Revised & Approved

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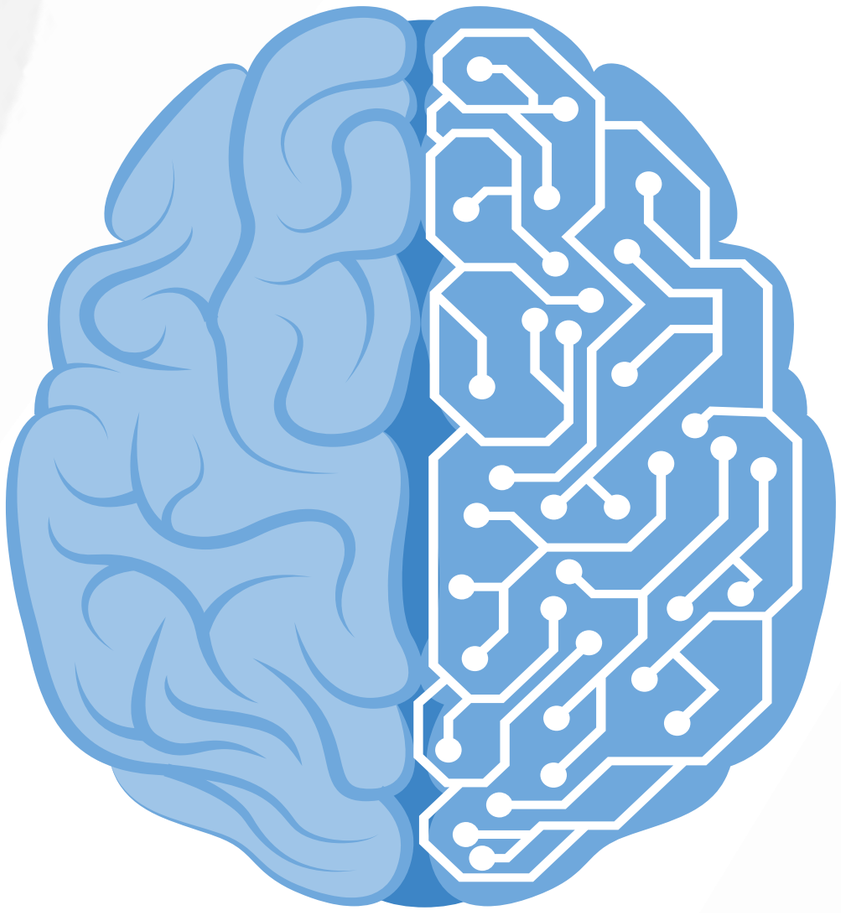
BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY



Sphingolipids And Myelin Structure

Editing File

Color Index

- Main Text
- Important
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- Dr.'s Notes
- Girls slides
- Boys slides

Happy Saudi national day!
Click on the picture to find a surprise and enjoy watching the video too

Objectives

Click on the objective to go to the related slide

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

Level 1 (with each lecture you will level up and it will get harder to find the scientist)

Hello my name is Johann Ludwig Wilhelm Thudichum, Find me in this lecture!
Then click me for more info about what I discovered.

Click the number between the [ ] to see the related notes.

Objective: 1

Background

Classes of sphingolipids

- Glycosphingolipids (Glycolipids) [1]
- Sphingophospholipids [2] e.g. Sphingomyelin

Phospholipids

- Essential component of membranes. [3]
- Cell transformation [4]
- Regulation of growth and development

Very antigenic:

- Blood group antigen
- Embryonic antigen
- Tumor antigen

Classes of phospholipids: (Based on the backbone)

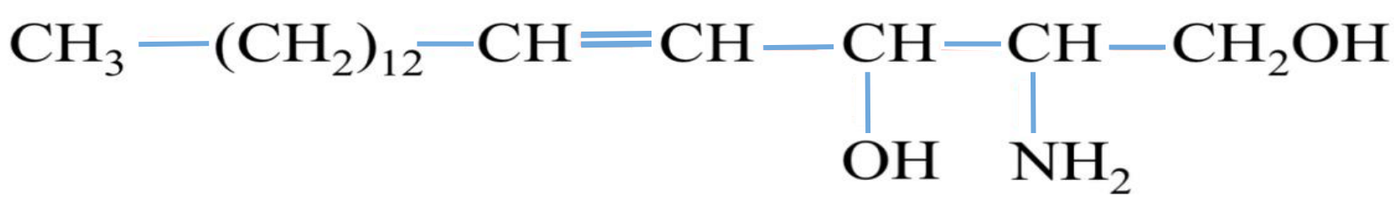
- Glycerol (from glucose)
- Sphingosine (from serine and palmitate)

