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carbohydratesisomersketone starchlipidproteinamine

Biochemistry 2

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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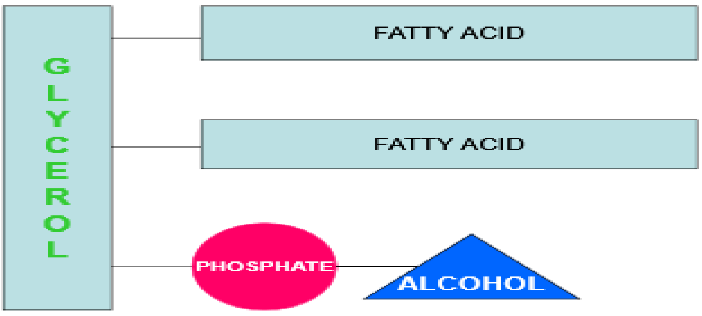
In this lecture we'll talk about the biosynthesis of glycerophospholipids (phoshoglycerides , phosphoacylglycerol), I'll try to make it full of fun.so, enjoy ☺

❖ First, let's view the constituents of **phospholipids** (phosphoacylglycerols):



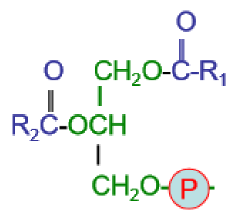
PHOSPHOACYLGLYCEROL

The components of **phosphoacylglycerol** are:

- glycerol
- 2 fatty acids
- Phosphate
- An alcohol

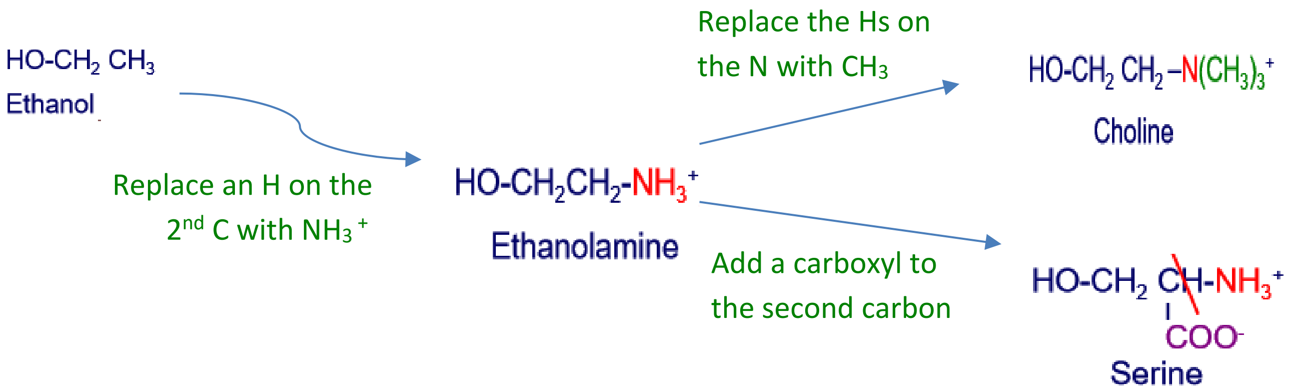
⇒Removal of the alcohol gives us a compound known as phosphatidic acid

❖ Phosphatidic acid is the parent compound of the different glycerophospholipids and also TAGs.

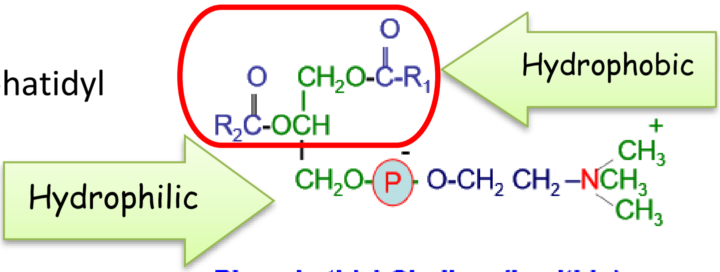

Phosphatidic Acid

- Its ionized form is called **phosphatidate**
- It can form **ester bonds** with alcohols to give different compounds. These alcohols can be either:
  - Amino alcohols: serine, ethanolamine, choline (-ine from amine)
  - Polyhydroxy alcohols: glycerol, inositol.
- The phosphate bonded to the alcohol is then called phosphatidyl- alcohol name (e.g. phosphatidyl choline)

