26

Biochemistry

Doctor 2017 | Medicine | JU

Sheet

Slides

Done By

Tala Saleh

Contributed in the Scientific Correction

Tamer Barakat

Contributed in the Grammatical Correction

...

Doctor

Faisal

Phospholipids

There are **two** classes of phospholipids:

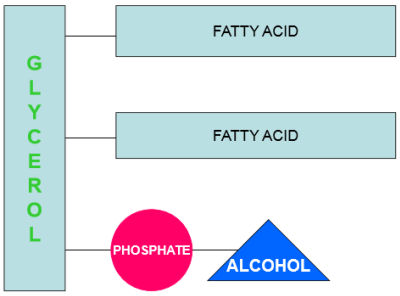
1- Those that have **glycerol** as a backbone, **Glycerophospholipids**.
2- Those that have **sphingosine** as a backbone, **Sphingophospholipids**.

Both classes are found as **structural** components of membranes, and both play a role in the generation of **lipid-signaling** molecules.

Glycerophospholipids

- The general structure of glycerophospholipids *(also known as phosphoacylglycerol)* consists of **4** components:

  a- Glycerol
  b- 2 Fatty acids
  c- Phosphate group
  d- Alcohol



- These components are linked together through **4 ester bonds**:

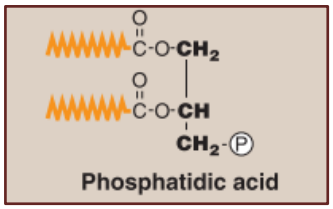
  a- 2 ester bonds between the **Glycerol** and the **2 Fatty acids**.

  b- 1 ester bond between the **Glycerol** and the **Phosphate group**.

  c- 1 ester group between the **Phosphate group** and the **alcohol**

  The last 2 bonds form a phosphodiester bond.

- The glycerol with the 2 Fatty acids (Diacylglycerol) and the phosphate group forms the **Phosphatidic acid**.

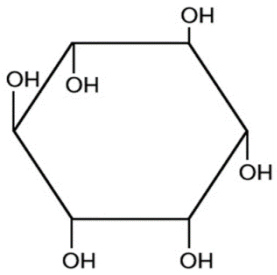


- **Different** alcohols bind to the phosphatidic acid forming different **phosphoacylglycerol**, these alcohols can be:

  a- Inositol (myo-inositol): is a 6-membered ring with **6** hydroxyl groups (not a sugar).

  b- Glycerol

  c- Amino-alcohols (-ine): **Ethanolamine**, **Serine**, **Choline**



Myo-Inositol

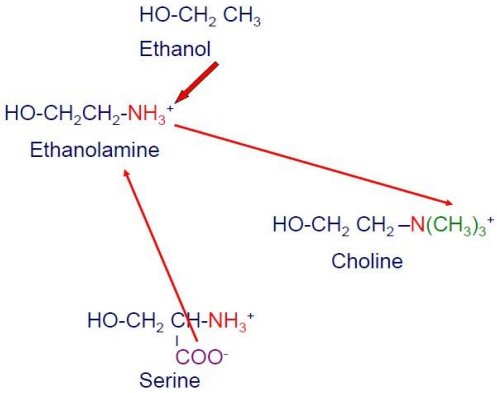
- When the **phosphatidic acid** binds with a certain **alcohol**, it is named as:

  Phosphatidyl- (serine/ethanolamine/inositol, etc.)

Only understand their structures:

The following is just to compare the structures; it is theoretical (not really how its synthesized)

- **Ethanolamine** is **ethanol** with an additional **amino group**.
- **Serine**, a common amino acid, is **ethanolamine** with a **carboxy group**.
- **Choline** is **ethanolamine** with **3** methyl groups.



Phosphatidyl Choline (Lecithin)

From its structure shown in the figure to the right, **two** regions are recognized:

- **Hydrophobic part (nonpolar):** Is the **tail**, which is made up of **two fatty acids**. It **cannot** dissolve in water.

  Kinks in fatty acids indicate the presence of **double bonds** *(in the cis configuration).*

- **Hydrophilic part (polar):** Is the **head**, which is made up of **phosphate along with choline molecules**. It **can** interact and dissolve in water since it is charged. It has both a **negative** charge (oxygen in phosphate) and a **positive** charge (nitrogen in choline).

