27

◉Sheet ○Slides

Done By

مُحَمَّد يُوسُف & Ahmad Attari

Contributed in the Scientific Correction

Abdallah Q& Razi

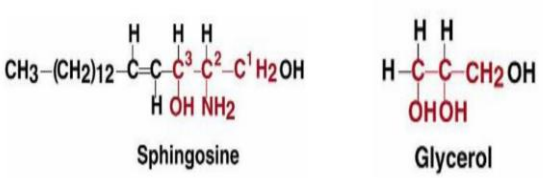
Contributed in the Grammatical Correction

Doctor

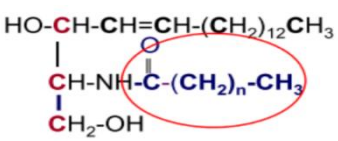
Faisal

Sphingophospolipids

- The backbone of sphingophospholipids is **sphingosine**, unlike glycerophospholipids with a glycerol as the backbone. Which 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 is attached to the backbone. The other long chain is part of the backbone (sphingosine) with no ester bonds involved.



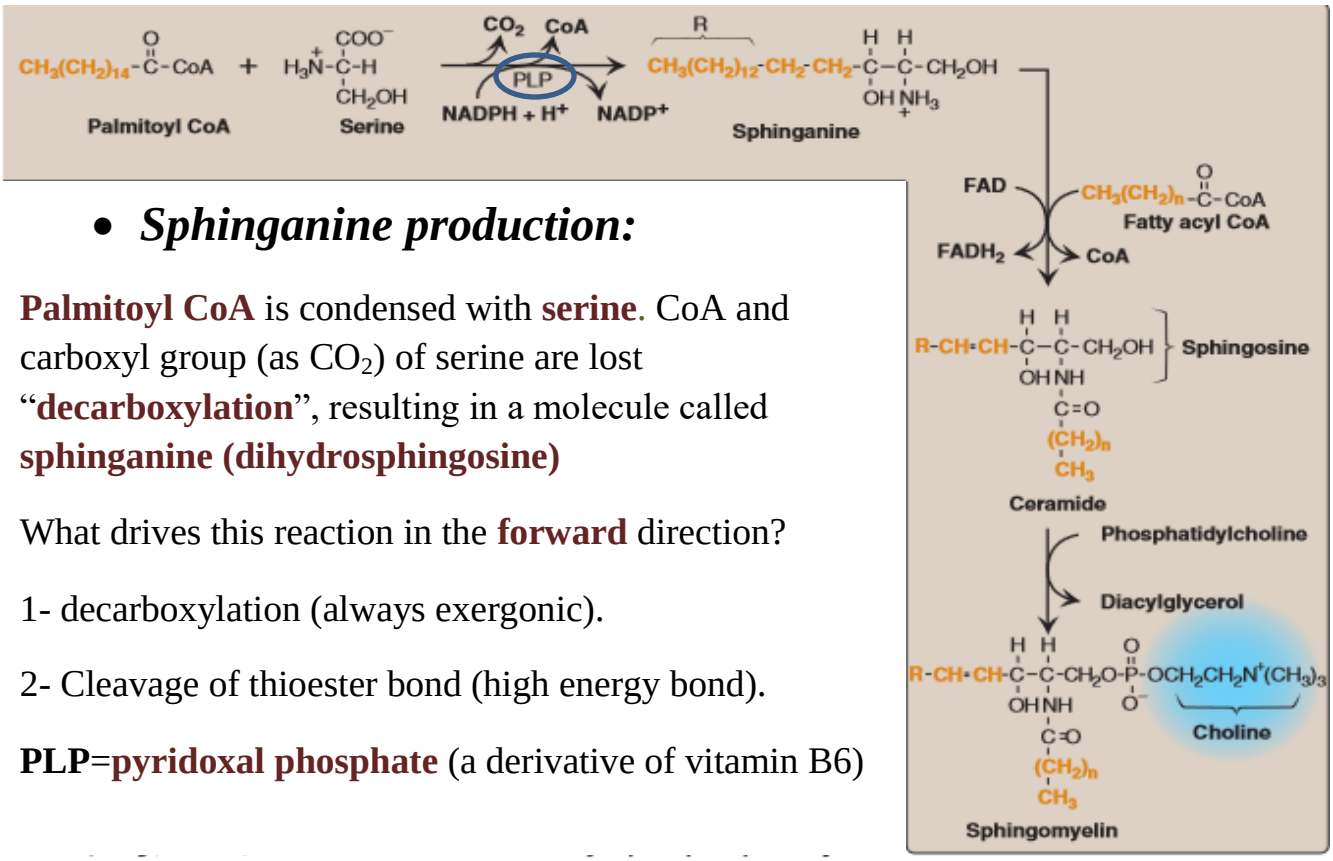
The 3 Functional groups on Sphingosine:

(-OH) on Carbon # 1 & 3

(-NH2) on Carbon #2

Synthesis of sphingolipids

This picture is an overview of the process:



- ***Sphinganine production:***

Palmitoyl CoA is condensed with **serine**. CoA and carboxyl group (as CO_2) of serine are lost "**decarboxylation**", resulting in a molecule called **sphinganine (dihydrosphingosine)**

What drives this reaction in the **forward** direction?

1- decarboxylation (always exergonic).

2- Cleavage of thioester bond (high energy bond).

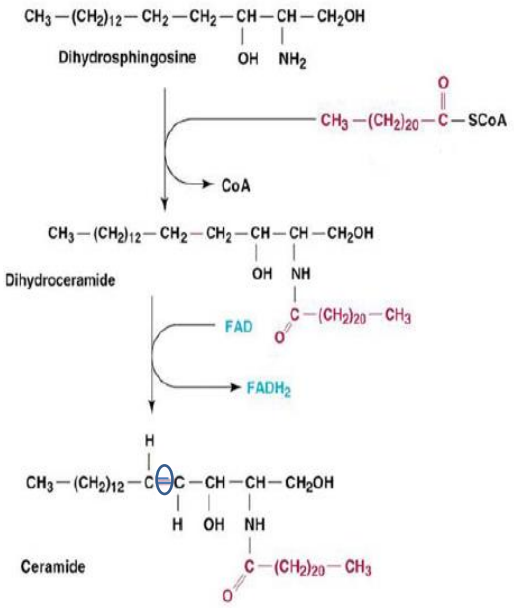
PLP=**pyridoxal phosphate** (a derivative of vitamin B6)

*By knowing that you start with palmitic acid and serine, you can predict the number of the carbons of sphingosine.

Palmitic acid (16 C) + serine (3 C) $\xrightarrow{CO_2}$ sphinganine (18 C)

Ceramide production:

Then **Dihydrosphingosine** reacts with **fatty acyl-CoA**, producing **dihydroceramide**. **The cleavage of the thioester bond** provides sufficient energy to drive this reaction (Condensation).



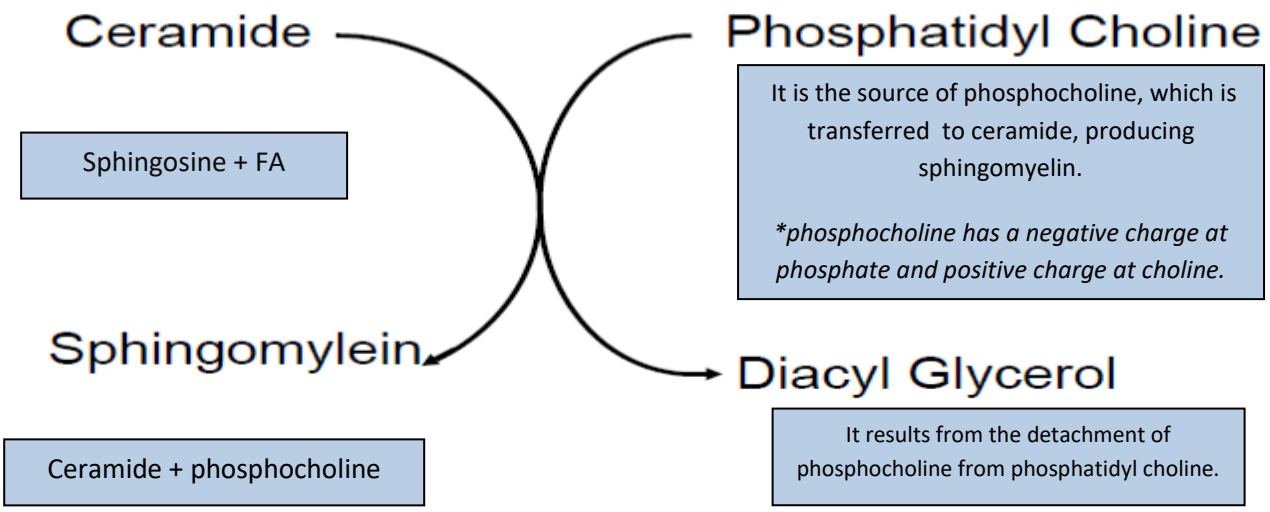
Note: the fatty acid is bound to the amino group at carbon 2 of the dihydrosphingosine by an amide bond.