Abundant in nervous tissue
Also exist extra-nervous tissue: e.g. Receptors for: [5]

- Cholera toxins
- Diphtheria toxins
- Viruses

Sphingosine Structure

Don’t memorize the structure



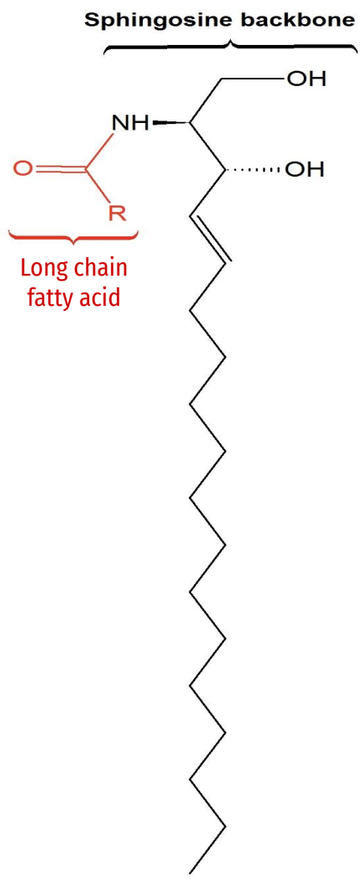
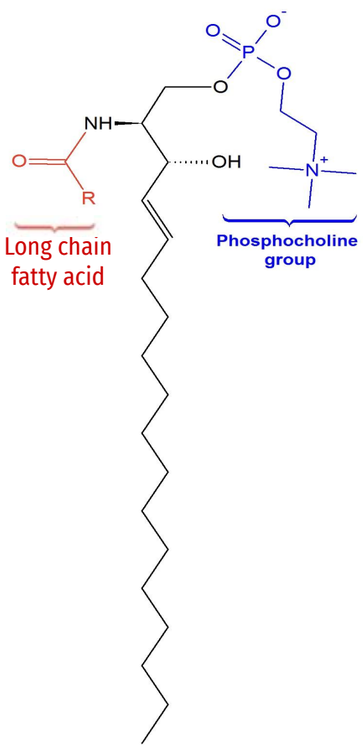
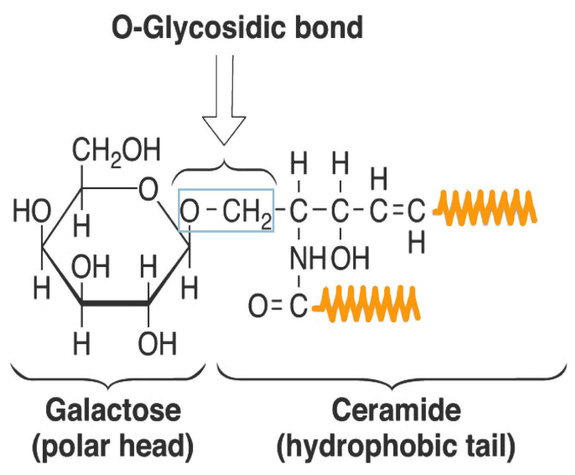
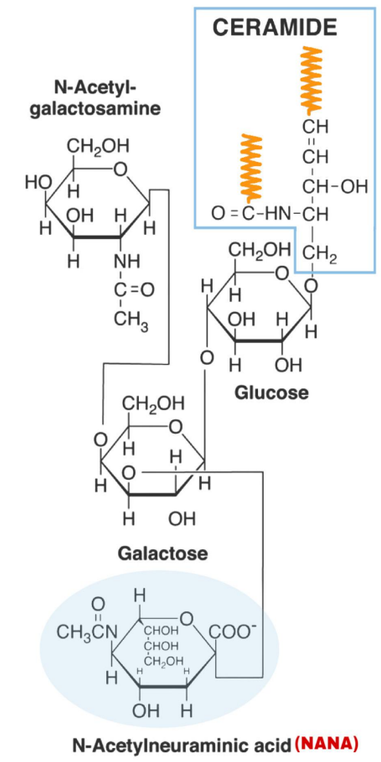
Long chain, unsaturated amino alcohol [6]

Click the number between the [ ] to see the related notes.