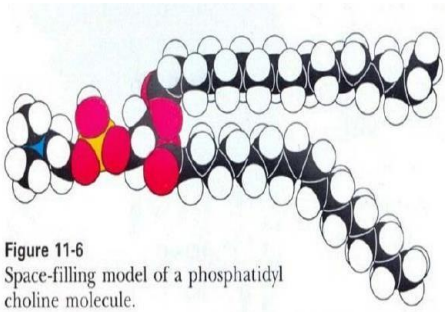
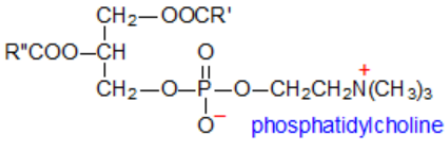


Figure 11-6
Space-filling model of a phosphatidyl choline molecule.

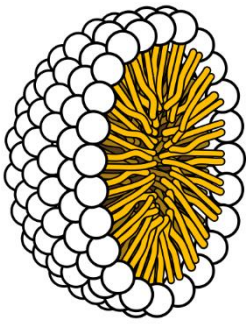


Action of Phospholipids in forming Micelles

- Phospholipids -*which are lipid molecules containing a phosphate group such as phosphatidylcholine*- when immersed in water, they **aggregate** through **nonpolar** interactions forming **micelles**.

  The **exterior part** is the **polar heads**, while the **interior part** is the **nonpolar tails**.

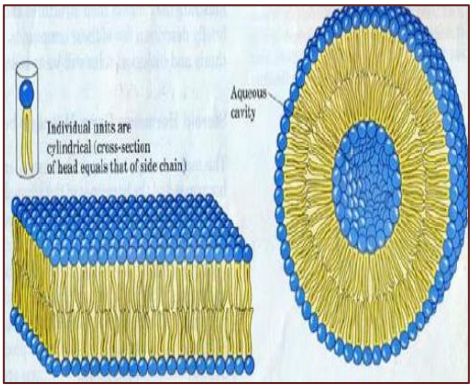
- Because of their **amphipathic** nature and their formation of **micelles**, they act as **emulsifying agents**, which are substances that integrate **nonpolar** molecules keeping them in suspension in water.



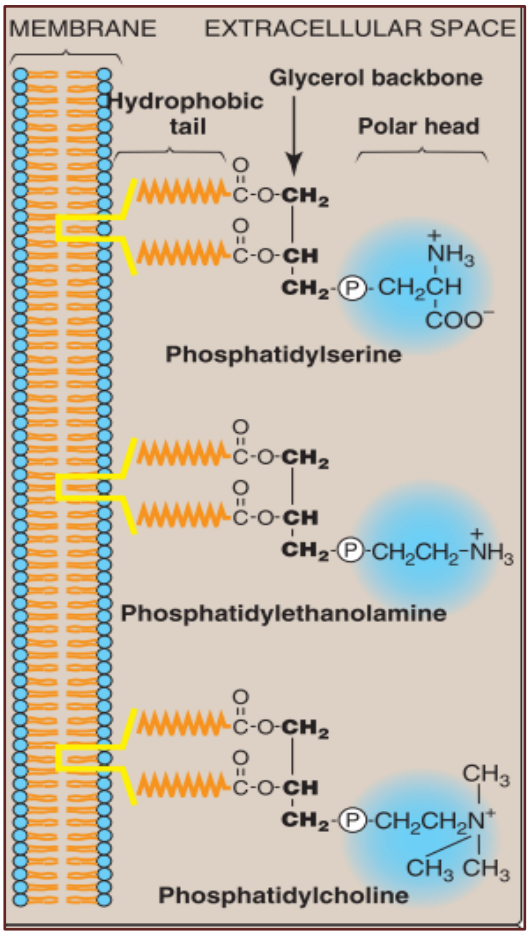
Note: ***Chocolate bars*** *contain* ***phosphatidyl choline*** *reducing the viscosity of chocolate. Also,* ***powder milk*** *contains phosphatidyl choline making it* ***water soluble****.*

- Phospholipids can also participate in forming **cell membranes** (lipid bilayer), and **liposomes**.

- Liposomes are structures with an **aqueous cavity**. They function as **transport vesicles** for **polar** molecules.



- **Cell membranes** in our body are made up of **phospholipids** *(phosphatidylethanolamine phosphatidylserine and phosphatidylinositol)* in different ratios and concentrations.



