L1

Neuropsychiatry Block

Sphingolipids and Myelin Structure

Editing File

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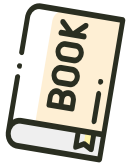
Objectives



1. Recognize the Sphingolipids class of lipids as regard their chemical structure, tissue distribution and functions.
2. Be familiar with the biochemical structure and function of myelin.
3. Learn the basics of biosynthesis of sphingolipids.
4. Be introduced to Sphingolipidoses.

Background:
Phospholipids

439: Polar head of the phospholipid helps in recognition and formation of receptors ——> exposed to extracellular environment (it may be attached to carb to act as receptor).

1

There are two classes of phospholipids based on the backbone:
1) Glycerol (from glucose)
2) Sphingosine (from serine and palmitate)

2

Essential component of membranes.
Glycerophospholipids are present within the lipid bilayer, while sphingolipids are present in the outer layer in communication with the extracellular compartment of the cell.

3

Abundant in nervous tissue.
Also exist in extra-nervous tissue: e.g receptors for:
1) cholera toxins
2) Diphtheria toxins
3) viruses

4

Regulation of growth and development

5

Very antigenic:

1) Blood group antigen
2) Embryonic antigen
3) Tumor antigen

6

Cell transformation.

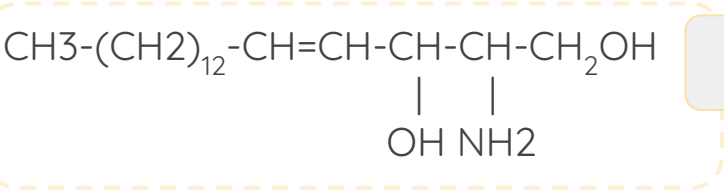
As when the cell transforms into a cancerous cell.
When the cell transforms its due to transformation of carbohydrate on its surface, therefore the merker is the carbohydrate on the surface.

Phospholipids form an essential component of cell membrane along with cholesterol and proteins.

Sphingolipids: Structure and Types

Sphingolipids are basically structures that have sphingosine as the backbone & are attached to fatty acids/ a lipid.

- **Sphingosine structure:**



Long chain, unsaturated amino alcohol

Long chain cause it has 18 Carbons, Unsaturated due to the presence of double bond, has an amino & alcohol groups.

The phospholipid that attaches to sphingosine, Actually attaches to it by the amino group.

- **Classes of sphingolipids:**

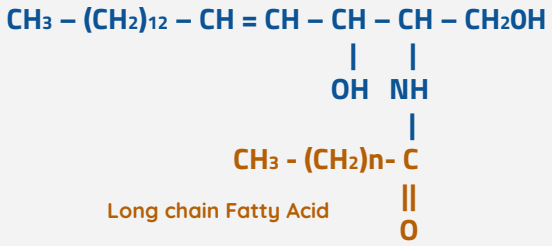
Glycosphingolipids (Glycolipids)	Sphingophospholipids E.g. Sphingomyelin
439: Glycolipid is formed by (Glycerol + 2 fatty acids group) and have carbohydrates attached to them (no phosphate group), Glycerol is formed by glucose.	439: Sphingolipid is formed by (sphingosine + 1 fatty acid group). Sphingosine is formed by (serine->amino acid) and (palmitate-> fat or oil). sphingophospholipids have phosphate group.

Types of Sphingolipids

1

Ceramide:

*Sphingosine + Fatty acid



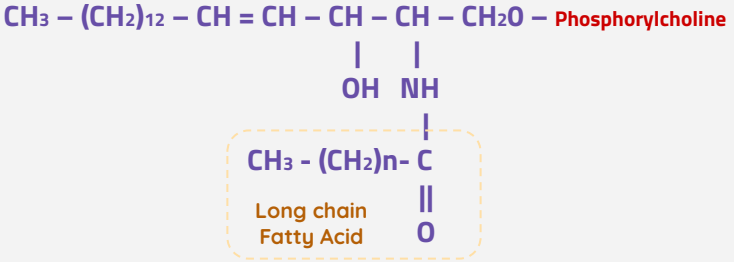
1) Ceramide play a key role in maintaining the skin's water-permeability barrier.
2) Decreased ceramide levels are associated with a number of skin diseases.

