

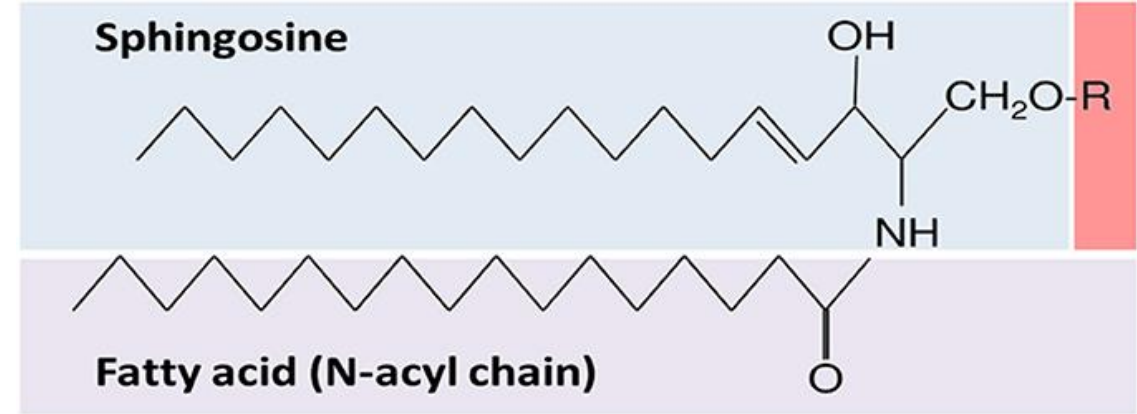
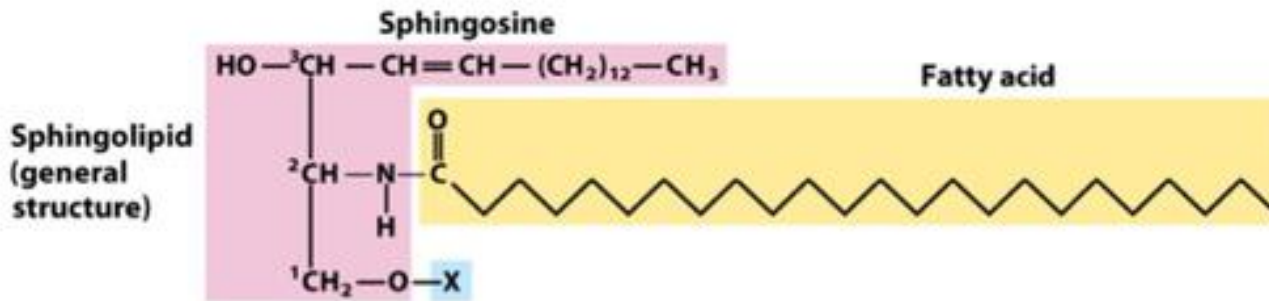
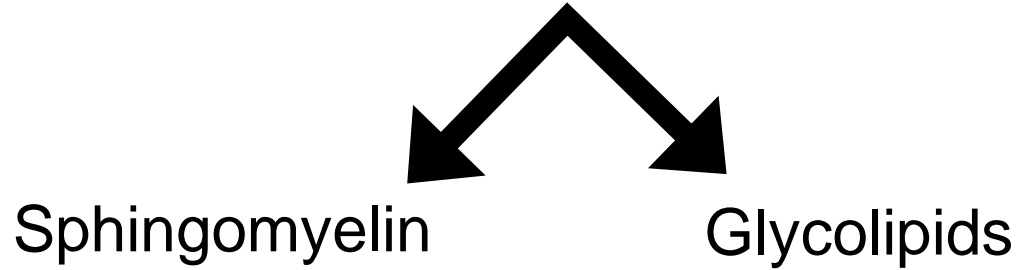
Metabolism of Sphingolipids

