◉Sheet ○Slides

Subject :	Glycophosphlipids
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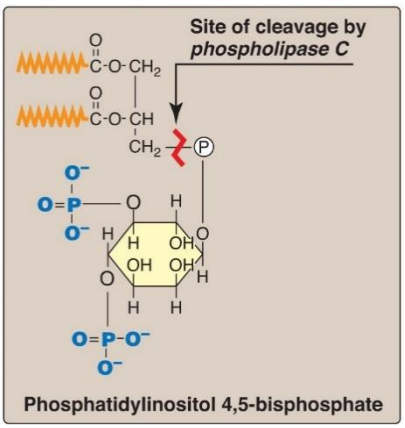
Number :	25

Functions of glycerophospholipids

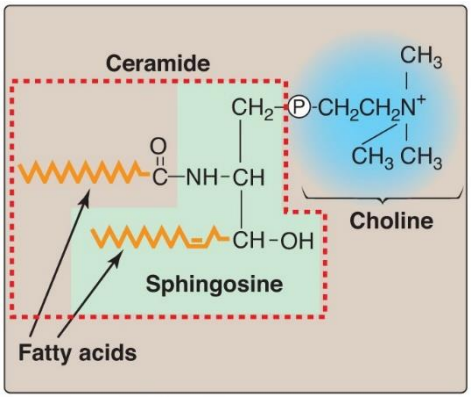
- **Emulsifying** agents.
- Major components of cell **membranes**.
- **Surfactant** action:
    - Surfactants are agents that lower the surface tension of water. Hydrogen bonds of water bring the water molecules together producing **surface tension**. If we put a drop of water on a glass plate, it forms a spherical shape, while if we put something that doesn't have surface tension, such as acetone or benzene, it spreads. The molecules of substances that have surface tension get close to each other and form droplets.
    - Surfactants are important in the lung. The smallest unit of the lung is the alveolus. At the end of respiration, alveoli are fully expanded. During expiration, the presence of surfactants allows the alveolus to remain **partially** deflated. Because of the presence of surfactants, water on the surface of the alveolus spreads and prevents the collapse of the alveolus. If the alveolus lacks surfactants (due to insufficiency in production or secretion), it will collapse, undergoing what is known as **atelectasis**. In newborns, this causes **respiratory distress**, and the newborn will have problems with respiration.
    - At the end of gestation, **pneumocytes** (alveolar cells) produce surfactants. Therefore, if the physician expects that the pregnant woman will deliver preterm, they will inject her with **glucocorticoids** that stimulate the production of surfactants.
    - The surfactant produced in alveoli is known as **dipalmitoylphosphatidylcholine** (DPPC or dipalmitoyl lecithin), which is composed of two palmitic acids and phosphatidylcholine. The presence of dipalmitoyl lecithin in the amniotic fluid indicates the maturity of the baby. This is done by measuring the ratio between DPPC to sphingomyelin (L/S ratio). If it was more than 2 then it is fully developed. This normally happens at the 32^{nd} week of development.

- Some phospholipids have **signaling** functions, such as platelet-activating factor.
    - The polar head group of phospholipids could be inositol, forming **phosphatidylinositol**. Addition of 2 phosphate groups to phosphatidylinositol gives **phosphatidylinositol 4,5-bisphosphate**. This phospholipid normally present in plasma membranes can undergo hydrolysis of the ester bond between glycerol and the phosphate group by **phospholipase C**. Phospholipase C is activated by certain signals, producing **1,2-diacylglycerol** (DAG) and **inositol triphosphate** (inositol 1,4,5-triphosphate, or IP3).DAG stays embedded in the membrane because it has the long hydrocarbon chains. These two molecules act as **2nd messengers**. Activation of *G protein* leads to activation of *phospholipase C*, producing DAG and IP3, *IP3* leads to the release of *calcium* from intracellular stores, calcium is going to activate *protein kinase C* to phosphorylate different targets depending on the signal that activated the pathway in the very beginning.



    - Another role for **phosphatidylinositol** is anchoring of peripheral membrane proteins. Peripheral membrane proteins need to be attached by a covalent bond, one of the ways of anchoring them is using the **GPI anchor**. GPI anchors are composed of phosphatidylinositol and another set of sugars that bind specifically to certain amino acids of peripheral membrane proteins. This allows free movement of the peripheral protein more than the integral membrane proteins.

Sphingolipids



Sphingolipids are either **Sphingophospholipids** or **glycosphingolipids**. Sphingophospholipids contain a phosphate group while glycosphingolipids don't. The backbone of sphingolipids is **sphingosine**, rather than glycerol.

