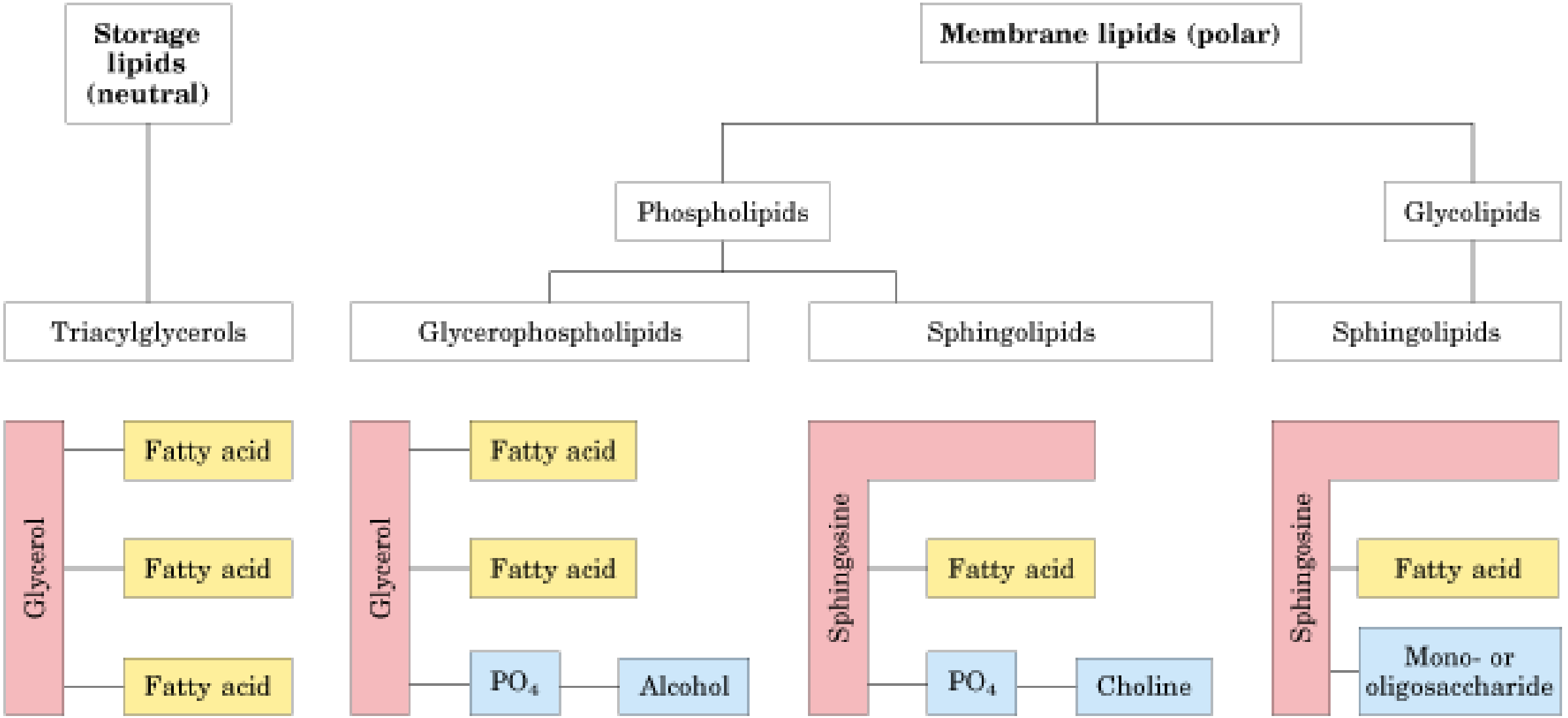
Metabolism of lipids VI:

Sphingolipids

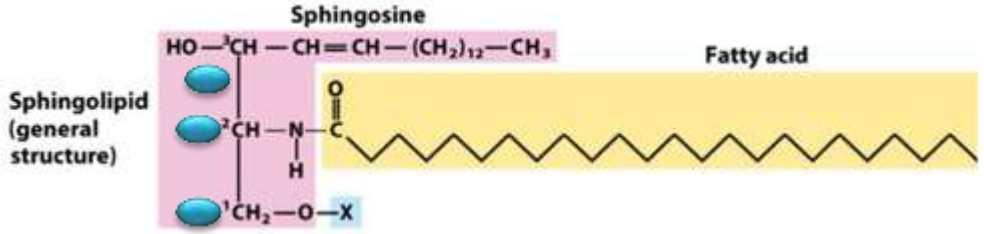
Prof. Mamoun Ahram

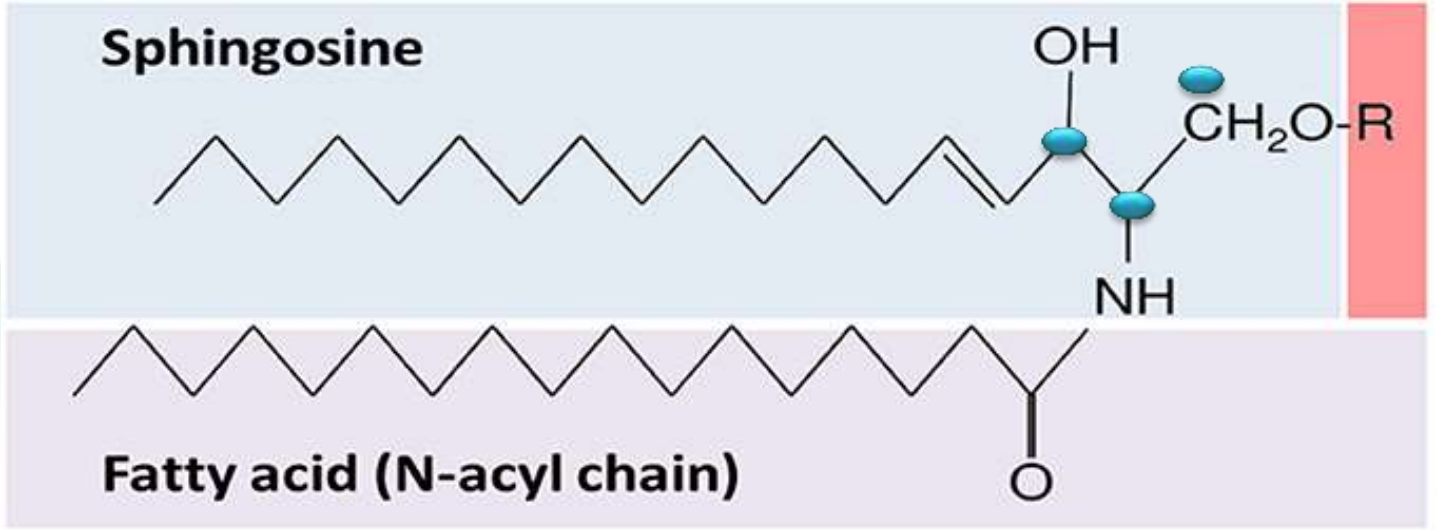
Resources

- This lecture
- Lippincott's Biochemistry, Ch. 17


Storage lipids (neutral)
Membrane lipids (polar)
Phospholipids
Glycolipids
Triacylglycerols
Glycerophospholipids
Sphingolipids
Sphingolipids
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
PO_4
Alcohol
Sphingosine
Fatty acid
PO_4
Choline
Sphingosine
Fatty acid
Mono- or oligosaccharide