Objective: 3

Don't memorize the structures but know the specific characteristics of each sphingolipids

Sphingolipids

Ceramide:[7] Sphingosine + Fatty acid	Sphingophospholipids	Glycosphingolipids	
		Cerebrosides:[8] Ceramide + Monosaccharide	Gangliosides:[9][10] Ceramide + oligosaccharides +NANA
 A Ceramide	 A Sphingomyelin	 Click on the pictures for more info	 Click on the pictures for more info
○ Ceramide play a key role in maintaining the skin's water-permeability barrier. ○ Decreased ceramide levels are associated with a number of skin diseases. Because of its effect Ceramide is actually a component in skin lotions.	Sphingomyelin is the **only significant sphingolipid in humans.**	e.g. Galactocerebroside. The polar head can either be glucose then we will call it glucocerebroside or galactose then we will call it galactocerebroside but galactose is more common.	e.g. G_{M2}: G=ganglioside; M=mono molecule of NANA; [11] 2=the monomeric sequence of the carbohydrate attached to the ceramide

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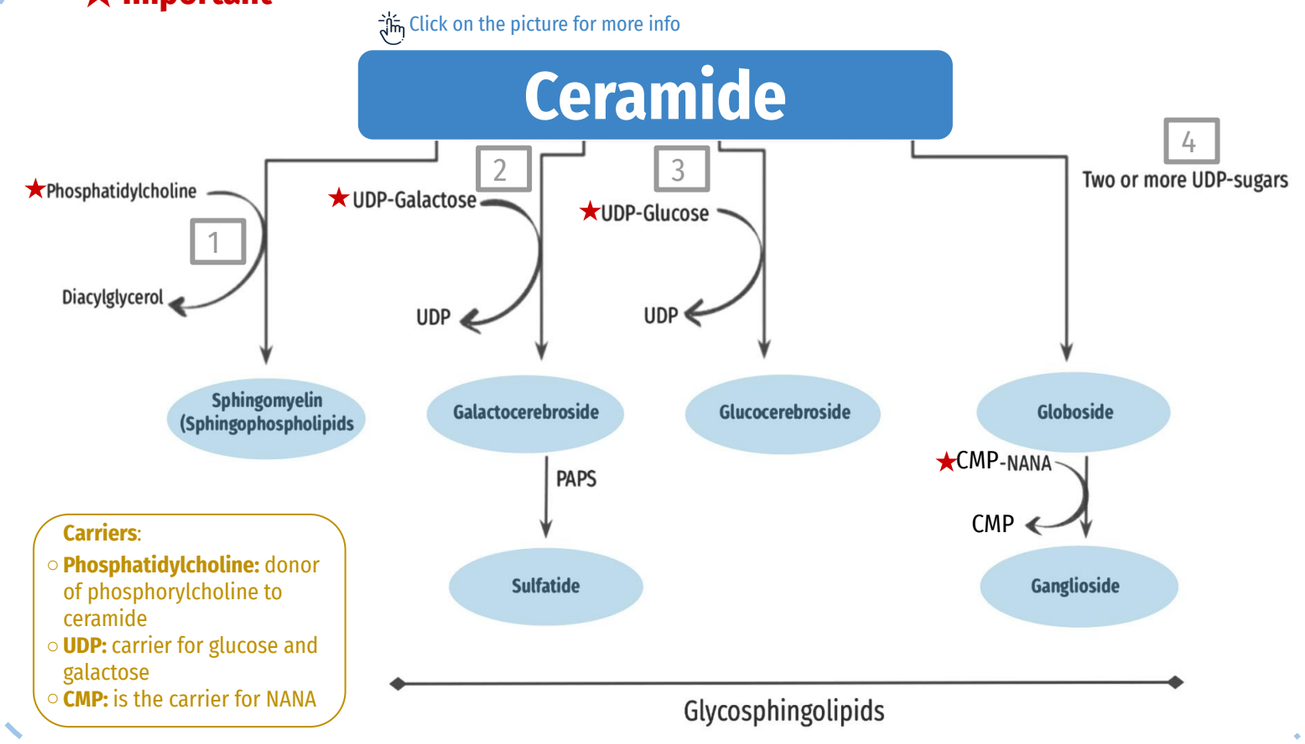
1. Phosphatidylcholine interacts with ceramide, diacylglycerol goes out and gives us sphingomyelin "the only important sphingophospholipid".
2. Galactose is added to ceramide by the carrier UDP "uridine diphosphate", UDP goes out and we get galactocerebroside. We can modify it further by adding a sulfate 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.