- dihydroceramide is **Oxidized** (desaturated), producing **Ceramide** and **FADH2**.

Sphingomyelin production:

Phosphatidyl Choline + Ceramide $\longrightarrow$ Sphingomyelin + Diacyl Glycerol

Note that Sphingomyelin is found in the cell membranes especially in the CNS.



Glycolipids

- Glycolipids are formed by linking **one or more sugars** to **ceramide**.

- They are sphingolipids, but **NOT** phospholipids

- Glycolipids are **amphipathic** in nature; they have a nonpolar part (long hydrocarbon chain + fatty acid) and a polar part (sugars) in their structure.

- since Glycolipids are amphipathic, they are suitable to be membrane components (found on the outer leaflet of the plasma membrane).

■ Major examples on glycolipids:

1. Ceramide + Glucose or Galactose → Cerebroside

*abundant in the cerebrum (cerebrum is a large part of the brain containing the cerebral cortex).

2. Ceramide + Sulfated Galactose → Sulfoglycosphingolipids

*sulfate group is added after Galactose

3. Ceramide + Oligosaccharide → Globoside

*sugars are added one at a time

4. Ceramide + Oligosaccharide with NANA → Ganglioside.

N-Acetylneuraminic Acid (NANA):

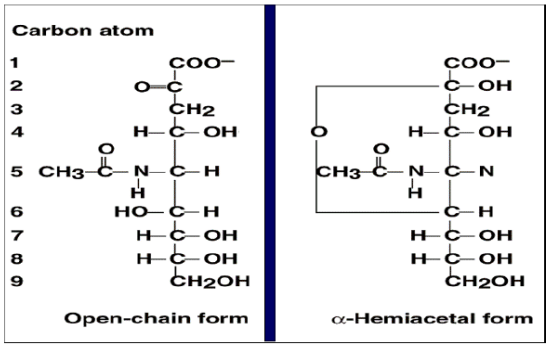
- 9 carbon sugar derivative.

- **acidic**; it has carboxylic group.

- **N**-Acytel refers to Acytel bound to Amino group. (Don't memorize the structure)

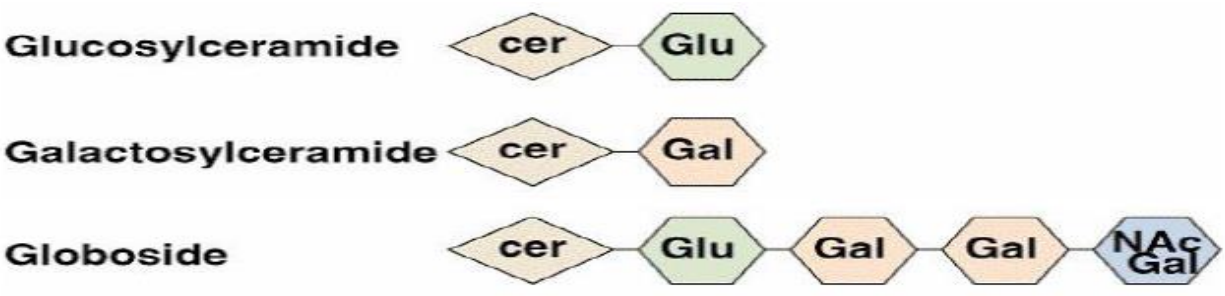
- It commonly known as **Sialic Acid**.