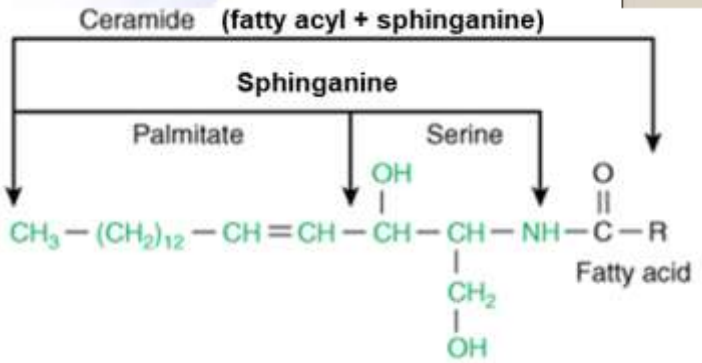
Structure of sphingolipids

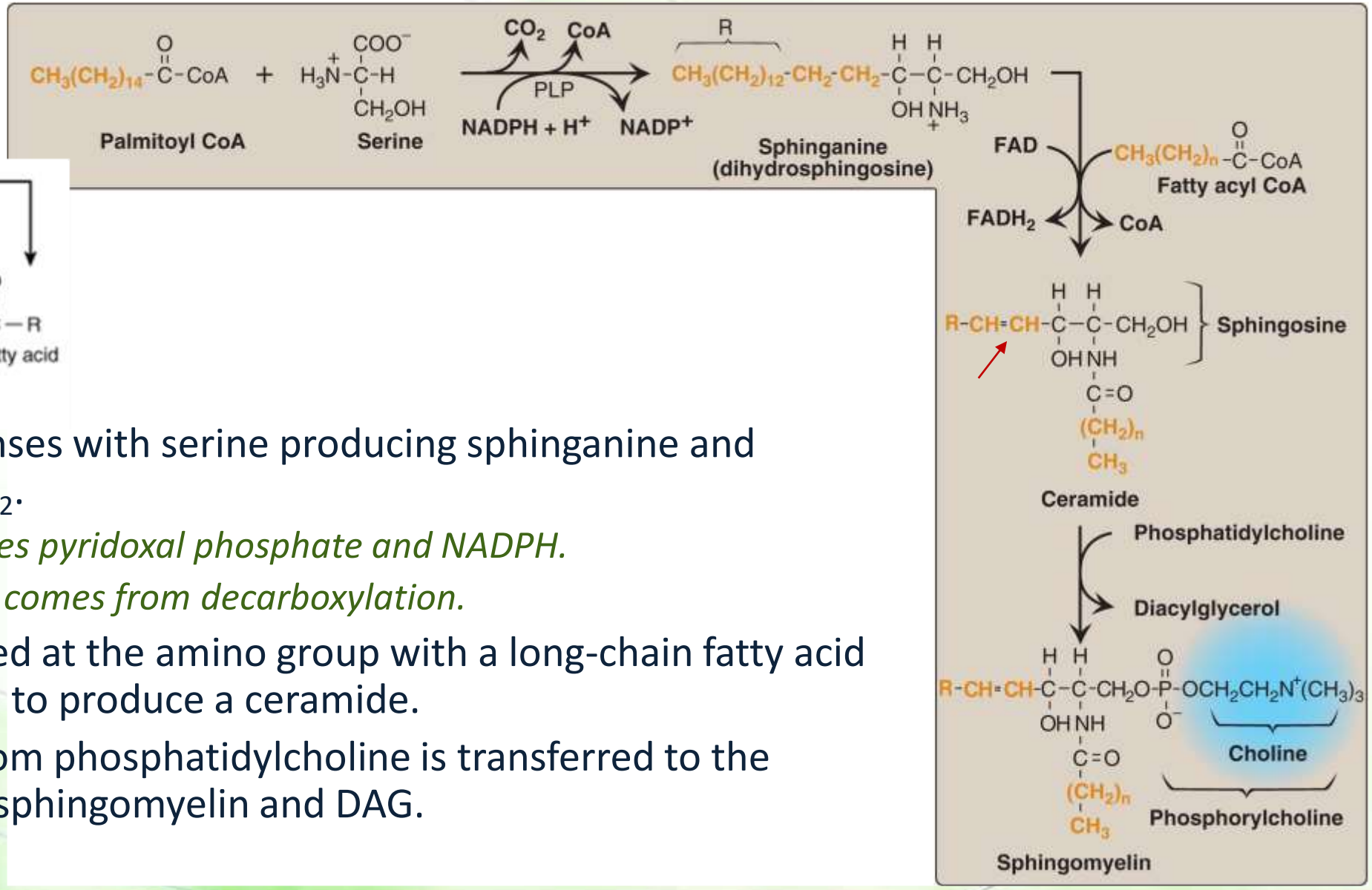




Substituent (R)	Sphingolipid
H	Ceramides
Phosphocholine	Sphingomyelins
Sugar (s) - Single sugar (glucose or galactose) - Lactose (disaccharide) - Oligosaccharide - Sugar + sulfate	Glycosphingolipids - Cerebrosides - Lactosylceramides - Gangliosides - Sulfatides

Synthesis of sphingomyelin



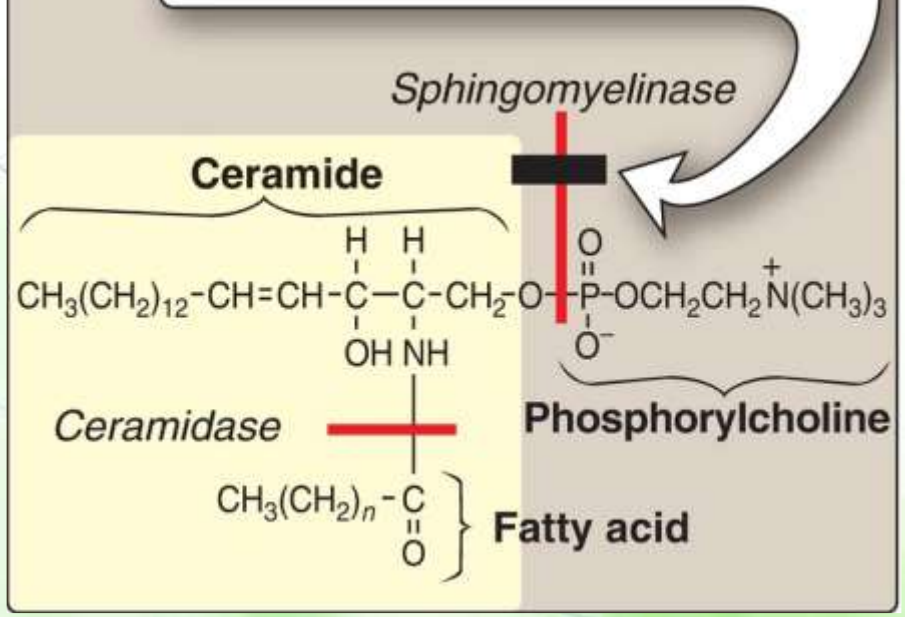


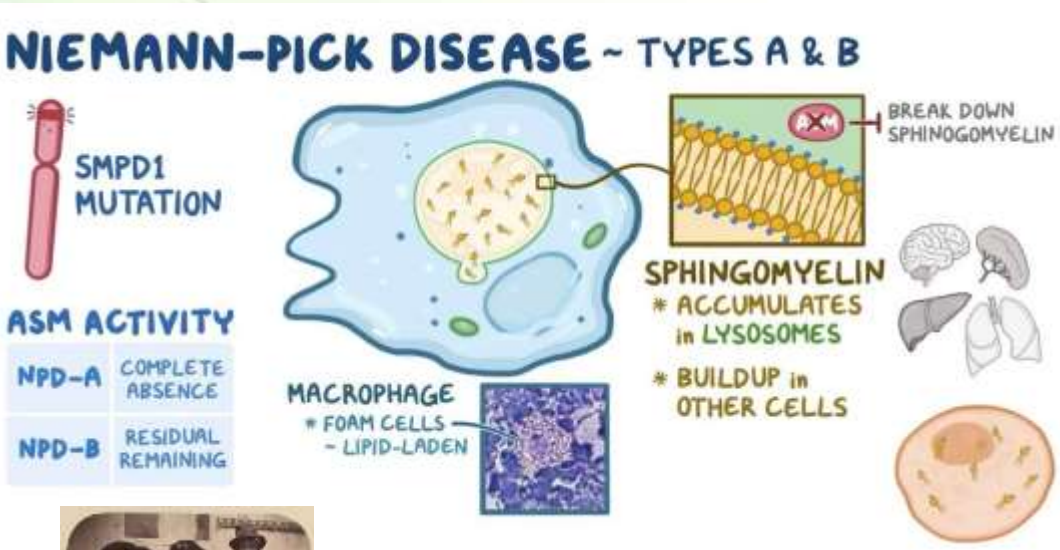
- Palmitoyl CoA condenses with serine producing sphinganine and releasing CoA and CO_2.
  - *The reaction requires pyridoxal phosphate and NADPH.*
  - *The needed energy comes from decarboxylation.*
- Sphinganine is acylated at the amino group with a long-chain fatty acid and then desaturated to produce a ceramide.
- Phosphorylcholine from phosphatidylcholine is transferred to the ceramide, producing sphingomyelin and DAG.