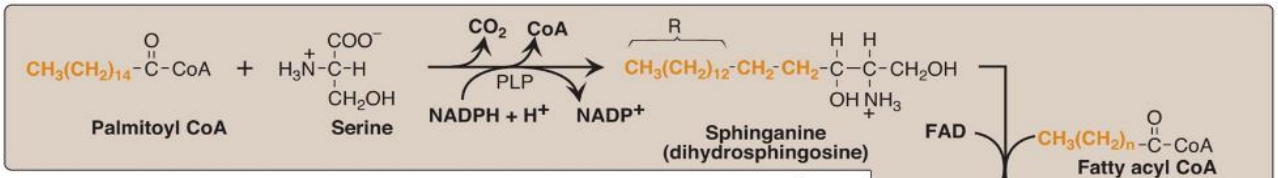
Sphingosine is an amino alcohol containing 18 carbon atoms (much larger than the glycerol molecule), 15 of which make up an unsaturated hydrocarbon chain connected to carbon #3 (the double bond is between carbon #4 and carbon #5). There is a hydroxyl group on carbon #1 and carbon #3, and an amino group on carbon #2. The structure of sphingosine resembles the structure of **monoacylglycerol**.

If we connect a fatty acid to the amino group on carbon #2 making an **amide bond**, the resulting molecule is called **ceramide**. The structure of ceramide resembles the structure of **diacylglycerol**.

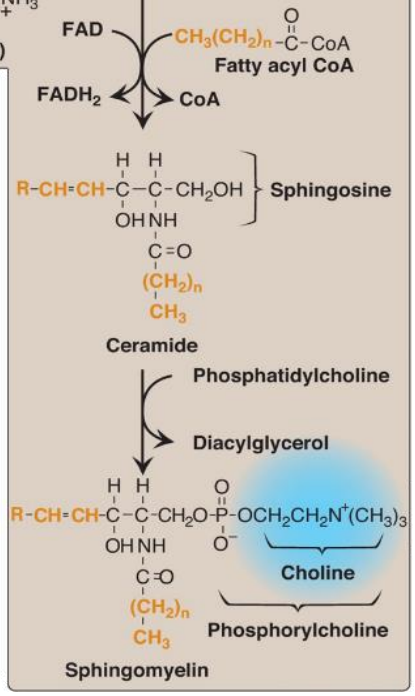
If we connect phosphocholine to the hydroxyl group on carbon #1, the resulting molecule is called **sphingomyelin**, and it is the only sphingolipid that has a phosphate group. Sphingomyelin is found in the myelin sheath of nerve fibers and animal cell membranes in general. The structure of sphingomyelin resembles the structure of phosphatidylcholine. They also have similar functions (constitute part of cell membranes).

Synthesis of sphingolipids

Palmitoyl CoA reacts with **serine** in a condensation reaction accompanied with the release of **CO2** (from decarboxylation of serine) producing a derivative of sphingosine called **sphinganine** (dihydrosphingosine). This condensation reaction requires the coenzyme **PLP** (most amino acid reactions require this coenzyme) and the reduction power of **NADPH**. The reaction is driven in the forward reaction by the release of CO2 and the hydrolysis of the high energy thioester bond between CoA and palmitic acid.

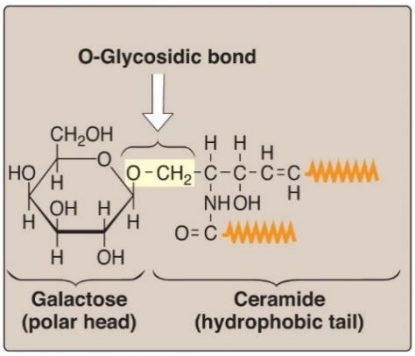


Next, an **acyl CoA** reacts with sphinganine producing **ceramide** (the parent compound of sphingolipids) and reducing FAD to **FADH2** (creating a double bond between carbon #4 and carbon #5).



The addition of different constituents to carbon #1 of ceramide produces different sphingolipids. For example, transferring phosphocholine to ceramide produces sphingomyelin. Phosphocholine isn't added directly, but instead, **phosphatidylcholine** reacts with **ceramide** producing **sphingomyelin** and **diacylglycerol**.

