Medical Committee
The University of Jordan

SLIDE SHEET

LECTURE#: 19

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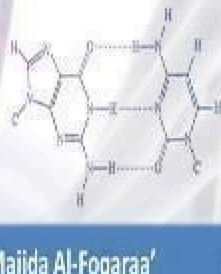
DONE BY: Esra'a Abu Haneieh

Biochemistry



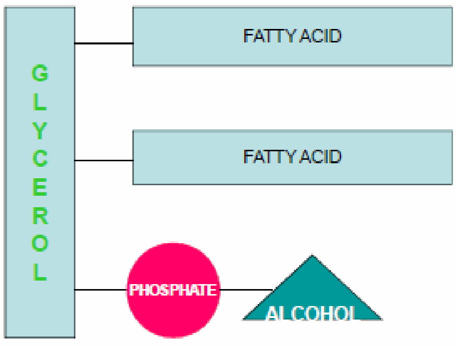
Majida Al-Foqaraa'

Biosynthesis Of Phospholipids

Today we will continue with phospholipids...

<u>* Structure of phospholipid:</u>

Formed from:
Glycerol that's esterified to 2 fatty acids at carbon #1&2, At carbon #3 is esterified to phosphate which in turn esterified to amino alcohol (ethanolamine, serine, choline, and inositol).

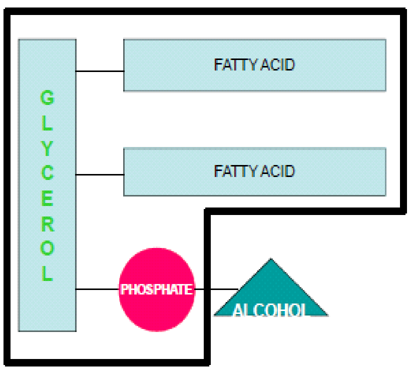


PHOSPHOACYLGLYCEROL

We've also talked about degradation of phospholipids, as they're degraded by enzymes called phospholipases (A1, A2, B, C, and D), each phospholipase is specific for an ester bond.

<u>Today, we'll talk about synthesis & some of the functions of phospholipids, in addition to being membrane components.</u>

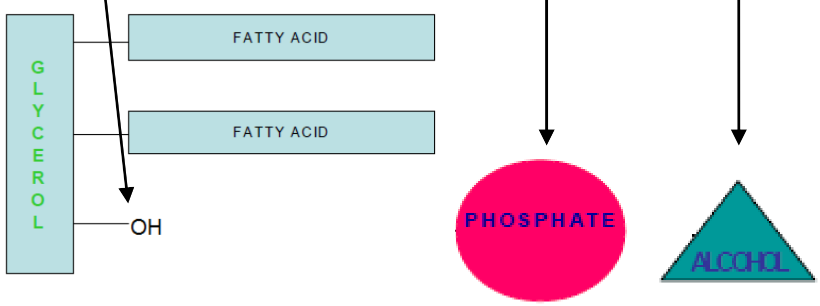
<u>* Synthesis</u>:
we said that **Phosphotadic acid** (synthesized by transferring 2 fatty acids [number #1&2] to glycerophosphate [glycerophospholipid without alcohol]) is a **common intermediate** in the synthesis of **TAG and Phosphoacylglycerol** .
Phosphotadic acid can form an ester bond with alcohol (serine, ethanolamine, choline, inositol), producing phospholipids [such as phosphatidyl choline, phosphatidyl ethalonamine, phosphatidyl inositol, etc].



* Phosphatidic acid is synthesized by addition of 2 FA one after the other to a glycerol phosphate by acyl transferases.

Biosynthesis of other glycerophospholipids:

Look at the components of glycerophospholipids: they are (diacylglycerol [alcohol 1] +phosphate+alcohol [alcohol 2]). Diacylglycerol by itself is an alcohol (alcohol 1) because it has a hydroxyl group.



Now how to join these components together?

The synthesis happens by one of 2 ways :

1- transfer of (activated form)**phosphyrlated - alcohol 1**(diacylglycerol)to alcohol 2

2- Transfer of ~ **phosphrylated - alcohol 2** to alcohol 1.

1st step,

How activated alcohol (phosphorylated alcohol) is synthesized?

Forming activated carrier (activated alcohol):

* We have CTP (Cytosine ribose TriPhosphate / Cytidine TriPhosphate), it's similar to ATP but instead of adenine it has cytosine (another nitrogenous base), it has a high energy compound because it contains 2 high energy bonds (between the 1st & 2nd phosphate and between 2nd & 3rd phosphate). Also, we have phosphorylated alcohol. Now, 2 phosphates from the terminal of CTP are removed/released and the last phosphate is added to the phosphate of alcohol-P so **CDP-alcohol** is now formed and the 2 terminal phosphates are released as **pyrophosphate**.

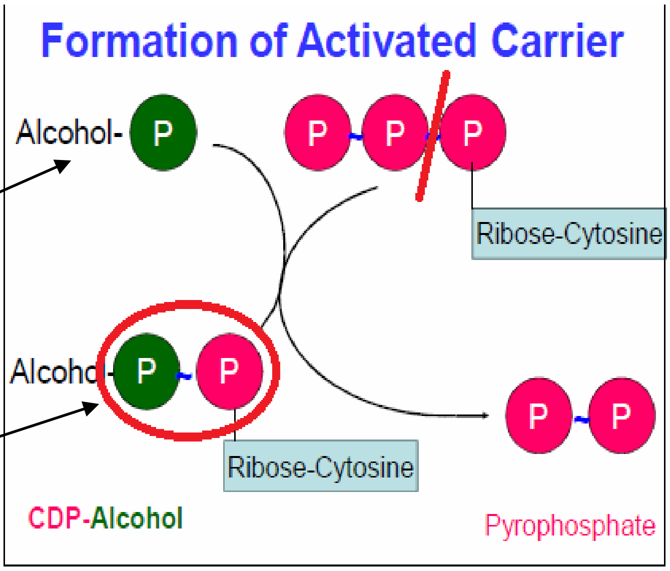
* **ΔG ~ 0** for this rxn, so it's a **reversible rxn**, But WHY **delta G is near to ZERO**? Because we are breaking a high energy bond and forming a new high energy bond.