Ceramide is the parent molecule for all sphingolipids

2

Sphingomyelin:

*Ceramide + phosphorylcholine



1)Sphingomyelin is the only significant sphingolipid in Humans.

Types of Sphingolipids cont.

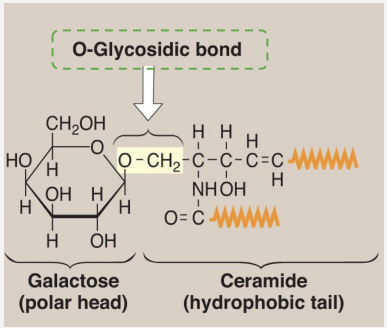
3

Cerebrosides:

***Ceramide + Monosaccharides**

e.g.
Galactocerebroside.

Same glycosidic bond as polysaccharides monomers



4

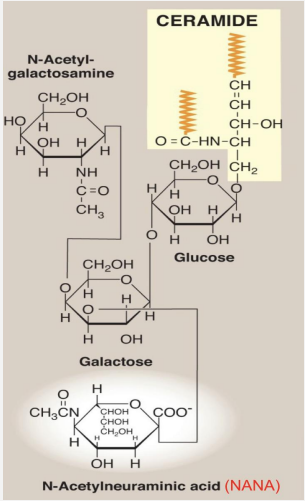
Gangliosides:

***Ceramide + oligosaccharides + NANA**

e.g. G_{M2}.

-G=ganglioside.
-M=mono molecule of NANA.
-2=the monomeric sequence of the carbohydrate attached to the ceramide.

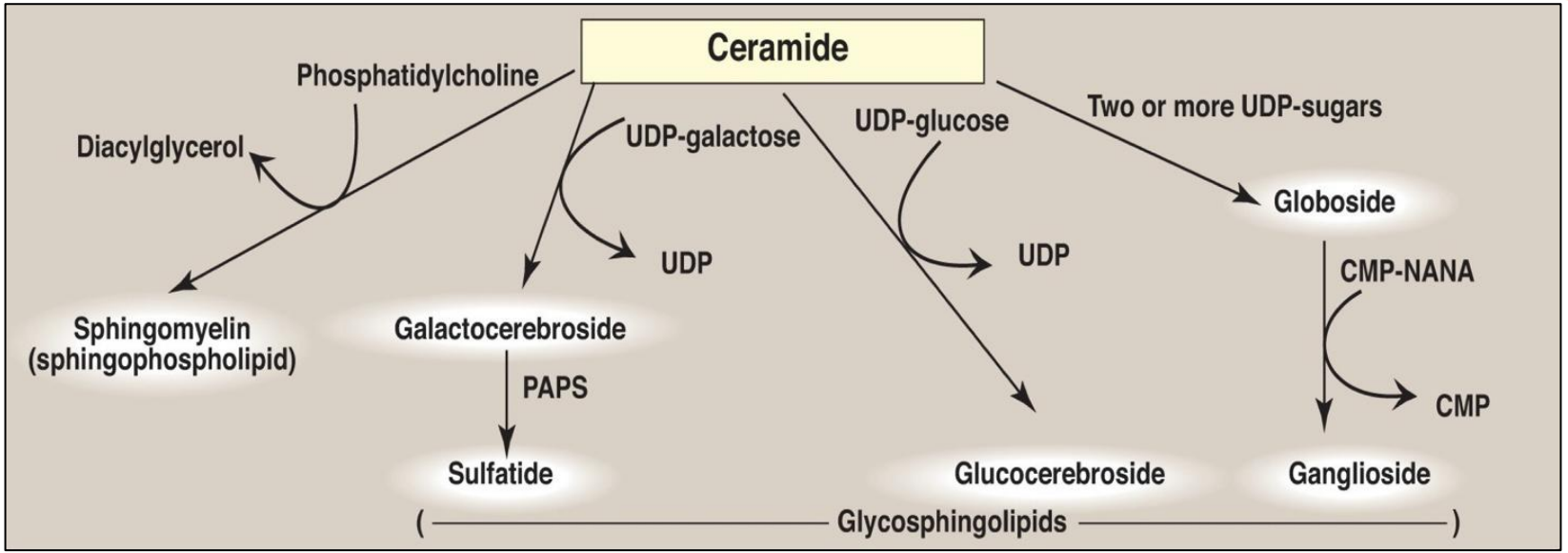
They're present in ganglionic cells, they're charged & acidic in nature due to the presence of NANA.