Degradation of phospholipids

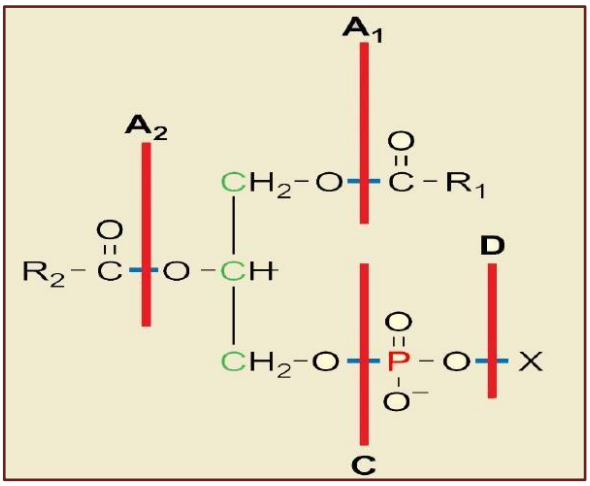
- Each **ester bond** discussed earlier in phospholipids, can be **hydrolyzed** through different enzymes known as **phospholipases**. Phospholipases hydrolyze the **ester** bonds **of phosphoglycerates** releasing **different** molecules, with each enzyme cleaving the phospholipid at a **specific site**:

1- **Phospholipase A1:** hydrolyzes the 1st ester bond (between glycerol and FA 1).

2- **Phospholipase A2:** hydrolyzes the 2nd ester bond (between glycerol and FA 2).

3- **Phospholipase C:** hydrolyzes the ester bond between glycerol and phosphate.

4- **Phospholipase D:** hydrolyzes the ester bond between alcohol and phosphate.

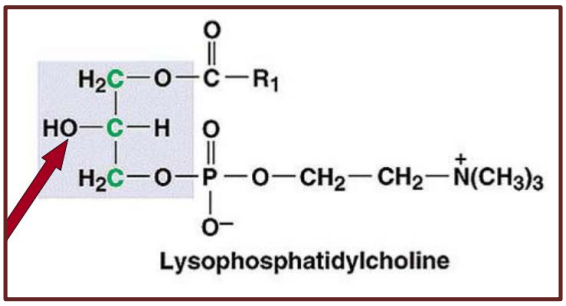


- The previous enzymes **do not work sequentially** since they work on **intact molecules**; PL-A2 doesn't work after PL-A1 and vice versa.

- However, the **removal** of the fatty acid from **carbon 1 or 2** of a phosphoglyceride through **PL-A1 / PL-A2,** produces a **lysophosphoglyceride** (a lysophospholipid), which is a substrate for **lysophospholipases** enzymes *(e.g. Phospholipase B).*

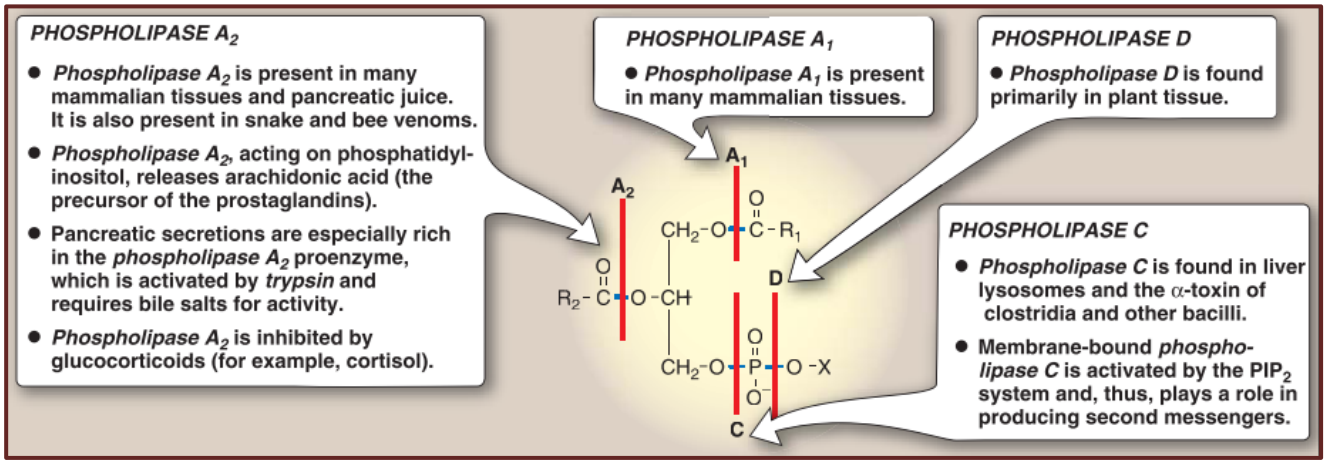
  Phospholipase B, removes the **remaining** fatty acid from a lysophosphoglyceride

  Example: Phosphatidylcholine **2nd ester bond** is hydrolyzed forming lysophosphatidylcholine. PL-B then works on lysophosphatidylcholine removing the **other FA**.