* How the rxn is made irreversible?

By rapid hydrolysis of pyrophosphate by pyrophosphatase (this pushes the rxn in the forward direction) → this is a common mechanism, so making CDP-Alcohol will be favorable by this mechanism. This

* This could be DAG joined to phosphate (phosphatidic acid) [phosphorylated alcohol 1] or phosphorylated choline or phophorylated ethanolamine... [phosphorylated alcohol 2]

* CDP-alcohol: activated form of phosphorylated alcohol because of the high energy bond.



* Now we have an activated form of phosphorylated alcohol (picture above shows how the activated carrier is produced), so in the next step we can easily transfer the phosphorylated alcohol to a new alcohol (here breaking of a high energy bond happens → so it can be easily done)

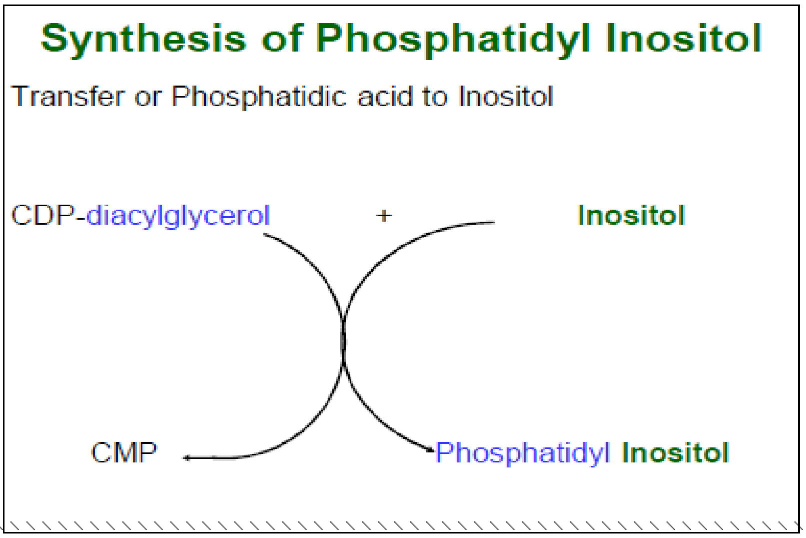
2nd step,

Transfer of phosphorylated alcohol to another alcohol, for example :

Synthesis of phosphatidyl inositol

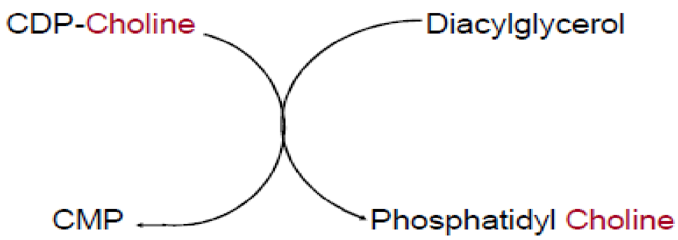
We have here CDP-DAG so we transfer phophorylated Diacylglycerol to inositol.

Diacylglycerol is not transferred alone! It's transferred along with a phosphate group, so what is transferred to inositol is a phosphatidic acid (diacylglycerol + phosphate group) in order to make phosphatidyl inositol. Then what remains is a CMP molecule because one phosphate group (from the 2 phosphates in the CDP-diacylglycerol molecule) is already transferred with diacylglycerol to the inositol.



Synthesis of Phosphatidyl choline

Transfer of phosphocholine (from CDP-choline) to DAG (alcohol 1), producing phosphatidyl choline and CMP (which remains from CDP-choline after transmission).



Synthesis of phosphatidyl ethanolamine

Same as phosphatidyl choline, but ethanolamine instead of choline...

So the strategy: transfer of phosphorylated alcohol (in activated form) to the other alcohol (two alcohols linked by phosphate) and this is how phosphatidyl choline & phosphatidyl ethanolamine are synthesized by utilization of ethanolamine and choline.

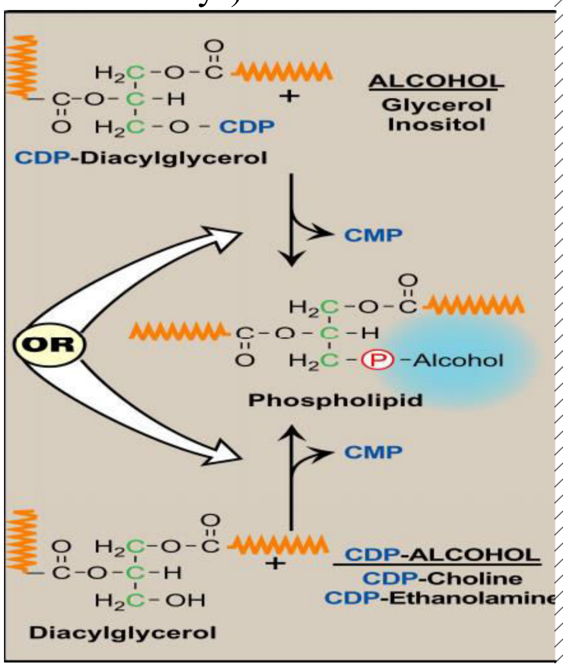
This pic is from the book to show the two strategies (methods or ways):

1) Transfer of phosphatidic acid to glycerol and inositol.

2) Transfer of phosphocholine or phosphoethanolamine to DAG to form phospholipid.

So each alcohol has a certain method, glycerol and inositol use the first one while choline and ethanolamine use the second one!

In this way we can synthesize the phospholipids by reutilization of choline and ethanolamine.