If you have one monosaccharide attached to ceramide then its called **"Cerebroside"**, but if you have two or more monosaccharides attached to ceramide we call it **"Globoside"**.

Important

Sphingolipids' Synthesis



☆Team 437:

1. Phosphatidylcholine interacts with ceramide and gives it phosphorylcholine, diacylglycerol goes out and gives us sphingomyelin "the only important sphingophospholipid".
2. Galactose is added to ceramide by the carrier UDP "uridine diphosphate", UDP goes out and we get galactocerebroside. We can modify it further by adding a sulfate group with the carrier PAPS, giving us sulfatide.
3. Glucose is added to ceramide by the carrier UDP, UDP goes out and we get glucocerebroside.
4. Two or more UDP sugars are added to ceramide and we get: globosides. If NANA was added to it by the carrier CMP "cytidine monophosphate", we get gangliosides.

Carriers:

1) Phosphatidylcholine: donor of phosphorylcholine to ceramide
2) UDP: carrier of glucose and galactose
3) CMP: carrier for NANA
4) PAPS : donor of sulfate group

Myelin

1

Definition:

Myelin is specialized cell membrane that ensheaths an axon to form a myelinated nerve fiber.

2

Production:

Myelin is produced by:

1) Schwann cells: in Peripheral nerves.

2) Oligodendrocytes: in CNS.

3

Composition:

Lipids (80%):

Main component: Cerebrosides

Other component: Sphingomyelin

Proteins (20%):

e.g. Myelin basic protein

439: Schwann cells envelope its membrane around the axon to make myelin sheath. While Oligodendrocytes send their dendrites to many axons.

4

Myelin Structure:

Fatty acid of Sphingomyelin: Myelin sheath:

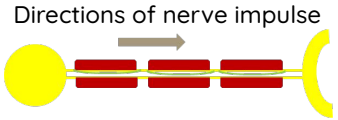
Very long chain fatty acids

Lignoceric 24:0, Nervonic 24:1(15)

5

Function:

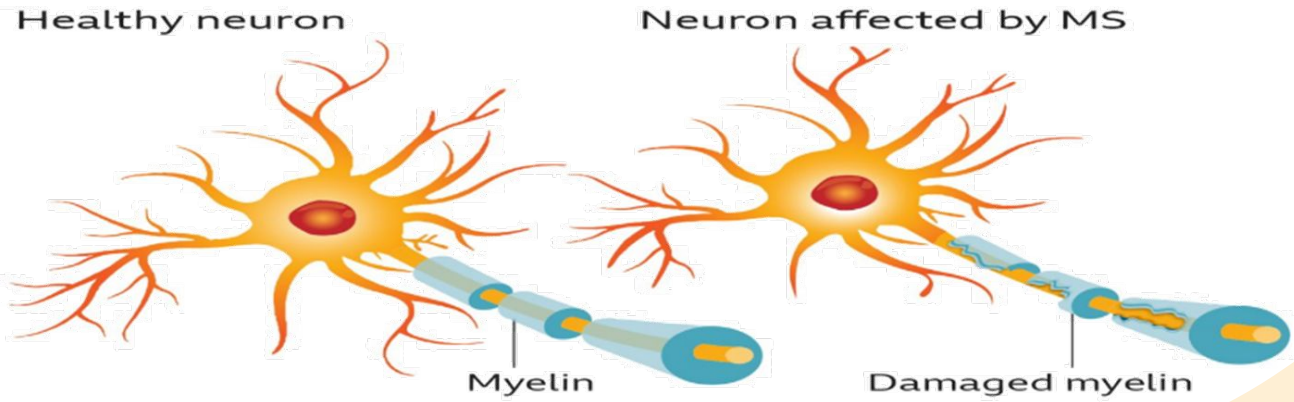
Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speeds up the transmission of impulses along axons.



Nervonic 24:1 (15): 24: Number of carbons. 1: Number of double bonds. (15): Location of the double bond

Multiple sclerosis

- Neuro-degenerative , autoimmune disease.
- Breakdown of myelin sheath (demyelination).
- Defective transmission of nerve impulses.



