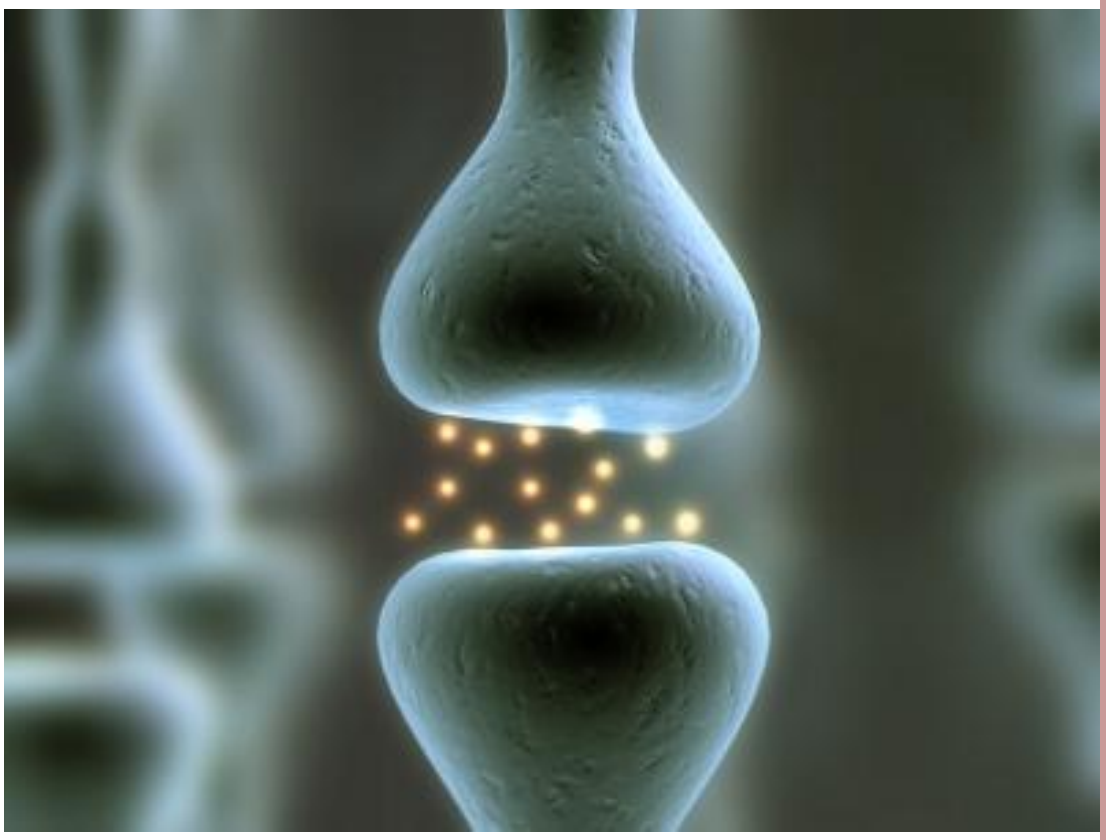
Biochemistry of the CNS



1st lecture:

Sphingolipids and Myelin Structure

Done by:

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Sphingolipids:

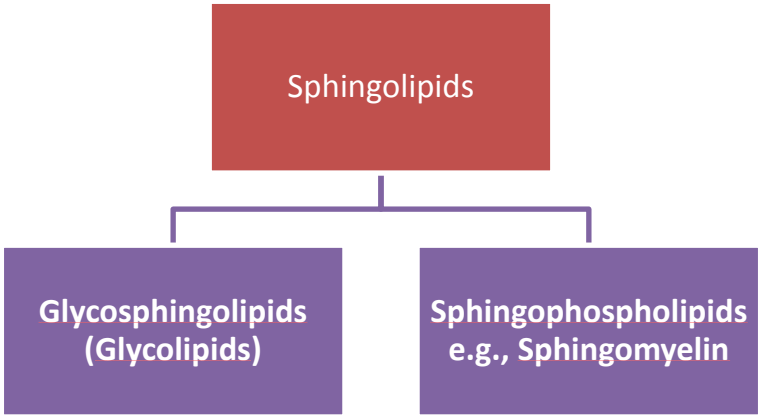
Background

* Shipngolipids are **complex lipids** found in the membrane phospholipid bilayer of the cell; they are essential component of the cell membrane.