❖ The structures of these glycerophospholipids are related to each other. This DOESN'T necessarily mean that they're converted to each other by modification in our bodies.



❖ Notice that all of these amino alcohols are positively charged (serine has both negative and positive charges). When they bond the **phosphatidic acid** (has a negative phosphate), they form amphipathic compounds that have both hydrophilic and hydrophobic sides.



Phosphatidyl Choline (Lecithin)

- For example here, the phosphatidyl choline.
- Phosphatidyl choline has a positively charged choline group attached to the negatively charged phosphate and 2 long hydrocarbon chains .
- Phosphatidyl choline is also called lecithin.

❖ This is a space filling model showing the amphipathy of phospholipids which makes it possible for them to form micelles (when we dissolve them in water), lipid bilayers or liposomes. (pictures are ordered like the names)

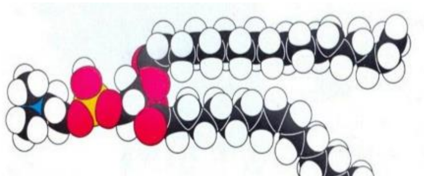
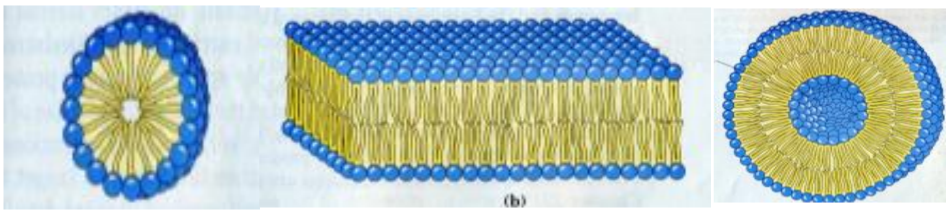


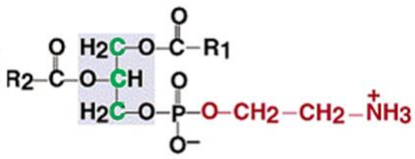
Figure 11-6
Space-filling model of a phosphatidyl choline molecule.



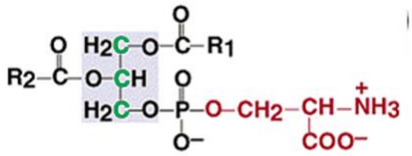
❖ Micelles are balls that have a hydrophilic surface and a hydrophobic center.
- If we mix oil with water, it'll TOTALLY separate. However, if we add an amphipathic substance like lecithin to the mixture, the oil will get into the micelles. Thus, lecithin solubilizes the TAG in water in a process called emulsification
- This will make the mixture **turbid**, because there are tiny balls of oil floating all over in the water which cause distortion of the light when it passes by it. The mixture is then called emulsion (مستحلب).
- So lecithin is an emulsifying agent, and a lipid bilayer component.

❖ We know that phospholipids are the main components of cellular membranes, but **phosphatidyl choline** is the main one of these.

- Phosphatidyl ethanolamine and phosphatidyl serine are the same as choline with polar heads and nonpolar sides.