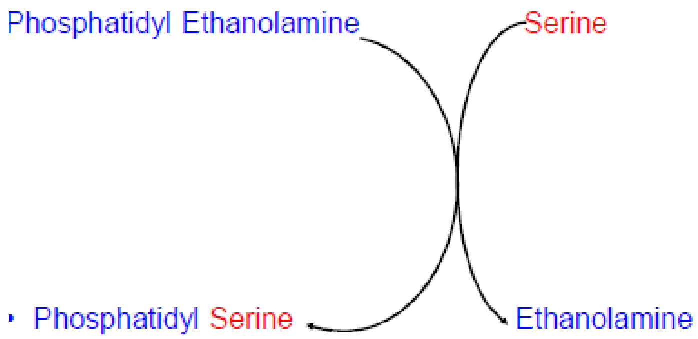
Now , how we can produce phosphatidyl serine ??

Alteration of polar head group

1) **Polar head group can be altered by the exchange of this polar head group**

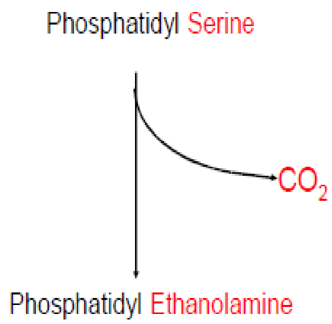
Ethanolamine is replaced or exchanged with Serine, we have phosphatidyl ethanolamine synthesized so we can remove the ethanolamine and put serine instead to produce phosphatidyl serine. So phosphatidyl serine is not synthesized by any of the two previous mechanisms. The synthesis is actually done by changing of the polar head group (alteration of polar head group). Ethanolamine is removed and Serine is replaced instead.

* Remember that serine is an alcohol, and it's an amino acid that has amino group, carboxyl group and hydroxyl group.



Alteration of polar head group

Can occur by
2) **Decarboxylation of Phosphatidyl serine** to form phosphatidyl ethanolamine**.**



We have said before that the relation between serine and ethanolamine is decaroxylation. So this is another way of producing phosphatidyl ethanolamine. Serine can go decarboxylation only when it is part of phosphatidyl Serine so it gives us phosphatidyl ethanolamine (we don't get ethamolamine be decarboxylation of serine but by ecarboxylation of phosphatidyl serine to give phosphatidyl ethanol amine).

Then if we need phosphatidyl serine again, we can produce it by exchange.

* A student asked: “why we don’t use carboxylation of phosphatidyl ethanolamine to produce phosphatidyl serine? Why by exchange not by carboxylation?

Carboxylation doesn’t happen because it needs ATP, biotin, carboxylase.

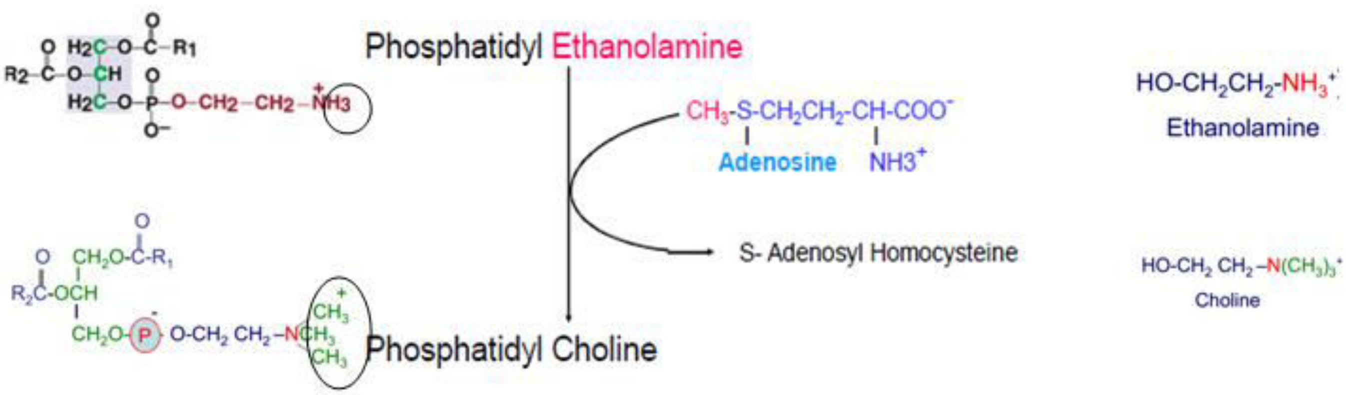
* Serine is readily available, it’s one of the common amino acids, just we put it instead of ethanolamine or we can utilize it. Just one molecule of ethanolamine can produce a lot of phosphatidyl ethanolamine by decarboxylation followed by exchange and so on.

3) **Methylation of Phosphatidyl Ethanolamine:** We can make make Phosphatidyl choline by this method. We said before that the relation between ethanolamine and choline is three methyl groups; so adding three methyl groups to ethanolamine when it is part of phosphatidyl ethanolamine gives us phosphatidyl choline.

* Replace 3 hydrogens by 3 methyl groups.

* Methylation: add methyl group (CH3)

* Methylation of phosphatidyl Ethanolamine, produce phosphatidyl choline.
(To make it easier, check the structures of alcohols at the beginning of slide #7)
* **SAM** (S- Adenosyl Methionine) is the active donor of methyl groups, each SAM donates one methyl group only.
SO we need **3 SAM's** to produce phosphatidyl choline.