Dr. Diala Abu-Hassan

Lippincott's Biochemistry, Ch. 17

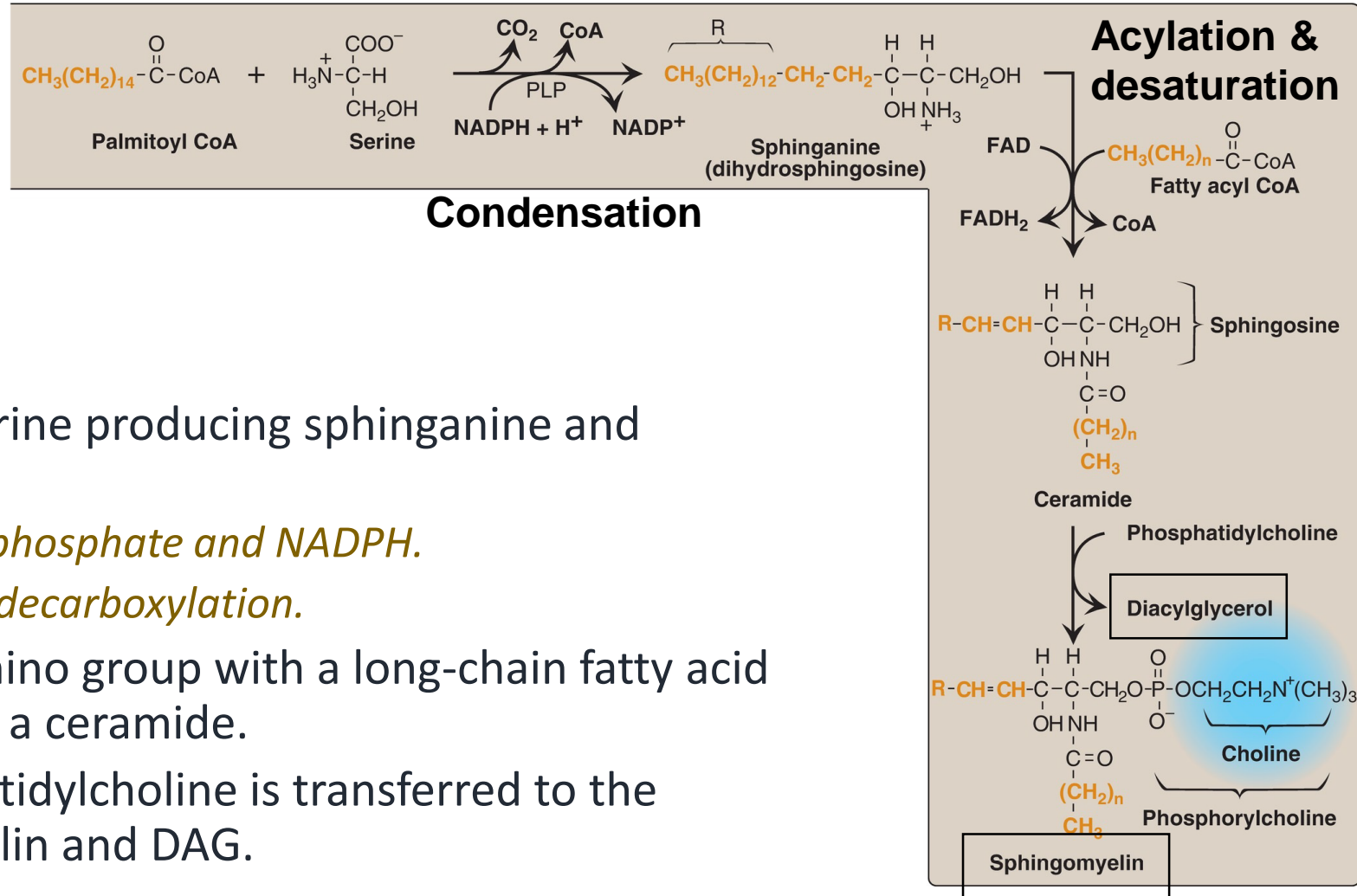
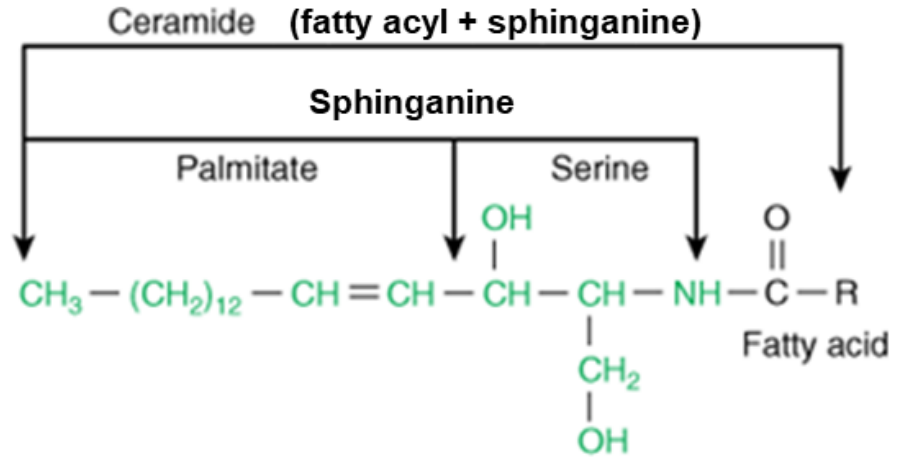


Structure of sphingolipids



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

Synthesis of sphingomyelin



- Palmitoyl CoA condenses with serine producing sphinganine and releasing CoA and CO₂.
 - *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.

Degradation of sphingomyelin and the deficiency of sphingomyelinase

- ✓ Sphingomyelin is degraded by sphingomyelinase, a lysosomal enzyme and a type of phospholipase C
- ✓ The ceramide is cleaved by ceramidase into sphingosine and a free fatty acid
- ✓ The ceramide and sphingosine released regulate signal transduction pathways by influencing the activity of protein kinase C and they also promote apoptosis.
- ✓ Niemann-Pick disease (Types A and B) is an autosomal recessive disease (lysosomal storage disease)
- ✓ Enlarger liver and spleen because of lipid deposits
- ✓ Type A is more severe than B
- ✓ Niemann-Pick disease occurs in all ethnic groups
- ✓ Type A is more frequent in the Ashkenazi Jewish population

