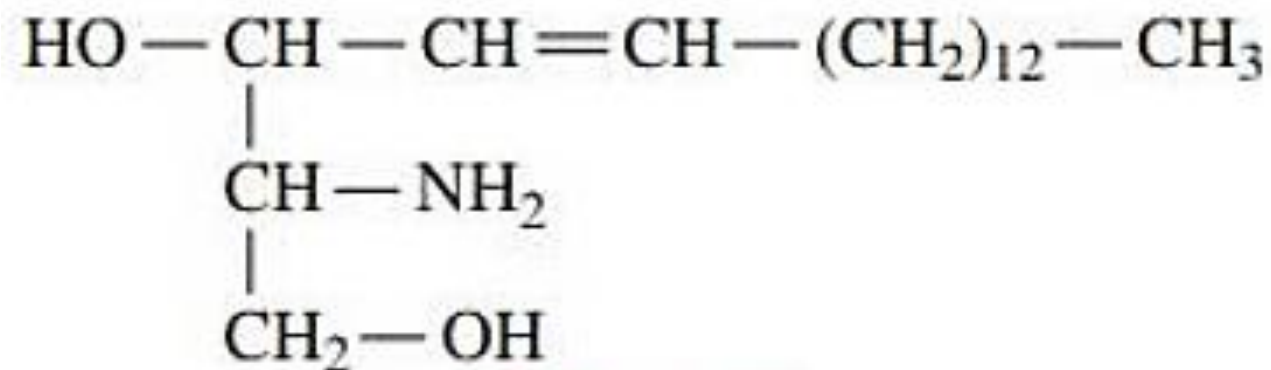


Medical Biochemistry
Sphingolipids and Myelin: From
Structure to Neurological
Disorders

Asst. Prof. Mohammed Hasan Eleyan
Faculty of Medicine
Al-Azhar University-Gaza





Sphingosine

Lipids Chemistry

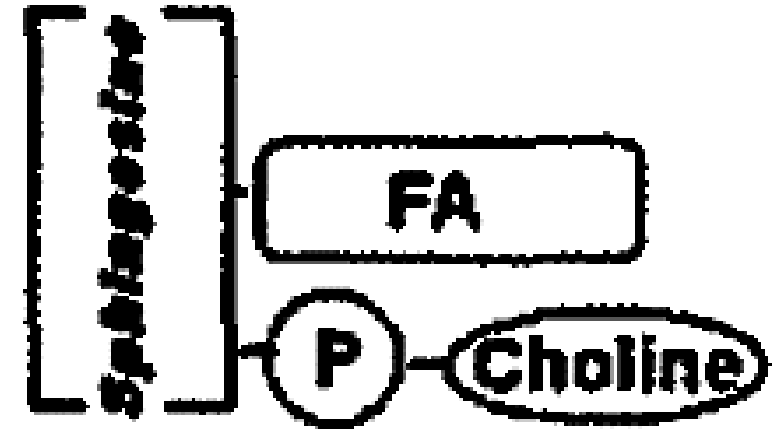
Complex (compound) lipids: Sphingophospholipids

Sphingophospholipids are a subclass of phospholipids that contain **sphingosine** (a long-chain amino alcohol) instead of glycerol as their backbone. They are key components of cell membranes, particularly in the nervous system.

Sphingomyelins

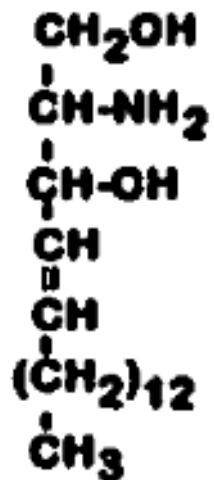
- Structure:

1. Sphingosine.
2. Fatty acid attached to amino group at position 2.
3. Phosphoric acid residue attached choline base
4. Function: It is present in high concentrations in brain and nerve tissue.