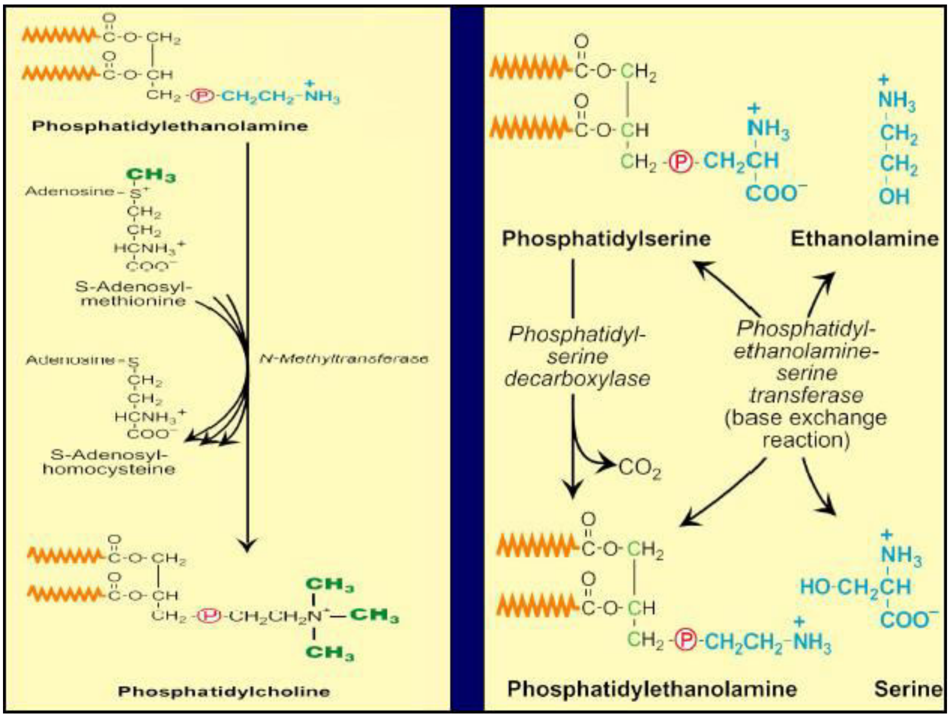


* The structure of SAM is adenosine (adenine+ribose) but instead of being bound to phosphate to make AMP, ADP, or ATP; it is bound with the Methionine (sulfur containing aminoacid; S-CH_3), so when methionine is linked to adenosine the compound is called S - Adenosyl Methionine; it is named so because the linkage is done through the sulfur atom.

* Many methylation reactions in the body occur by transfer of methyl group from this active donor of methyl groups.

* What is unique about SAM, which made it a good methyl donor?
(S) Atom is attached by 3 bonds (usually attaches 2 bonds); this makes the molecule unstable so the transfer of methyl group will be easy.
After transferring of three CH3 group to phosphatidyl ethanolamine to make phosphatidyl choline, S- Adenosyl Homocysteine will remain (Homocysteine is similar to Cysteine but with addition CH_2).
We will take this reaction again in the metabolism of aminoacids.

This figure from the book summarizes the reactions we took



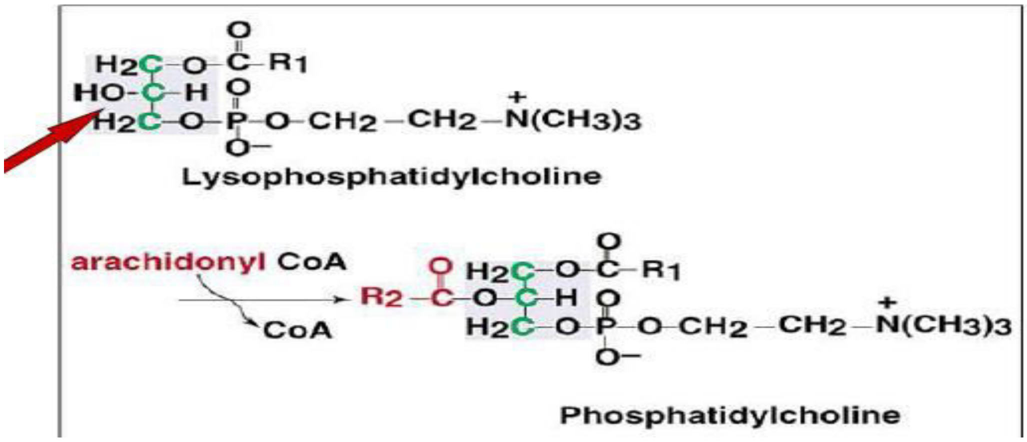
Remodeling of phospholipids:

Changing of fatty acid.
* one of its purpose is to modulate the fluidity of membrane by removing saturated fatty acid and adding unsaturated one for example .

*The fatty acid that's usually change is the one that's found at position #2

- look at the structure of Lysophosphatidylcholine , this is phosphotidyl choline that has lost Fatty acid at carbon #2 , it is a product of phospholipase A2 and a substrate of phospholipase B.

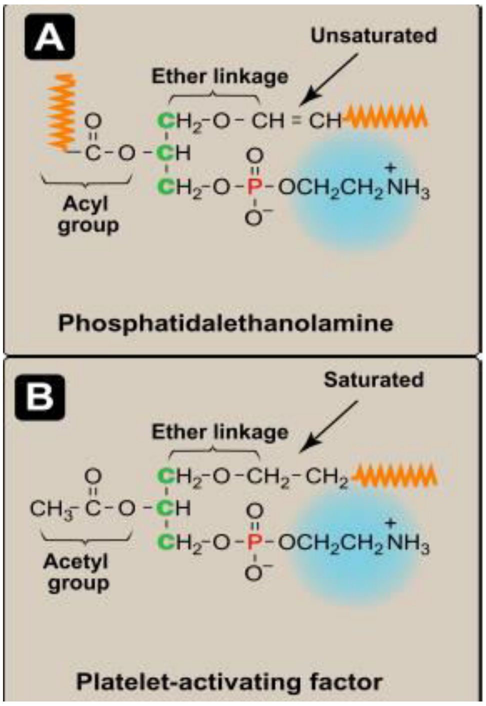
- This can accept now new fatty acid; ex: arachidinoic acid that is linked to coenzyme A to produce phosphatidylcholine.



Look at these structures :

A) Phosphatidalethanolamine: It is a phospholipid but it has ether bond instead of ester bond or carboxyl bond.
this makes the phospholipid more resistant to hydrolysis,

found in some phospholipids of the membrane of mitochondria for example .
This type of phospholipids is called; ether-glycerophospholipids.