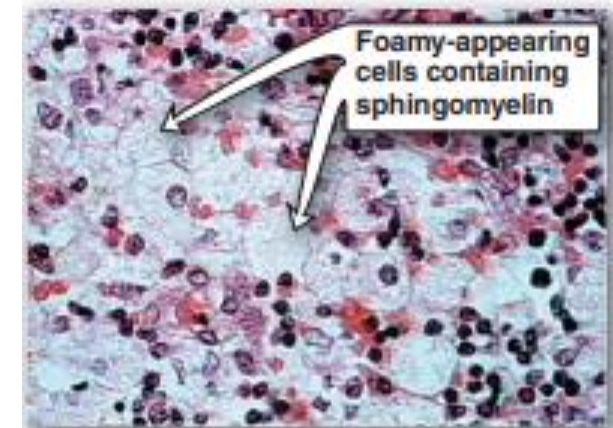
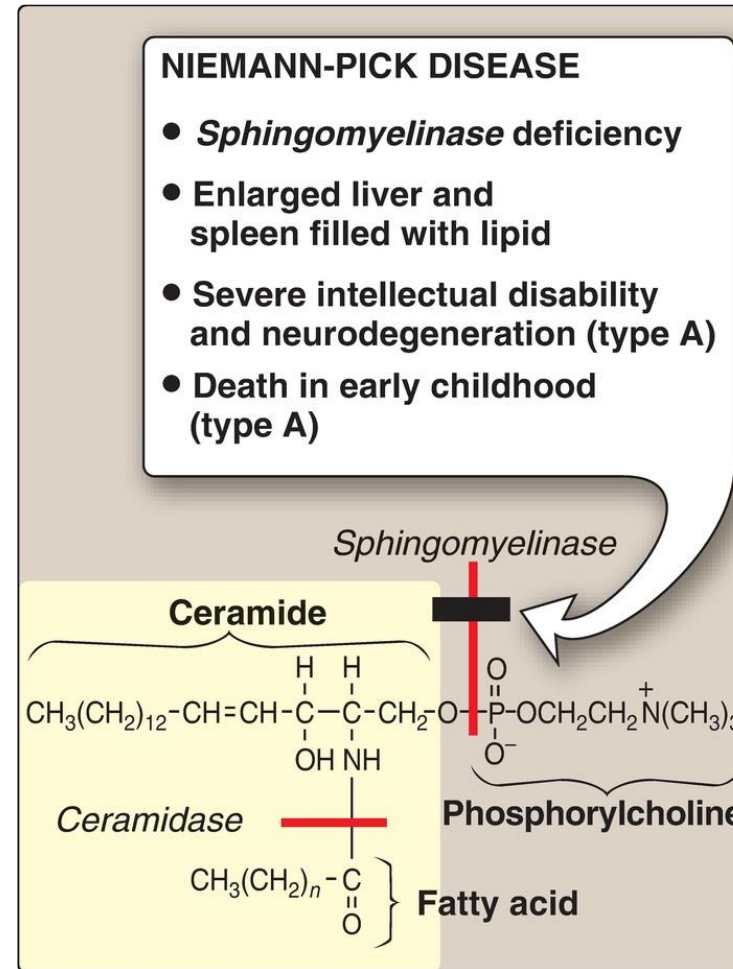
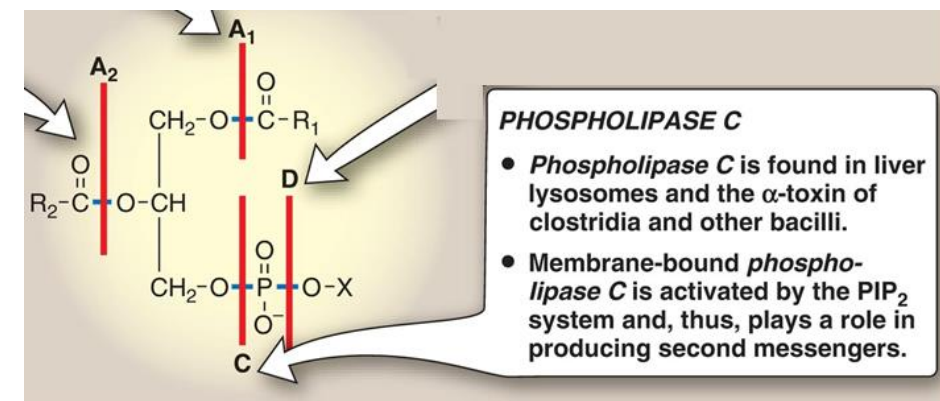
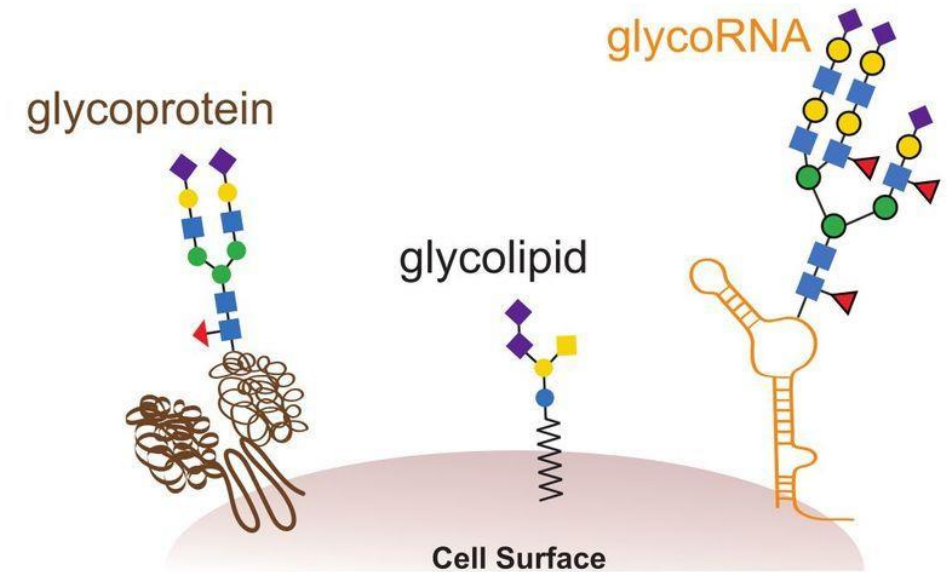
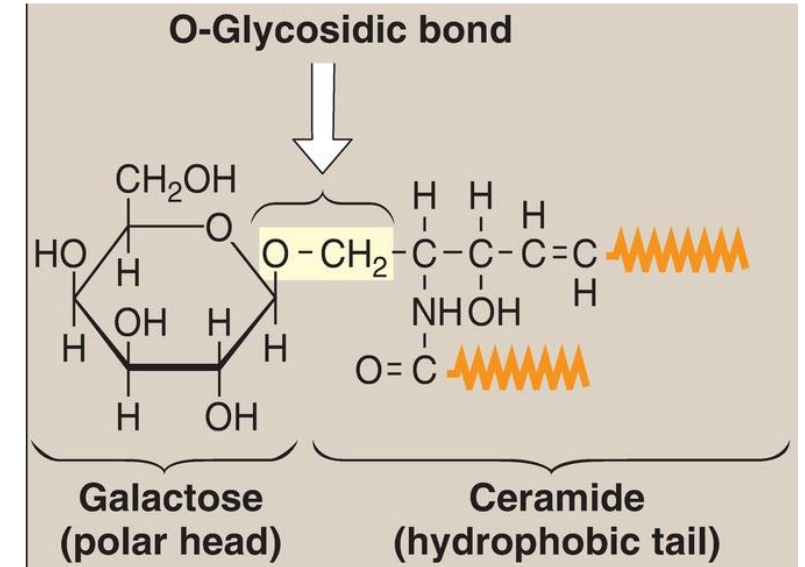


Figure 17.13
Accumulation of lipids in spleen cells from a patient with Niemann-Pick disease.

Glycosphingolipids (glycolipids)

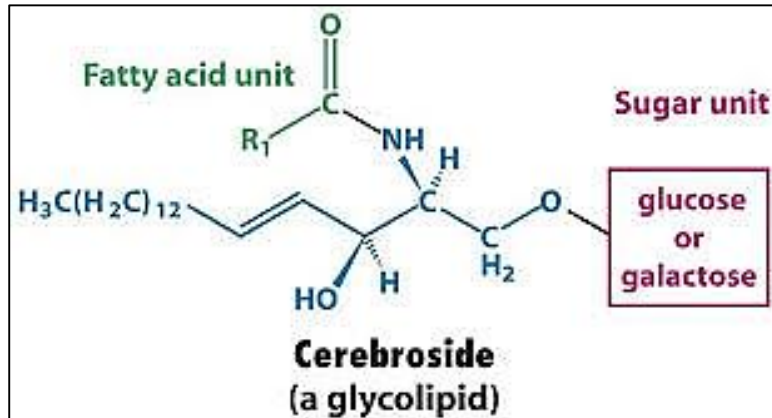
- They are made of ceramide (precursor).
- A sugar(s) is attached to ceramide by an O-glycosidic bond.
- The number and type of carbohydrate moieties determine the type of glycosphingolipid.
- They are localized in the outer leaflet of the plasma membrane and exposed extracellularly (adhesion, recognition,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