★ Important

Click on the picture for more info



Carriers:
- **Phosphatidylcholine:** donor of phosphorylcholine to ceramide
- **UDP:** carrier for glucose and galactose
- **CMP:** is the carrier for NANA

Click the number between the [ ] to see the related notes.

Objective: 2&4

Myelin

Definition

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

Production [12]

Myelin is produced by:

Schwann cells:
in Peripheral nerves.

Oligodendrocytes:
in CNS.

Composition

Myelin composition:

Lipids (80%):
Main component:
Cerebrosides
Other component:
Sphingomyelin

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

Myelin sheath

Fatty acid of Sphingomyelin:

Myelin sheath:
Very long chain fatty acids

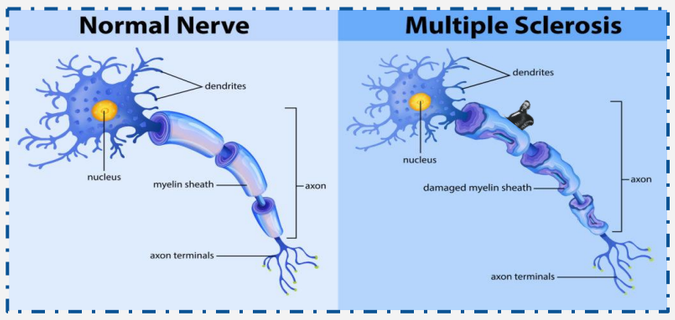
Lignoceric 24:0
Nervonic 24:1(15) [18]

Function

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

Multiple sclerosis

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



Sphingolipidoses

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

- Synthesis is (**Normal**), but Degradation is (**Defective**)
- Progressive, **early death**
- **Autosomal recessive** (mostly)[15]
- Substrate accumulates in organs
- Phenotypic and genotypic variability [13][14]
- Rare, Except in **Ashkenazi Jewish**

Diagnosis

1. Measure enzyme activity:
1.1 Cultured fibroblasts or peripheral leukocytes.
1.2 Cultured amniocytes or chorionic villi (prenatal).[16]
2. Histologic examination.
3. DNA analysis.[17]

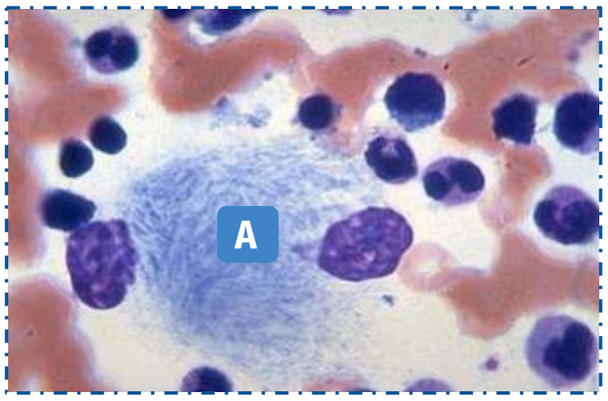
Treatment

e.g. for Gaucher disease: (it will be explained in the next slide)
1. Replacement Therapy (e.g. recombinant human enzyme).
2. Bone marrow transplantation.

Sphingolipidoses

Gaucher Disease:

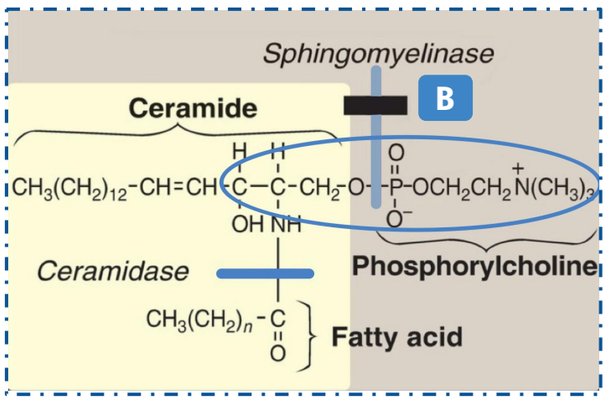
Click on the picture for more info



A The "crumpled tissue paper" appearance of the cytoplasm of Gaucher cells is caused by enlarged, elongated lysosomes filled with glucocerebroside.