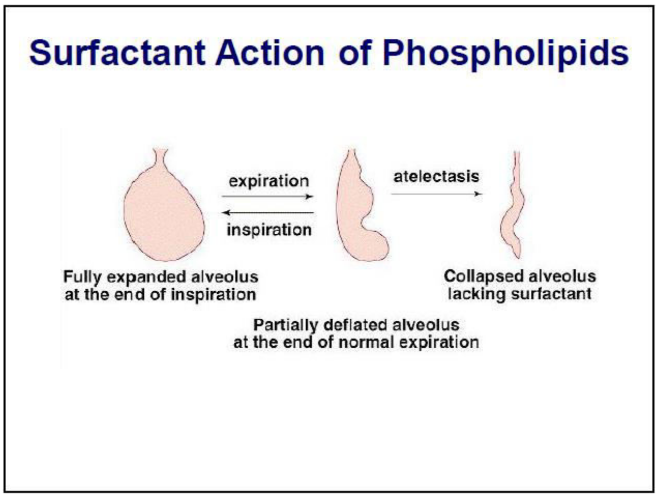
<u>B) platelet activating factor .</u>
This is again an ether-phospholipid (ether bond)
It is characterized by presence of acetic acid (acetyl group)
at carbon #2; it is known as platelet activating factor.
So phospholipids in addition to being membrane components can be like signal molecules (hormones) that act on platelets.

Surfactant action of phospholipids:

-Surfactant : surface tension lowering agent = reduce the surface tension.

Surface tension :
when we put drop of water on a glass plate, the drop of water will not spread all over the surface, it will form a droplet that you will see by your naked eyes due to presence of large number of **hydrogen bonds** connecting water molecules together = high surface tension , but another molecules like acetone, ethanol (alcohol) or benzene spread on plate of glass because of lower surface tension & less hydrogen bonding .

** This function is important in the lung
the functional unite there is alveolus, **it will be inflated in the inspiration and partially deflated in expiration, the alveoli will not collapse when the oxygen exits of them** due to the presence of surfactant because there is a water layer covering the cells of alveoli without surface tension..

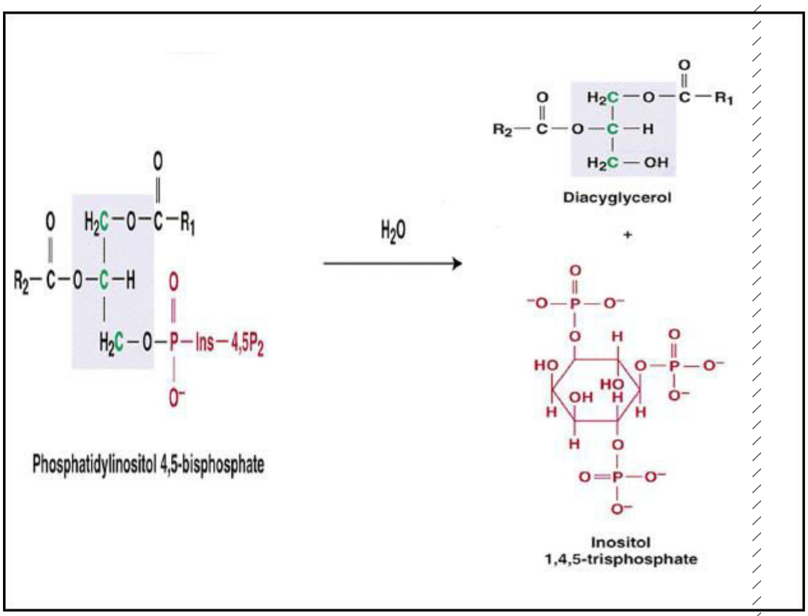


** if the surfactant is not present small water molecules will bring the wall of the alveoli together due to the surface tension = totally collapsed >>> inspiration become so difficult / problems in respiration .

** The synthesis of the phospholipids that lower the surface tension starts at the late stage of pregnancy (in the last stage of fetal life), if fetus is born premature >> presence of surfactant is not enough >> suffering of respiratory problems of new born (difficulty in breathing).
When delivery is suspected as premature (premature labor , before 30-32 weeks of gestation) , physicians usually inject corticosteroids to enhance the synthesis of surfactants.

Another function of phospholipids is **:**

Source of single molecules (2ndary messengers) .



-phosphatidylinositol: phospholipid; two fatty acids and glycerol connected to inositol with two addition phosphate group on carbon atoms #4&5 so it is called phosphatidylinositol 4,5-bisphosphate.
-is found in the interior leaflet of plasma membrane and by the action of phospholipase C that hydrolyzes the ester bond between glycerol and phosphate we get DAG & inositol 1,4,5 trisphosphate ,

This happens upon binding of some hormones to cell surface receptors >> stimulate phospholipase C2 to produce these products; the action of these is to stimulate protein kinase C so they are signal molecules that tell the cells that there are hormones outside upon binding

the last function:
to a protein or carbohydrates with the membrane (it can act to anchor the proteins to the membrane)

This is phosphatidalinositol connected to some carbohydrates, oligosaccharides, ethanolamine, glucose then it is connected to a protein which is an extracellular enzyme that is covalently bound to the membrane of the cell so the function of the phospholipid is to anchor proteins (The doctor was explaining this about a slide but we did not find it on the slides given to us).

. **SO the main function of phospholipids are :**

1) membrane components .
2) emulsification >> micelles formation .
3) signal molecule (platelet activating factor) ".
4) Surfactant agent .
5) a source of single molecules (secondary messengers).
6) to link protein or carbohydrates with the membrane .

بضع دقائق من وقتك , ارفع كفيك للسماء ادع الله لنفسك و ادعوه لأمتك , ادعوه لأناس بيننا يتألمون لكن بصمت يا رب أعنا ..

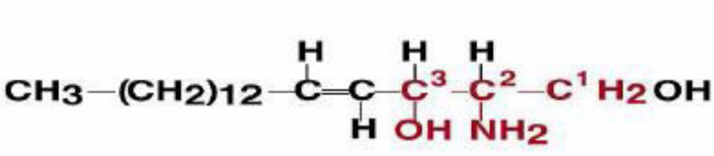
Metabolism of Sphingolipids

Sphingophospholipids

Glycosphingolipids

The thing that is used to distinguish sphingolipids from glycerophospholipids is the presence of Sphingosine while glycerol is present in glycerophospholipid.