Types of glycolipids

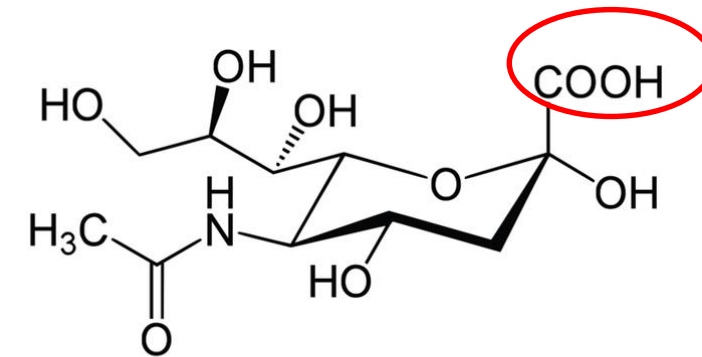
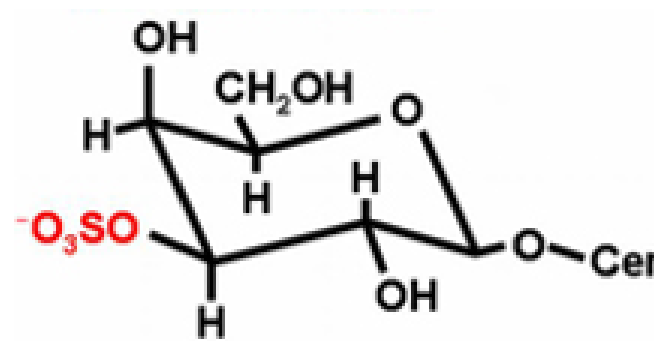
Neutral glycosphingolipids

- **Cerebrosides** are the simplest.
- Gluco- or Galactocerebrosides

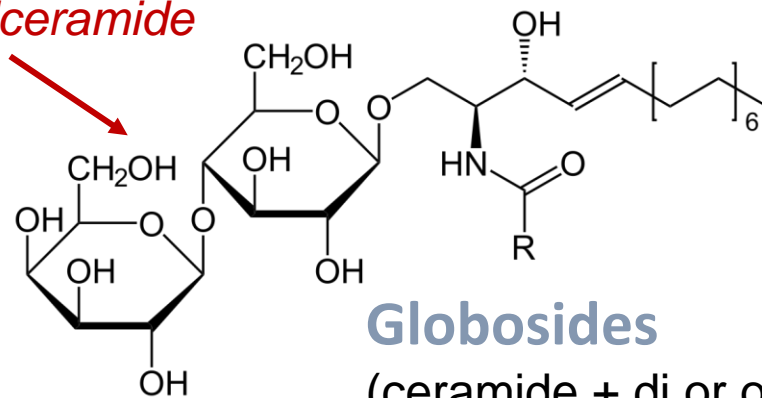


Acidic glycosphingolipids (**gangliosides**)

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

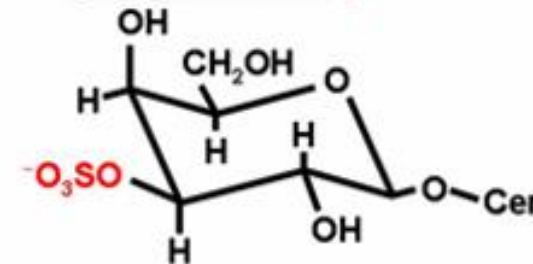
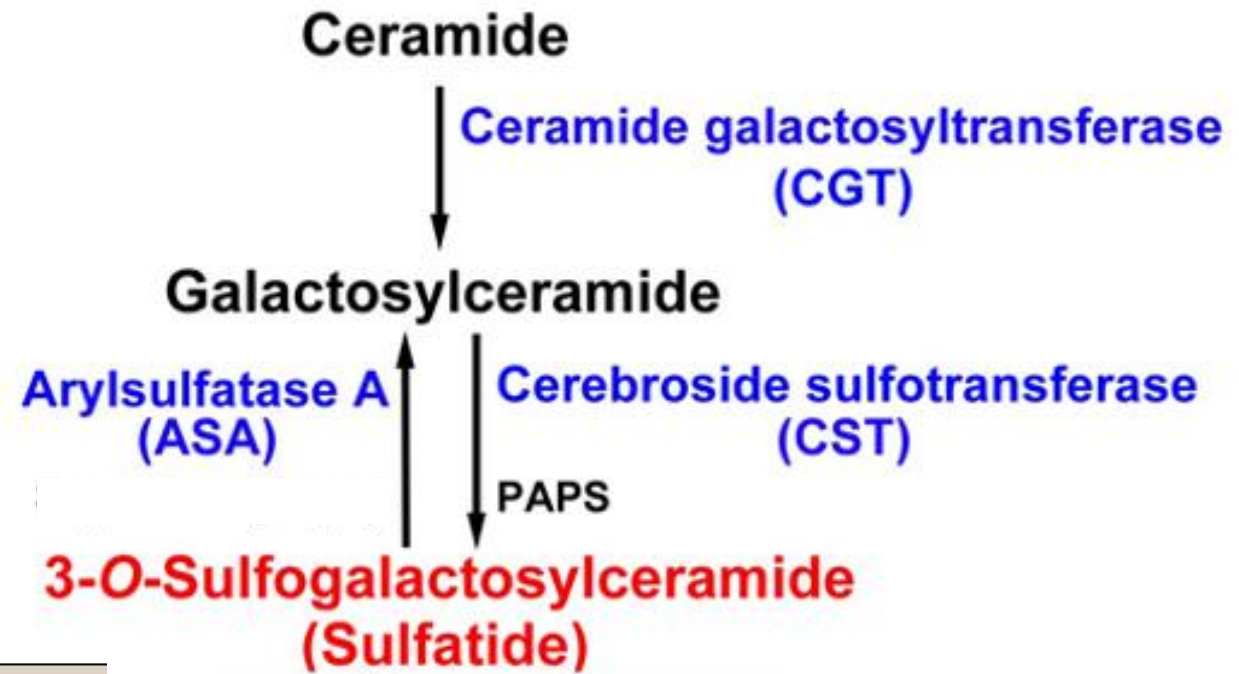
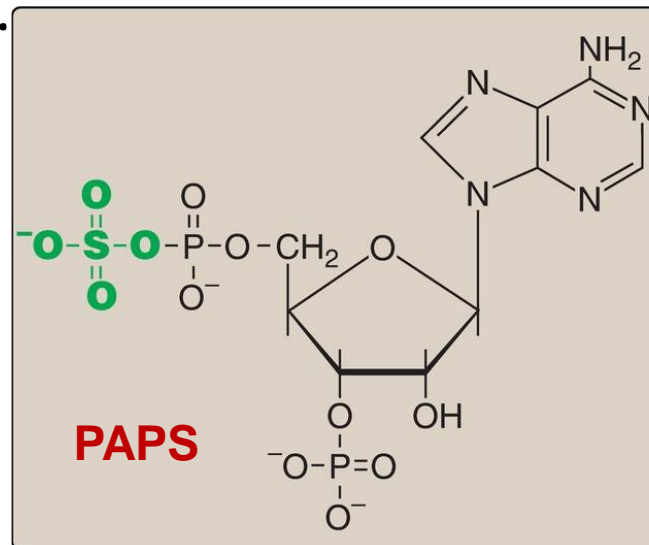