- They are abundant in nervous tissue
- Found in extra-nervous tissue: e.g., Receptors for: Cholera toxins , Diphtheria toxins , Viruses *these receptors are sphingolipids in nature*.
- They play a major role in the regulation of growth & development; abnormal shingolipids lead to defective growthand may sometimes lead to death.
- They are very antigenic; they stimulate the immune response in our body. Eg:Blood group antigen , Embryonic antigen, Tumor antigen. *the chemical structure of these antigens is sphingolopdis*.
- They are important in cell transformation, such in the transformation of the normal cell to a cancerous cell; Changes in the sphingolipid structure may transform a regular cell into a cancerous cell.

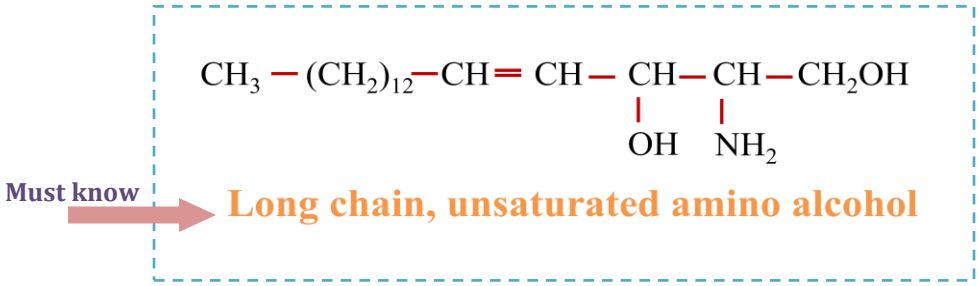
sentences in black are copied from the lecture, the rest is explanation.

Key Principles:



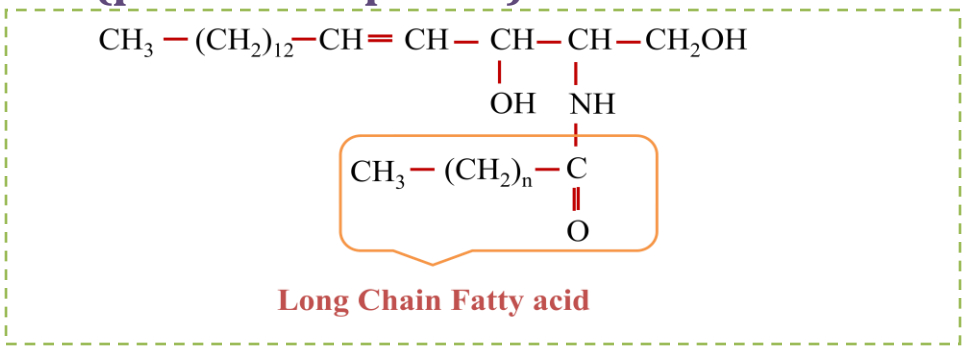
Structures: you do not need to memorize these structures, they are only to help you understand the formation of myelin..

*Sphingosine:



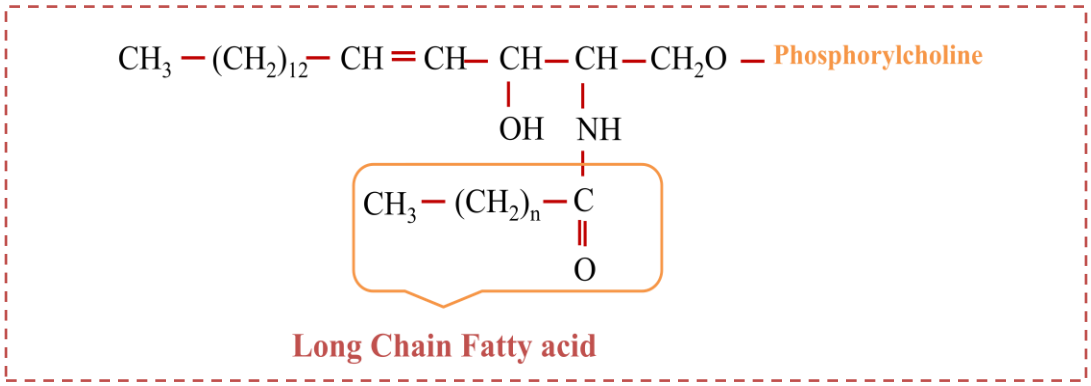
*by adding a fatty acid we get :

*Ceramide(parent compound):



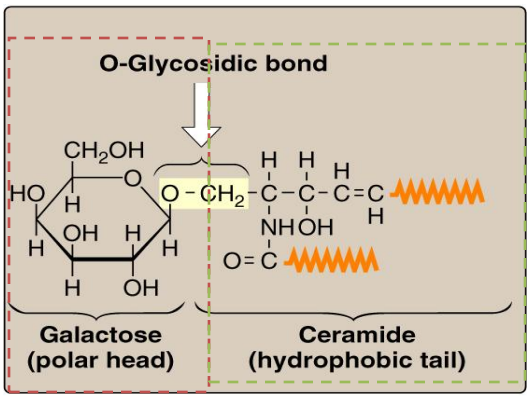
*by adding phosphorylcholine we get:

*Sphingomyelin:



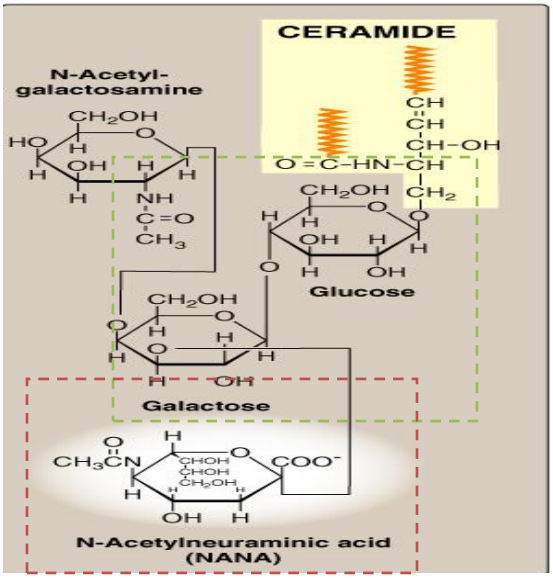
*by adding a monosaccaride to a ceramide molecule we get cerebroside.

Eg: Galactocerebroside (galactose + ceramide):



*by adding an oligosaccharide (more than one saccharide molecule) and a NANA molecule (N-acetylneuraminic acid) to a ceramide molecule we get:

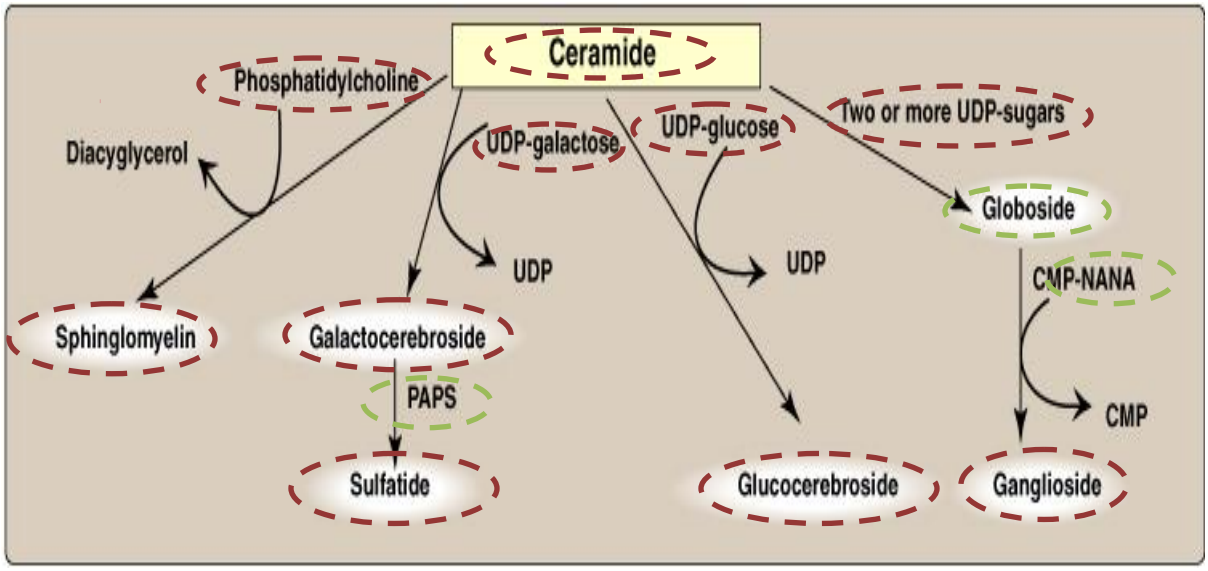
*Gangliosides:



Summary of the previous structures: *must memorize*

- Ceramide = Sphingosine + fatty acid
- Sphingomyelin = Ceramide + Phosphorylcholine
- Cerebrosides = Ceramide + Monosaccharides
- Gangliosides = Ceramide + oligosaccharides + NANA

*Sphingolipids' Synthesis: (summary) *this graph contains repeated info only, must know encircled details



*Myelin structure:

*Myelin is a member of the sphingolipids group. It is a sphingolipid that contains alcohol sphingosine.

*Myelin is a specialized cell membrane that ensheathes an axon to form a myelinated nerve fiber which help in increasing the conduction velocity.