All sphingolipids contain sphingosine = amino alcohol
They can be Sphingophospholipids or Glycosphingolipids.
- look at the structure of sphingosine , you should be able to recognize it; understanding the structure gives you many information about the molecule.
-Hydroxyl group at C#1 ,amino group at C#2 , hydroxyl group at C#3 .
- Long hydrocarbon chain; 18 Carbon atoms.

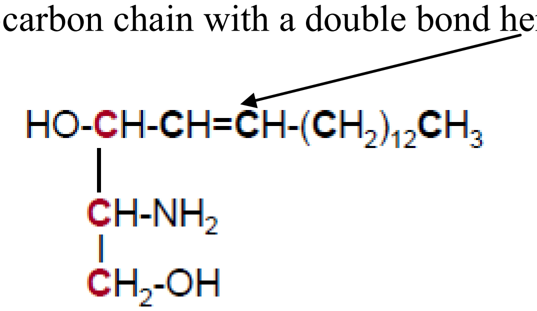


Sphingosine

- there is some similarity with glycerol , hydroxyl groups at C #1&3 but carbon #2 in sphingosine has amino group while in glycerol it has hydroxyl group.

Glycerol

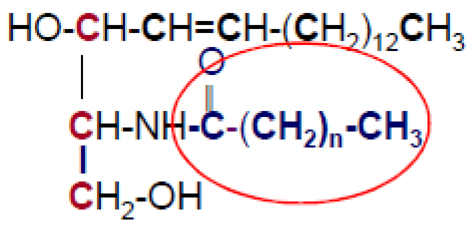
You can draw sphingosine in this shape; you can find that it could be like a glycerol connected to a long hydrocarbon chain with a double bond here.



Ceramide :

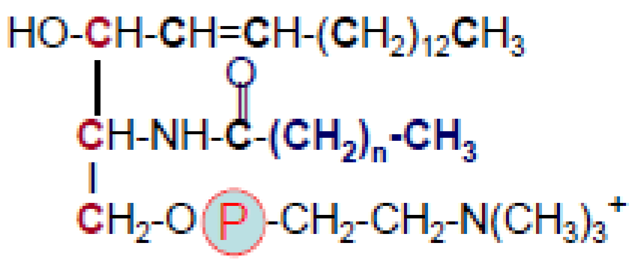
Fatty acid joined to sphingosine at amino group forming amide bond. So the name Ceramide tells that it contains an amide bond.

amide bond: means that there are amine with fatty or carboxylic acid.



Ceramide is similar to DAG but thea fatty acid at carbon #1 is replaced by long hydrocarbon chain.

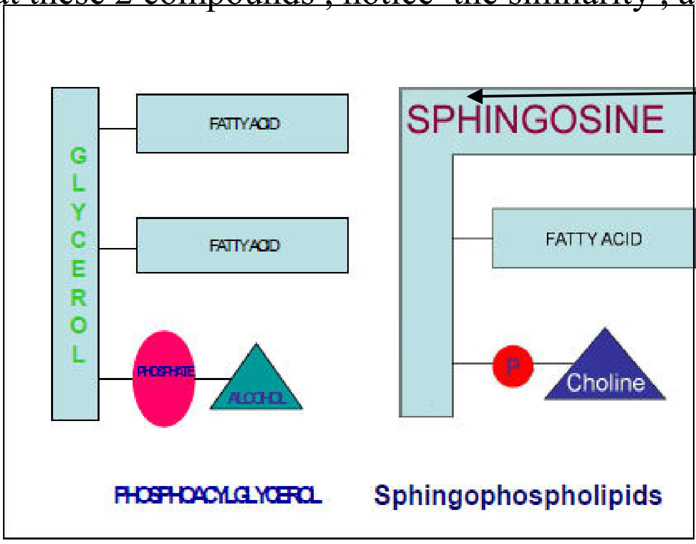
Sphingomyelin: is phosphocholine ester of Ceramide



Sphingosine + Fatty acid at the amino group = ceramide
Ceramide + phosphorylcholine = sphingomyelin

Written by Isra'a Abu Haneieh

Look at these 2 compounds , notice the similarity , and recognize the differences …



There is no ester bond here. Here the fatty acid is replaced by long hydrocarbon chain in the same molecule.

*** phosphoacylglycerol :**

- glycerol esterified to two fattay acids , phosphate and alcohol …

*** sphingophospholipid :**

- sphingosine esterified to 1 fatty acid , phosphate and choline …

- it looks like that the 1st fatty acid of phosphoacylglycerol is replaced by long H-C chain in sphingosine .

*** space filling modeles of phosphatidyl choline and sphingomyelin showing the similarity ..:** they are very much similar together in space filling model.

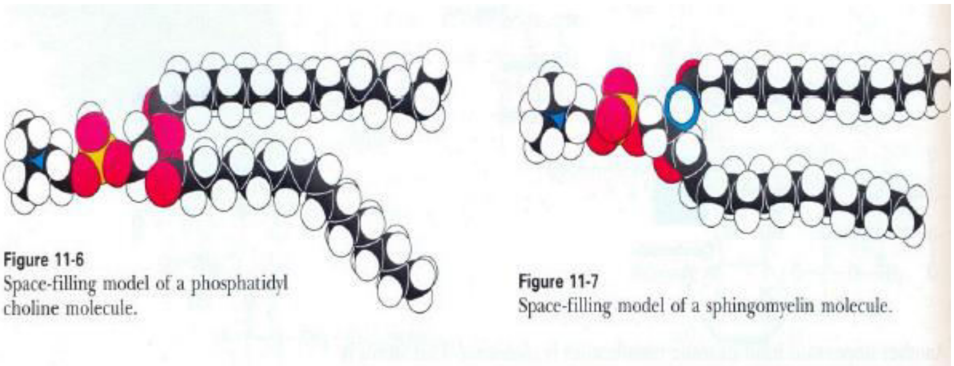


Figure 11-6
Space-filling model of a phosphatidyl choline molecule.

