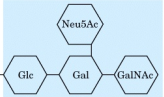
Sphingolipid (general structure)	$\begin{array}{c} \text{Sphingosine} \\ \text{HO}-^3\text{CH}-\text{CH}=\text{CH}-(\text{CH}_2)_{12}-\text{CH}_3 \\ \text{^2CH}-\text{N}-\text{C} \\ \quad \quad \quad \\ \text{H} \quad \quad \quad \text{O} \\ \text{^1CH}_2-\text{O}-\text{X} \end{array}$	
	Fattyacid	
Name of sphingolipid	Name of X	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	$\begin{array}{c} \text{O} \\ \\ -\text{P}-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}^+(\text{CH}_3)_3 \\ \\ \text{O}^- \end{array}$
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	

Table 2: Sphingolipid structure and common head groups. Source: Lafer, Eileen. “Membrane Lipids I and II: Glycerophospholipids and Sphingolipids.” Lecture. San Antonio, Texas. December 6, 2011

Sphingomyelin is a common sphingolipid that is prominent in the myelin sheaths of neurons. The head groups have a large effect on overall lipid structure, which is why phosphatidyl choline (glycerophospholipid) and sphingomyelin (sphingolipid) look so similar (Figure 1.2.4).

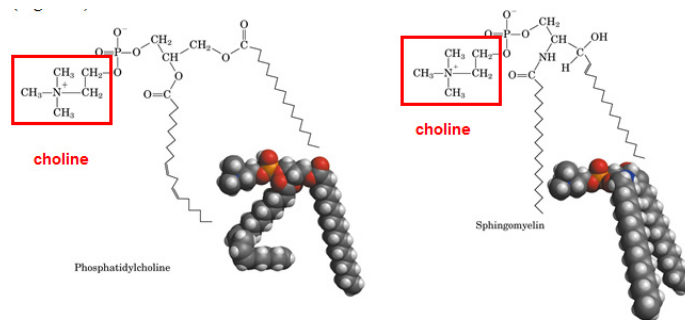


Figure 1.2.4: Both phosphatidylcholine and sphingomyelin have a choline head group attached to a phosphate group. Despite the different backbone molecule, the two molecules are remarkably similar in shape. Source: Lafer, Eileen. “Membrane Lipids I and II: Glycerophospholipids and Sphingolipids.” Lecture. San Antonio, Texas. December 6, 2011

III. GLYCOLIPIDS

Glycolipids contain a sub-group of sphingolipids that have a similar backbone structure to phosphosphingolipids (Figure 1.2.3), but have a mono- or oligosaccharide bound to the Csn-3 position instead of a phosphate-choline group (Table 2). Glycosphingolipids

are especially relevant to neuronal membranes, where D-glucose is added to the hydroxyl group of ceramide to create GlcCer. If the headgroup has any (one to four) silica acid(s) attached to it, the new molecule is referred to as a ganglioside [2].

Interestingly, the carbohydrate head group portions of sphingolipids are what define the human blood groups. The oligosaccharide head groups are composed of D-glucose (Glc), D-galactose (Gal), N-acetyl-D-galactosamine (GalNAc), and fucose (Fuc). The addition of an extra GalNAc creates the A antigen/blood type, and the addition of a Gal creates the B antigen/blood type (Figure 1.2.5).

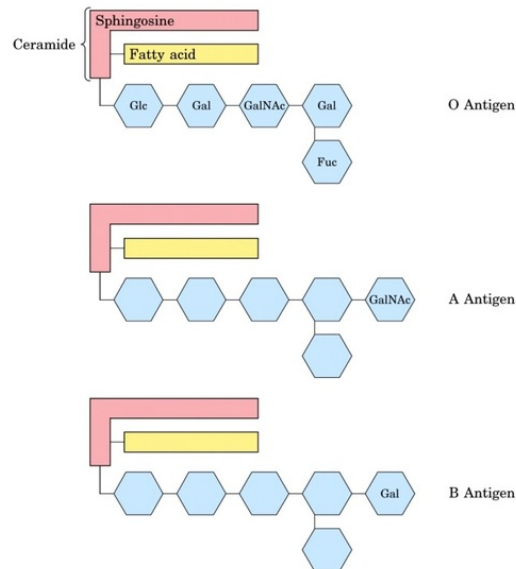


Figure 1.2.5: Blood group types in humans are determined by the glycolipid headgroup; source: Lafer, Eileen. "Membrane Lipids I and II: Glycerophospholipids and Sphingolipids." Lecture. San Antonio, Texas. December 6, 2011

STEROLS

Sterols in mammals stem primarily from cholesterol (Figure 1.2.6) and its derivatives. Sterols are subdivided primarily based on biological function; steroids, a set of important hormones and signaling molecules [5] can also be subdivided by the number of carbons in the core skeleton. Estrogens fall into the C_{18} family, while androgens make up the C_{19} family [4]. A broad representation of sterols can be seen below (Figure 1.2.6).