*Myelin is produced by:

Schwann cells	⇨	Peripheral nerves
Oligodendrocytes	⇨	CNS

*Myelin composition:

-Lipids (80%): Main component: Cerebrosides

Other component: Sphingomyelin

-Proteins (20%): e.g., Myelin basic protein (MBP)

*Fatty acid of Sphingomyelin:

-Myelin sheath: **Very long** chain fatty acids:

Eg:	Lignoceric	24:0
	Nervonic	24:1

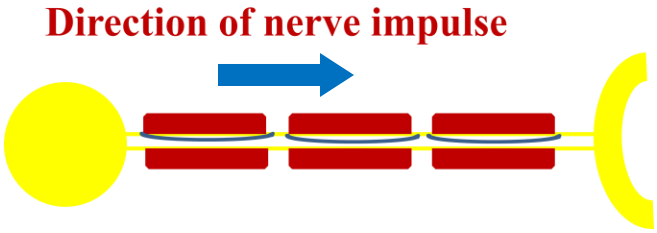
-Gray matter**: Long** chain fatty acid

Eg:	Stearic	18:0

*do not memorize the number of carbon atoms nor the position of the double bond.

*Myelin function:

Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speeds up the transmission of impulses along axons.



Multiple sclerosis:

It is a Neuro-degenerative, auto-immune disease caused by the breakdown of myelin sheath (demyelination) which leads to defective transmission of nerve impulses.

Sphingolipidosis: *are heterogeneous group of inherited disorders of lipid metabolism affecting primarily the central nervous system*

In these diseases, Synthesis of sphingolipids is (Normal). However, the degradation is (Defective). This will lead to accumulation of substrates in the organs. The diseases are progressive and eventually cause early death. They are rare and passed as autosomal ressisive disorders except in Ashkenazi Jewish. They show Phenotypic and genotypic variability.

Diagnosis: *since the problem mainly is in the breakdown of the enzymes, we can diagnose clinically by measuring the enzyme activity*

- Measure enzyme activity

  From: Cultured fibroblasts or peripheral leukocytes

  Cultured amniocytes (prenatal)

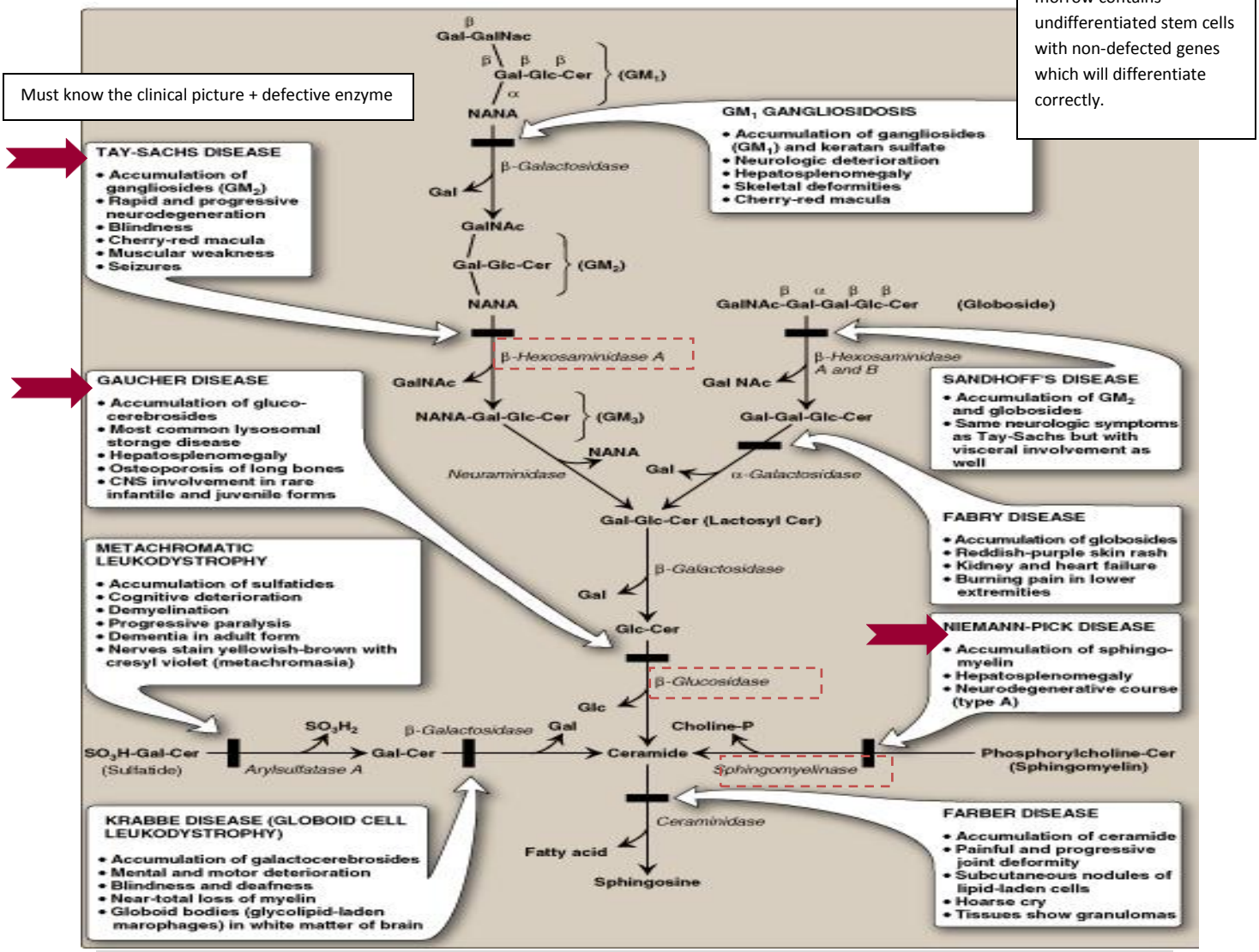
- Histologic examination *example next page "**Gaucher Disease**"*
- DNA analysis