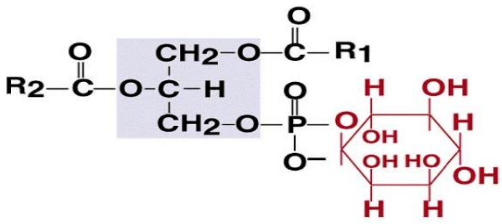


Phosphatidyl ethanolamine

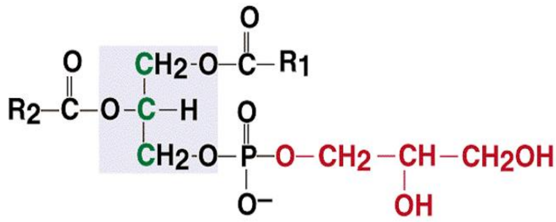


Phosphatidyl serine

- Phosphatidyl inositol has a polar head, but has no positive charge because of the lack of the amine. Also, phosphatidyl glycerol as well.



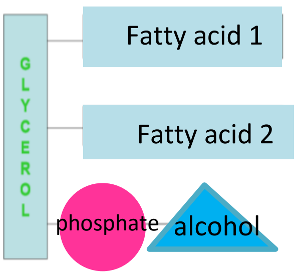
Phosphatidylinositol



Phosphatidylglycerol

Degradation of phospholipids:

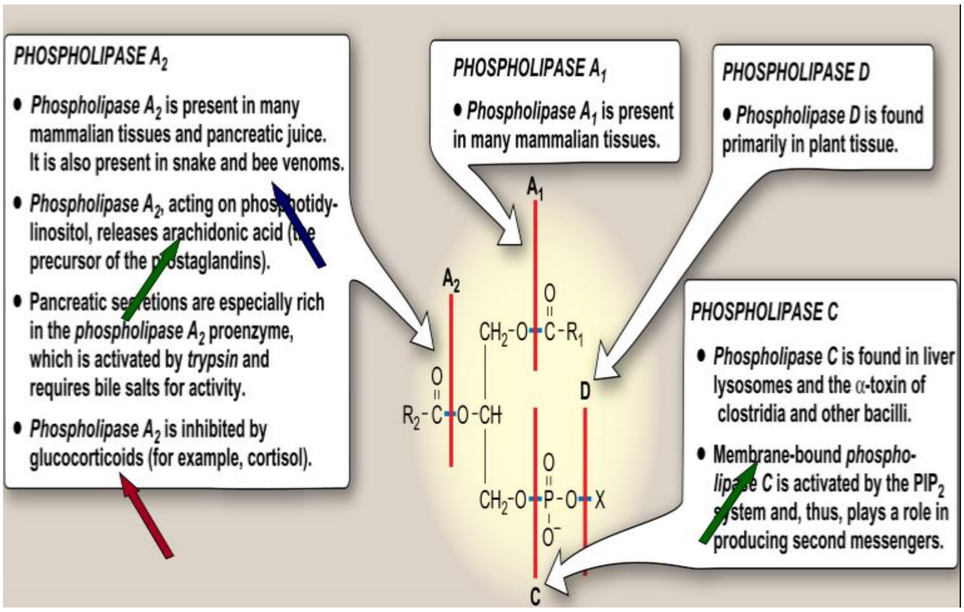
- The molecule of phospholipids has **4 ester bonds** and is made of **five components**.



  - To degrade an ester bond we need enzymes called phospholipases.
    - Phospholipase A1 → first ester bond between **Glycerol and 1st FA.**
    - Phospholipase A2 → breaks ester between 2nd FA and glycerol.
    - Phospholipase C → breaks bond between **glycerol and phosphate.**
    - Phospholipase D → breaks bond between phosphate and alcohol