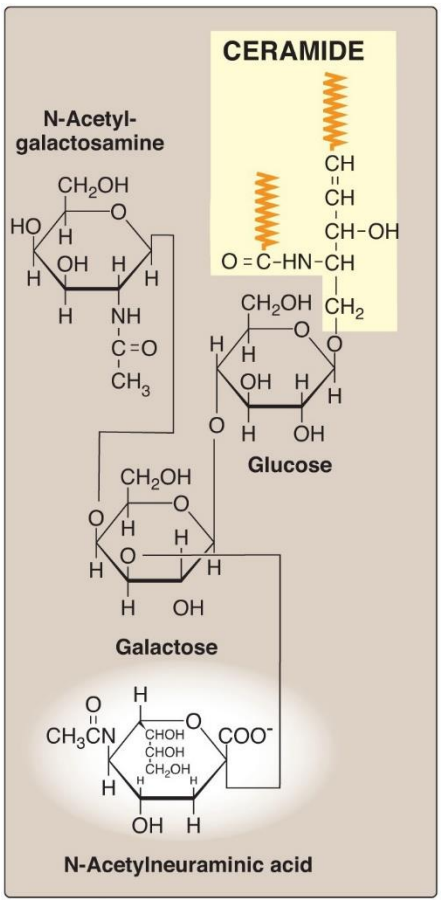
Glycosphingolipids are produced by linking one or more sugars to ceramide. Addition of glucose or galactose to ceramide produces **cerebrosides** (glucocerebroside or galactocerebroside). Addition of sulfate to galactose gives **sulfoglycosphingolipids** (sulfatides). Addition of oligosaccharides to ceramide **globosides**. Globosides containing **N-Acetylneuraminic acid** (NANA, or sialic acid) are called **gangliosides**. Gangliosides are memebrane components found on the outside of the cell membrane.



N-acetylneuraminic acid is a 9 carbon sugar connected to an acetyl group.

Sphingomyelin, cerebrosides, globosides are all **neutral** sphingolipids meaning they don't possess a charge on the head group. However, sulfatides contain a sulfate group connected to the galactose and are thus **charged** sphingolipids.

The figure to the right represent the ganglioside GM2. The subscript M, D or T indicates whether there is one (mono) , two (di) or three (tri) molecules of NANA. The number subscript refers the sequence of the sugars attached to the ceramide. The lower the number is, the longer the sequence will be (the reason will be explained later).



The active donor in glycosphingolipids synthesis is **UDP-sugar**. However, the active donor of N-Acetylneuraminic acid is **CMP-N-Acetylneuraminic acid**.

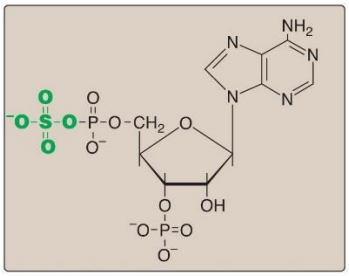
Ceramide + UDP-galactose → galactocerebroside + UDP

Ceramide + UDP-glucose → glucocerebroside + UDP

These reactions catalyzed by enzymes called **glycosyltransferases**. The enzyme which adds glucose is different from the one which adds galactose, so that each enzyme is specific for the type of sugar added.

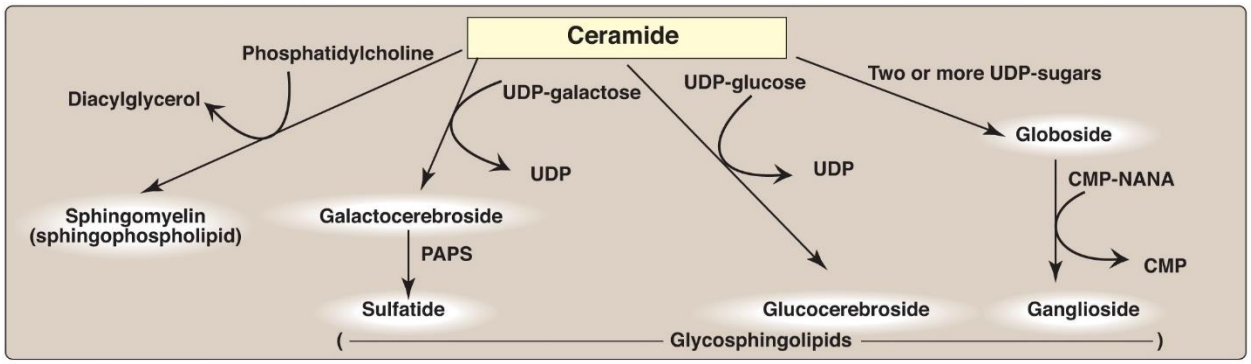
The sequence of sugars in glycolipids and glycoproteins carries important information, such as receptors, interaction with viruses or interaction with cells. For example, the difference between blood groups is the type of glycolipid.