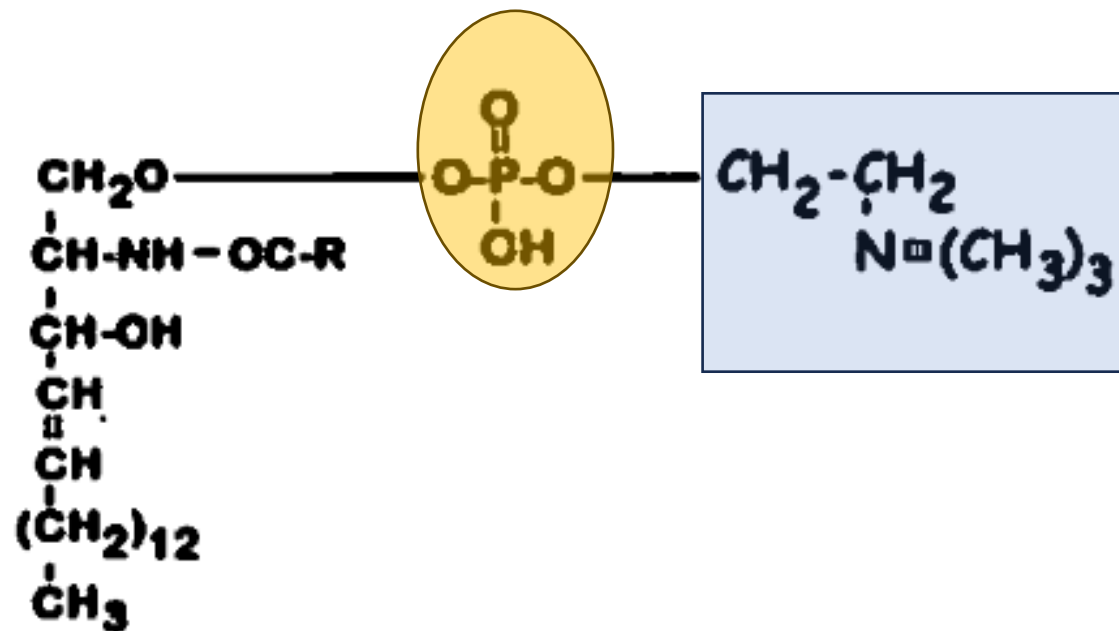


Sphingomyelin

Sphingomyelins



Sphingosine



Sphingomyelin

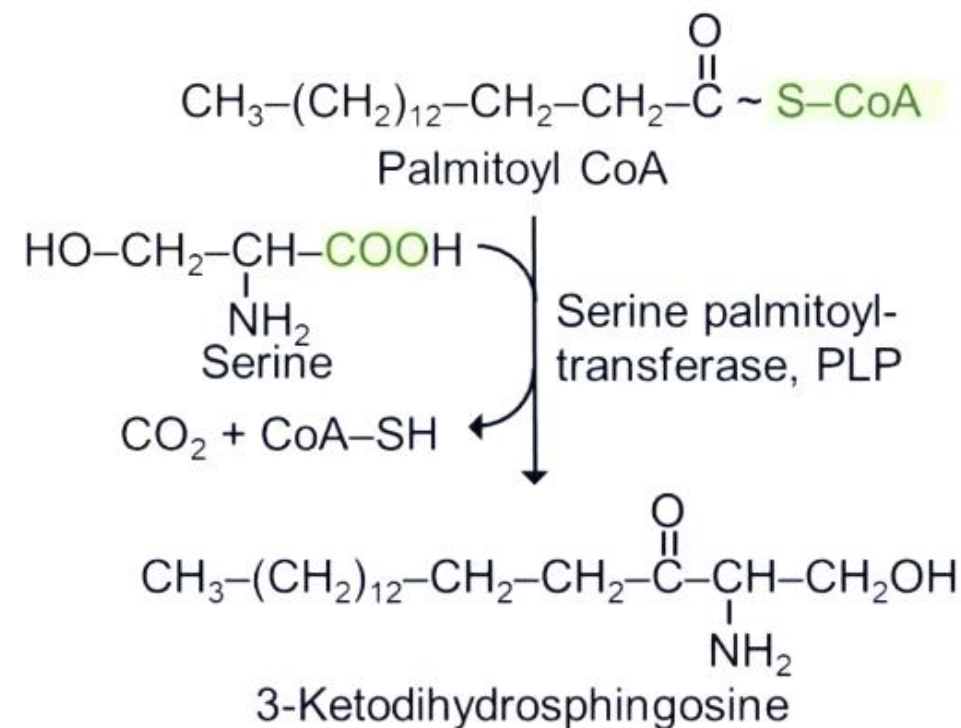


Synthesis of sphingolipids



The First Reaction in Sphingolipid Biosynthesis

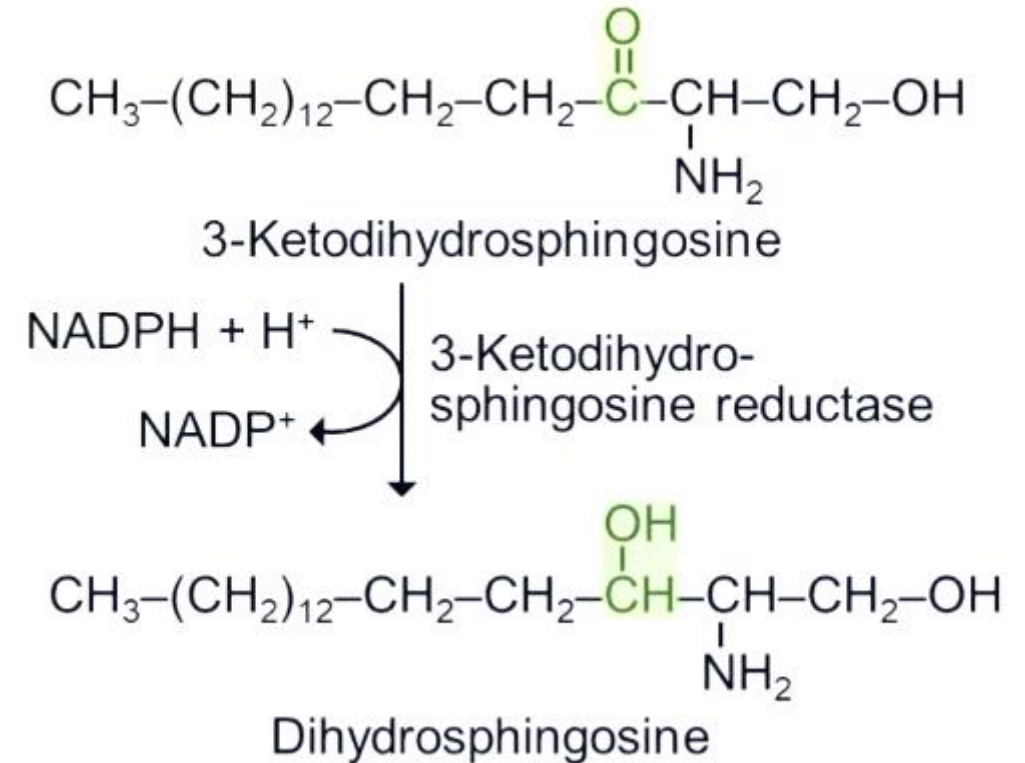
- The first reaction occurs between serine and palmitoyl CoA
- Serine is decarboxylated
- CoA is released from palmitoyl CoA
- The product of the first reaction is 3-keto dihydrosphingosine
- This is the rate-limiting reaction of sphingolipid synthesis
- The reaction is catalyzed by serine palmitoyltransferase (SPT)
- SPT is a pyridoxal phosphate-dependent enzyme





Reduction of 3-Keto-dihydrosphingosine to Dihydrosphingosine

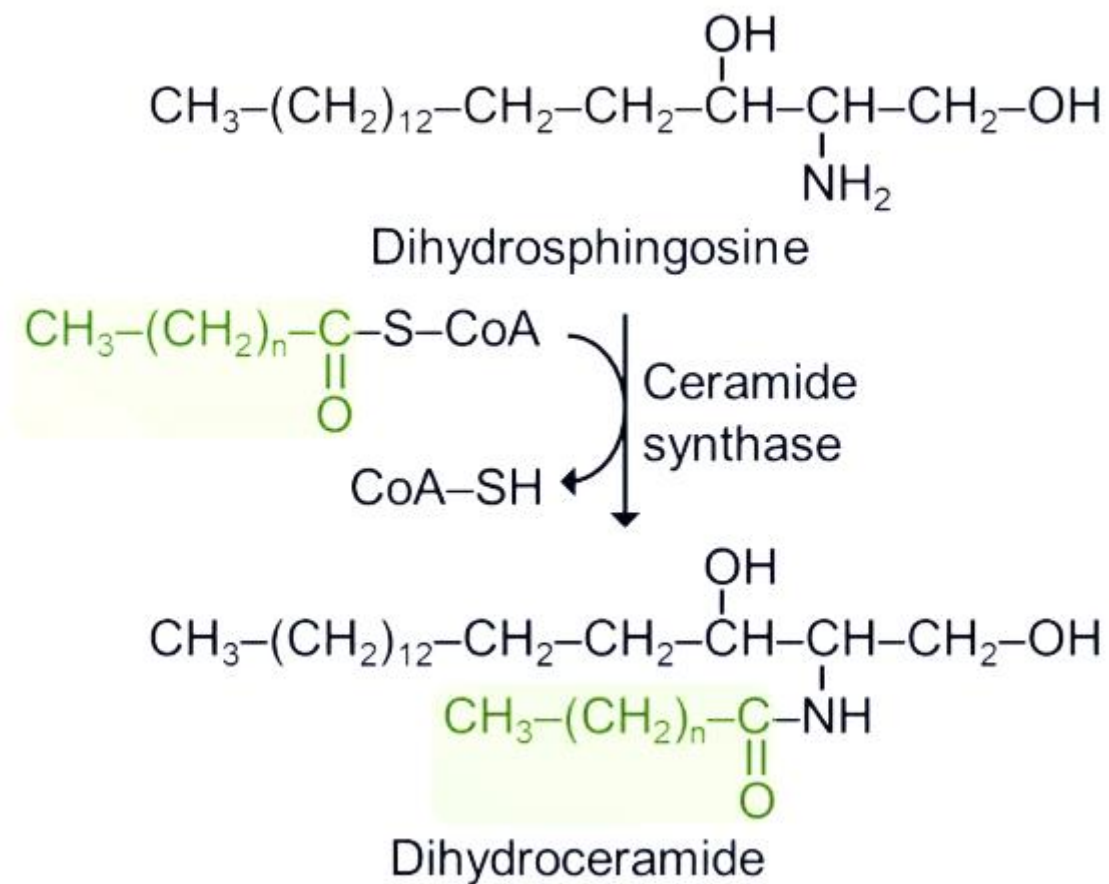
- 3-Ketodihydrosphingosine is reduced to dihydrosphingosine (sphinganine)
- 3-ketodihydrosphingosine reductase is NADPH-dependent





Acylation of dihydrosphingosine (sphinganine) to form dihydroceramide.