N-AcetylNeuraminic Acid (NANA)



- **Types of glycolipids:**

A. neutral sphingolipids: (*they are called "neutral", because carbohydrates don't carry positive or negative*, but they are polar, and have non polar regions as well (Amphipathic) Thus, could be found in membranes.



B. Acidic Sphingolipids:

1- Sulfatides:

These sulfoglycosphingolipids are sulfated Galactocerebrosides that are **negatively charged** at physiologic pH.

2- Gangliosides:

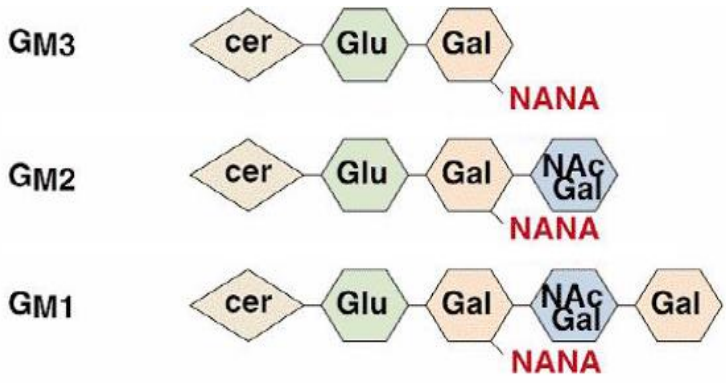
- Gangliosides are derivatives of ceramide oligosaccharide and contain one or more molecules NANA (from CMP-NANA).

- They are found primarily in the **ganglion cells of the CNS**, particularly at the **nerve endings**.

- **G** stands for **gangliosides**, **M** stands for **mono** sialic acid.

- If it is **Di** sialic acid, it is called **GD**. However, GM is the most common.

The designation GM3,GM2,GM1 is discussed later on.

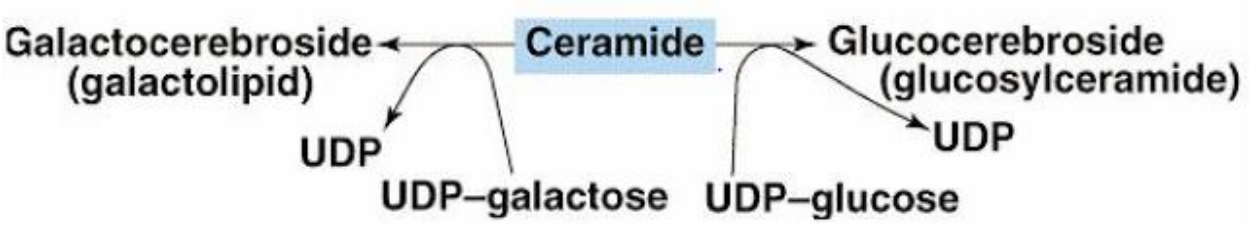


■ **To synthesize glycolipids, we need activated donors.**

After activating the sugar (shown below) a specific glycosyltransfer**ase** transfers the sugar to the acceptor (ceramide).

Activated Donors in Glycolipids Synthesis:

- UTP + Glucose→***UDP-Glucose***
- UTP + Galactose→***UDP-Galactose***
- UTP + N-Acetylgalctoseamine→ ***UDP-N-Acetylgalctoseamine***
- CTP +NANA→***CMP- N-Acetylneuraminic Acid***



- Galactose is transferred from UDP-Galactose to ceramide to form Galactocerebroside. UDP is liberated.

- **Galactosyltransferase** catalyze this reaction.

- Glucose is transferred from UDP-Glucose to ceramide to form Glucocerebroside. UDP is liberated.