Lactosylceramide

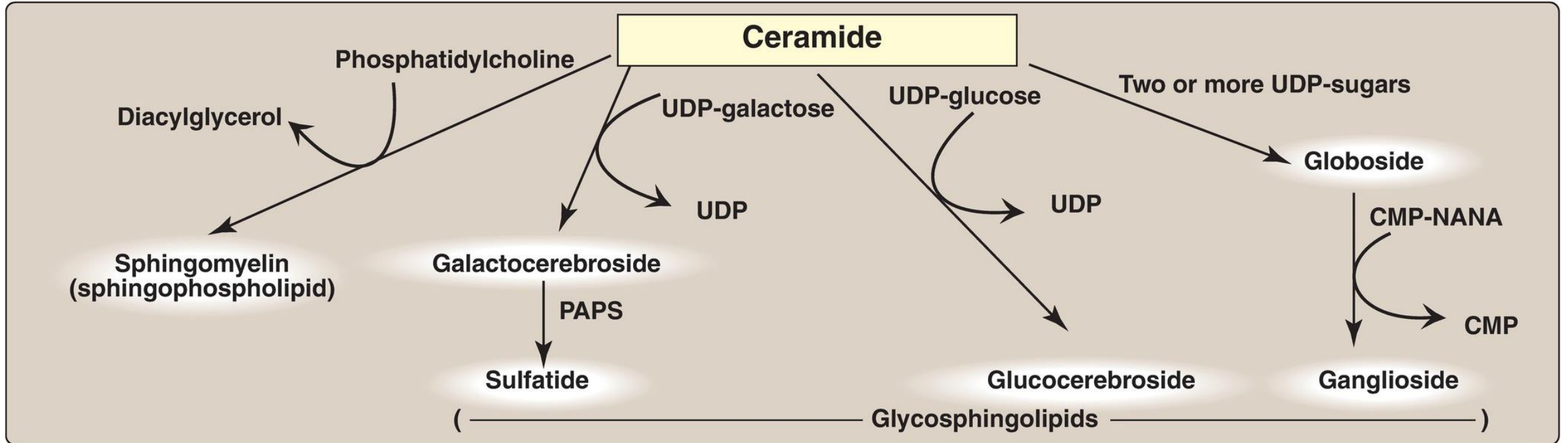


Synthesis of Glycosphingolipids and Sulfatides

- 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.

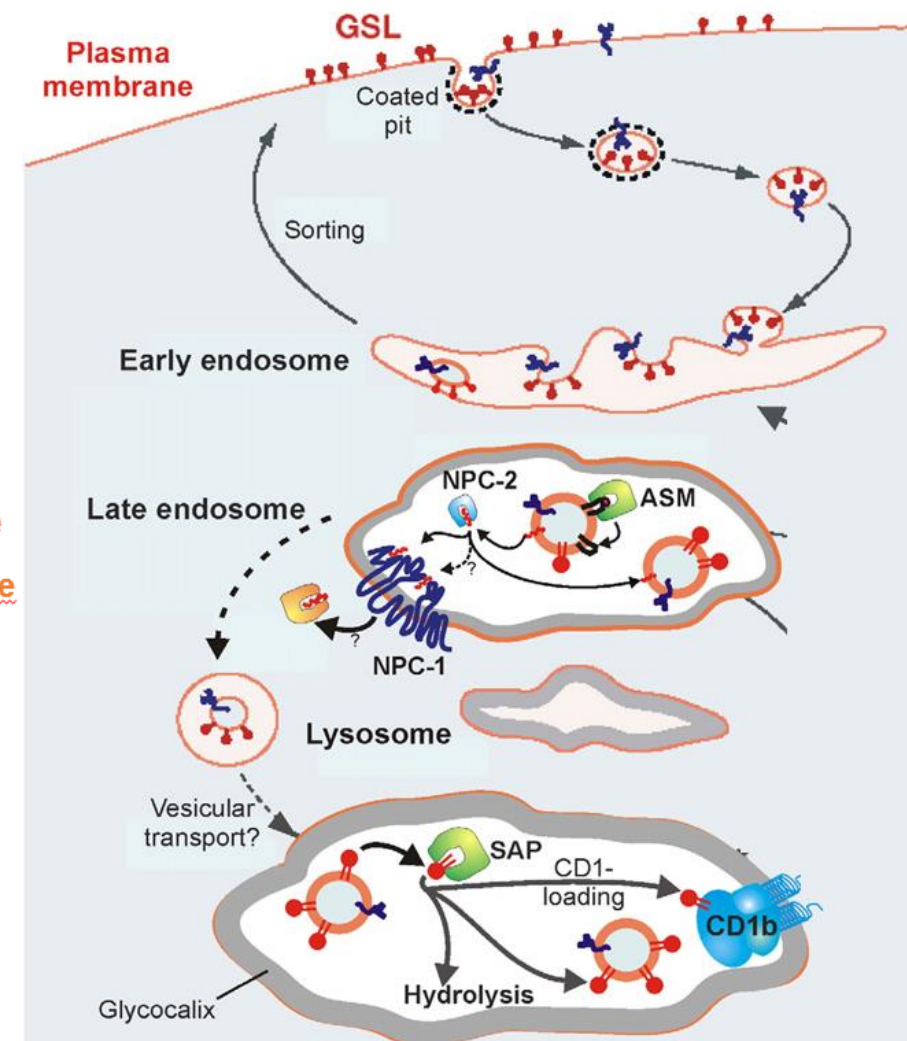
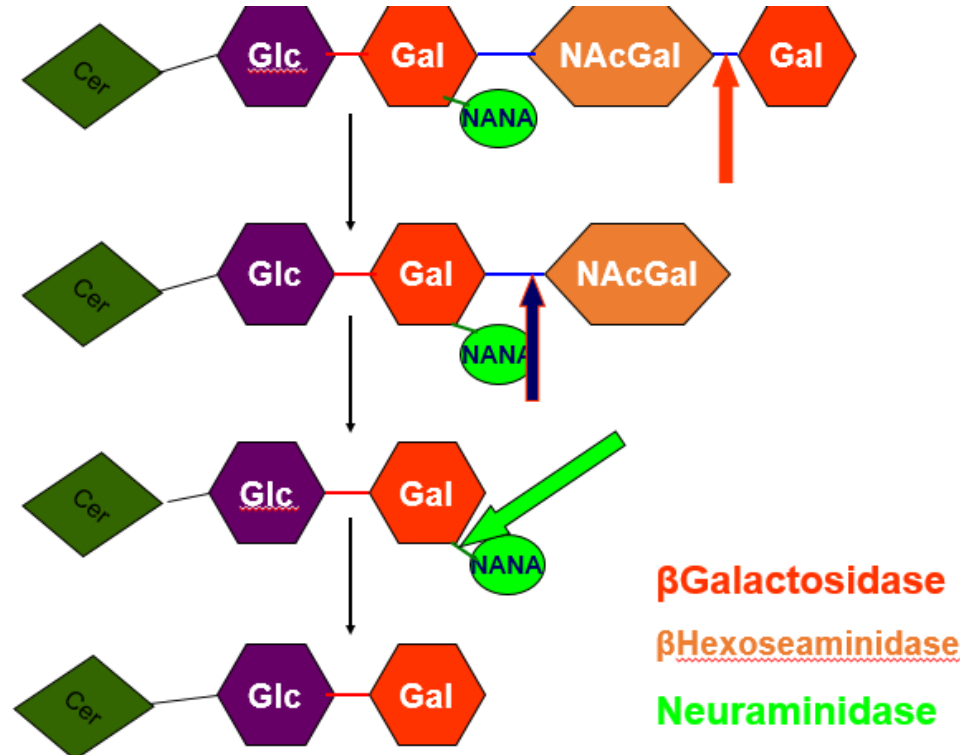