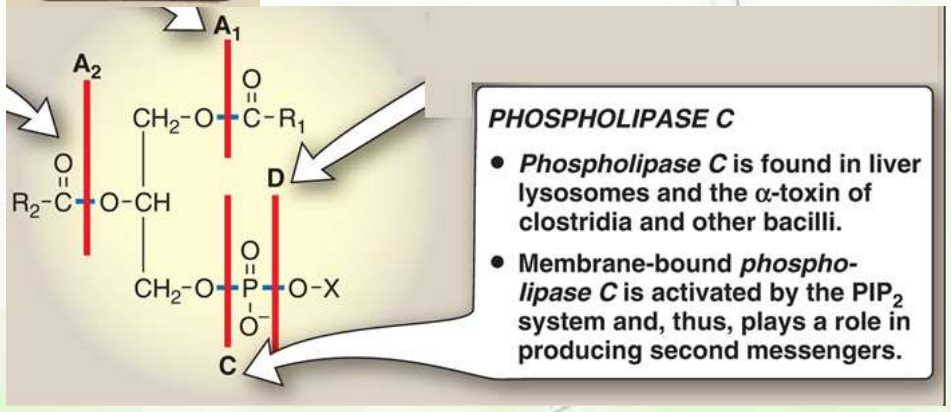
Deficiency of sphingomyelinase

NIEMANN-PICK DISEASE

- *Sphingomyelinase* deficiency
- Enlarged liver and spleen filled with lipid
- Severe intellectual disability and neurodegeneration (type A)
- Death in early childhood (type A)

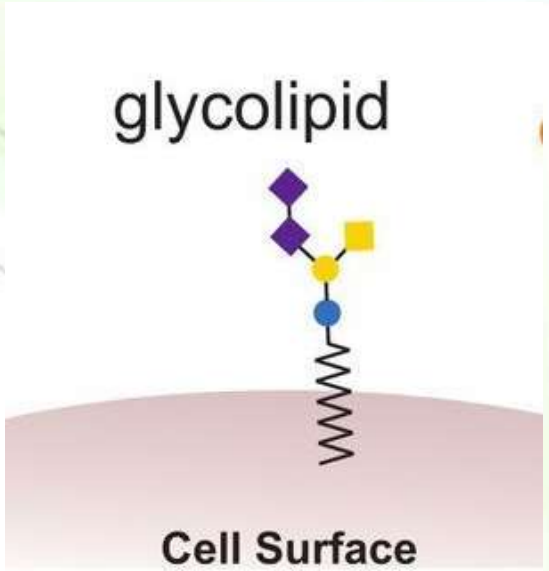


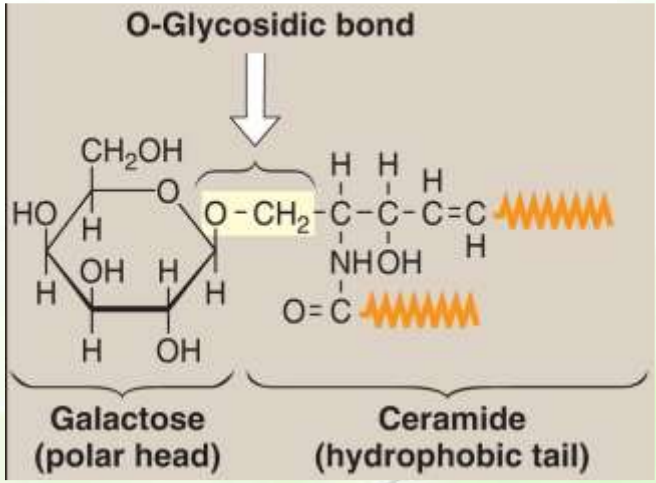




Glycosphingolipids (glycolipids)

- They are made of ceramide (precursor).
- A sugar(s) is attached to ceramide by an O-glycosidic bond.
- The number and type of carbohydrate moieties determine the type of glycosphingolipid.
- They are localized in the outer leaflet of the plasma membrane and exposed extracellularly (adhesion, recognition, and signaling).
- Their hydrophobic ceramide tail inserts into the outer phospholipid leaflet, while the glycan headgroup extends outwardly.

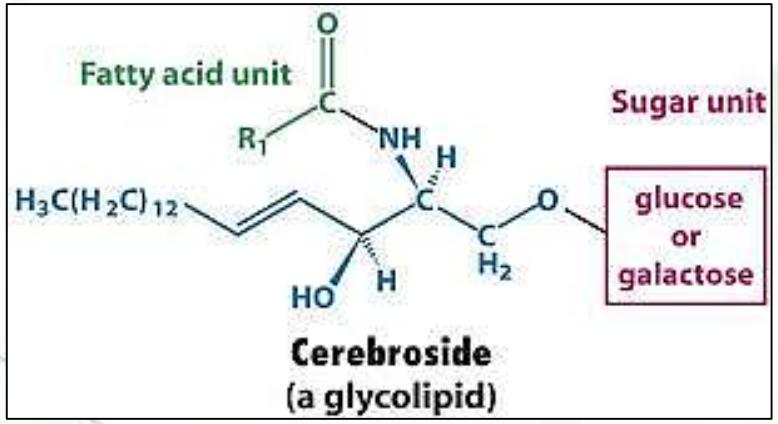




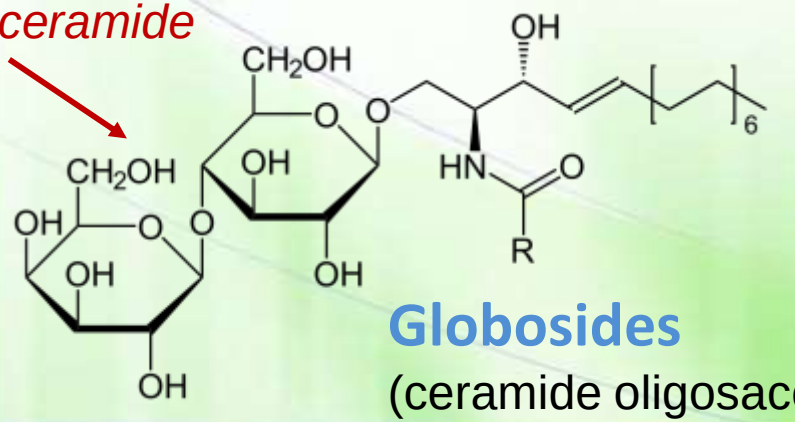
Types of glycolipids

Neutral glycosphingolipids

- **Cerebrosides** are the simplest.



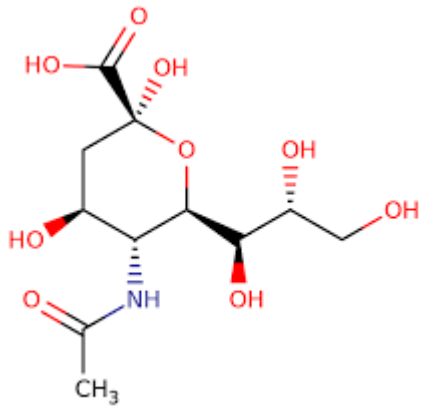
Lactosylceramide

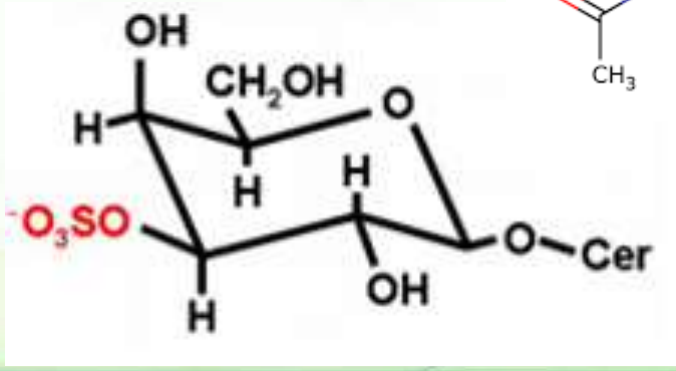


Globosides
(ceramide oligosaccharides)

Acidic glycosphingolipids (gangliosides)

- They are negatively charged at physiologic pH due to attachment of N-acetylneuraminic acid ([NANA], a sialic acid, in gangliosides or by sulfate groups in sulfatides.