Niemann-pick disease:

Click on the picture for more info

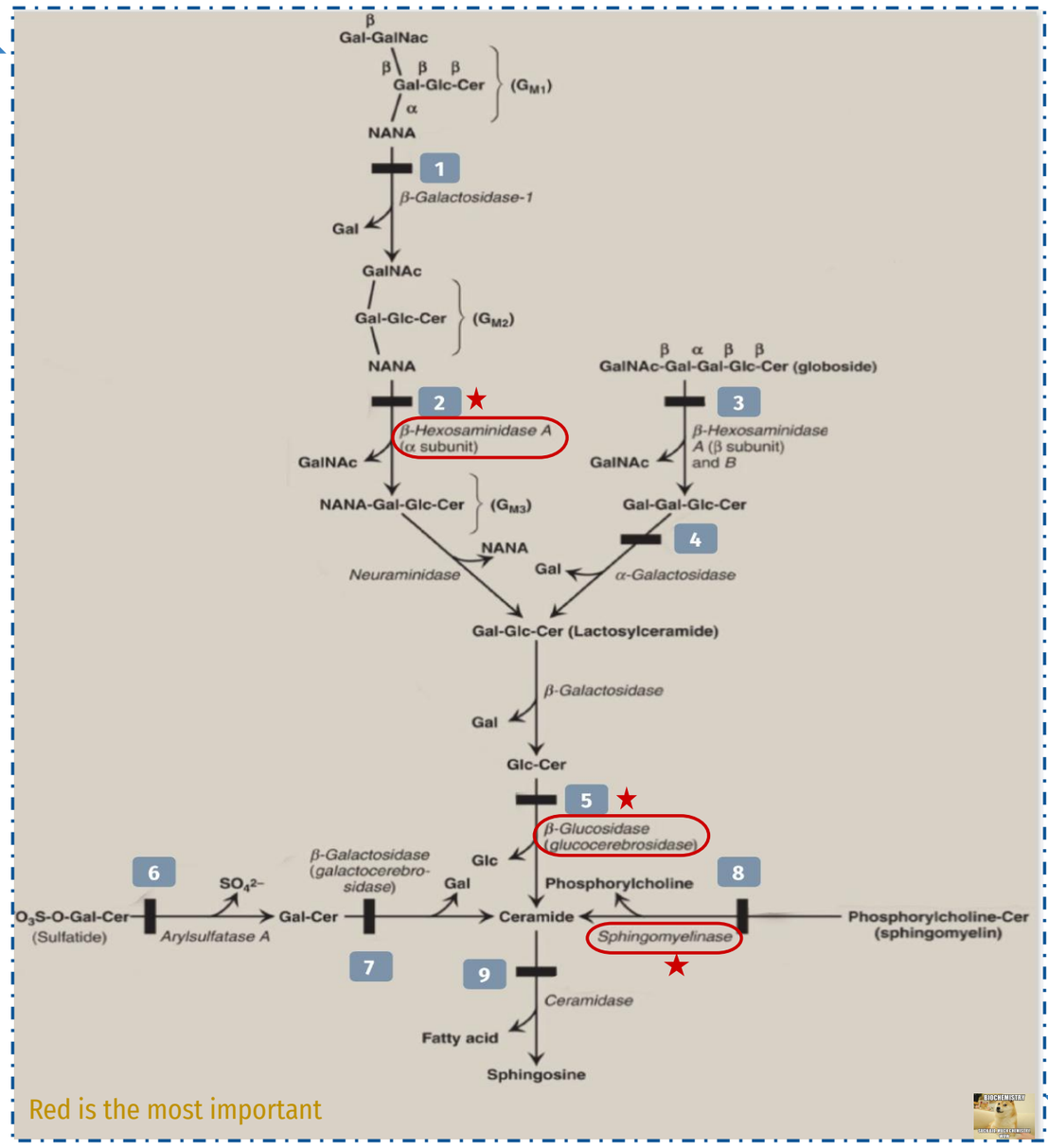


B

Sphingomyelinase deficiency

1. Enlarged liver and spleen filled with lipid
2. Severe intellectual disability and neurodegeneration (Type A)
3. Death in early childhood (Type A)