Synthesis of Glycosphingolipids and Sulfatides



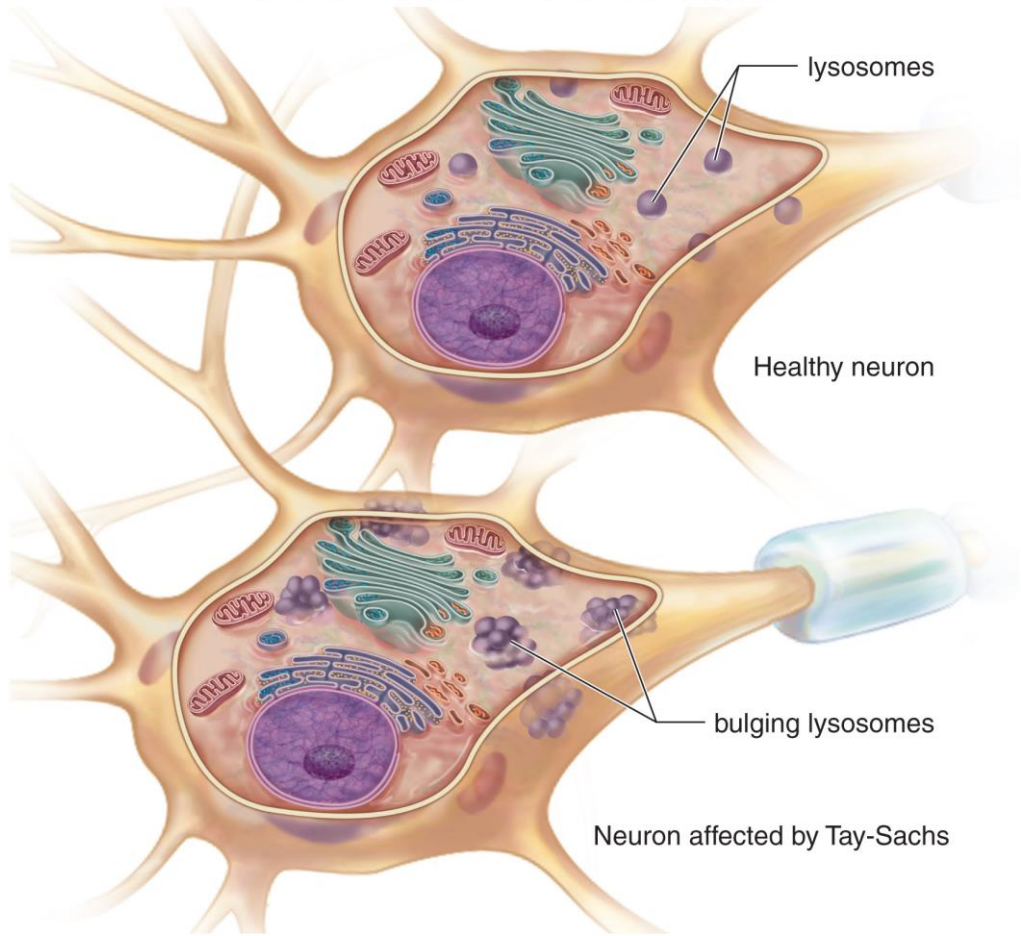
Glycosphingolipid (GSL) degradation

- Glycosphingolipids are phagocytosed into the endosomes that fuse with the lysosomes.
- 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”.
- Sialidase (neuroaminidase) is the glycosidase that removes sialic acid during ganglioside degradation



Application: Sphingolipidoses (lysosomal disease)

- Sphingolipidoses: **lysosomal** diseases characterized by mutations in genes that encode lysosomal hydrolases or activator proteins engaged in the intralysosomal **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.