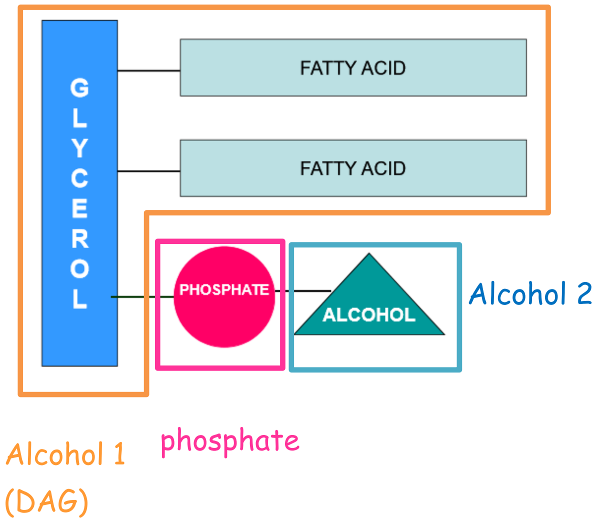
- phospholipase A2 produces lysophosphatidylcholine, if the starting compound was phosphatidyl choline. (-lyso because it resulted from lysis of the plasma membrane).
  - Phospholipase B acts on lysophosphatidylcholine to remove the other FA. It actually works after the action of either A1 or A2. However, A1 and A2 don't work after each other.
- Phospholipase A2 is present in snakes' and bees' venom. Remember in inflammation how phospholipases are inflammatory mediators because they release arachidonic acid? Well, this is what their venom does. It inflames!

Extra (interesting) information about phospholipases (focus on A2):



Biosynthesis of phospholipids:

- We already discussed the structure of glycerophospholipids and how phosphatidic acid is the first intermediate in their synthesis. Let's have a different look at the structure and components:



The main principle of glycerophospholipids' synthesis is the **transfer** of a phosphorylated activated alcohol to the other alcohol.

This can be done in two possible strategies.

1st Transfer ~(Phosphate-Alcohol1) to Alcohol2

or

'Phosphorylated alcohol''

2nd Transfer ~(Phosphate-Alcohol2) to Alcohol1

How does it work?

- First, **formation of the activated carrier** by the transfer of phosphorylated alcohol to CTP. The **goal of activation** is to create a high energy bond that'll produce a lot of energy when it breaks.

❖ The **phosphorylated alcohol** is added to the first phosphate of a CTP molecule (it binds to the first phosphate), **displacing a pyrophosphate in the process**. Producing CDP-alcohol (the active carrier of alcohol)

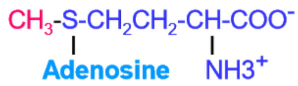
- Since in this reaction a high energy phosphodiester bond is broken and another high energy phosphodiester bond is formed. we expect ΔG to be nearly zero.
- To guarantee that the reaction goes in the forward direction, one of the products is **continuously removed** from the environment of the reaction.
- The product removed is pyrophosphate , by an enzyme called pyrophosphatase

Specifications:

- Synthesis of phosphatidyl inositol (DAG-phosphate-inositol):
  CDP-diacylglycerol (CMP-phosphatidic acid) can be transferred to **inositol** to produce **phosphatidyl inositol** and CMP. In this reaction, the **first strategy** is followed (refer back to the box in the previous page). By transferring the first alcohol (**diacylglycerol**) in its activated form (**CMP-phosphate-DAG**) to the second alcohol (**inositol**).
- Synthesis of phosphatidyl choline and phosphatidyl ethanolamine are similar:
  They follow the second strategy where CDP-alcohol2 is transferred to DAG producing phosphatidyl choline or phosphatidyl ethanolamine and CMP.
- Synthesis of phosphatidyl Serine:
  Serine is an **amino acid** and it has an **OH group in its side chain** making it an alcohol. It's synthesized by **exchanging ethanolamine** in phosphatidyl ethanolamine with **serine**.
  Despite serine's structural relativity to ethanolamine we CAN'T produce phosphatidyl serine by only carboxylating ethanolamine
  - However, we CAN produce **phosphatidyl ethanolamine** by decarboxylating phosphatidyl serine.
- How to get phosphatidyl choline from phosphatidyl ethanolamine?
  - **Phosphatidyl choline** is used in membranes and also in making acetylcholine which is used as a **neurotransmitter**.
  - The body can synthesize choline, but not in a sufficient amount. So we still need to acquire it from diet.