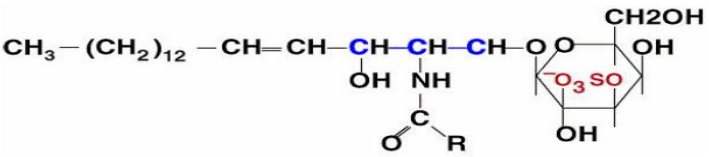
- **Glucosyltransferase** catalyze this reaction.

- Whether **glc.** or **gal**. is added to ceramide depends on the **presence** and **specificity** of the enzyme.

Note: notice that they just differ in OH position in the ring (glucose is below, galactose is above).

Note:The sequence of sugars is important, it gives some sort of identity to the cell, and gives the ability of some molecules to bind to the cell.

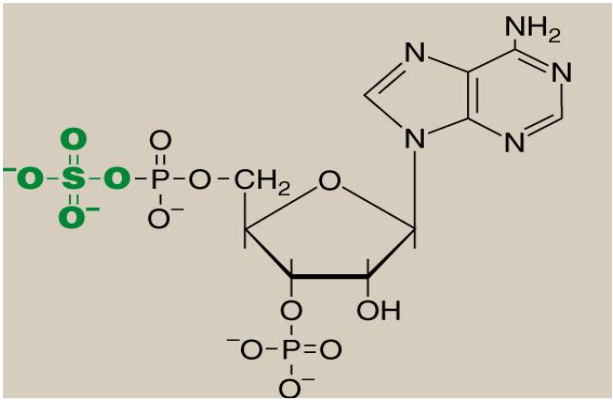
Transfer of sulfate group to Galactocerebroside produces Sulfogalactocerbroside (sulfatide)



*Sulfate group donor:

- Present in all reactions that involve adding sulfate groups.

- similar to ADP, but instead of a 2nd phosphate, there is a **sulfate** group



3Phosphoadenosine 5 Phosphosulfate PAPS

(the name is not important)

What is the significance of glycolipids?

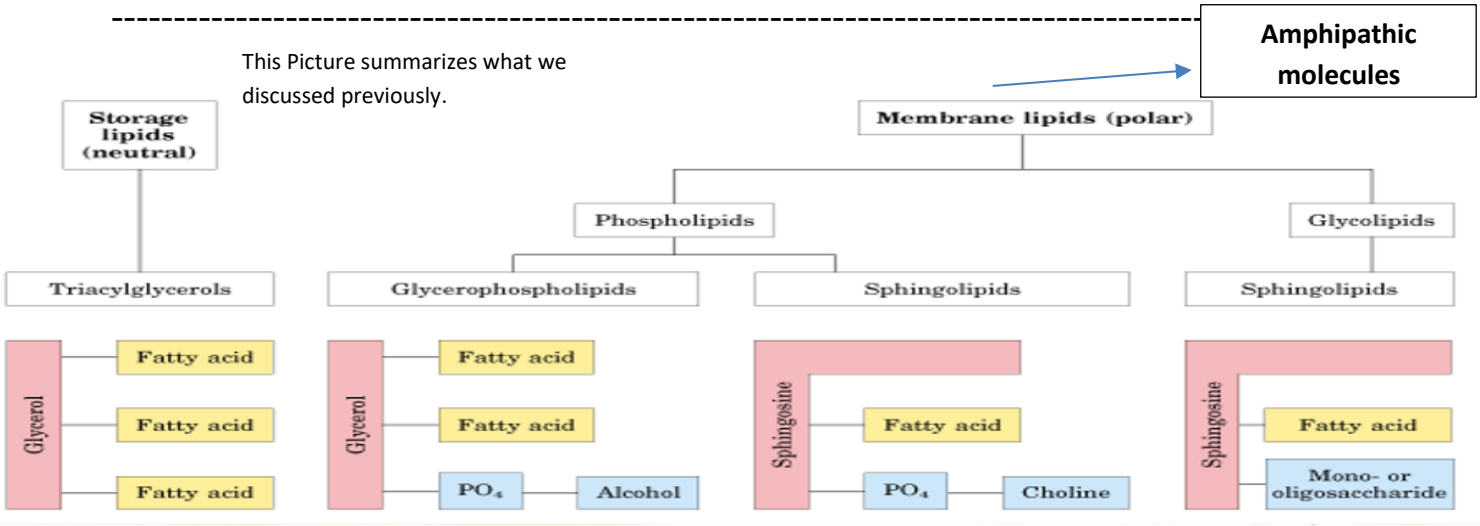
A. Since they are found on the outer layer of the membrane, they play a role in;