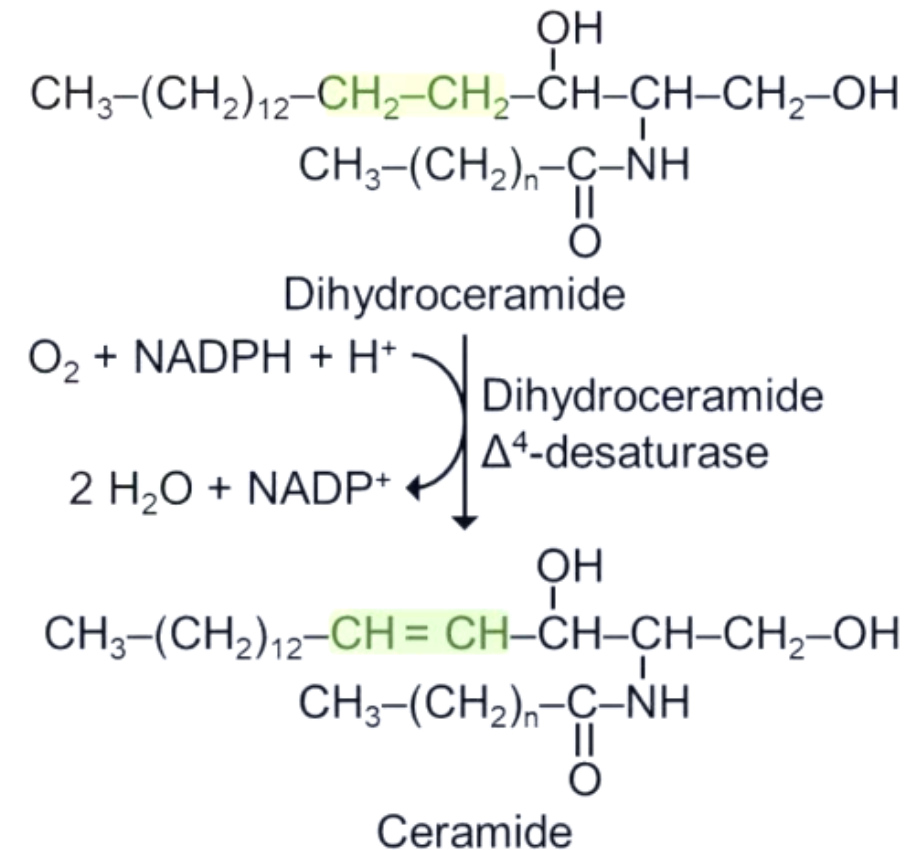
- Ceramide synthase adds a fatty acyl group to dihydrosphingosine
- The product is dihydroceramide
- There are six of different ceramide synthases in human beings
- They add fatty acids of different chain lengths to dihydrosphingosine





Desaturation of dihydroceramide to form ceramide.

- Two hydrogen atoms are removed from dihydroceramide forming a double bond
- Dihydroceramide is converted into ceramide
- The reaction is catalyzed by dihydroceramide Δ^4 -desaturase





Functions of Ceramide

- Ceramide is a central molecule in sphingolipid metabolism.
- It serves as the precursor for complex sphingolipids such as sphingomyelin, cerebroside, and gangliosides.
- Ceramides are also involved in cell signaling, apoptosis, and membrane structure.
- Different ceramide synthases add different fatty acids to sphingosine
- This results in the formation of different species of ceramide



Transport of Ceramide to the Golgi Apparatus

- **Ceramide is synthesized in the endoplasmic reticulum (ER).**
- Ceramide is **hydrophobic** and **insoluble in water**, making it unable to freely diffuse through the cytosol.
- **Transport Mechanisms:**
 1. **Vesicular Transport:** Ceramide is packaged into vesicles in the ER and transported to the Golgi apparatus.
 2. **Ceramide Transfer Protein (CERT):** A cytosolic protein that binds ceramide and transports it from the ER to the Golgi apparatus.
- In the Golgi apparatus, ceramide is used to synthesize **complex sphingolipids**.



Ceramide is a central molecule in sphingolipid metabolism

Synthesis of:

1. Sphingosine,
2. Sphingomyelin,
3. Glycosphingolipids (cerebrosides, sulphatides (Sulfolipids) and gangliosides)

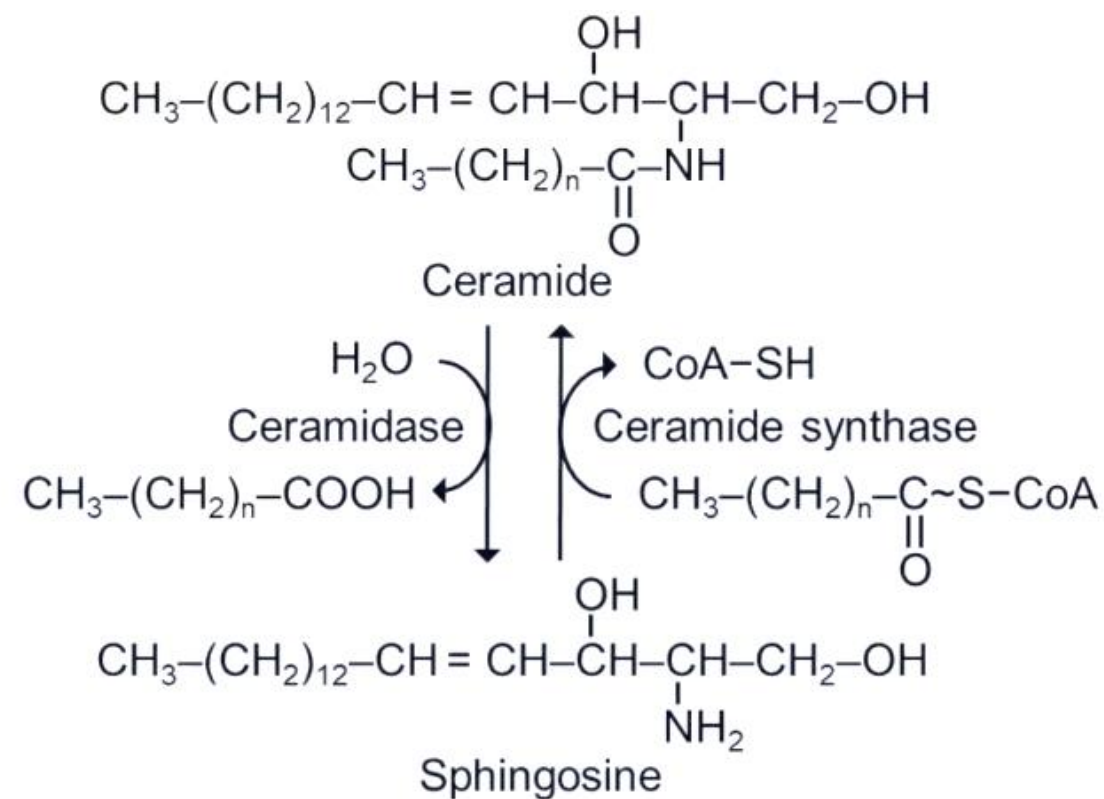


Synthesis of Sphingosine



Hydrolysis of ceramide to release sphingosine and a free fatty acid

- The amide bond ($-\text{CO}-\text{NH}-$) in ceramide is cleaved by the addition of a water molecule (H_2O).
- This releases **sphingosine** (the sphingoid base) and a **free fatty acid**.
- Sphingosine is a **bioactive signaling molecule** involved in regulating cell growth, apoptosis, and inflammation.
- It serves as a precursor for **sphingosine-1-phosphate (S1P)**, a potent signaling molecule that regulates immune cell trafficking, vascular function, and cell survival.