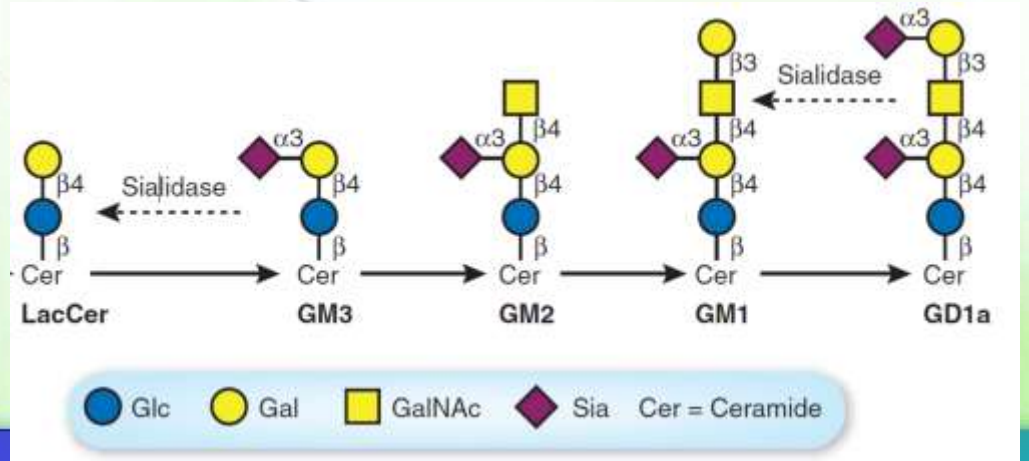


More on gangliosides and sulfatides

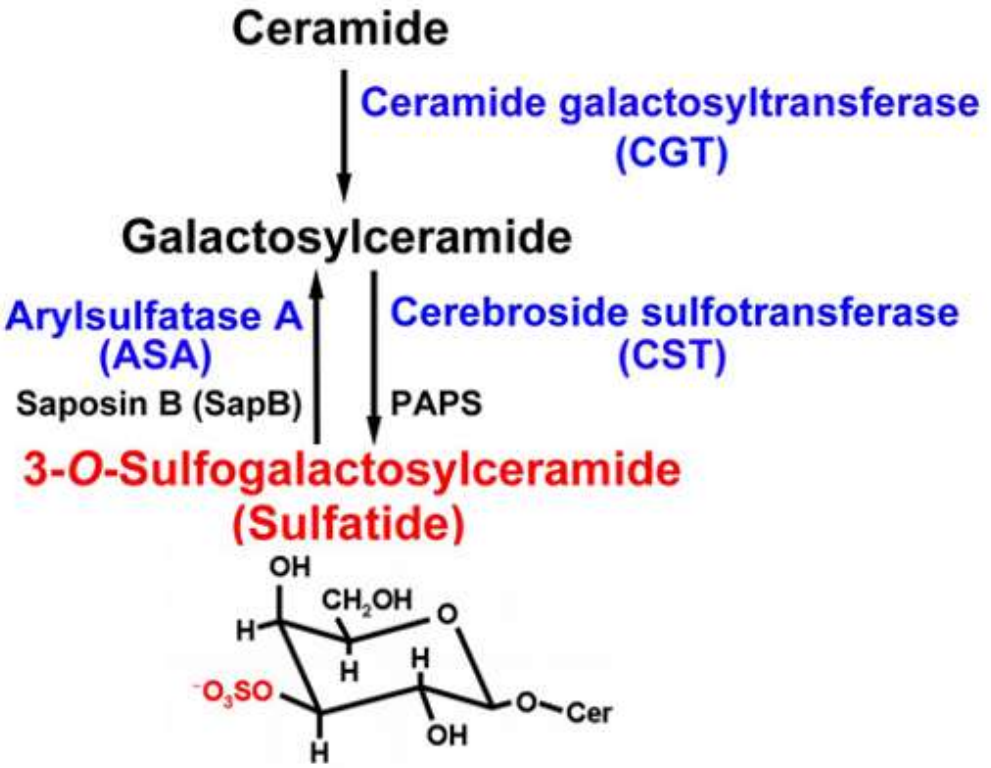
https://chat.openai.com/share/b7c23fa3-71d4-4d6e-bb09-7c90df1d1876

Gangliosides

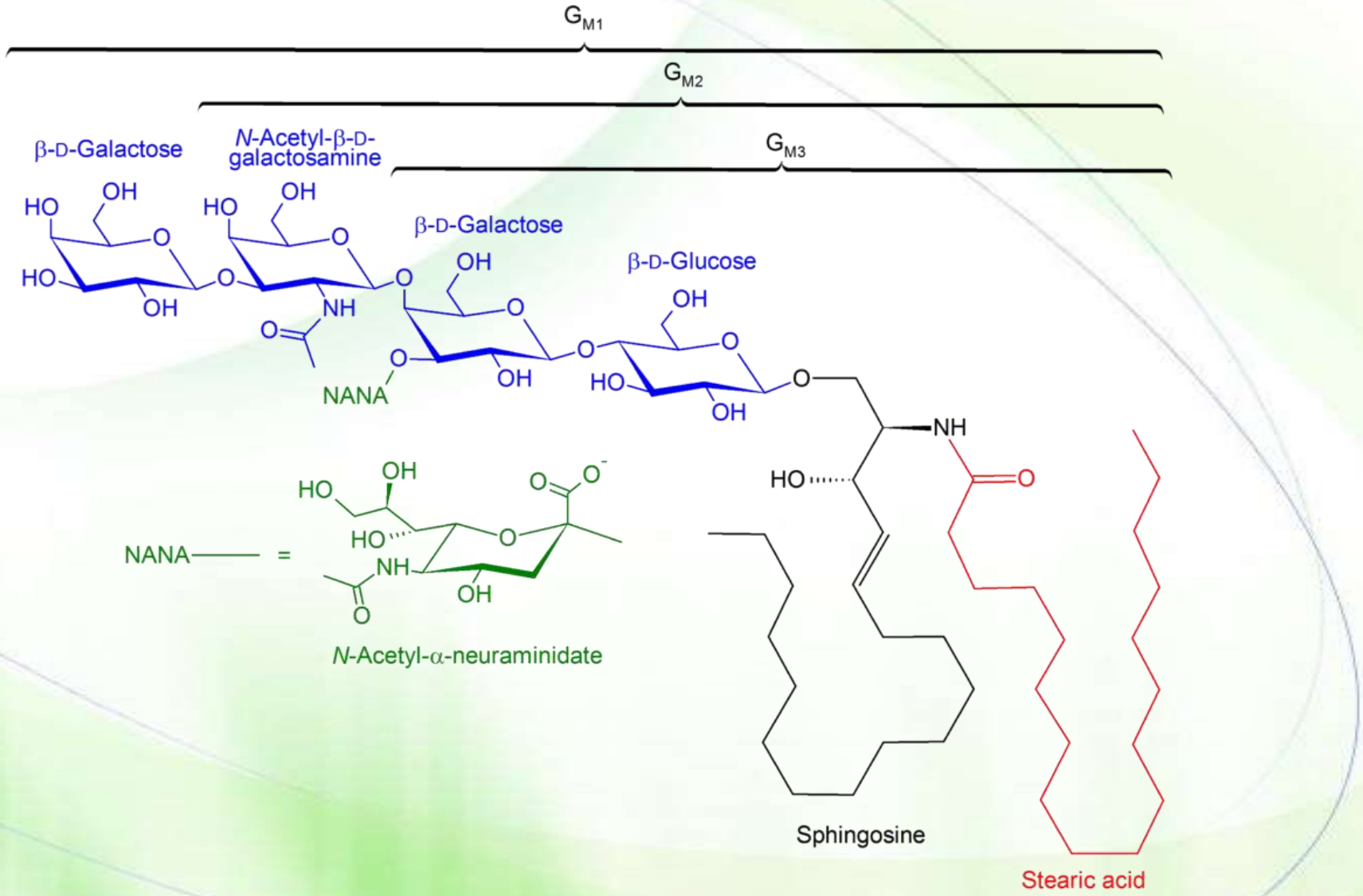
- They are designated as G (for ganglioside) plus a subscript (M, D, T, or Q) to indicate the number of sialic acid molecules: 1 (mono), 2 (di), 3 (tri), or 4 (quatro), and then numbers to indicate **indirectly** the number of sugar residues subtracted from 5:
  - GM1 contains 5–1 = 4 sugar residues
  - GD3 contains 5–3 = 2 sugar residues