Click on the picture for more info



Red is the most important

1	Gangliosidosis : Accumulation of gangliosides Gm1 and keratan sulfate • Neurologic deterioration • Hepatosplenomegaly • Skeletal deformities • Cherry-red macula in infantile form.
2	**Tay-Sachs disease :** **Accumulation of gangliosides Gm2 • Rapid, progressive, and fatal neurodegeneration• Blindness • Cherry-red macula • Muscular weakness •Seizures • Deficiency of activator protein Beta-Hexosaminidase A (Gm2 activator) in some cases.**
3	Sandhoff disease : Accumulation of Gm2 and globosides • Same neurologic symptoms as Tay-Sachs (including red macula) but visceral involvement as well.
4	Fabry disease (X linked) : Accumulation of globosides • Red-purple skin rash • Kidney and heart failure • Burning pain in lower extremities • Enzyme replacement therapy.
5	**Gaucher disease :** **Accumulation of glucocerebrosides • Most common lysosomal storage disease • Hepatosplenomegaly • Osteoporosis of long bones • CNS involvement in rare infantile and juvenile forms • Enzyme Beta-glucosidase replacement therapy.**
6	Metachromatic leukodystrophy Accumulation of sulfatides • Cognitive deterioration • Demyelination • Progressive paralysis and dementia in infantile form • Nerves stain yellow-brown with cresyl violet • Deficiency of activator protein (saposin B) in some cases.
7	Krabbe disease (globoid cell leukodystrophy) : Accumulation of galactocerebrosides • Mental and motor deterioration • Blindness and deafness • Near-total loss of myelin • Globoid bodies (glycolipid-laden macrophages) in white matter of brain.
8	**Niemann-pick disease (A+ B) :** **Accumulation of sphingomyelin • Hepatosplenomegaly • Neurodegenerative course (Type A) • Cherry-red macula. •caused by a missing or malfunctioning enzyme called sphingomyelinase**
9	Farber disease : Accumulation of ceramide • Painful and progressivejoint deformity • Subcutaneous nodules of lipid-laden cells • Hoarse cry • Tissues show granuloma.

Doctors' Notes

Click the note to go back to the related slide

[1] glycolipid is formed by (Glycerol + 2 fatty acids group) and have carbohydrates attached to them (no phosphate group), Glycerol is formed by glucose

[2] 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.

[3] Phospholipids form an essential component of cell membrane along with cholesterol and proteins. Sphingolipids abundantly present in nerve tissues

[4] Carbohydrates in phospholipids serve as biomarker for cell transformation. "e.g. when the cell transformed into cancer cell".

[5] Polar head group of the phospholipid helps in recognition and formation of receptors (head) ——> exposed to extracellular environment (it may be attached to carb to act as receptor

[6] (Long chain = 18 carbon ,Unsaturated due to double bond . The NH2 will be attached to other molecules)

[7] Ceramide is the parent molecule for all sphingolipids.

[8] Monosaccharide can be either glucose or galactose, and the majority of cerebrosides in the membranes are galactocerebroside. When we have monosaccharide we call it cerebroside when we have 2 or more monosaccharides units we call it globoside

[9] Gangliosides are present in ganglionic cells.

[10] Cerebrosides are neutral "not charged", but gangliosides are -ve charged so they are acidic.

[11] Nana molecule (common name is Sialic acid) in one ganglioside can vary in number, for example if we have 2 (**D**i) NANA the **M** (**M**ono) in G**M**2 will be replaced by a **D** (G**D**2).

[12] Schwann cells envelope its membrane around the axon to make myelin sheath. While oligodendrocytes send their dendrites to many axons.

[13] Phenotypic variability means that the enzyme is completely absent or present but have little activity.