Synthesis of sphingomyelin & Catabolism

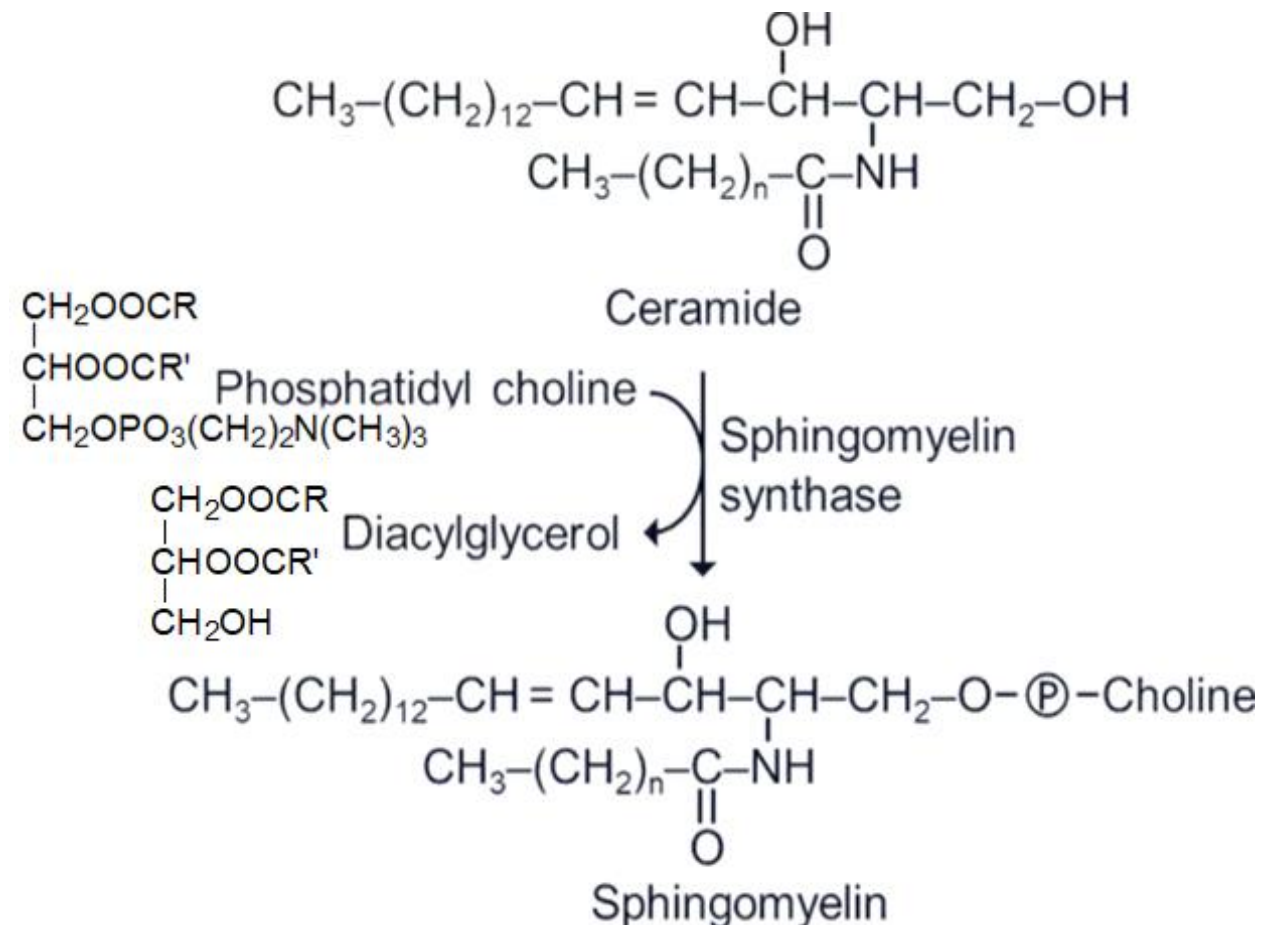


Synthesis of sphingomyelin

- Sphingomyelins are a diverse group of lipids, and their diversity arises from the variation in the **fatty acid component** attached to the ceramide backbone.
- The main fatty acids in sphingomyelins are palmitic acid and stearic acid
 1. **Sphingomyelin with Palmitic Acid (C16:0)**
 2. **Sphingomyelin with Stearic Acid (C18:0)**

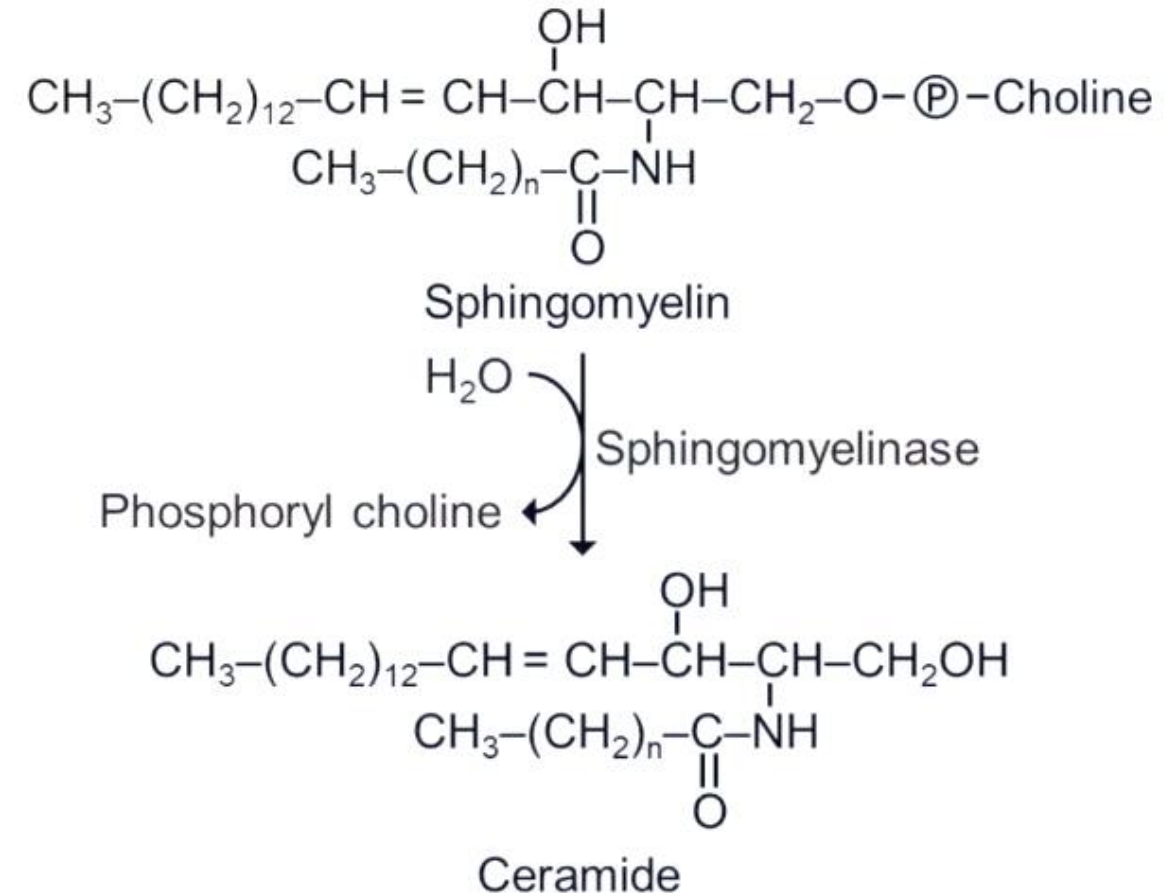
Sphingomyelin synthesis

- Phosphoryl choline is transferred from phosphatidylcholine to ceramide
- Phosphoryl choline is converted into diacylglycerol (DAG)
- Ceramide is converted into sphingomyelin
- **Sphingomyelin synthase** is the enzyme responsible for this reaction.
- There are two isoforms of sphingomyelin synthase: **SMS1** (Golgi) and **SMS2** (plasma membrane).



Catabolism of Sphingomyelins

- The phosphodiester bond in sphingomyelin is hydrolyzed to release ceramide and phosphocholine by Sphingomyelinase





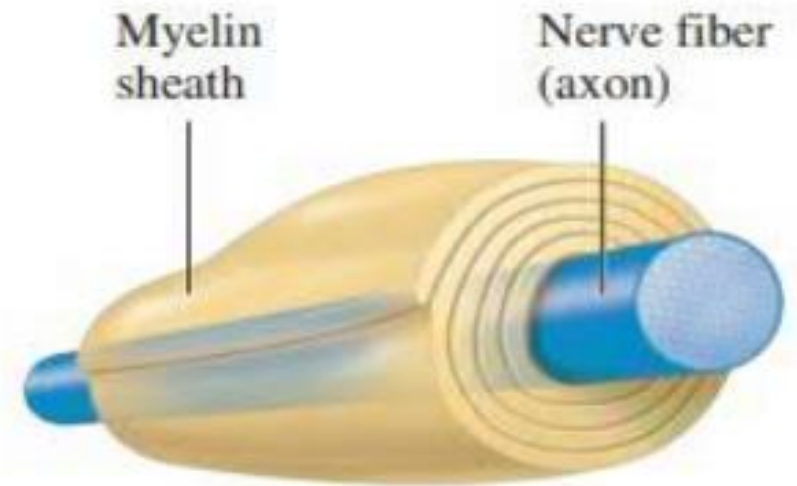
Multiple Sclerosis

- **Multiple Sclerosis (MS)** is a chronic autoimmune disease that affects the central nervous system (CNS), leading to the destruction of the **myelin sheath** surrounding nerve fibers.
- The symptoms of multiple sclerosis include **muscle weakness** with **loss of coordination and vision**, depending on the amount of damage.