> ***Note:*** *A lysophospholipid is any derivative of a **phospholipid** in which **one** of the **acyl groups** has been removed by **hydrolysis**.*

More information on phospholipases mentioned by the doctor, refer to the information in the following picture too.



Phospholipase A2:

- Commonly found in **snakes** and **bees venoms**. When present in the body, after a bite, phospholipases act on phospholipids of the **cell's membranes**, producing **lysophospholipids**.

  They are called lysophospholipids because they cause **cell lysis**.

- It has strong **detergent action**; it can hydrolyze (degrade) the **plasma membrane** of the cells leading to necrosis.
- PL-A2, also acts on **phosphatidylinositol** releasing **arachidonic acids**, which are precursors for the synthesis of **Prostaglandins**.
- PL-A2 is inhibited by **glucocorticoids** (e.g. Cortisol); this is how Cortisol works as an **anti-inflammatory** agent, since it **prevents** the release of **arachidonic acid** which is the precursor of inflammatory signals.

Phospholipase C:

- It is a membrane-bound phospholipase, which releases **diacylglycerol** (DAG) and **inositol triphosphate** (IP3).

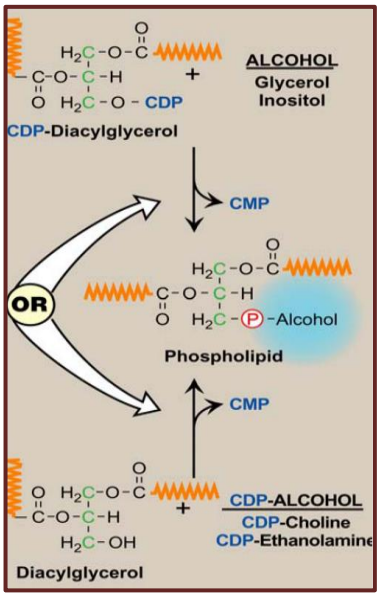
Biosynthesis of Phosphoacylglycerol

- **Phosphatidic acid** is the common intermediate and main precursor in the biosynthesis of phosphoacylglycerides. To synthesize a **glycerophospholipid**, an **alcohol** should be added to the phosphatidic acid.
  Recall: *Phosphatidic acids is a precursor for both **TAG** and **Phospholipids**.*

- Ways of the **biosynthesis of glycerophospholipid** involves either:

  1- Donation of **phosphatidic acid** from **CDP-diacylglycerol** to an **alcohol**.

  2- Donation of the **alcohol** from **CDP-alcohol** to **diacylglycerol**.



- In both cases, the **CDP-bound** structure is considered as an **activated** intermediate *(activated carrier)*, which is added to an **inactivated** intermediate, and cytidine monophosphate (**CMP**) is released as a **side product** of glycerophospholipid synthesis.

- Thus, either **alcohol** or **diacylglycerol** are activated through the **linkage to CDP**, to be **added** forming a **glycerophospholipid**.

The activation of alcohol occurs as follows:

CTP + Alcohol-P → CDP-Alcohol + PP

- Notice that a **high energy** bond in **CTP** was **broken down**, forming a **high energy** bond in **CDP-Alcohol**, so the value of delta G will be almost **zero**; meaning that the reaction is **reversible**.

- However, the **pyrophosphate** is rapidly **consumed** through hydrolyzation. Thus, continuously **decreasing** its concentration causing a shift in the reaction to the **right** making the reaction **irreversible** *(the forward reaction is favored).*

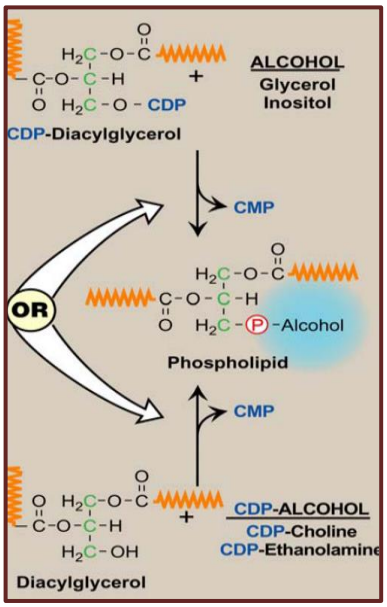
> ***Note:*** *This is similar in principle to the **activation of sugars** by their attachment to uridine diphosphate (UDP) instead of CDP.*

Synthesis of Phosphatidylinositol (PI)

Please refer to the figures to understand each process.