Sphingolipidoses

Ses = accumulation

-A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.

-Lysosomal lipid storage diseases caused by these deficiencies are called sphingolipidoses.

Synthesis **(Normal)**; Degradation **(Defective)**.

Phenotypic and genotypic variability.

Substrate accumulates in organs..

Autosomal recessive **(mostly)**.

Progressive, early death.

Rare, **Except in** Ashkenazi Jewish.

• **Usually only a single sphingolipid accumulates in the involved organs in each disease.**

Sphingolipidoses

Diagnosis:

- Measure enzyme activity:
  - Cultured fibroblasts or peripheral leukocytes.
  - Cultured amniocytes or chorionic villi (prenatal- If the parents are affected or carriers).
- Histologic examination.
- DNA analysis.

Treatment:

e.g. for Gaucher disease:

- Replacement Therapy (e.g. recombinant human enzyme).
- Bone marrow transplantation

Sphingolipidoses

Important!
Focus on diseases in this slide and their :

- Accumulated lipid
- Enzyme
- Features

1. Tay-Sachs disease:

Accumulation of gangliosides Gm2

• Rapid, progressive, and fatal neurodegeneration • Blindness

• Cherry-red macula • Seizures • Muscular weakness •

Deficiency of activator protein Beta-Hexosaminidase A (Gm2 activator) in some cases.

2. Gaucher disease :

Accumulation of glucocerebrosides

• Most common lysosomal storage disease

• CNS involvement in rare infantile and juvenile forms

• Enzyme Beta-glucosidase replacement therapy.

• Hepatosplenomegaly

• Osteoporosis of long bones

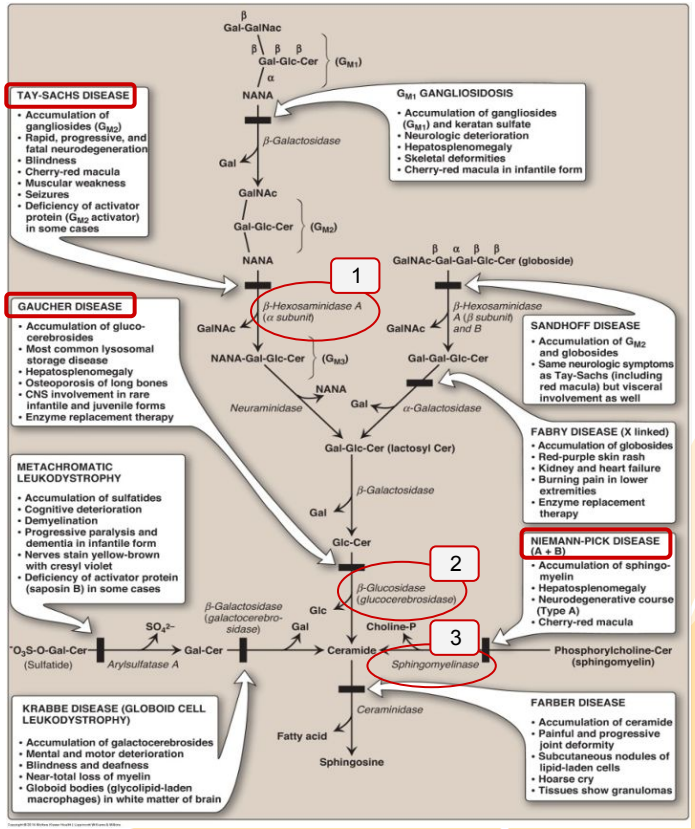
3. Niemann-pick disease (A+ B) :

Accumulation of sphingomyelin

• Hepatosplenomegaly • Cherry-red macula.