Multiple Sclerosis

- Sphingomyelin is **lost** from the myelin sheath.
- As the disease progresses, the myelin sheath deteriorates.
- **Scars form on the neurons and impair the transmission of nerve signals.**



Normal myelin sheath



Damaged myelin sheath



When the myelin sheath loses sphingomyelin, it deteriorates and the transmission of nerve signals is impaired.



Niemann Pick's disease

- It is **accumulation** of large amounts of **sphingomyelin** in brain, liver, spleen, and bone marrow due to deficiency of **sphingomyelinase enzyme**.
- It leads to **mental retardation** and death in early life.





Synthesis of glycosphingolipids & Catabolism



Synthesis of glycosphingolipids

- Glycosphingolipids are made up of ceramide and one or more **carbohydrate groups**
- These carbohydrate groups can range from a monosaccharide to complex oligosaccharides.
- The main glycosphingolipids are cerebrosides, sulphatides (Sulfolipids) and gangliosides.



Glycosphingolipids

Cerebrosides



Cerebrosides

- They are called **simple glycolipids**.

- Upon hydrolysis ,they give:

1. Sphingosine.
2. Fatty acid.
3. Sugar (usually galactose or glucose).

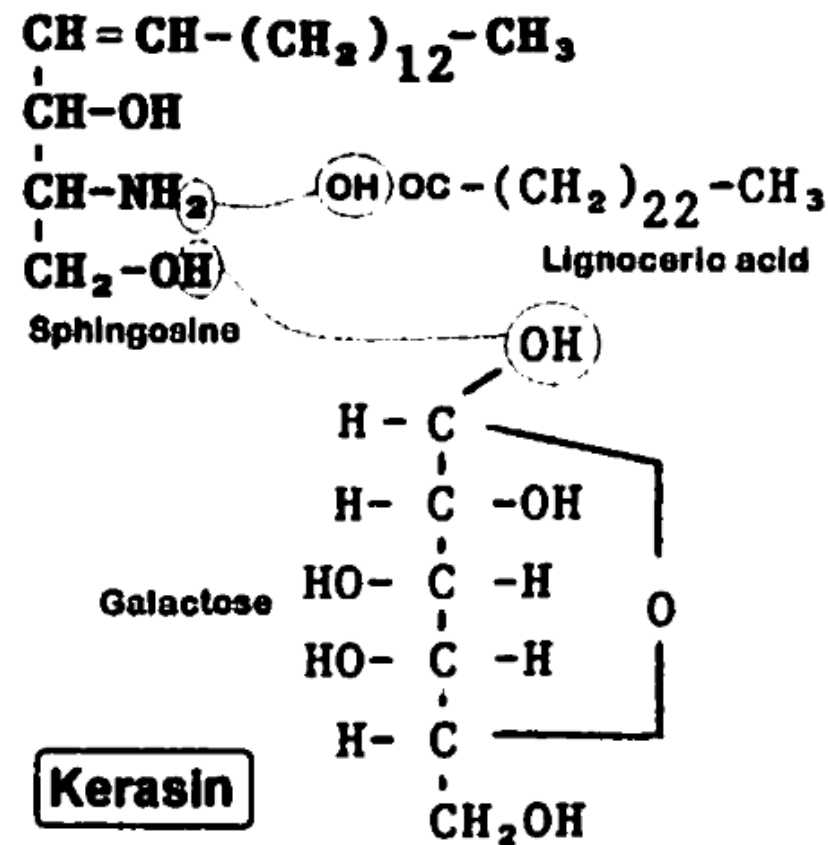
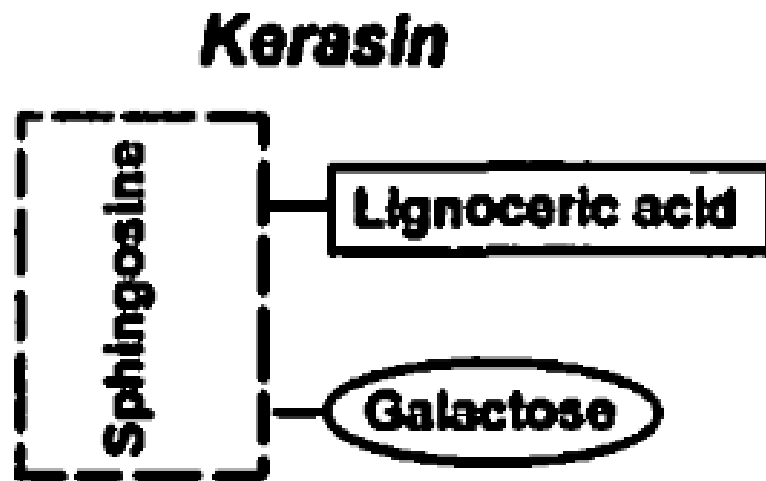
Cerebrosides having galactose are called galactocerebrosides

A few cerebrosides contain glucose and called glucocerebrosides

- According to the type of fatty acid, they may be:

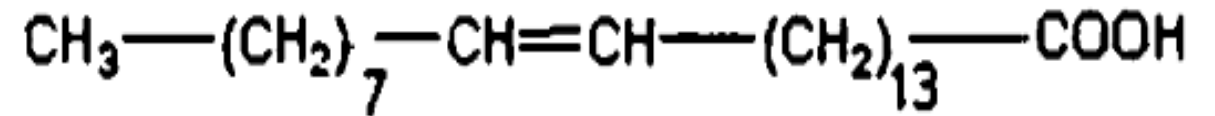
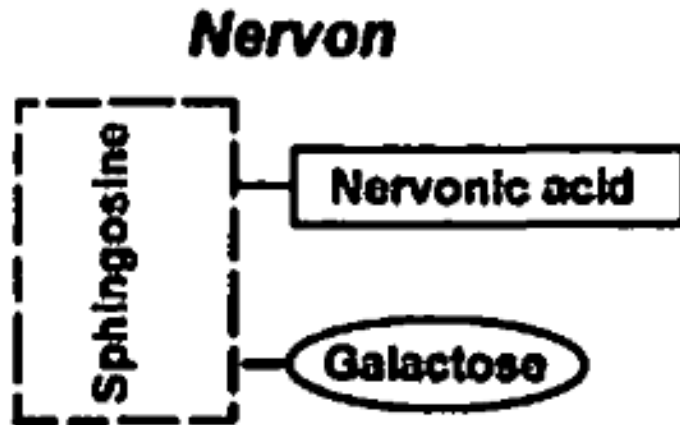
Kerasin

- Kerasin: The fatty acid is **lignoceric acid** (C24: saturated)



Nervon

- Nervon: The fatty acid is **nervonic acid**
(C24 unsaturated, ω^9)

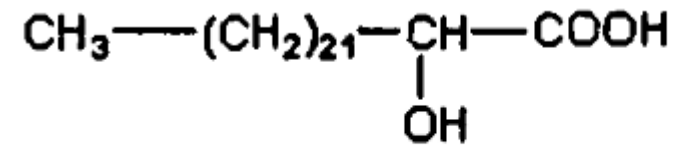
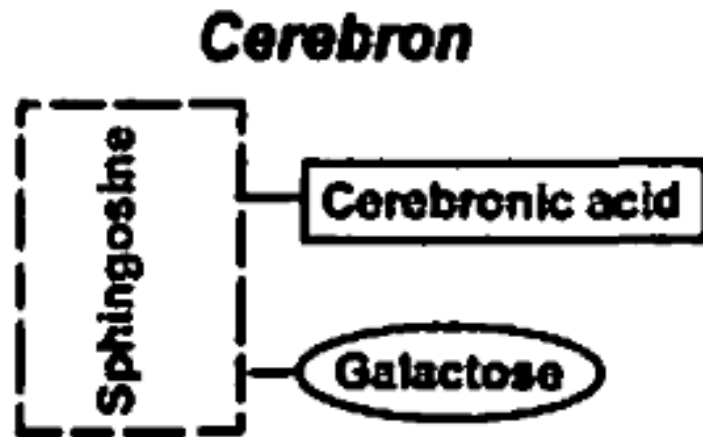