1- recognition and cell-cell interaction, which depends on the sequence of carbohydrates.

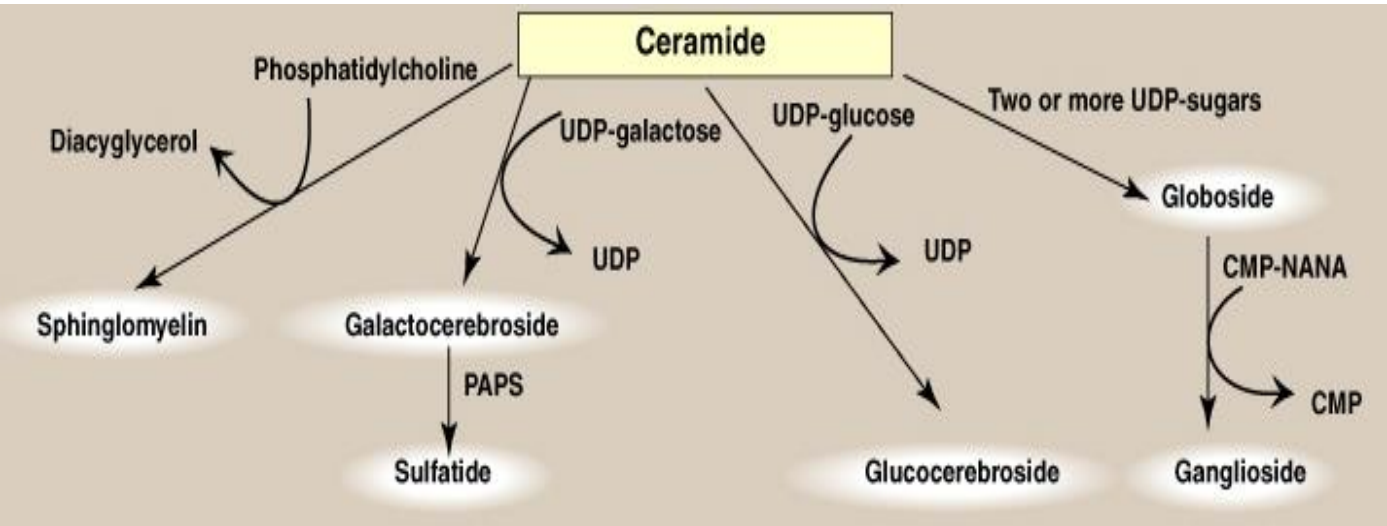
2- cell-virus interaction, some viruses invade the cell after binding to certain glycolipids.

B. blood groups depend on glycolipids (Sphingolipids).

This Picture summarizes what we discussed previously.



This is a very useful summary on sphingolipids synthesis (make sure you study it thoroughly)



Degradation of sphingolipids

- occurs by **hydrolytic enzymes**, that are **specific** for the sugar.