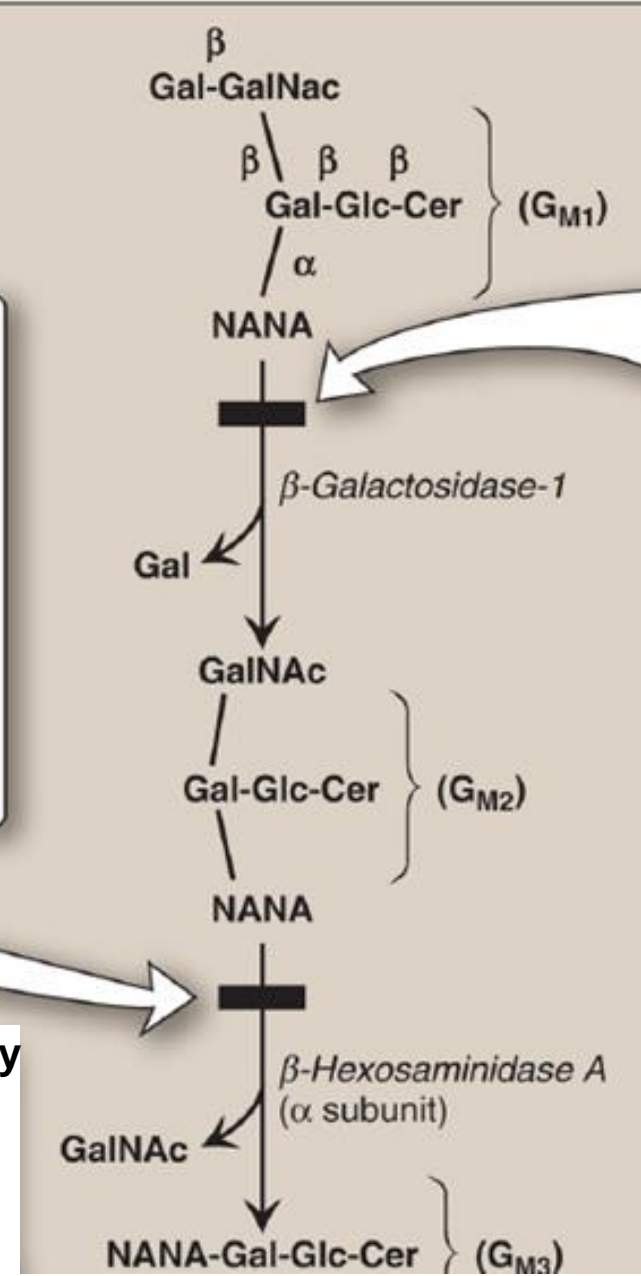


TAY-SACHS DISEASE

- Accumulation of gangliosides (G_{M2})
- Rapid, progressive, and fatal neurodegeneration
- Blindness, seizures
- Excessive startle response
- Muscle weakness
- Cherry-red macula
- Deficiency of activator protein (G_{M2} activator) in some cases

Hexosaminidase A deficiency

Tay-Sachs disease



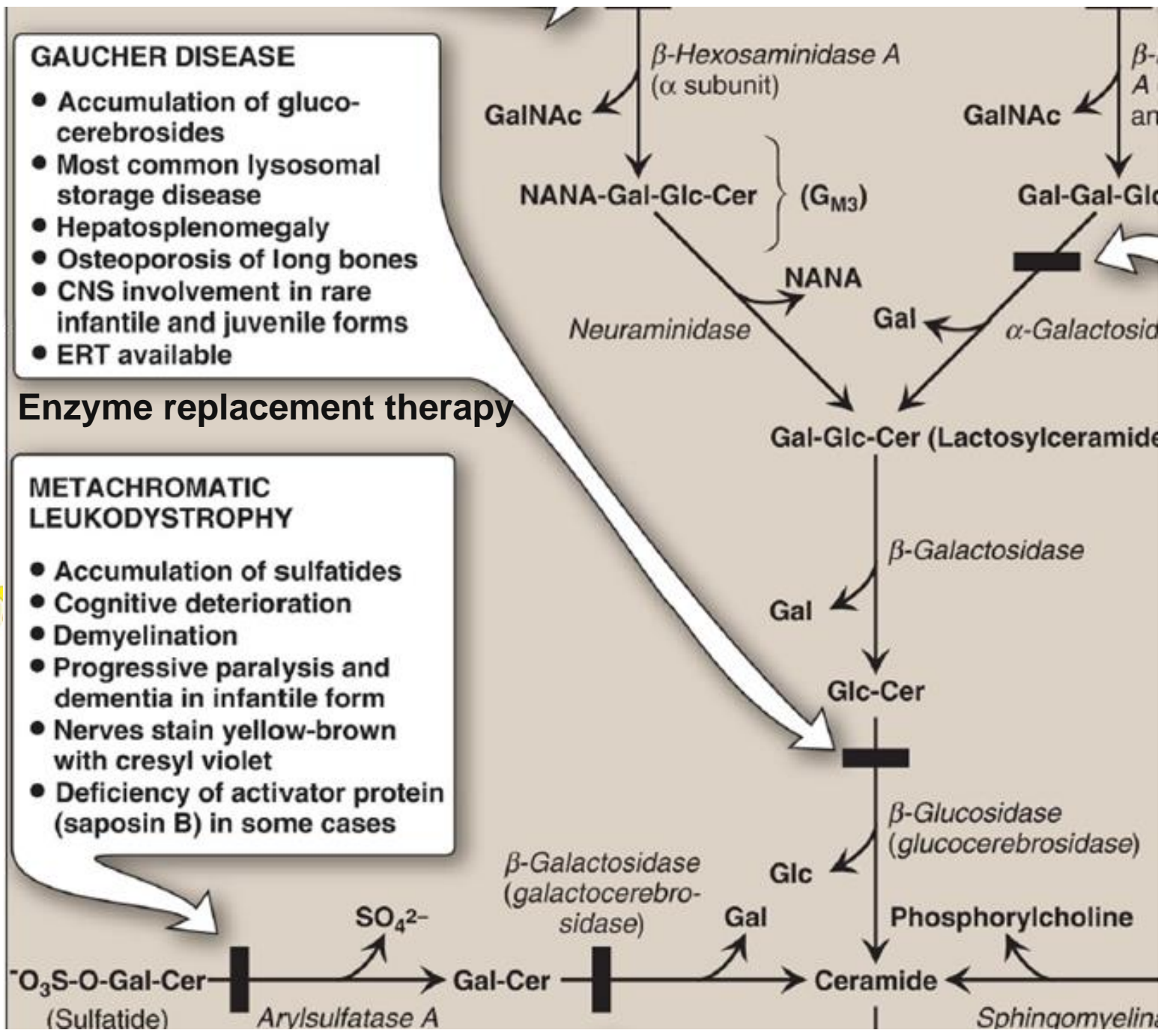
Gaucher disease

* MOST COMMON LYSOSOMAL STORAGE DISORDER

- GAUCHER DISEASE**
- Accumulation of glucocerebrosides
 - Most common lysosomal storage disease
 - Hepatosplenomegaly
 - Osteoporosis of long bones
 - CNS involvement in rare infantile and juvenile forms
 - ERT available