- To produce choline, we first convert **phosphatidyl ethanolamine** to **phosphatidyl choline** by transferring three methyl groups to the amine nitrogen.
- The donor of methyl groups is our dear old **SAM (S-adenosyl methionine).**

- SAM's structure:
  - Look at the name. **S-adenosyl** → an **adenosine** bound to the **S** of the amino acid **methionine**'s side chain. And a methyl attached to that same S atom (the methyl is an original part of the side chain).



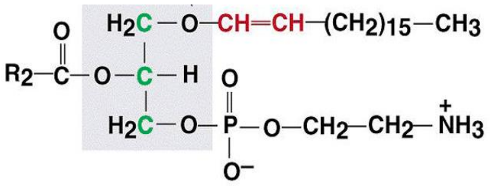
  - SAM is the active donor of methyl groups
    Active donor= high energy group carrier.
  - What makes SAM special in donating methyl groups is that it **has 3 groups attached to the sulfur** which we know is bivalent. (this is unstable)
  - After CH_3 is removed what remains of SAM is an AA called homocysteine (cysteine like) with an adenosine attached to the S still. (S-adenosyl homocysteine)
  - 3 SAMs are required to convert **phosphatidyl ethanolamine** to **phosphatidyl choline**.

Remodeling of phospholipids: changing the fatty acids:

- Normally the fatty acid in the middle is an unsaturated fatty acid.
  - Removal of the second fatty acid by phospholipase A2 produces **Lysophosphatidylcholine**.
  - The second FA can be replaced by arachidonic acid, and the donor of it is **Arachidonyl CoA.**

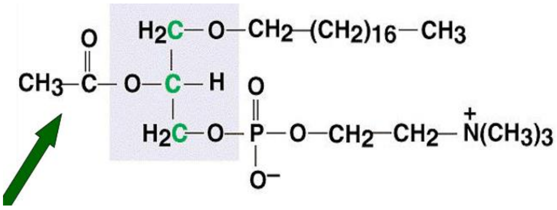
- Arachidonic acid in the plasma membrane serves as a precursor for prostaglandins.
  - Releasing arachidonic acid from plasma membrane is the starting reaction in the synthesis of **prostaglandins**.

Other phospholipids:



Ether glycerophospholipids

What's unique about this molecule is that it has **an ether bond** rather than an ester bond between the first fatty acid and glycerol, because there is an alkene between C1 and C2 instead of a carbonyl on C1. This bond CANNOT be hydrolysed by phospholipases (which are esterases)



Platelet-activating factor:

Here there's an ether bond with the first carbon and instead of an unsaturated fatty acid there's **an acetic acid on the second.**

It's a signal molecule produced by WBCs for platelet aggregation and inflammatory events.

Phosphatidylethanolamine (can be present with ether linkage instead of an ester linkage) and platelet-activating factor both have ether linkage.

Surfactant Action of phospholipids: (detergent action)

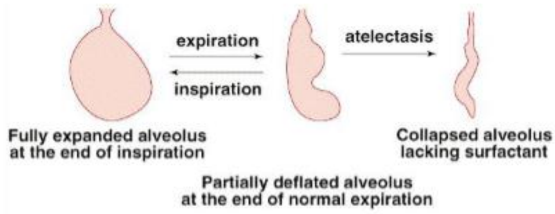
- They lower (break) the surface tension of water.
  - For example: if we have a droplet of water on a surface, it'll have a spherical shape. However, if we add ether, chloroform or acetone to that drop it'll **spread.**

The surfactant action of phospholipids is important in the lungs. How?

The main unit of lung function is called an **alveolus**. During respiration the air gets out and the **alveolus gets only partially deflated** due to some surfactant action that causes the spread of a thin layer of water all over inside the alveolus.

- Without this surfactant action, the water would tend to form a droplet; causing the collapse of the alveolus, this collapse would lead to **reinflation requiring more negative pressure to occur** (needs deeper, harder breaths).