Sulfatides

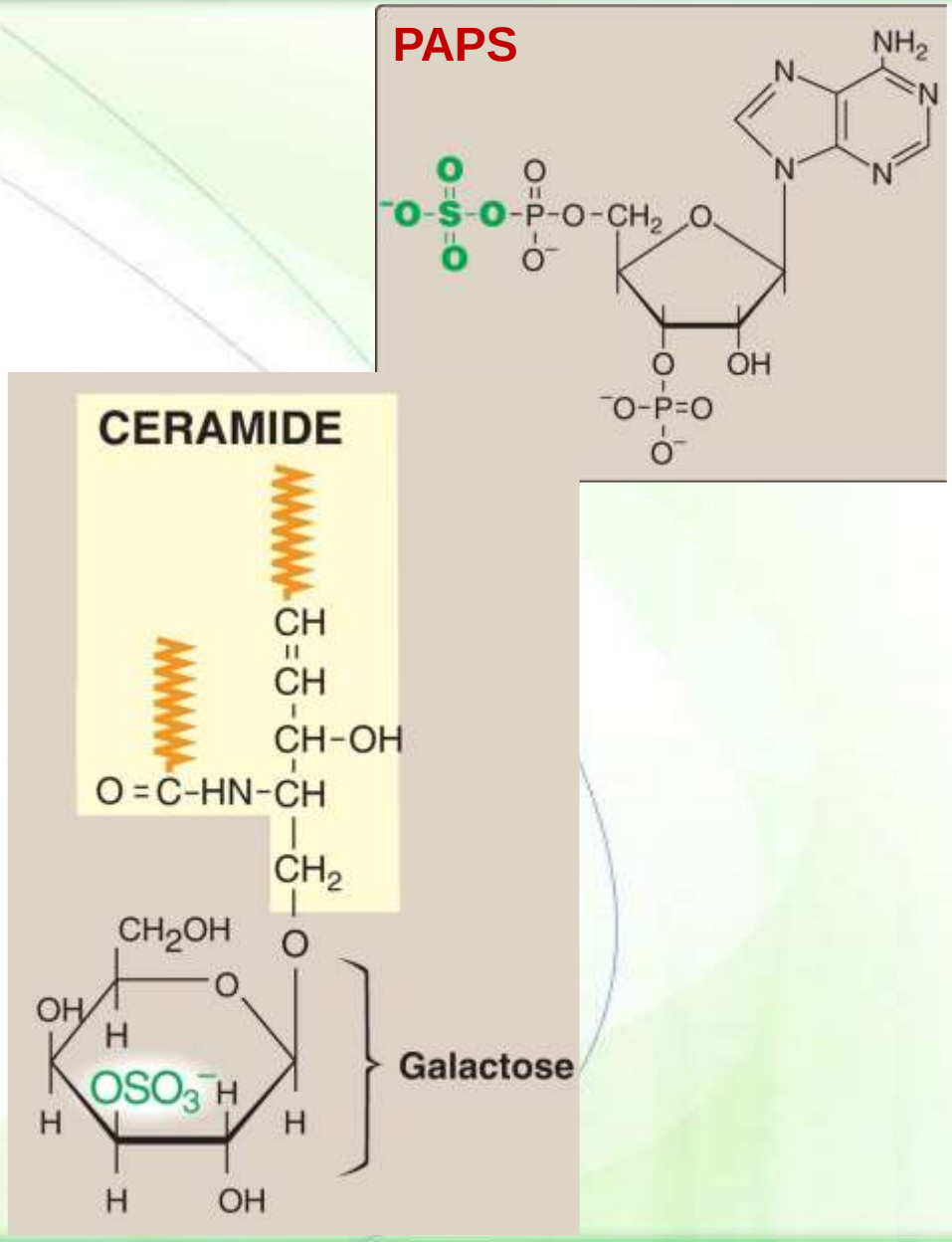


An example

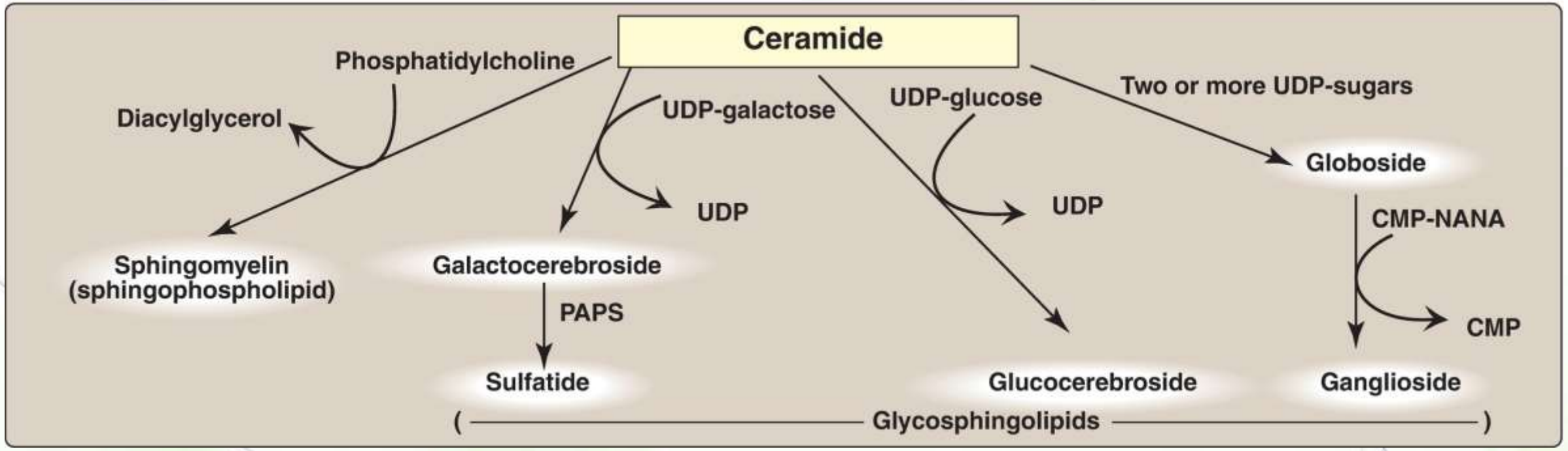

G_{M1}
G_{M2}
G_{M3}
β-D-Galactose
N-Acetyl-β-D-galactosamine
β-D-Galactose
β-D-Glucose
NANA
NANA —— =
N-Acetyl-α-neuraminidate
Sphingosine
Stearic acid

Synthesis of glycosphingolipids I

- Synthesis of glycosphingolipids occurs primarily in the Golgi apparatus by sequential addition of glycosyl monomers transferred from UDP-sugars to the acceptor molecule by glycosyltransferases.
- A sulfate group from the sulfate carrier 3′-phosphoadenosine-5′-phosphosulfate (PAPS), is added by a sulfotransferase to a galactose in a galactocerebroside, forming the sulfatide galactocerebroside sulfate.