Figure 11-7
Space-filling model of a sphingomyelin molecule.

- space filling modele is important because it reflects some of the molecule properties (always there is a relationship between the function and structure; any structure can give you details about the function).

- both are membrane components.

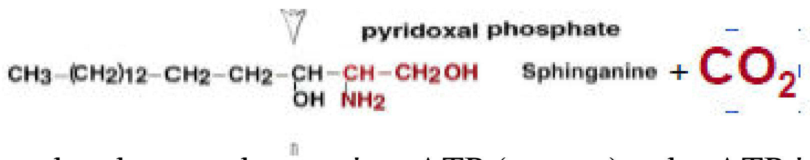
- all plasma membranes and all our cells have sphingomyeline, mainly in myeline sheaths and in shwan cells that wrap around the axon of neurons, if myeline is lost from some nerves or neurons >> multiplesclerosis التصلب المتعدد أو التصلب اللويحي.

<u>* Synthesis of sphingomyelin and sphingolipids in general:</u>

1)

Here you have Palmitic acid connected to Coenzyme A this active form of Palmatic acid is called Palmitoyl CoA + and here you have the amino acid L-serine

Condensed together with lose of CO2 , producing sphinganine (dihydrosphingosine)



- Alway joining two molecules together equires ATP (energy); why ATP is not required?

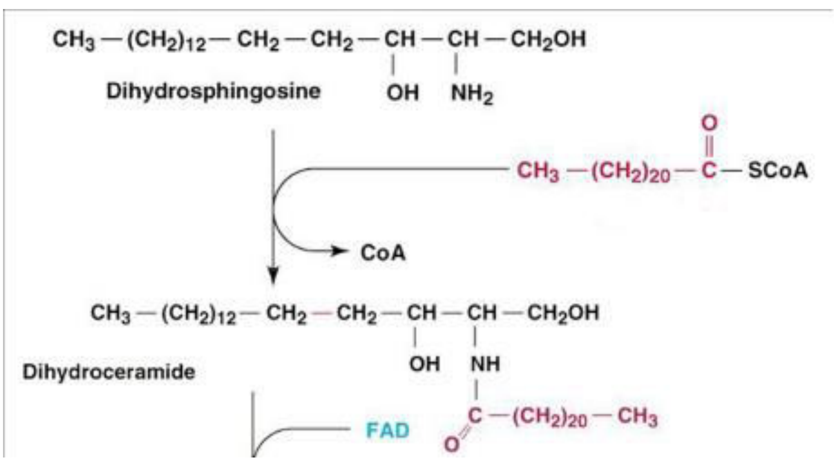
1- Because there is breaking of high energy bond (S~CoA)

2- releasing of CO2 (decarboxylation usually make the rxn irreversible)

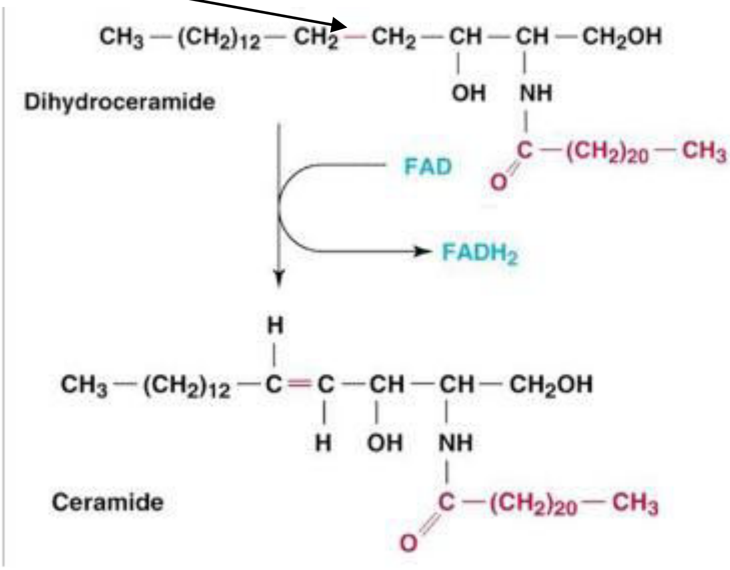
2) Dihydrosphingosine accept F.A from acyl-CoA (usually is one of the very long fatty acids that are found in CNS) **producing Dihydroceramide** (no double bond)

- how many carbons are in this Fatty acid ??

22 carbon atoms = very long H-C chain .

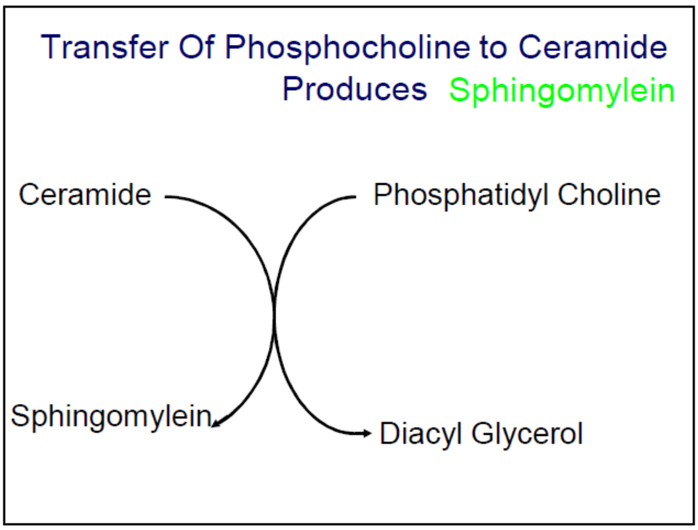


3) Dihydroceramide is converted to ceramide by introduction of double bond here into dihydrosphingosine; Ceramide is produced (with double bond).