So, surfactant action of phospholipids has a crucial role in normal lung function.



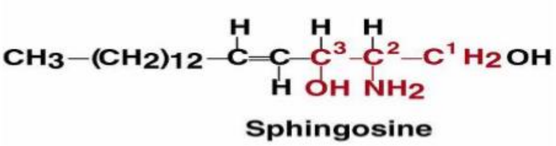
- At the 32^{nd} week of gestation, the fetus starts to synthesize this surfactant. Which is **dipalmitoyl lecithin** (a phospholipid with its 2 FAs being **palmitic acid)**

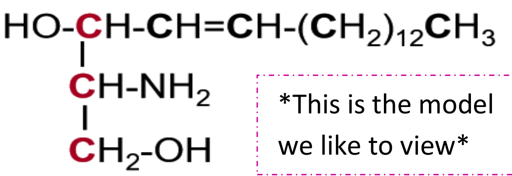
In preterm infants (born in the 7^{th} and 8^{th} months of gestation) the lung isn't perfectly formed yet, so the baby may face Respiratory Distress Syndrome.
When a doctor suspects preterm delivery, S/He would give **Glucocorticoids** to stimulate the synthesis of this surfactant. During life outside the womb, we produce it regularly.

Metabolism of sphingolipids:

- These molecules - unlike glycerophospholipids which contain glycerol- contain **sphingosine.**
- **They're divided into:**
    - Glycosphingolipids (they don't contain phosphate, they contain sugar)
    - Sphingophospholipids (they contain phosphate)

First, sphingosine:



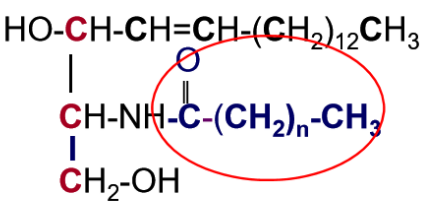


This is the model we like to view

It's a long amino-alcohol, formed with 18 carbons.

- C'1 has an OH group
- C'2 has an amine group (amino-alcohol)
- C'3 has an OH group.
- And it's connected to C'4 from the long carbon chain.

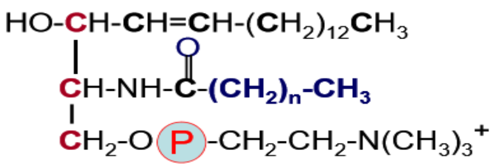
- It's very similar to mono acyl glycerol, in it's starting form.
    - However, sphingosine can bind a second FA on its second carbon by an amide bond. (it's a bond between an amine group and a carboxyl group)



This is ceramide:

Ceramide indicates the type of the bond connecting the fatty acid to the sphingosine (amide bond).

- If we add phosphocholine to **ceramide**, we'll have a new molecule called Sphingomyelin.



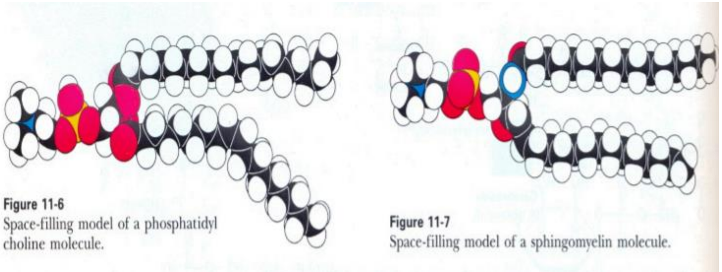
This is Sphingomyelin:

It's a phosphocholine added to ceramide.