• Neurodegenerative course (Type A)

• caused by a missing or malfunctioning enzyme called sphingomyelinase



Sphingolipidoses

4. Metachromatic leukodystrophy:

Accumulation of sulfatides

- Cognitive deterioration
- Progressive paralysis and dementia in infantile form
- Nerves stain yellow-brown with cresyl violet
- Deficiency of activator protein (saposin B) in some cases.
- Demyelination

5. Krabbe disease (globoid cell leukodystrophy) :

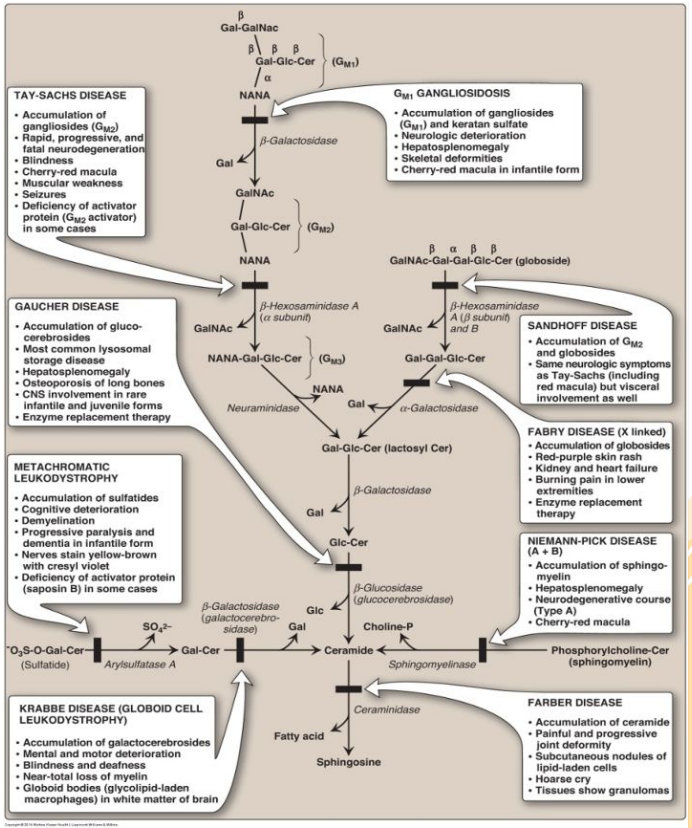
Accumulation of galactocerebrosides

- Mental and motor deterioration
- Near-total loss of myelin
- Globoid bodies (glycolipid-laden macrophages) in white matter of brain.
- Blindness and deafness

6. Sandhoff disease :

Accumulation of Gm2 and globosides

- Same neurologic symptoms as Tay-Sachs (including red macula) but visceral involvement as well.



Sphingolipidoses

All sphingolipidoses diseases are autosomal recessive EXCEPT fabry disease which is an X-linked disease.

7. Fabry disease (X linked) :

Accumulation of globosides

- Red-purple skin rash
- Burning pain in lower extremities.
- Kidney and heart failure
- Enzyme replacement therapy.

8. Gangliosidosis :

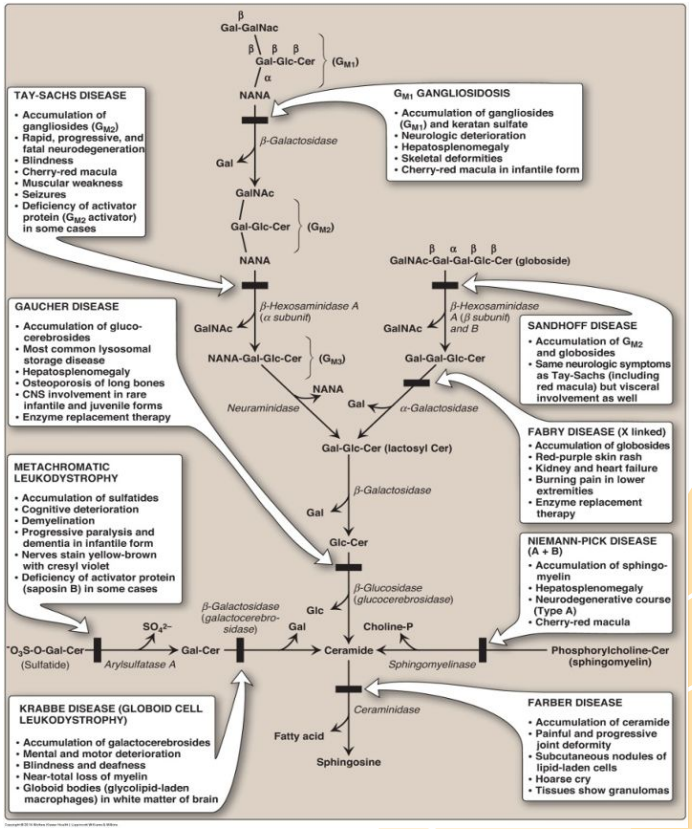
Accumulation of gangliosides Gm1 and keratan sulfate