Example on the 1st way of the biosynthesis of glycerophospholipid.

- PI is synthesized from **free inositol** and **CDP-diacylglycerol** as shown in Figure.



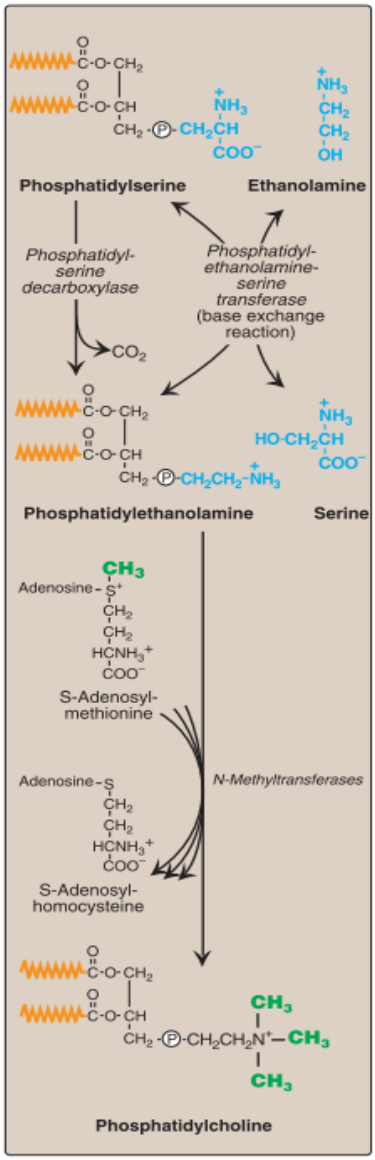
Synthesis of Phosphatidylcholine and Phosphatidylethanolamine (PC & PE)

Example on the 2nd way of the biosynthesis of glycerophospholipid.

- These synthetic pathways involve the **phosphorylation** of **choline/ethanolamine** by kinases, followed by conversion to the **activated** form, CDP-choline / CDP-ethanolamine.
- Finally, the **activated** form (CDP-Alcohol) reacts with a molecule of **diacylglycerol,** leaving CMP as a **by-product.**

Synthesis of Phosphatidylserine (PS)

- The primary pathway for synthesis of PS is through alteration of polar head groups (base exchange reaction), in which the **ethanolamine** in **PE** is exchanged for **free serine** forming **PS.**
- The **decarboxylation** of **phosphatidylserine**, resynthesizes **Phosphatidylethanolamine.**



Synthesis of Phosphatidylcholine (PC) "another way"

- PS is **decarboxylated** to PE, by PS decarboxylase. **PE** then undergoes **three methylation** steps to produce **PC** where S- Adenosylmethionine is the methyl group donor.
  (3 molecules of it are needed to produce 1 PC from PE)
- **S- Adenosylmethionine**, is a sulfur contain sulfur containing amino acid joined to adenosine. The sulfur in it holds a positive charge making the compound **unstable**, thus it is used as a methyl donor, since it **easily** loses the **methyl** group.
- When S-Adenosyl methionine (SAM) loses the methyl group, it becomes **S-adenosyl homocysteine.**

Remodeling of Phospholipids

Phospholipases are responsible not only for degrading phospholipids, but also for **remodeling** them.

1- **Phosphatidylcholine** can be regenerated through the addition of **arachidonic acid** in the form of **arachidonyl CoA** to **lysophosphatidylcholine**.