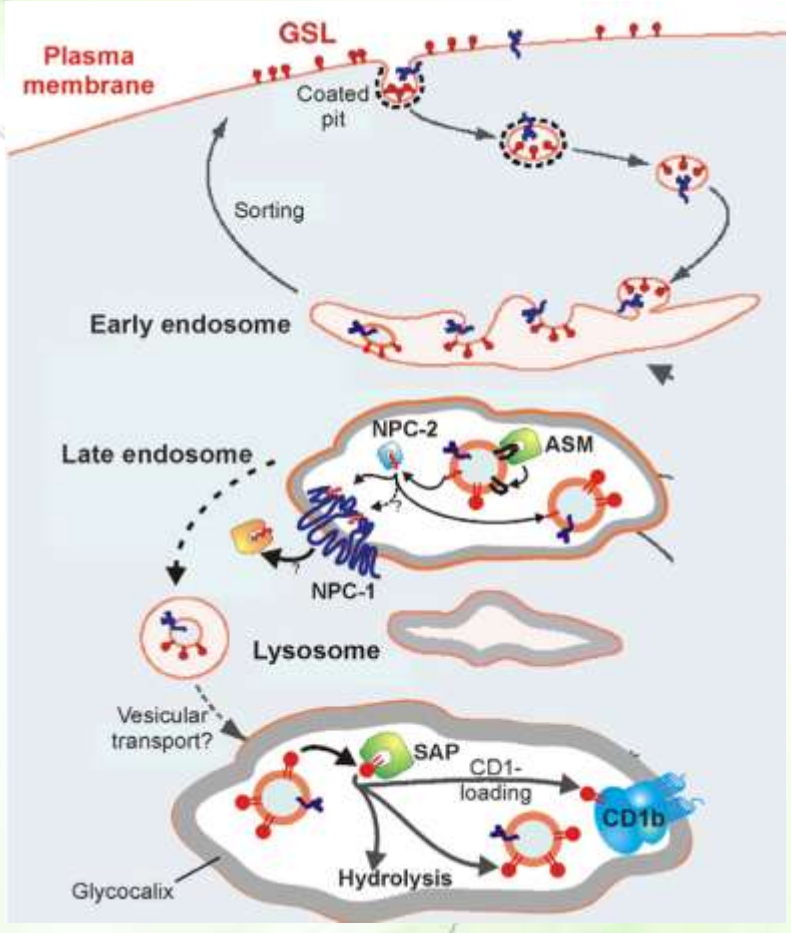


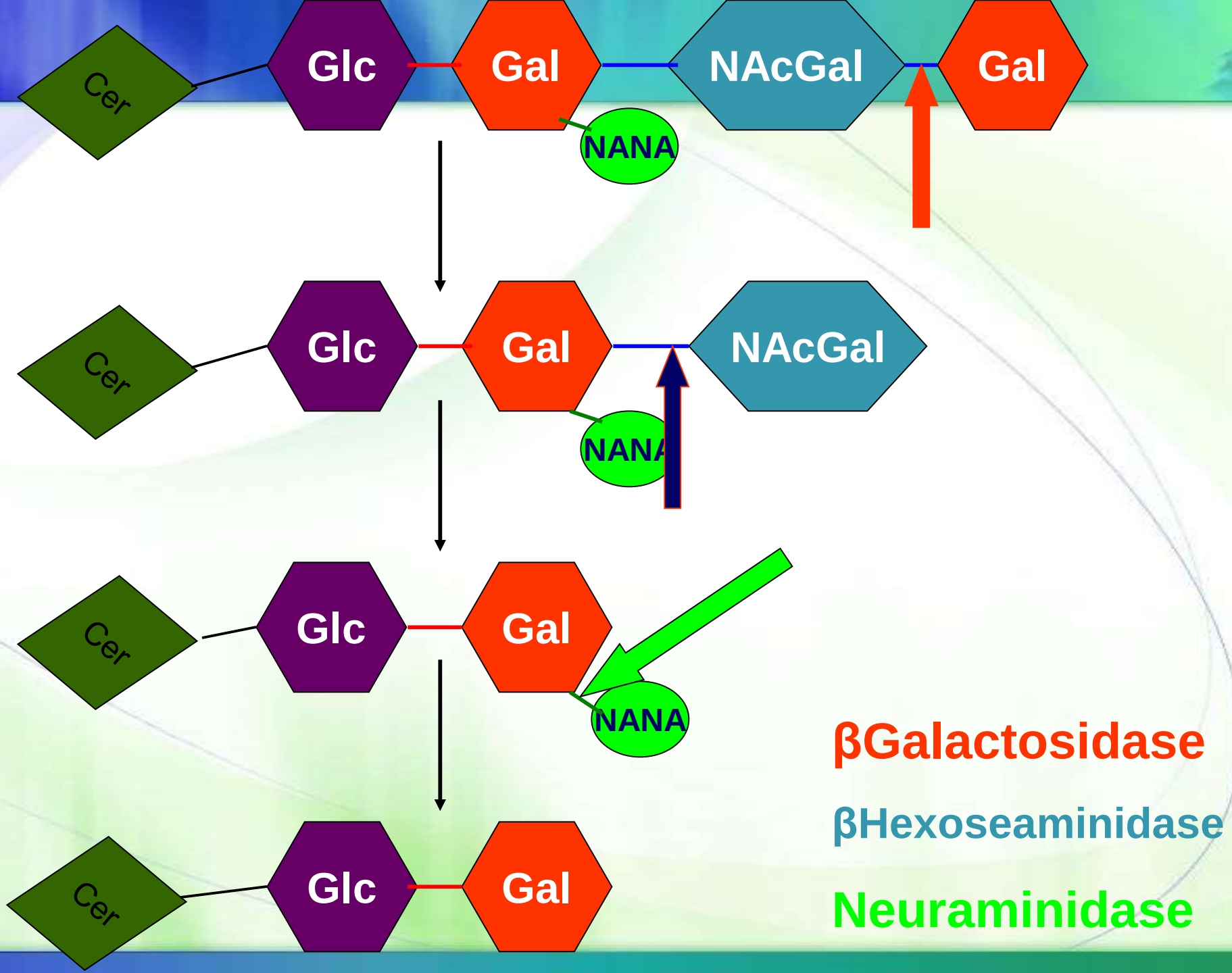
Synthesis of glycosphingolipids II



Glycosphingolipid degradation

- Glycosphingolipids are phagocytosed into the lysosomes that fuse with the phagosomes.
- The lysosomal hydrolases remove the sugars sequentially starting with the last one added and ending with the first one added.
- Defect in the degradation of glycosphingolipid, glycosaminoglycans, and glycoproteins causes “lysosomal storage diseases”.