- Neurologic deterioration
- Cherry-red macula in infantile form.
- Hepatosplenomegaly
- Skeletal deformities

9. Farber disease :

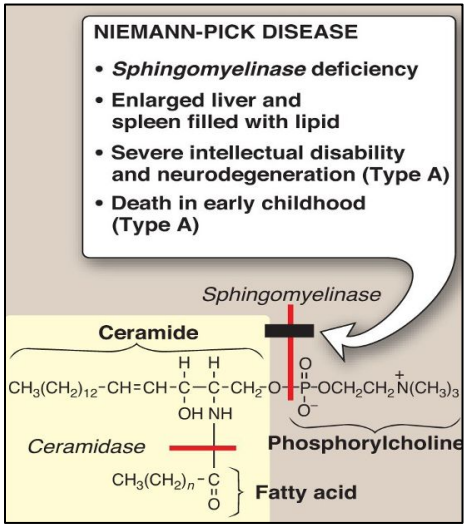
Accumulation of ceramide

- Painful and progressive joint deformity
- Subcutaneous nodules of lipid-laden cells
- Hoarse cry
- Tissues show granuloma.

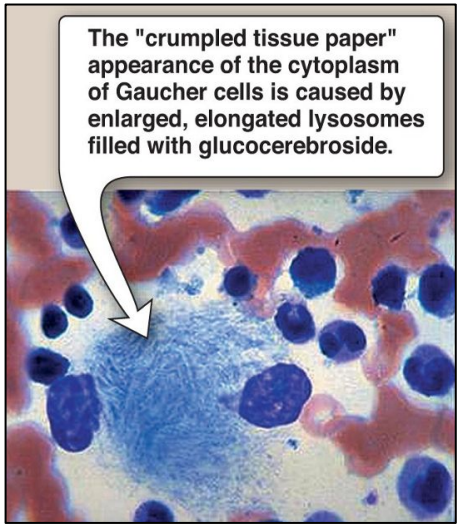


Sphingolipidoses

Niemann-pick disease



Gaucher Disease



Summary!

Take Home Messages

- 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 also found extra-neural.
- Myelin sheath insulates the nerve axon to avoid signal leakage and speed up impulse transmission.
- Sphingolipidoses are rare genetic diseases due to defective degeneration of sphingolipids.

MCQs

Q1: Accumulation of Sphingomyelin is found in?							
A	Niemann-pick disease	**B**	Tay-Sachs disease	**C**	Gaucher disease	**D**	Fabry disease
Q2: ..... is composed of a Ceramide attached to a monosaccharide.							
A	Cerebroside	**B**	Sphingomyelin	**C**	Sphingosine	**D**	Ganglioside
Q3: Which of the following contains N-acetylneuraminic acid?							
A	Cerebroside	**B**	Sphingomyelin	**C**	Sphingosine	**D**	Ganglioside
Q4: Accumulation of Gangliosides GM2 is due to deficiency of?							
A	Activator protein (saposin B)	**B**	Beta-Hexosaminidase A	**C**	Sphingomyelinase	**D**	Beta-glucosidase
Q5: Which of the following carriers is for NANA?							
A	PAPS	**B**	UDP	**C**	CMP	**D**	Phosphatidylcholine

1) A
2) A
3) D
4) B
5) C

SAQ

Q6: Name 3 Sphingolipids and mention their components?

Answer:

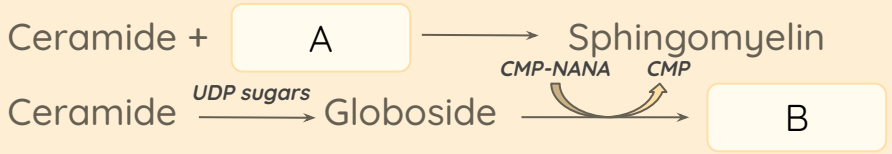
1- Sphingomyelin= Ceramide + Phosphorylcholine
2- Cerebrosides= Ceramide + Monosaccharide
3- Gangliosides= Ceramide + oligosaccharides +NANA

Q7: Name three conditions that lead to the accumulation of sphingolipids?