Nervonic acid (C 24:1 Δ^{16})



Cerebron

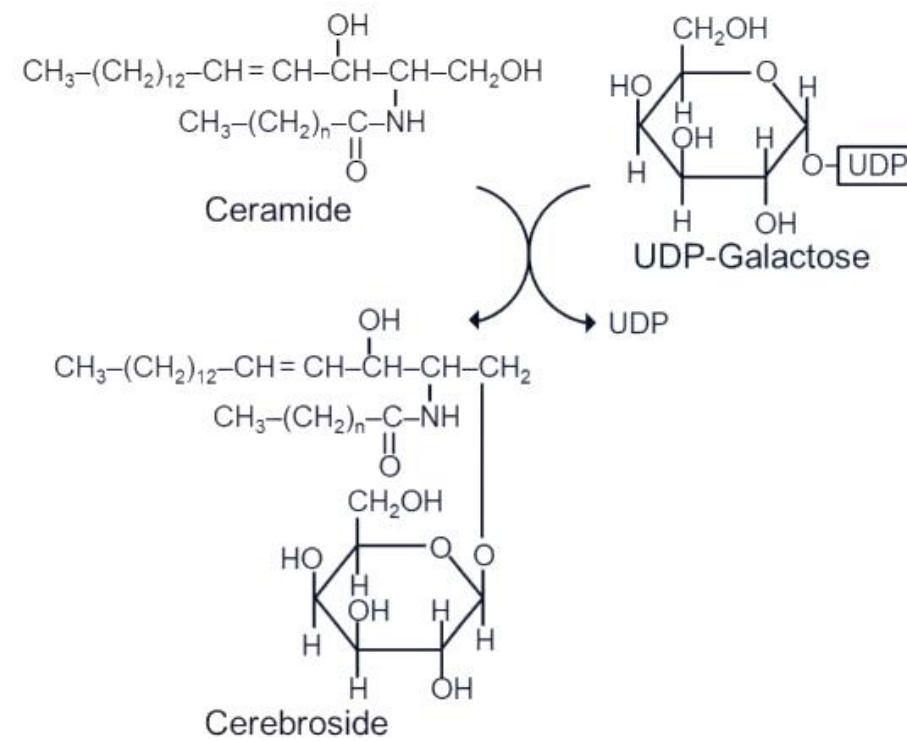
- Cerebron: The fatty acid is **cerebronic acid** (C24-hydroxy saturated).



Cerebronic acid (C₂₄ saturated OH)

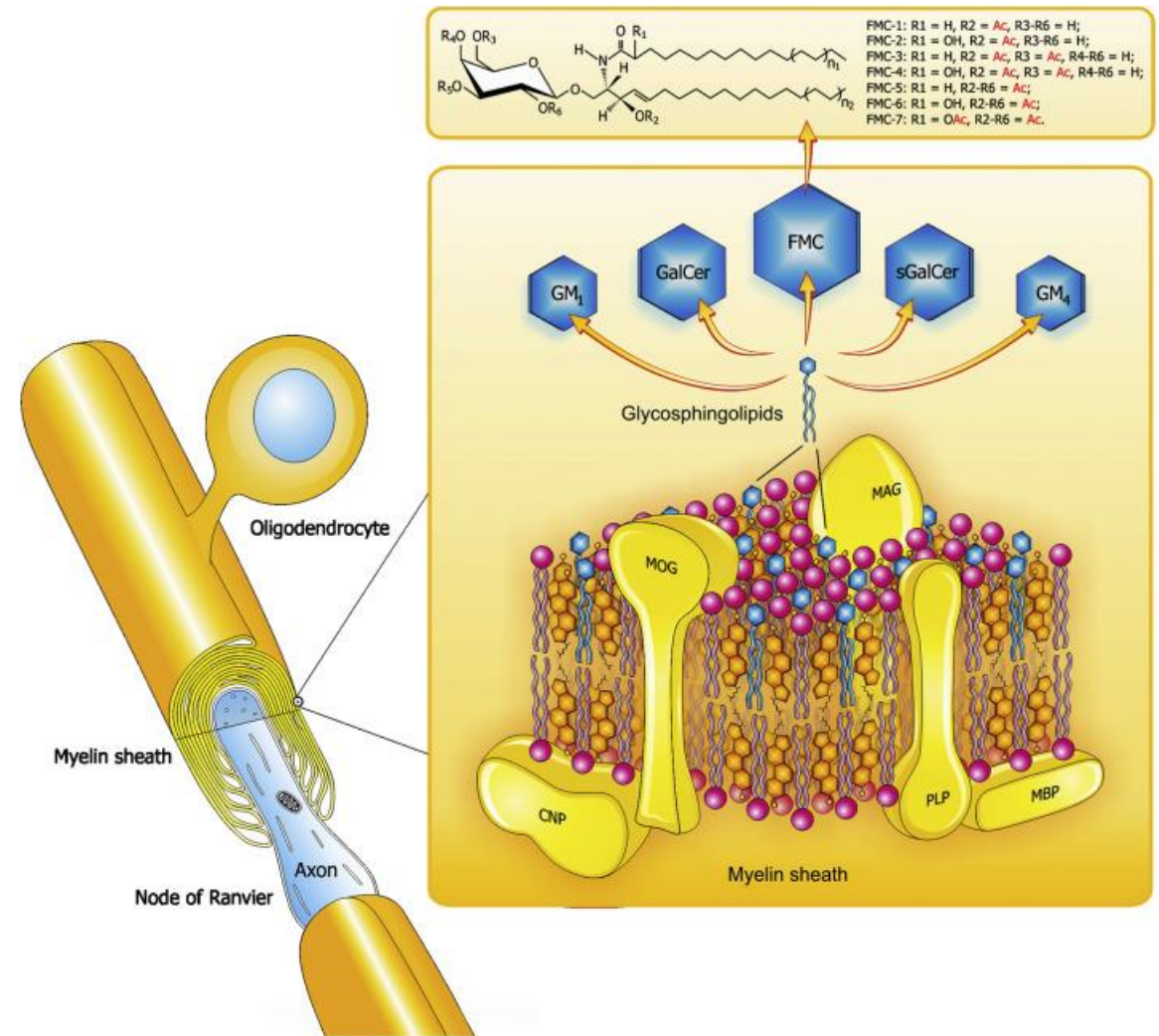
Synthesis of Galactocerebrosides

- Ceramide + UDP-Galactose → Galactocerebroside + UDP
- The galactose moiety from UDP-galactose is transferred to ceramide.
 - This forms a glycosidic bond between the galactose and the hydroxyl group (–OH) at position 1 of ceramide.
- Galactosylceramide synthase (UDP-galactose:ceramide galactosyltransferase).



Functions of Cerebrosides

- Cerebrosides are present in many tissues especially in the **brain and myelin of nerve fibers.**
- They act as **insulators of nerve impulse.**





Functions of Cerebrosides

- Galactocerebroside is involved in signaling pathways such as:
 1. PI3K/Akt Pathway: Regulates cell survival and growth.
 2. MAPK/ERK Pathway: Controls cell proliferation and differentiation.
- Membrane Structure:
 - Galactocerebroside contributes to the stability and integrity of the plasma membrane.



Gaucher's disease (Autosomal recessive):

- Def: Accumulation of cerebroside in tissues due to deficiency of “ β glucocerebrosidase” enzyme.
- Consequences: **Affect normal function** of tissues where it is accumulated.
- Manifestations: mental retardation, hepatomegally and bone disorder.