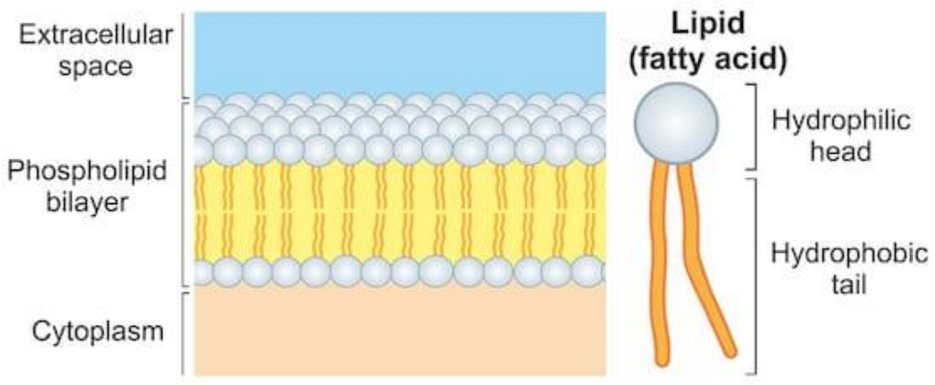
[14] Genotypic variability means mutation in the enzyme's gene which will reduced enzyme activity or loss of its activity.

[15] All sphingolipidoses diseases are autosomal recessive EXCEPT fabry disease which is X linked disease.

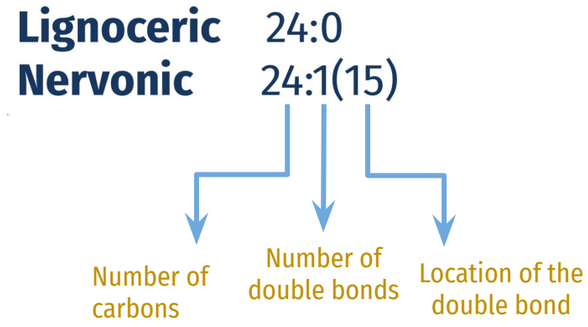
[16] If the parent are carrier of the enzyme mutation or they are going to be affected we can apply prenatal diagnosis.

[17] If you know all the gene mutations that could lead to the disease then you can apply DNA analysis
For ex: if there are 10 mutations and we know 3 then we can't do it.

Extra (related to note [5])



[18]



Summary

Sphingolipids

Ceramide: Sphingosine + Fatty acid

Play a central role in maintaining the skin's water permeability

- Decreased ceramide levels are associated with a number of skin diseases

Sphingophospholipids

Sphingomyelin :
Ceramide + Phosphorylcholine

Sphingomyelin is the only significant sphingolipid in humans

Glycosphingolipids

Cerebrosides:
Ceramide + Monosaccharide

e.g. Galactocerebroside

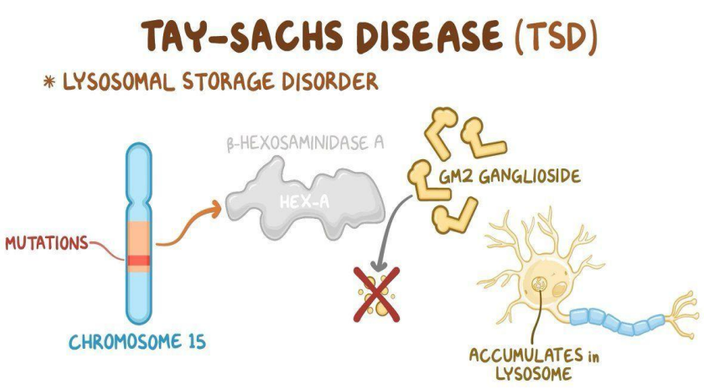
Gangliosides:
Ceramide + oligosaccharides +NANA

E.g. GM2:
G= ganglioside;
M= mono molecule of NANA;
2= the monomeric sequence (position) of the carbohydrate attached to the ceramide

Sphingolipidoses

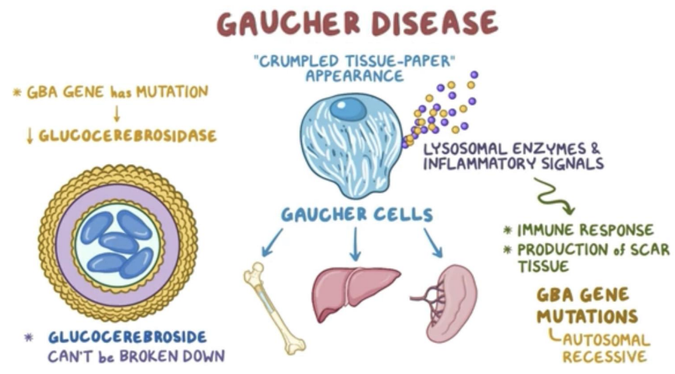
TAY-SACHS DISEASE

- Accumulation of gangliosides (GM2).
- Deficiency of the enzyme β-Hexosaminidase A
- Rapid, progressive and fatal Neurodegeneration.
- Cherry-red macula "red spot found in the Retina"
- Muscular weakness.
- Seizures
- Deficiency of activator protein (GM2) in some cases.