Enzyme replacement therapy

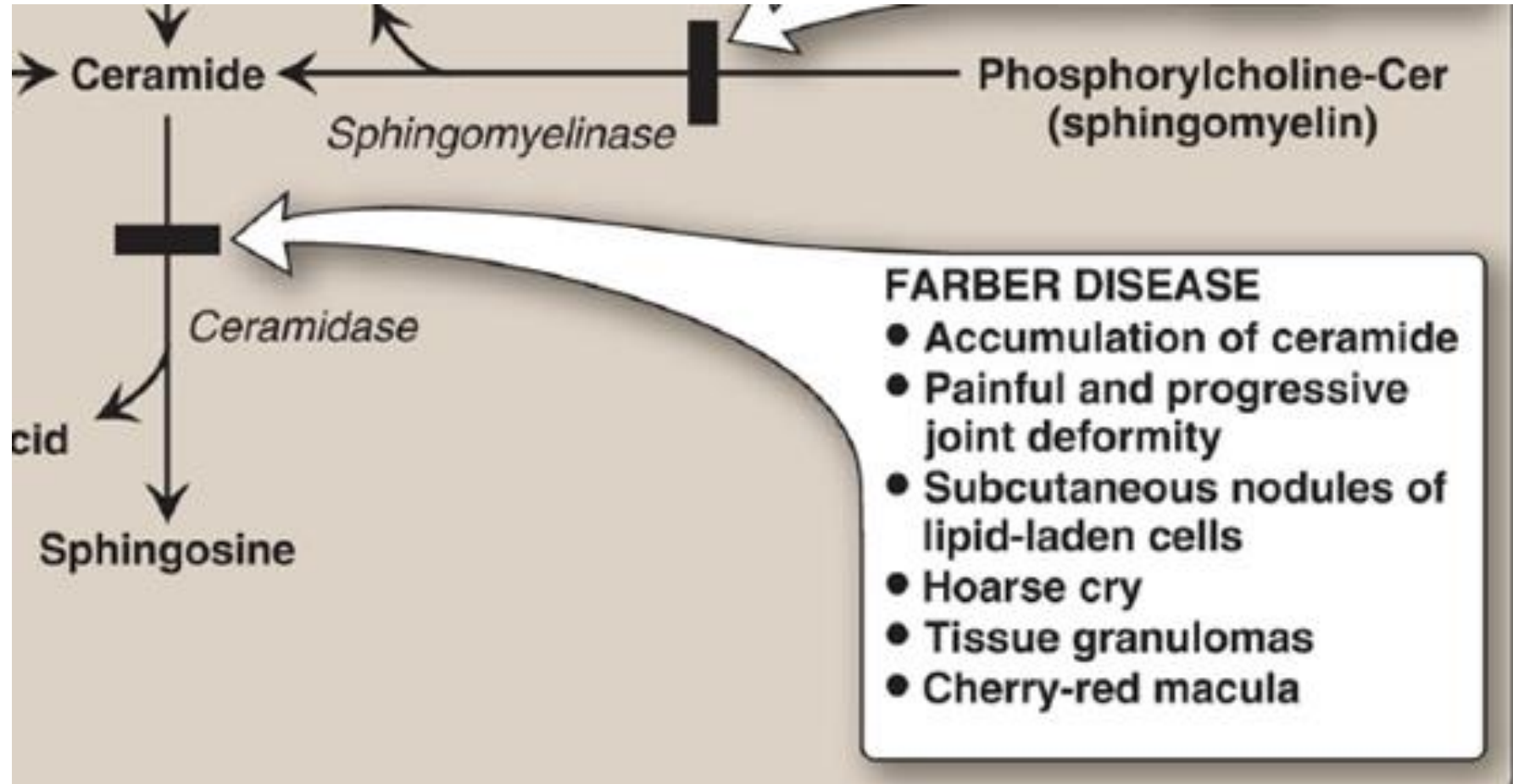
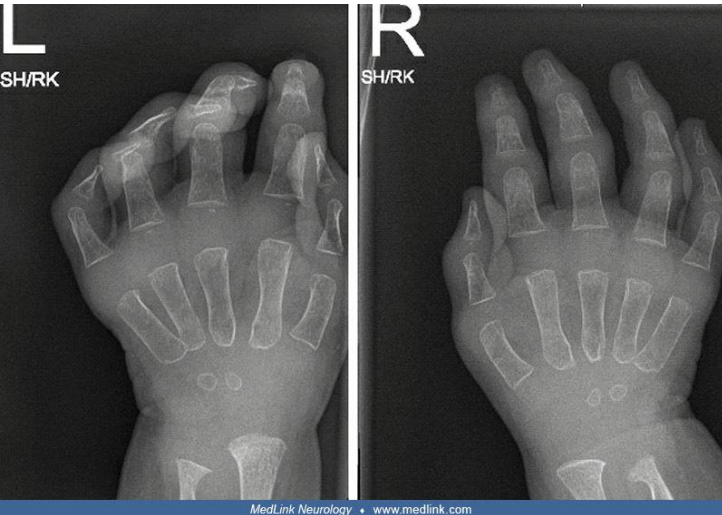
- METACHROMATIC LEUKODYSTROPHY**
- Accumulation of sulfatides
 - Cognitive deterioration
 - Demyelination
 - Progressive paralysis and dementia in infantile form
 - Nerves stain yellow-brown with cresyl violet
 - Deficiency of activator protein (saposin B) in some cases



Farber disease



Deformed joints



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: reducing the amount of glucocerebroside produced in the body pharmacologically