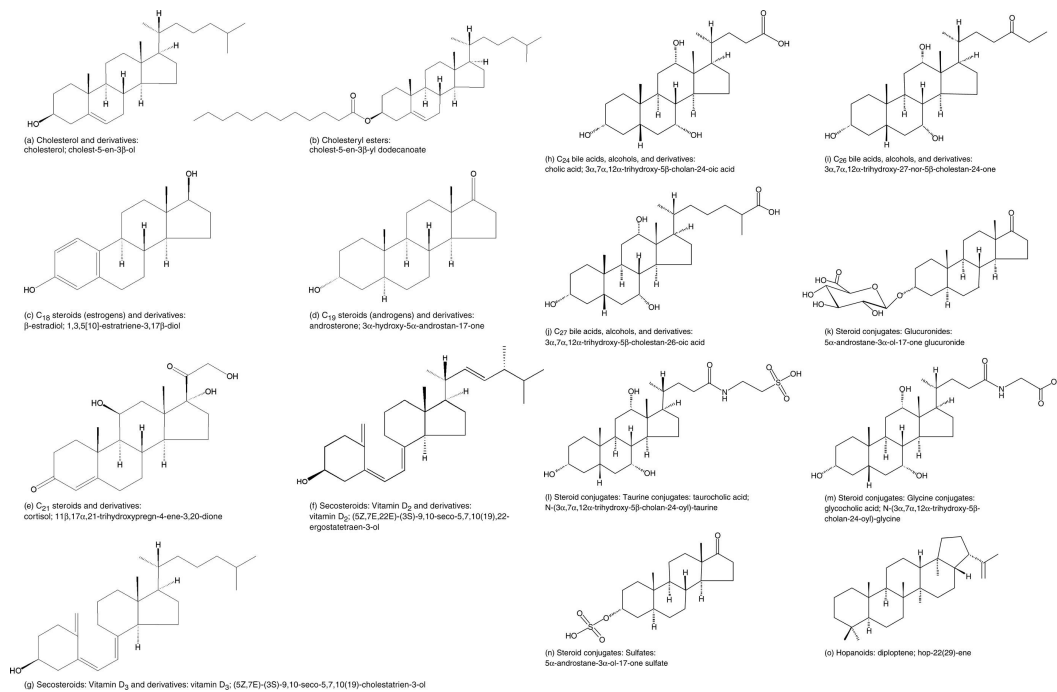


Figure 1.2.6: Representative structures for sterol lipids; source: Fahy E et al. J. Lipid Res. 2005;46:839-862, ©2005 by American Society for Biochemistry and Molecular Biology

CHARGED HEADGROUPS

Many lipids (both glycerophospholipids and sphingolipids) have **charged headgroups**. This charge is incredibly important in determining headgroup behavior, as it affects repulsion with other molecules and other membrane characteristics. For example, phospholipid headgroups interact with other membrane proteins like the P-glycoprotein multidrug transporter, which is linked to cancer resistance [6]. Similarly, charge density and headgroup structure influence membrane rigidity [7], create variation in protein-lipid interactions and liposome membrane mobility [8], and determine the ability of lipid-DNA complexes to transfect DNA *in vitro* [9].

There are many negatively charged headgroups, whereas positive charges are much less common. Phosphatidic acid is a dynamic headgroup that is uncharged below pH 4, but has a -1 charge at physiological (human) pH and a -2 charge above pH 14. Similarly, phosphatidylserine has a -1 charge and phosphatidylcholine is zwitterionic (Figure 1.2.7).

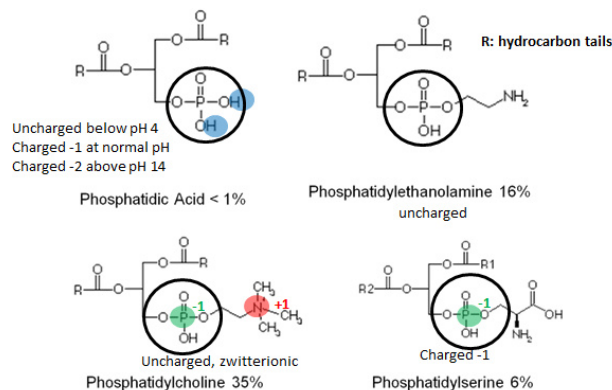


Figure 1.2.7: Headgroups found in cell membranes with various charges. Percentages represent relative abundance in human red blood cell membranes. Source: Faller, Roland. "Introduction to Membrane and Lipid Fundamentals." Lecture. Davis, CA. April 3, 2014

The presence and concentration of charge has direct effects on headgroup orientation. If the electric surface charge of a membrane is positive, the N⁺ component of the P—N dipole (see phosphatidylcholine, Figure 1.2.7) moves toward the water phase, which

causes a large ($>30^\circ$) change in orientation of the phosphate segment. A negative surface charge has the opposite effect, moving the N^+ end of the dipole toward the interior area of the membrane [10]. The orientation of lipids, and therefore the movement of headgroups, is important for lipid-protein binding and membrane topology. Finally, headgroup charge is notably related to membrane curvature. Studies have shown that the negatively charged headgroups phosphatidic acid and phosphatidylserine favor negative membrane curvature when excess ion are present (due to charge repulsion) and nearly flat surfaces in pure water. However, it is important to consider salt and pH conditions, as these may have an effect on the data [1, 11, 12].

CONCLUSION

In summary, there are three major membrane lipid groups: sterols, glycolipids, and phospholipids. These groups are determined based on the molecular backbone of the lipid. A variety of headgroups can then attach and alter structure and function. Many of these membrane lipids are directly associated with cellular processes, and therefore present health risks if perturbed. One case study showed that higher levels of plasma sphingolipids increases risk or occurrence of lung cancer [13]. Headgroups also largely affect biological functions due to their ability to be charged, and often to change charge at different various pH values.

References

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