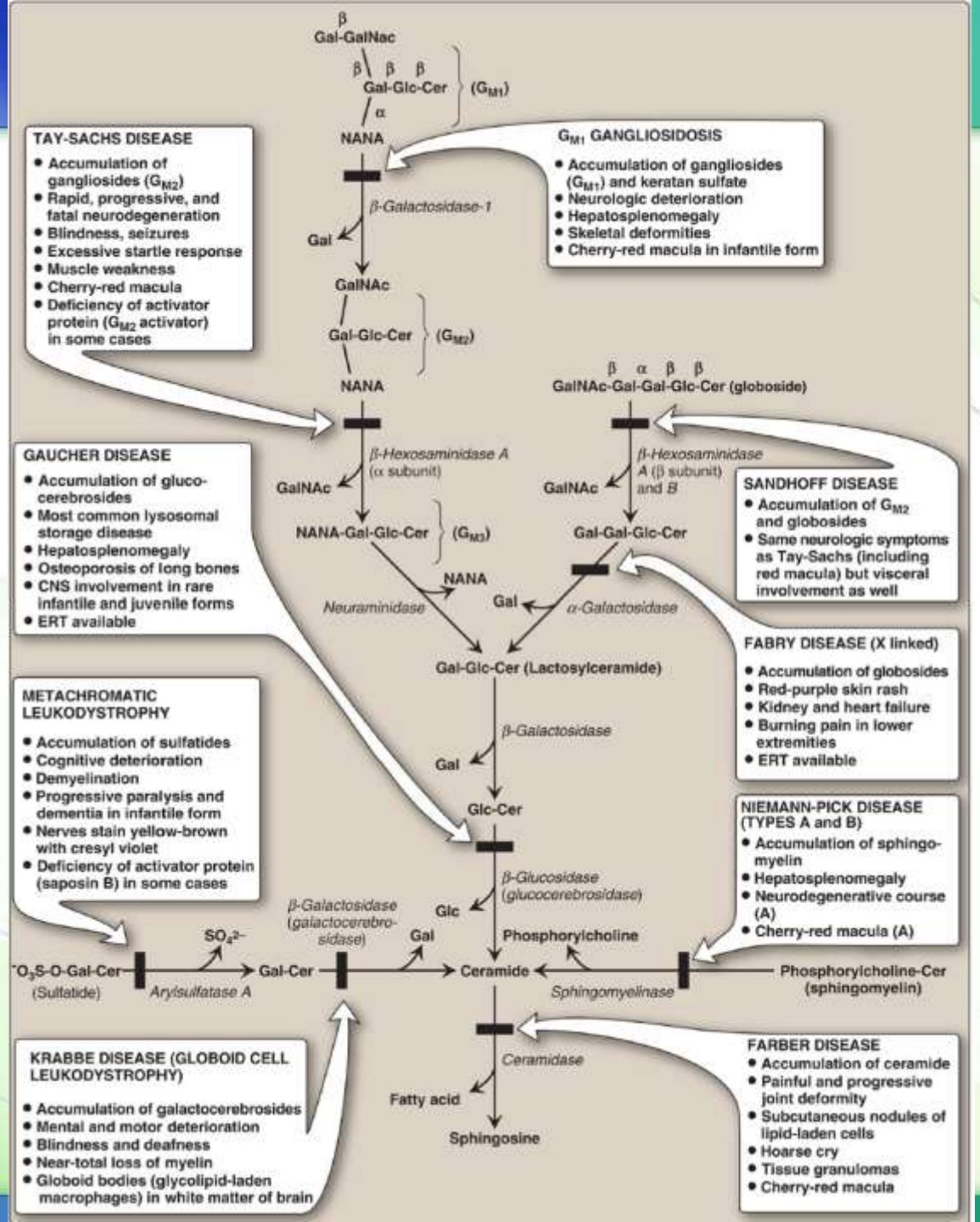
βGalactosidase

βHexoseaminidase

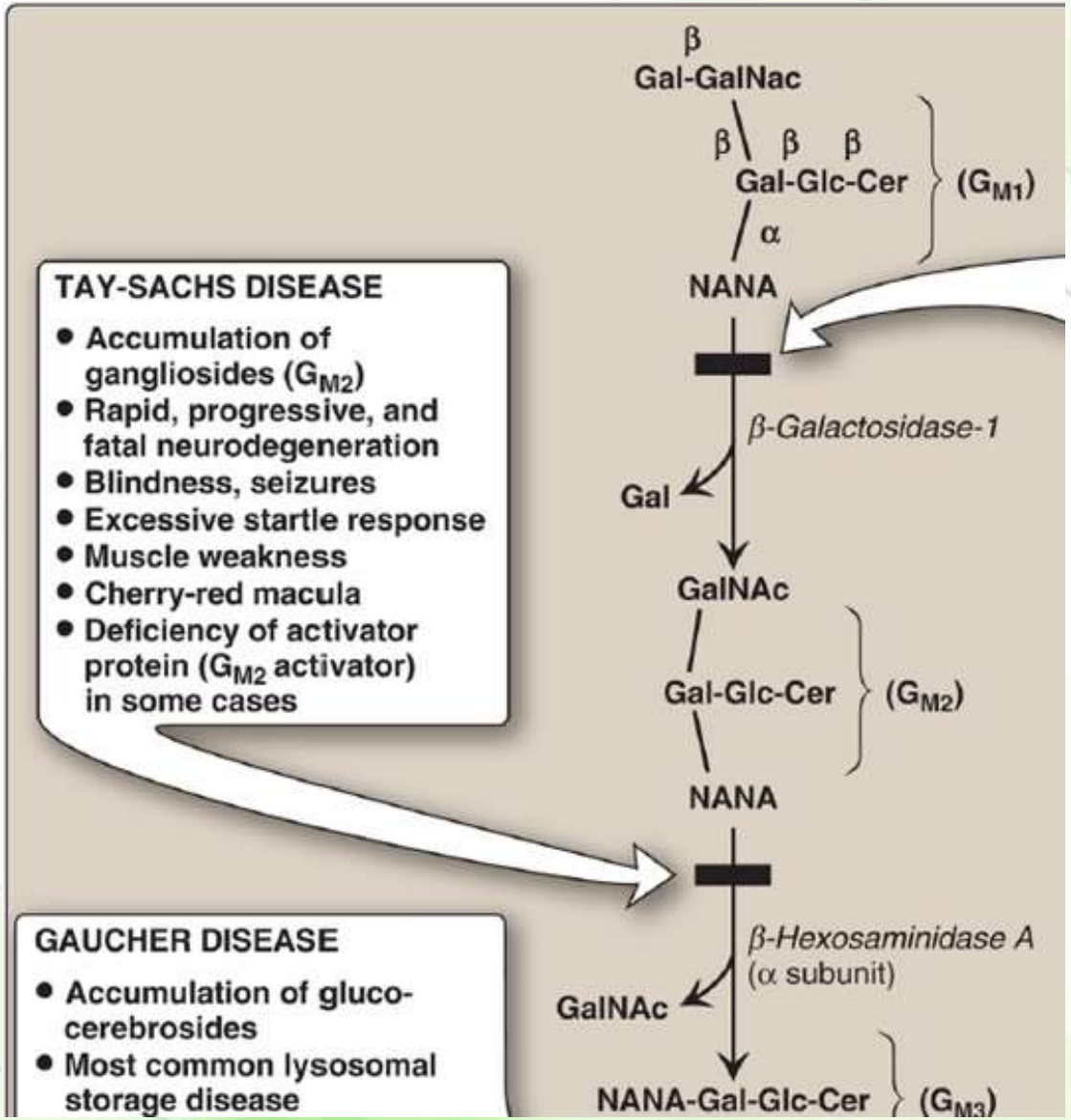
Neuraminidase

Sphingolipidoses

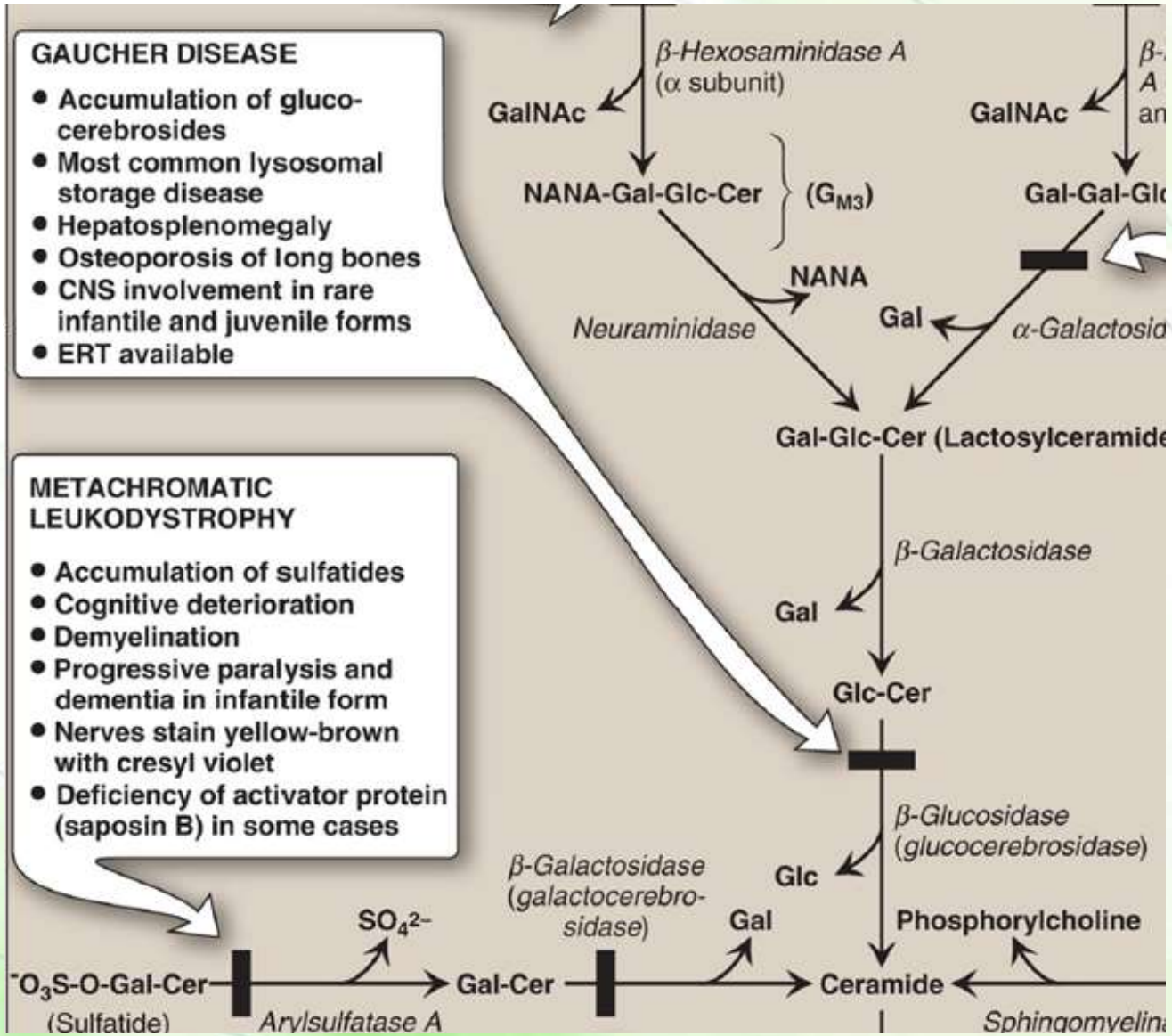
- Sphingolipidoses: disorders related to defective degradation of sphingolipids
- Usually, only a single sphingolipid (the substrate for the deficient enzyme) accumulates in the involved organs.
- The disorders are progressive becoming more severe with aging and can be fatal.
- There is extensive phenotypic variability due to:
  - Allele heterogeneity: different mutations within the same gene (different alleles)
  - Locus heterogeneity: different genes are defective (locus = position, location).
- They are autosomal-recessive disorders, except for Fabry disease, which is X linked.
- The incidence of sphingolipidoses is low in most populations, except for Gaucher and Tay-Sachs diseases, which, like Niemann-Pick disease, show a high frequency in the Ashkenazi Jewish population.