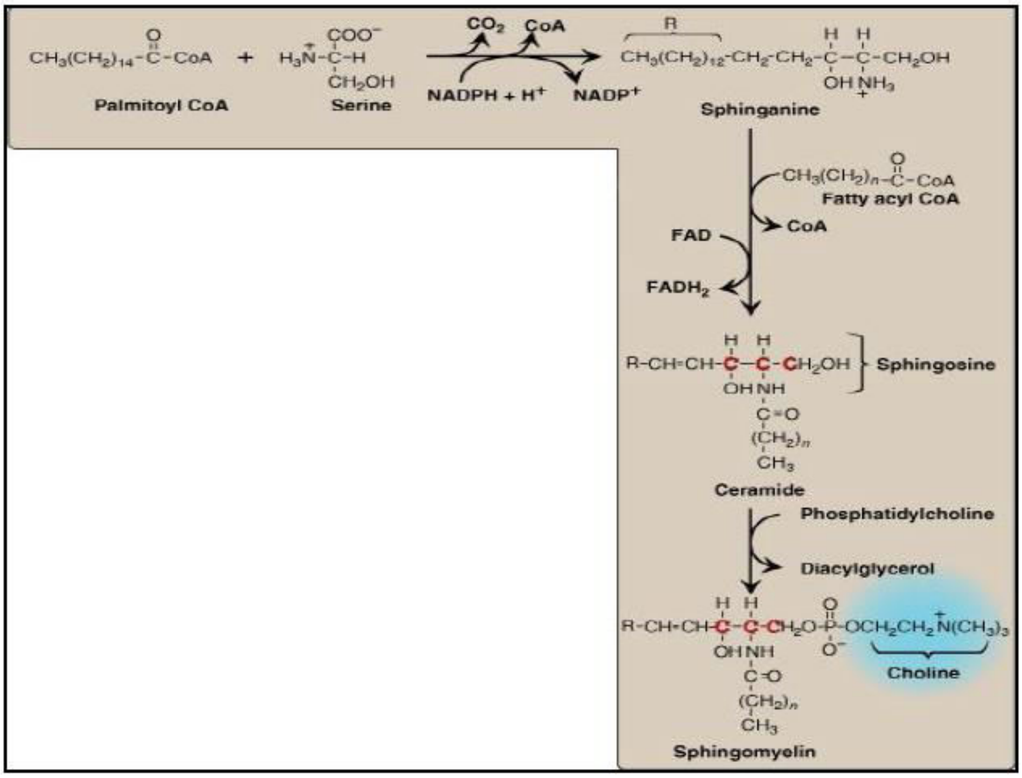


4) Transfer of phosphocholine to Ceramide produce sphingomylein.

When phosphatidylcholine loses phosphorylcholine and gives it to the ceramide to convert it to sphingomylein, it releases DAG. If you understand the structures and the components, you will know the products without the need to memorize them.
In the incomplete/makeup exam this question will come:
Ceramide with phosphotidylcholine produce?? DAG and Sphingomylein.



This summary map is from the book: Structures are not required for their sake but for helping you to understand.



We have finished now from sphingophospholipids (caontain phosphate).

<u>Glycolipids:</u>

- Dont have phosphate .

- formed by linking of one or more sugar to ceramide .

Ceramide + Glucose or Galactose **= Cerebroside .**

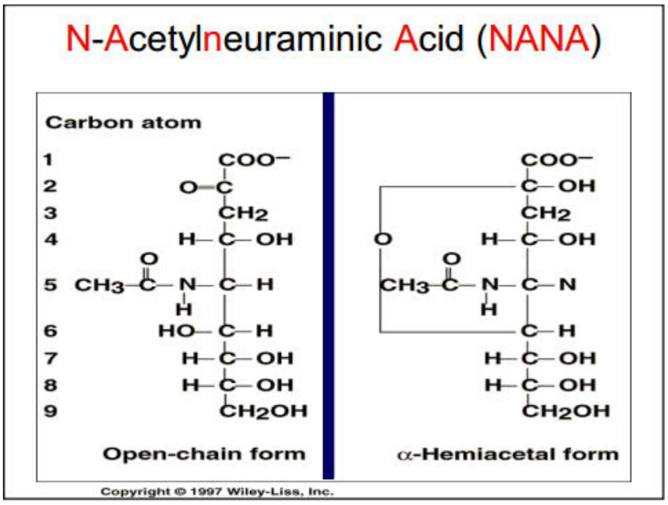
Ceramide + Oligosaccharide **= Globoside .**

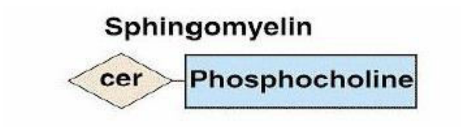
Ceramide + Oligosaccharide with NANA **= Ganglioside**

-oside = sugar connected by glycosidic bond to alcohol (sugars added to ceramide).

Some drugs are glycosides like digoxin which is used for the heart and aminoglycosides which are antibiotics.

- NANA : N-acytylneuraminic acid (Sialic acid / acidic sugar) it has a carboxyl group.

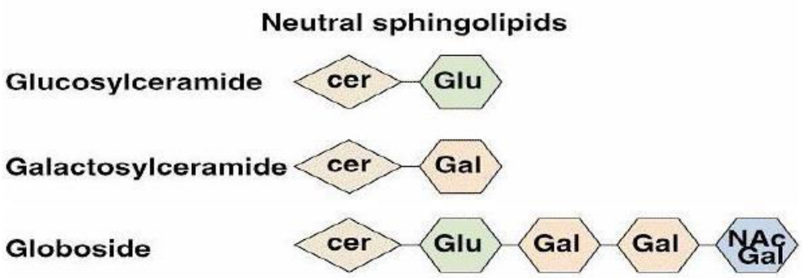




Ceramide with pohsphocholine = sphingomyleine.

* **natural sphingolipids :** no negative charge; they don't have phosphate or acidic sugars

they have carbohydrates:



* when we add sulfate **>> acidsphingolipid** (presence os sulfate gives it a negative charge**).**

* if there is NANA with oligosaccharide **>>Ganglioside .**

- You are not required to know the sequence,
 just know that there is NANA in each of these.

- GM ; G = ganglioside... M = mono NANA