Transfer of a sulfate group to galactocerebroside produces sulfogalactocerebroside. The donor of the sulfate group is **3'-phosphoadenosine-5'-phosphosulfate** (PAPS).

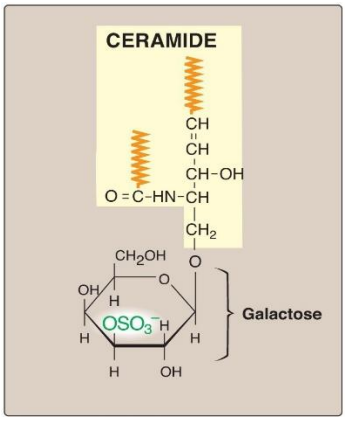


A deficiency in one of the enzymes required for the synthesis is not compatible with life.

The figure below summarizes the production of different types of sphingolipids.



Degradation of sphingolipids

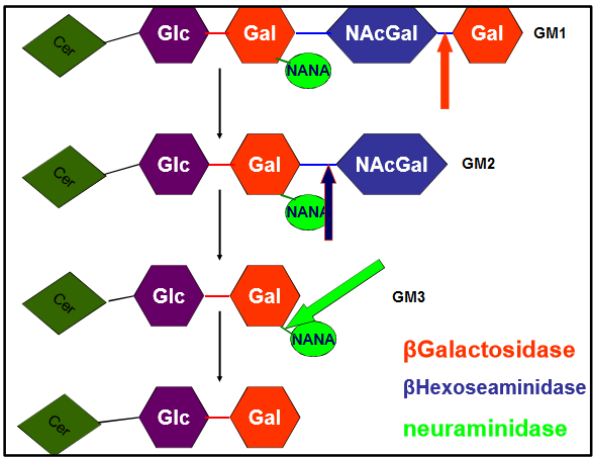


Degradation of sphingolipids doesn't happen for the purpose of getting energy, but for the **turnover** of cell membranes. All of the cell's constituents undergo turnover, so there is a balance between the synthesis and degradation.

Degradation occurs by hydrolytic enzymes (α-galactosidase, β-galactosidase, neuraminidase, hexosaminidase) that are specific for the sugar they hydrolyze.

The cell engulfs part of the membrane by endocytosis producing an endocytic vesicle. This endocytic vesicle fuses with a **lysosome** which contains the hydrolytic enzymes required for the degradation. These enzymes are firmly **bound** to the lysosomal membrane so as not to leave the lysosome and enter the cytosol. The pH inside the lysosome is 3.5-5.5, so the enzymes are only active inside the lysosome and are not active in the cytosol. This is important for regulation, to prevent the enzymes from degrading cell contents. Degradation occurs by a **stepwise** sequential process. The last sugar to be added in the synthesis is the first one to be degraded.

β-galactosidase hydrolyses the bond between galactose and the rest of the compound. After that **β-hexosaminidase** hydrolyzes the bond that connects N-acetylgalactosamine. **Neuraminidase** hydrolyzes the bond that connects NANA independent of its position. (whether it is terminal or not).



The number subscript is given according to the degradation pathway. The longer ganglioside comes first in the degradation pathway, so it's given the lower number.

Sphingolipidoses (lipid storage diseases)

It is accumulation of sphingolipids due to a deficiency in a lysosomal hydrolytic enzyme. Most of these diseases are **autosomal recessive** diseases. Autosomal as in related to autosomes (not the sex chromosomes). Recessive means that two copies of the defective gene must be present for the disease to develop. Enzyme deficiencies are usually recessive, because when one normal gene is present, 50% of the enzyme level is present which is in most cases sufficient because enzymes work at a fast rate, and degradation is a **slow** process.

Accumulation happens in lysosomes because hydrolysis happens there. Although the accumulation happens in all tissues, the **brain** is mainly affected because nervous tissues cannot regenerate. Also cells with no nuclei, like RBCs, are badly affected. The extent of deficiency is the same in different tissues, so a biopsy from any tissue will give the same result.

Sphingomyelin is degraded to ceramide and phosphocholine by the action of **sphingomyelinase**. Ceramide is degraded by **ceramidase** giving sphingosine and a fatty acid. Examples on sphingolipidoses:

- **Tay-sachs disease** (common): accumulation of G_{M2} leads to blindness and seizures. This disease is seen in the Jewish population of the US (Ashkenazi Jews).
- **Gaucher disease** (most common): accumulation of glucocerebrosides.
- **Niemann-pick disease:** accumulation of sphingomyelin.