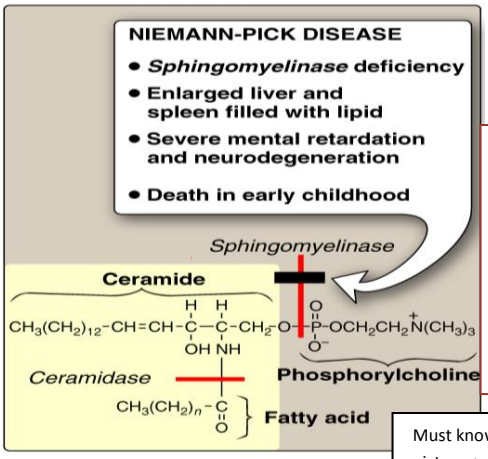
Treatment:

- Replacement Therapy: Recombinant human enzyme *replacing the defective enzyme*
- Bone marrow transplantation: specially in Gaucher disease

For your information: bone morrow contains undifferentiated stem cells with non-defected genes which will differentiate correctly.

Must know the clinical picture + defective enzyme





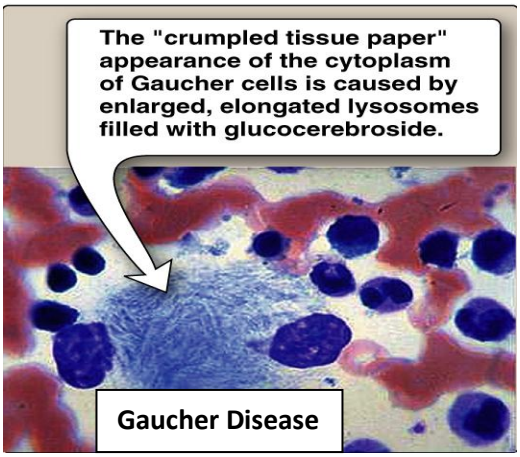
-Phenotypically variant (type A and type B).

-type A is more severe with CNS involvement.

- type A May cause early death.

Must know the clinical picture + defective enzyme

Sphingolipids and Myelin Structure



Take home massages:

- Sphingolipids are complex lipids that includes sphingo-phospholipids and glycolipids
- Ceramide is the precursor of all sphingolipids
- Sphingolipids are present mainly in nerve tissue, but they are found also extra-neural.
- Myelin sheath insulates the nerve axon to avoid signal leakage and speed up impulse transmission
- Sphingolipidosis are rare, genetic diseases due to defective degradation of sphingolipids

Further explanation of the previous diseases:

***Tay-Sachs disease**:

-accumulation of gangliocytes due to defect in B-hexosaminidase A.

-rapid and progressive neurodegeneration.

-affects the area around the optic nerve which may cause blindness

- cherry-red macula is seen by karyo-scopy.

-cause muscular weakness and seizures.

***Gausher disease:**

-hepatosplenomegaly.

-have special histologic appearance *shown above*

-Osteoporosis in young age

-Rare CNS involvement. However, may be involved in infants and juvenile.

-Most common lysosomal storage disease

-accomulation of glucose cerebrosides due to defect B-glucocerebrosidase