Glycosphingolipids

Sulpholipids

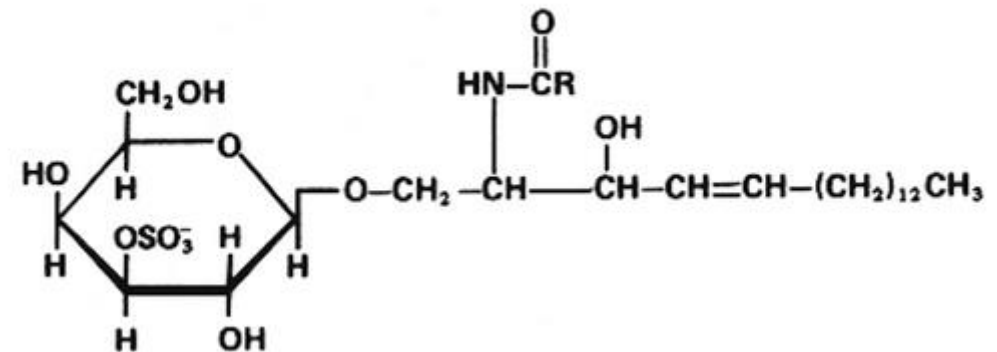


Sulfolipids

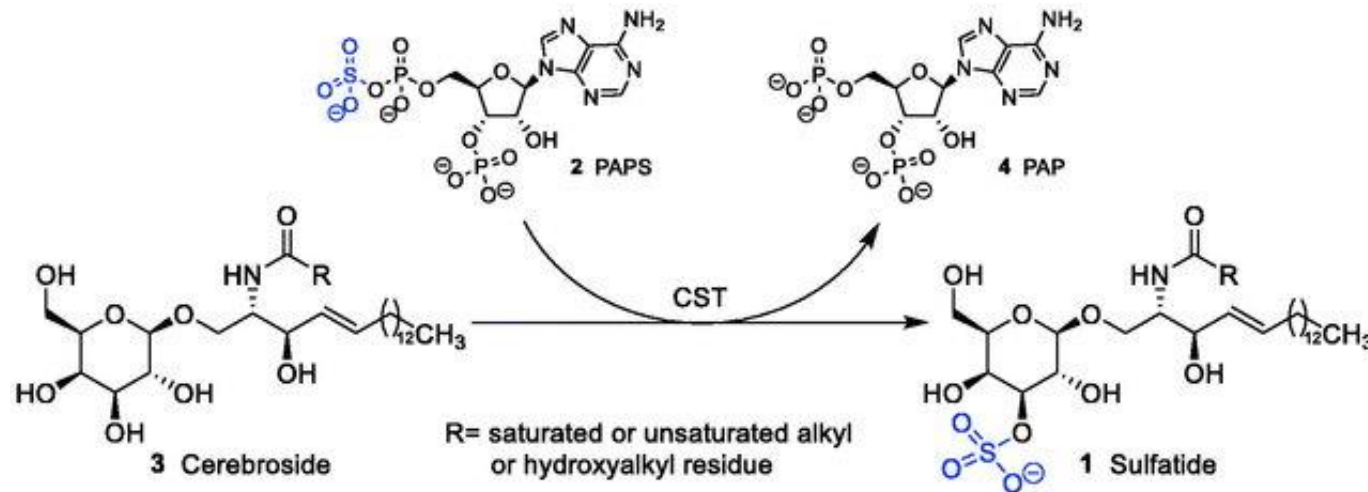
- Sulfolipids are a subclass of **glycosphingolipids** containing a **sulfate group** attached to the sugar moiety.

contained in **brain lipids** and present in low levels in liver, lung, kidney, spleen, skeletal muscle and heart

Function: Membrane Stability and Antioxidant Properties

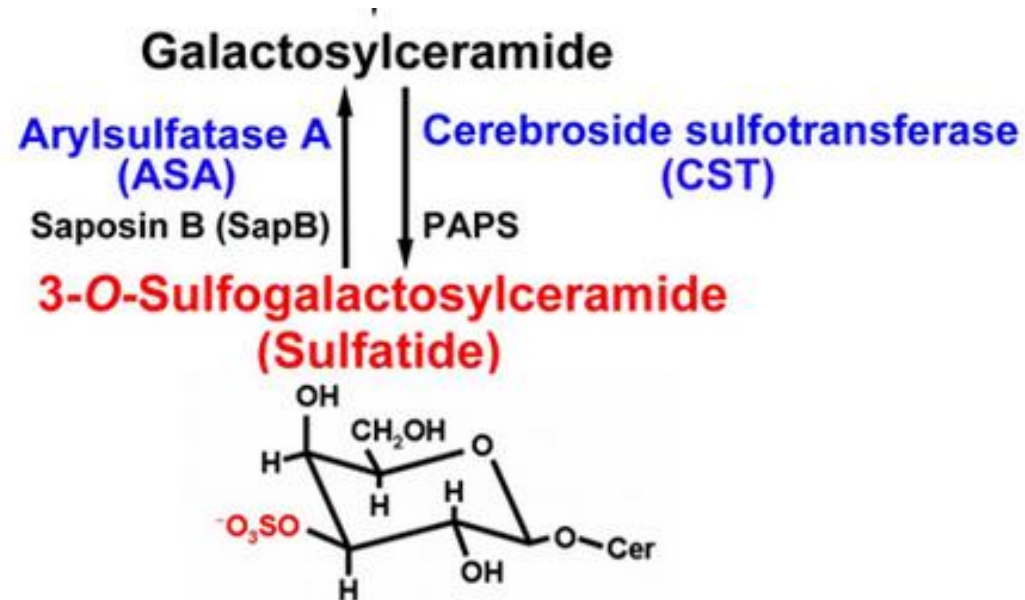


Synthesis of sulphatides



- Sulphatides are synthesized from galactocerebrosides and activated sulphate (3'-Phosphoadenosine-5'-phosphosulfate (PAPS))
- The sulphate group is transferred from PAPS to carbon 3 of galactose.
- Enzyme: Cerebroside sulfotransferase (also called galactosylceramide sulfotransferase).

Catabolism of sulfatides



- The catabolism of sulfatides involves the hydrolysis of the **sulfate ester bond** that links the sulfate group to the galactose moiety in sulfatide.
- This reaction is catalyzed by the enzyme **arylsulfatase A** and produces **galactocerebroside** and **sulfate**.