Function of sphingolipids:

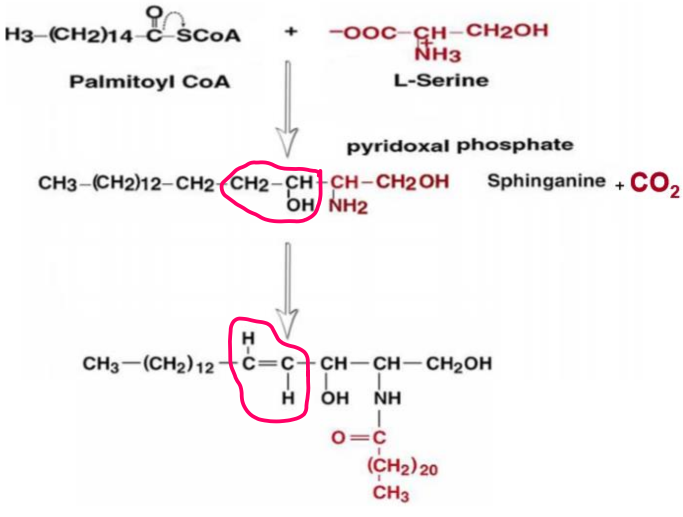
since their sructure has a great resemblence to PAGs (hydrocarbon chain & polar head) they're similar in function to them. So, they're **cell membrane components.**

- They can form micelles and lipid bilayers like PAGs.
- Sphingomyelin is present in all animal cells' membranes. However, they're very rich in **myelin sheath** of myelinated neurons.



Synthesis:

- Sphingosine comes from a condensation reaction between **serine** and **palmitic acid**.
  What drives this reaction in the forward direction are two things:
  1) the release of CO2 (decarboxylation)
  2) the cleavage of a thioester bond (of palmitoyl CoA. **The active donor of palmitic acid**)



After the reaction between serine and palmitoyl CoA, dihydrosphingosine is produced (notice the second formula, there's no double bond)

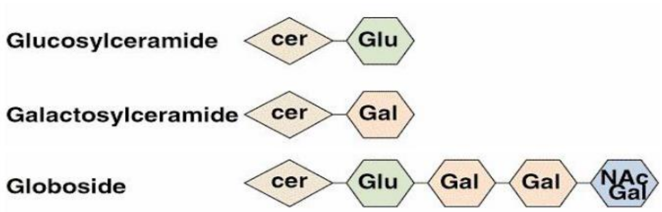
Then, fatty acid is added and the double bond is introduced (by dehydration)→ **ceramide** is formed.

Finally, it has 18 carbons:
3 serine + 16 palmitoyl - 1 CO2 =18

- Transfer of phosphocholine from phosphatidylcholine **to ceramide** produces sphingolmylein + DAG

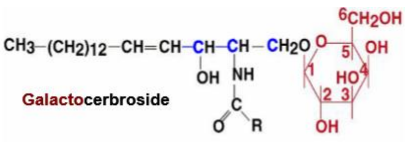
- Glycolipids (ceramide +sugar): first, neutral sphingolipids

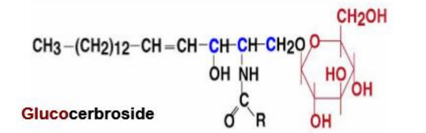
Glycolipids are formed by **linking one or more sugars to ceramide**
(there's NO phosphate in their structure)



- Whatever the length of the sugar. Sugar units are always added one at a time and by a **sugar specific enzyme**.
- -oside means sugar bound by a glycosidic bond to an alcohol.

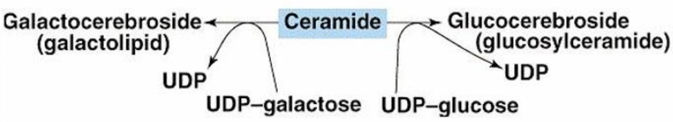
Cerebrosides – found especially in neuronal tissue. (ceramide linked to glucose or galactose)



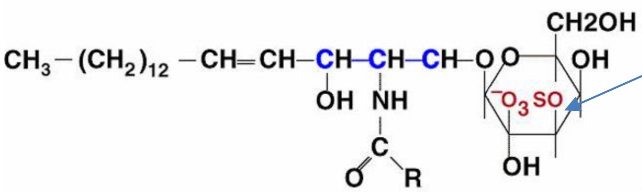


* Notice that, even though the difference between glucose and galactose is very mild (the orientation of OH on carbon 4), their presence gives different information and they're added by 2 different specific enzymes.