GAUCHER DISEASE

- Accumulation of glucocerebroside .
- Deficiency of the enzyme β-glucosidase (glucocerebrosidase).
- Most common.
- Causes osteoporosis in long bones
- hepatosplenomegaly "in liver and spleen".
- Causes crumpled tissue paper appearance of the cytoplasm.
- Treated with replacement therapy and bone marrow transplantation.

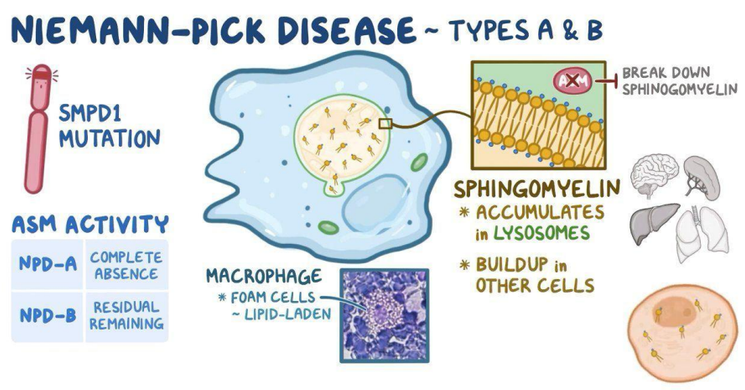


NIEMANN-PICK DISEASE (A+B)

- Accumulation of sphingomyelin.
- Sphingomyelinase deficiency.
- hepatosplenomegaly
- Cherry-red macula .
- It has two types, A and B:

- Type A is more severe because the enzyme has almost no activity, it causes severe intellectual disability and death in early childhood.

-Type B is less severe, has a later onset and causes little to no neurodegeneration.



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

1- Deficiency in beta Hexosaminidase A results in:

A-niemann-pick disease
B-Gaucher disease
C-Tay-sachs disease
D-Sphingomyelin

2- A Neurodegenerative, auto-immune disease that involves the breakdown of myelin sheath:

A-Multiple sclerosis
B-Fabry disease
C-Niemann-pick disease.
D-Tay-sachs disease.

3- Patient with sphingomyelinase deficiency will most likely develop:

A-Gaucher disease.
B-Farbry disease.
C-Tay-sachs disease.
D-Niemann-pick disease.

4- Gaucher disease results from deficiency of which ONE of the following enzymes:

A-Beta hexosaminidase A
B-Sphingomyelinase
C-Beta glucosidase
D-Saposin B

5- in the CNS myelin produced by :

A-Oligodendrocytes
B-Schwann cells
C-macrophages
D-astrocytes

6- Which one of the following is NOT a diagnosis procedure for Sphingolipidoses:

A-DNA analysis
B-PCR
C-Measurement of enzyme activity
D-Histologic examination

Answers key

1- C 2- A 3- D 4- C 5- A 6- B

🧠 SAQs

1- What is the cause of Sphingolipidoses?

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

2- What is the product and byproduct of Phosphatidylcholine + Ceramide?

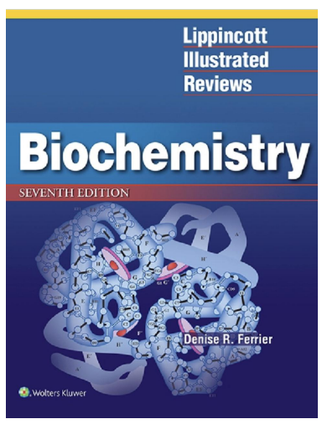
-The product is sphingomyelin and byproduct diacylglycerol

3- A 10 month old male is brought to the pediatrician by his mother who is concerned about his lack of interaction. He was previously playful and happy but now hardly ever smiles. On examination, he is found to have poor muscle tone and a Cherry red macula. Deficiency of which enzyme is most likely?

- Deficiency of the enzyme β-Hexosaminidase

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.