Answer:

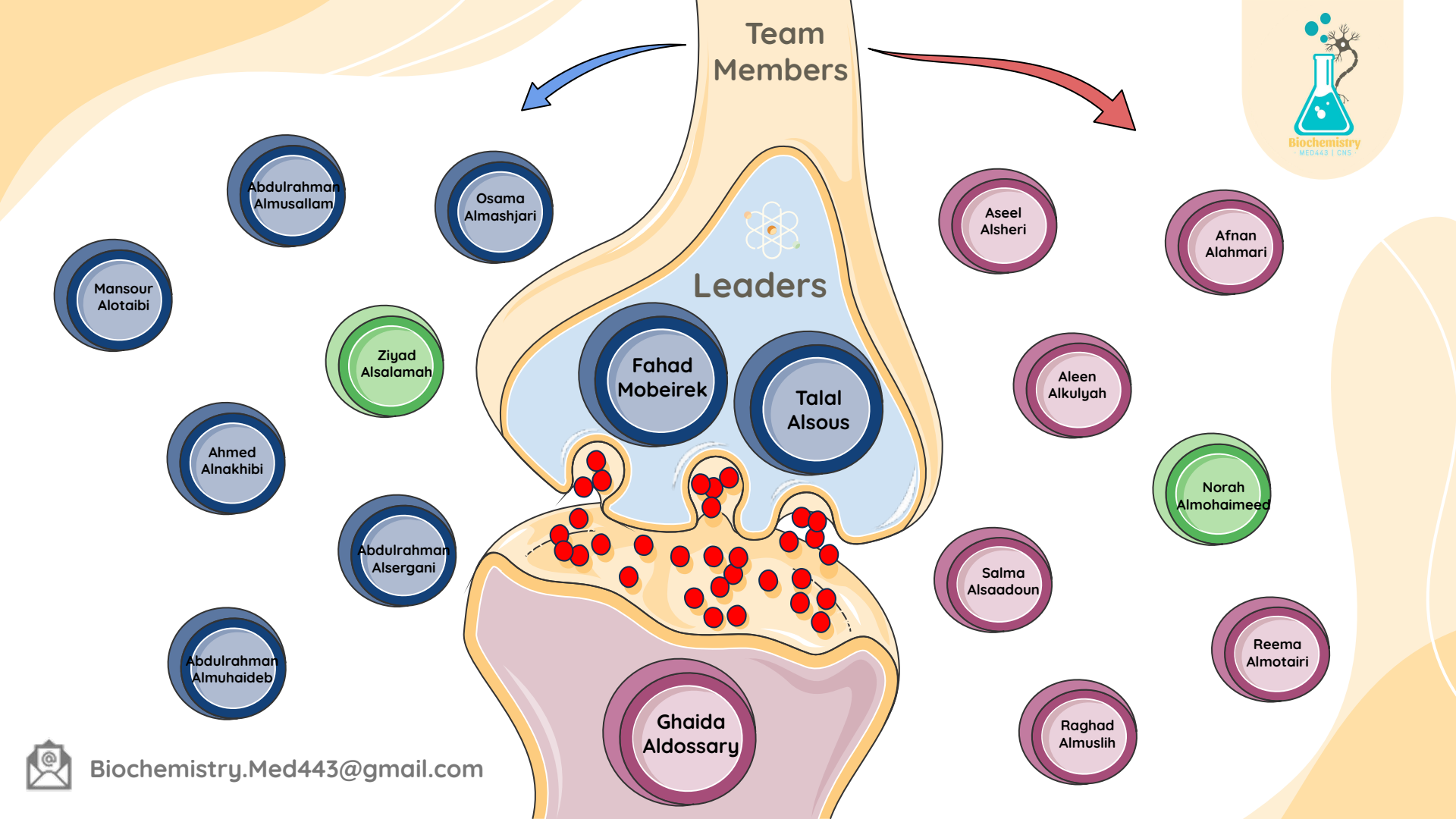
1- Tay-Sachs disease
2- Gaucher's disease
3- Niemann-Pick disease (A+B)

Q8: Fill in the empty boxes:



Answer:

A- Phosphatidylcholine
B- Gangliosides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