The activated donors of Glu and Gal are: UDP-Glucose and UDP-Galactose

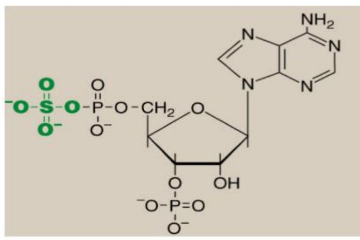


Transfer of a Sulfate Group to Galactocerbroside Produces an acid sphingolipid called Sulfogalatocerbroside (Sulfatide)



Notice the sulfate group.

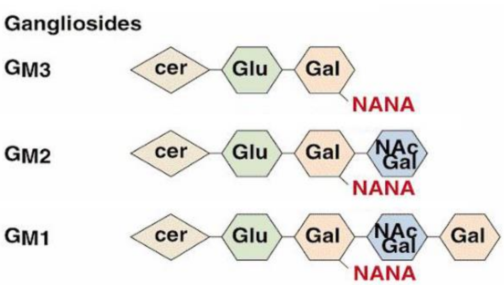
The active donor of sulfate is a molecule called PAPS



3 Phosphoadenosine 5 Phosphosulfate PAPS

Gangliosides: related to ganglion ☺

They contain longer sugar chains, each sugar is added SEPARATELY .



Activated donors are: UDP-Glucose, UDP-Galactose, UDP-N-Acetylgalctoseamine

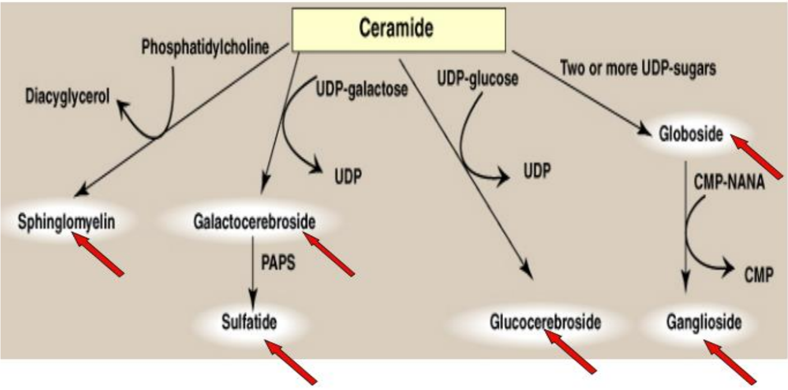
CMP-N-Acetylneuraminicacid

About NANA

It's a carbohydrate derivative. **An acid with 9 carbons**, found in the **gangliolipids**.

—————————————————

Summary:



- Sugars are there on the outer leaflet of cell surfaces to give **identity**, to differentiate, to receive and contact, to let viruses in. They're not just there for the sake of having a sugar, they're there in a carefully organized manner, and chosen to indicate certain information.

The ABO blood groups are dependent on glycolipids. group is information, it's identity.

Enzymes adding sugars are specific for **the sugar**, for **the substrate to which the sugar is added**, and for **the sequence**. the sequence is determined by many enzymes, each is specific for one sugar at a time.

Notes :-

- **Inositol** is composed of a 6 carbon ring with 6 OH groups.
- **Ethanolamine** is a primary amine**, choline** is quaternary and all of them are positively charged because of the presence of the basic amino group**.**
- **Amination (**adding an amino group) of ethanol **doesn't** lead to ethanolamine in our body
- **Phospholipases A1 and A2** can't work after each other, so if we want to hydrolyse the ester bond of the 1st FA we use A1 **or** A2 then we use B for the 2nd FA
- **Adenosine = adenine + ribose**

Good luck