  - alpha galactosidase; Hydrolyzes Alpha Glycosidic bonds

  - Beta galactosidase

  - neuraminidase

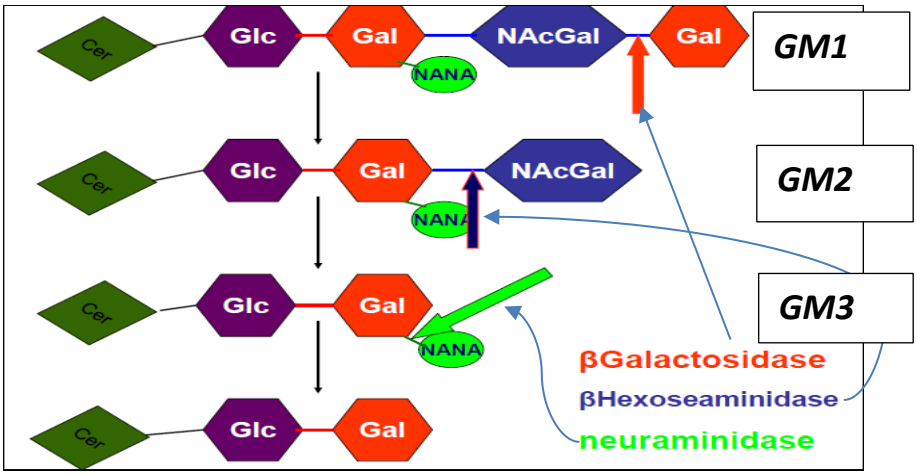
  - Hexoaminidase

- These enzymes are **firmly bound** to the **lysosomal membrane**; to prevent them from degrading cell constituents that are found in the cytosol
- The pH Optimum (3.5-5.5) (acidic media); that means even if they escape from the lysosome, they won't be active in other body compartments (at physiological pH).

Note: remember that the lysosome is an organelle found in the cell and has the function of digestion of molecules that are taken by endocytosis.

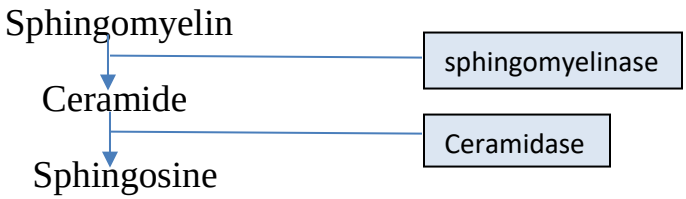
Note: Degradation is more important for us than synthesis.

- degradation is a **stepwise sequential** process; sugars are removed one at a time.
- **"Last on, first off"** Meaning that the last one added during synthesis, is the first one removed during degradation



- The designation GM1,2,3 depends on the degredation sequense (Since degredation is more important than synthesis;it is used in designantion).

Degradation of Sphingomyelin



Sphingolipidoses:

- The inability to degrade sphingolipids due to **defection/inhibition/inactivation** in one of the enzymes in the degradation pathway.
- They used to be known as Lipid Storage Diseases because lipids were seen within the cell.
- Accumulation of specific lipid substrate of the defective enzyme leads to the destruction of the cell **(apoptosis)**.
- **Brain is the most affected**; as brain cells do not regenerate.
- Extent of enzyme deficiency is the same in different tissues
- Most of them are inherited on the **somatic chromosome** (not x-linked).
- Inherited as Autosomal Recessive Disease

Note: Autosomal Recessive disease means two copies of an **abnormal gene** must be present in order for the disease or trait to develop, So, a person could be completely normal while carrying an abnormal gene (1 Copy).

- **We are going to talk about the most important *Sphingolipidoses*:**
  -The doctor said that you are **NOT** required to know what the defective enzyme is nor the substrate that accumulates.

A. *Tay-Sachs disease* (*common disease*)

- Occurs due to accumulation of gangliosides (GM2)

- Rapid and progressive neurodegeneration, which leads to blindness, cherry red macula, muscular weakness and seizures

- It mostly affects the Jews in eastern European countries.

B. *Gaucher disease*

- Accumulation of glucocerebrosides .

- It is the **most** common lysosomal storage disease. (Focus on this sentence)

- Hepatosplenomegaly (simultaneous enlargement of both the liver (hepatomegaly) and the spleen (splenomegaly).

- Osteoporosis of long bones (a condition that weakens bones, making them fragile and more likely to break).

- CNS involvement in rare infantile and juvenile forms.

C. *Niemann-Pick disease*

- accumulation of sphingomyelin

- Hepatosplenomegaly

- neurodegenerative course (type A)

Good luck ☺

You'll Never Walk Alone