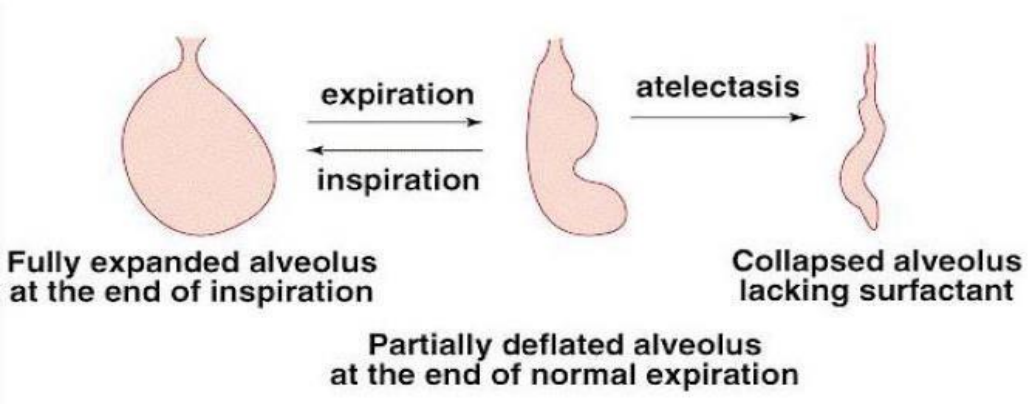
2- When fatty acids are connected to **glycerol** through an **ether bond** instead of an **ester bond**, they form **Ether Glycerophospholipids**.

   The platelet activating factor, is an ether glycerophospholipids, where carbon #1 forms an **ether bond**, while carbon #2 of the glycerol is connected to an **acetic acid**. Thus, phospholipids can act as **precursors** of **signal molecules**.

3- Phospholipases A1 and A2 remove specific fatty acids from membrane-bound phospholipids, which can be **replaced** with alternative fatty acids using fatty acyl CoA transferase. This mechanism is used as one way to create a unique lung surfactant.

Surfactant actions of phospholipids

- Surface tension results from **hydrogen bonds** between water molecules, each water molecule can form **4** hydrogen bonds therefore large number of hydrogen bonds makes the water droplet form a **dome like shape** on a surface instead of **spreading** like other liquids that lack surface tension.
- Surfactants are substances that **lower** the **surface tension**. They are important in the **lungs**, where the **alveoli** are lined with a thin water film. The surface tension of water **squeezes** the alveolus while the **surfactants** coating it **prevents** the alveoli from **collapsing**.
- Also, surfactants **reduce** the **effort** needed to **expand** the lungs (increase lung compliance).



- Lung surfactants (mainly phosphatidylcholine) start forming during the **fetal life** after the 32th week of gestation. If the baby was born **before** that, there would be insufficient pulmonary surfactants causing newborn **respiratory distress syndrome**.

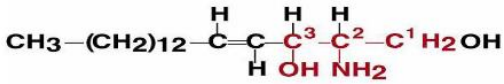
  This can be avoided if the physician predicted that the baby will be delivered early, and so injecting the mother with **glucocorticoids** which **accelerate** the **maturation** of the lungs.

The functions of Glycerophospholipids stated up till now are:

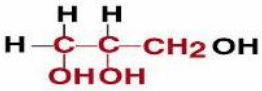
1- Components of cell membranes.
2- Sources of arachidonic acids.
3- Signaling molecules: Platelet activating factor, for platelets aggregation.
4- Emulsifiers.
5- Surfactants.

Sphingophospholipids

- The backbone of **sphingophospholipids** is **sphingosine**, unlike glycerophospholipids with a glycerol as the backbone.



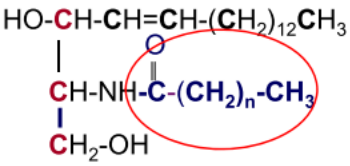
Sphingosine



Glycerol

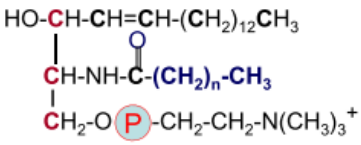
- **Sphingos-ine,** contains an **amine group** and is an amino alcohol. The amine group can form an **amide bond** with a carboxyl group forming **Ceramide**. The ceramide structure is **common** between all sphingophospholipids.

- The ceramide looks like **diacylglycerol**, except that at carbon #2 in ceramide there's an **amide bond** whereas in diacylglycerol it is an **ester bond**. Furthermore, only **one** FA attaches to the backbone. The other long chain is **part** of the **backbone** (sphingosine) with **no** ester bonds involved.



Sphingomyelin

The addition of **phosphorylcholine** to the 3rd carbon in **ceramide** forms **sphingomyelin**. It is similar in structure to phosphatidylcholine, having some functions in common such as being part of the **cell membrane** and forming **micelles**. Sphingomyelin is present in **large quantities** in the **membrane of neurons** (myelin sheath).



Good Luck ♥