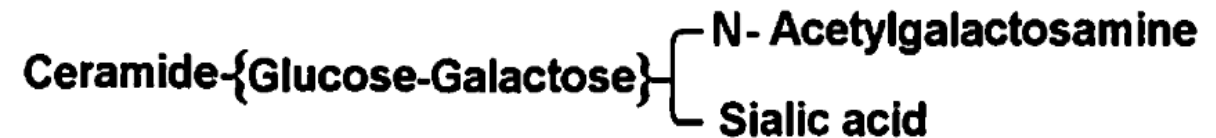
Glycosphingolipids

Gangliosides



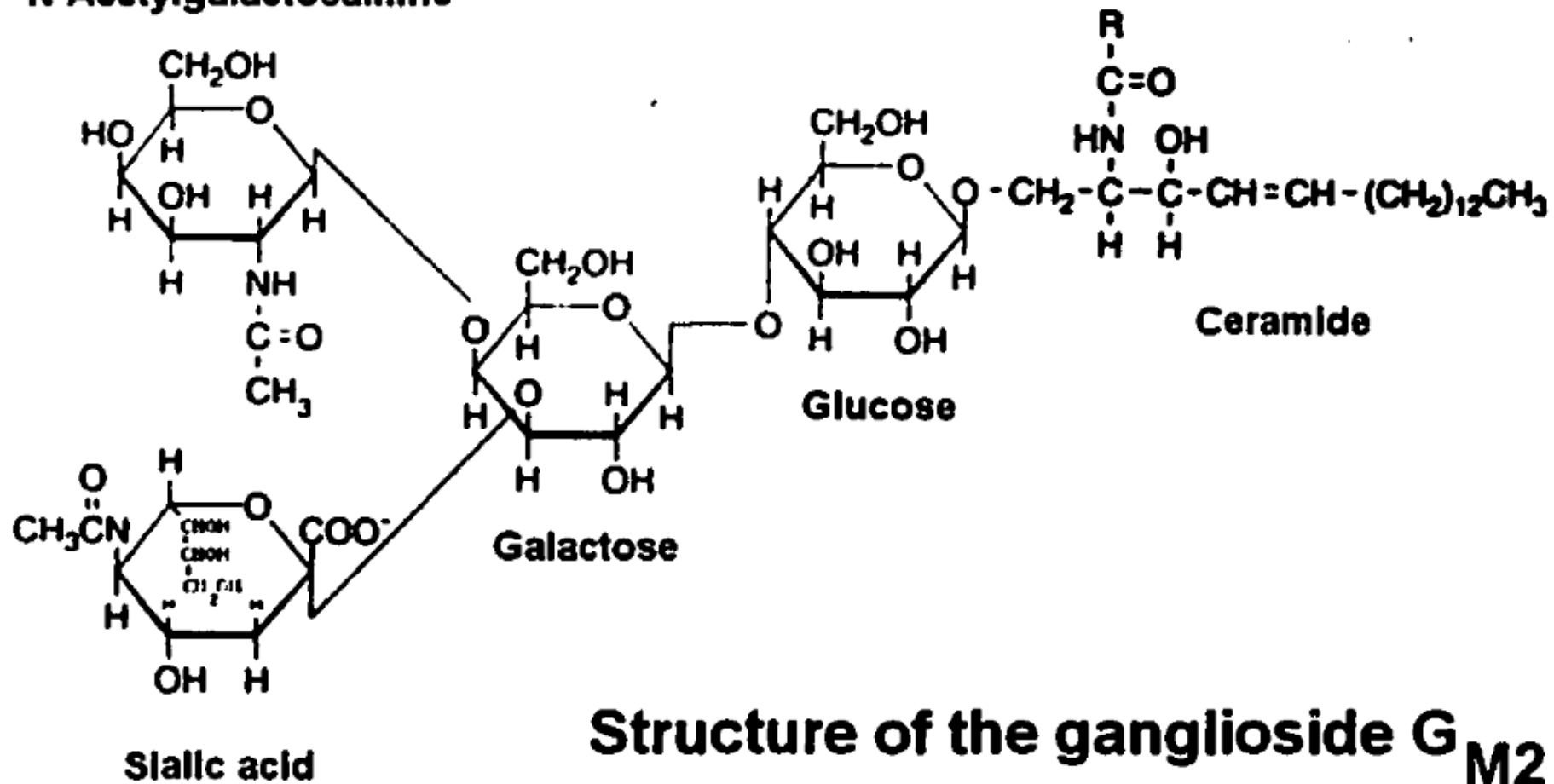
Gangliosides:

- They are called complex glycolipids, because they contain in addition to hexose (glucose, galactose, and N-acetylgalactosamine), one or more sialic acid molecules.
- Upon hydrolysis they give:
 1. Ceramide (sphingosine and fatty acid).
 2. Hexoses (glucose and galactose).
 3. Hexosamines:
 - Sialic acid (N-acetylneuraminic acid).
 - N-acetylgalactosamine.



Ceramide-{Glucose-Galactose} $\left\{ \begin{array}{l} \text{N-Acetylgalactosamine} \\ \text{Sialic acid} \end{array} \right.$

N-Acetylgalactosamine

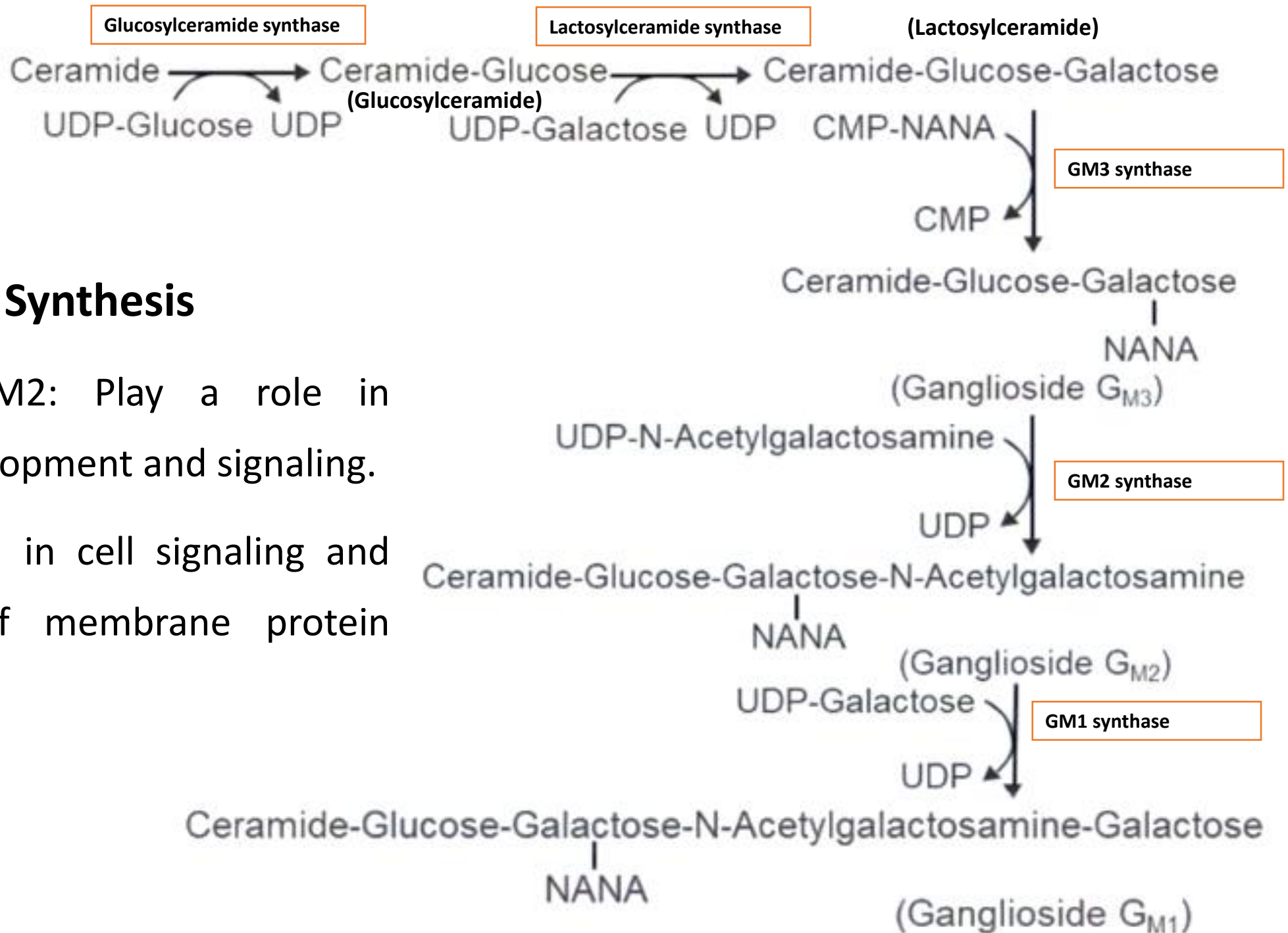


Structure of the ganglioside G_{M2}



Ganglioside Synthesis

- GM1 and GM2: Play a role in neuronal development and signaling.
- GM3: Involved in cell signaling and modulation of membrane protein function.





Functions of gangliosides:

1. They act as **receptors at cell membrane** (back to CHO).
 2. They are present in **high concentration in brain**.
- Degradation: By **hexosaminidase enzyme**.



Tay Sachs disease (Autosomal recessive):

- Accumulation of gangliosides (GM2) in brain and intestine due to deficiency of **hexosaminidase enzyme**.
- Manifestations: **mental retardation, hepatomegally, blindness and death in early life.**





Thanks