β
Gal-GalNac
β β β
Gal-Glc-Cer
(GM1)
α
NANA
GM1 GANGLIOSIDOSIS
• Accumulation of gangliosides (GM1) and keratan sulfate
• Neurologic deterioration
• Hepatosplenomegaly
• Skeletal deformities
• Cherry-red macula in infantile form
TAY-SACHS DISEASE
• Accumulation of gangliosides (GM2)
• Rapid, progressive, and fatal neurodegeneration
• Blindness, seizures
• Excessive startle response
• Muscle weakness
• Cherry-red macula
• Deficiency of activator protein (GM2 activator) in some cases
β-Galactosidase-1
Gal
GalNAc
Gal-Glc-Cer
(GM2)
NANA
β α β β
GalNAc-Gal-Gal-Glc-Cer (globoside)
β-Hexosaminidase A (α subunit)
GalNAc
β-Hexosaminidase A (β subunit) and B
GalNAc
GAUCHER DISEASE
• Accumulation of gluco-cerebrosides
• Most common lysosomal storage disease
• Hepatosplenomegaly
• Osteoporosis of long bones
• CNS involvement in rare infantile and juvenile forms
• ERT available
NANA-Gal-Glc-Cer
(GM3)
Gal-Gal-Glc-Cer
SANDHOFF DISEASE
• Accumulation of GM2 and globosides
• Same neurologic symptoms as Tay-Sachs (including red macula) but visceral involvement as well
NANA
Neuraminidase
Gal
α-Galactosidase
Gal-Glc-Cer (Lactosylceramide)
FABRY DISEASE (X linked)
• Accumulation of globosides
• Red-purple skin rash
• Kidney and heart failure
• Burning pain in lower extremities
• ERT available
β-Galactosidase
Gal
Glc-Cer
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
β-Glucosidase (glucocerebrosidase)
NIEMANN-PICK DISEASE (TYPES A and B)
• Accumulation of sphingo-myelin
• Hepatosplenomegaly
• Neurodegenerative course (A)
• Cherry-red macula (A)
β-Galactosidase (galactocerebro-sidase)
Glc
Gal
Phosphorylcholine
SO4 2−
⁻O3S-O-Gal-Cer
(Sulfatide)
Arylsulfatase A
Gal-Cer
Ceramide
Sphingomyelinase
Phosphorylcholine-Cer
(sphingomyelin)
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
Ceramidase
FARBER DISEASE
• Accumulation of ceramide
• Painful and progressive joint deformity
• Subcutaneous nodules of lipid-laden cells
• Hoarse cry
• Tissue granulomas
• Cherry-red macula
Fatty acid
Sphingosine

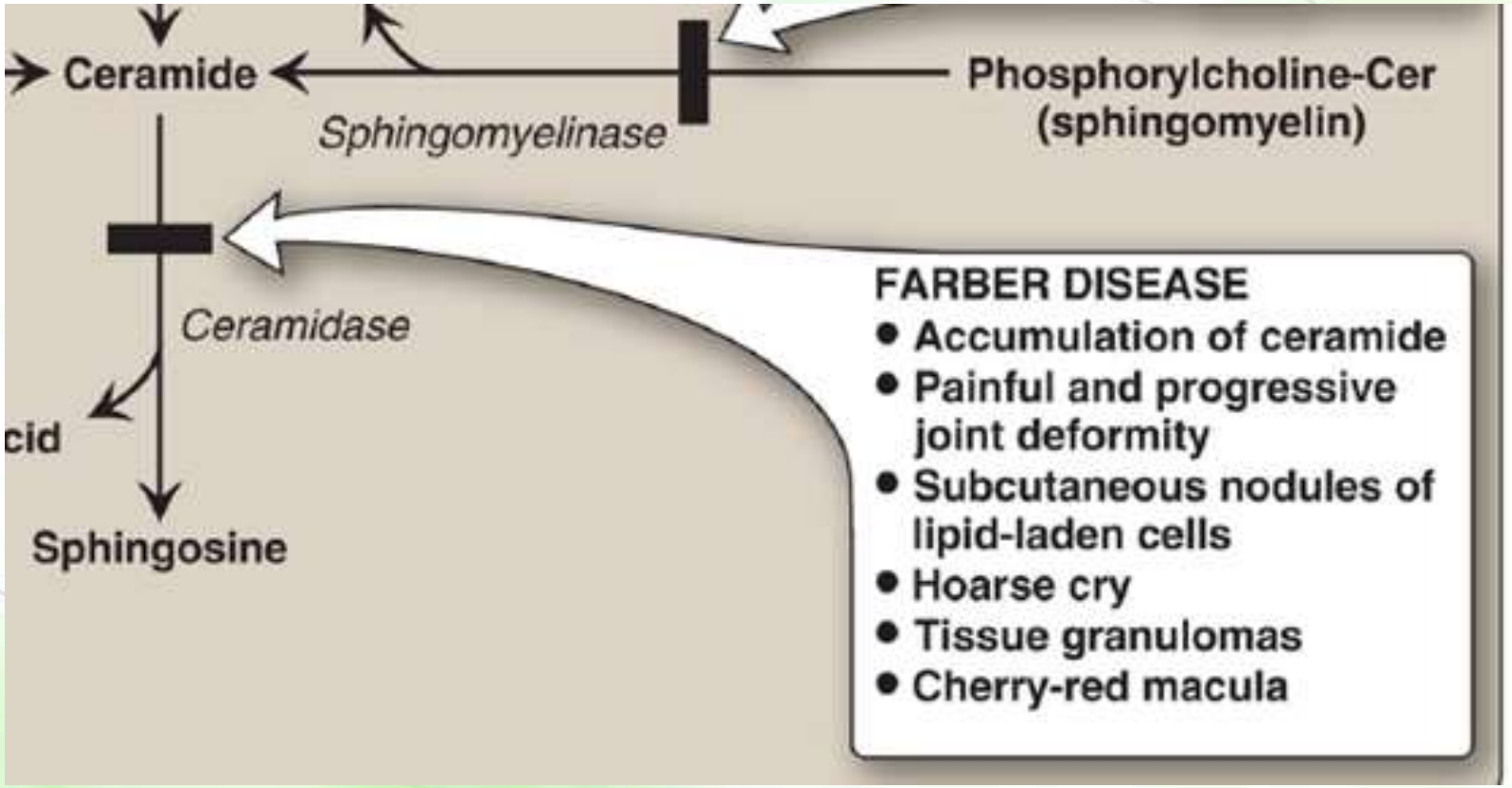
Tay-Sachs disease



Gaucher disease



Farber disease



Diagnosis and treatment

- Diagnosis:
  - Measure enzyme activity in cultured fibroblasts or peripheral leukocytes
  - Analyzing DNA
- Treatment:
  - Recombinant human enzyme replacement therapy
    - Gaucher disease and Fabry disease (expensive)
  - Bone marrow transplantation:
    - Gaucher disease
- Substrate reduction therapy
  - Gaucher disease: Pharmacologic reduction of glucosylceramide