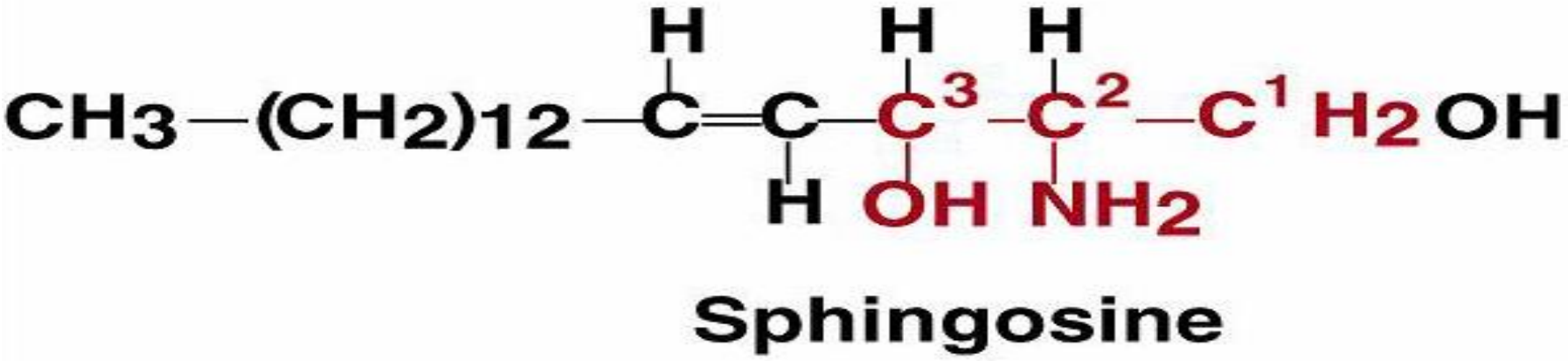
Metabolism of Sphingolipids

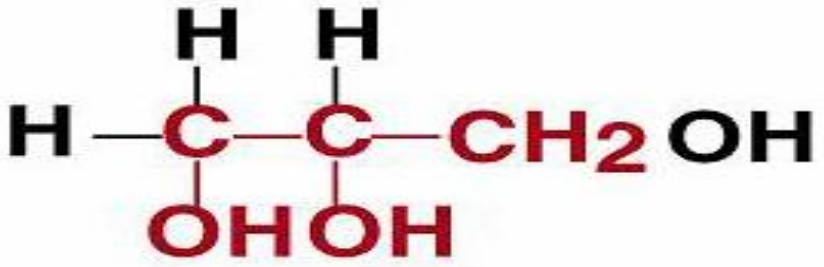
Sphingophospholipids

Glycosphingolipids

Sphingosine; Amino Alchol

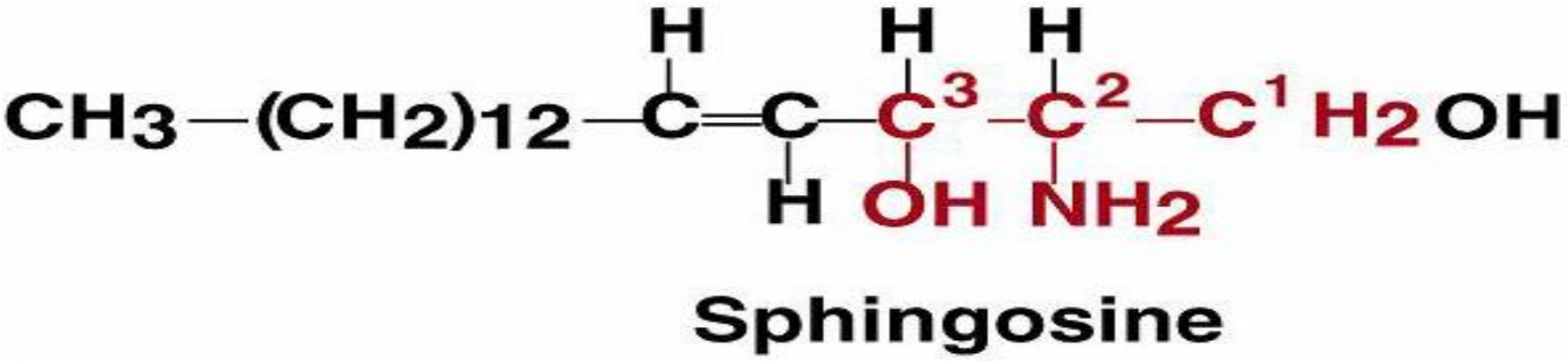


Sphingosine



Glycerol

Sphingosine; Amino Alchol



HO-**C**H-**C**H=**C**H-(**C**H_2)$_{12}$**C**H_3

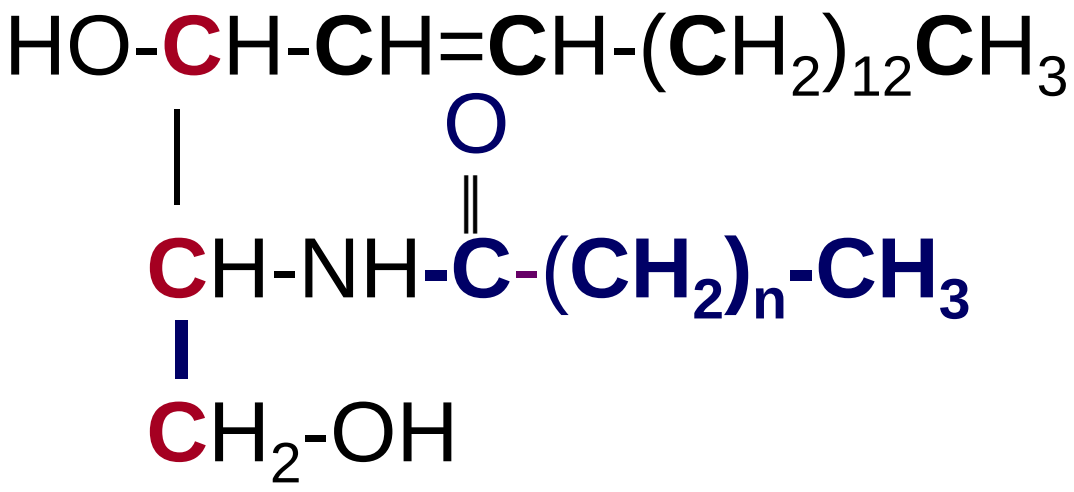
|

CH-NH_2

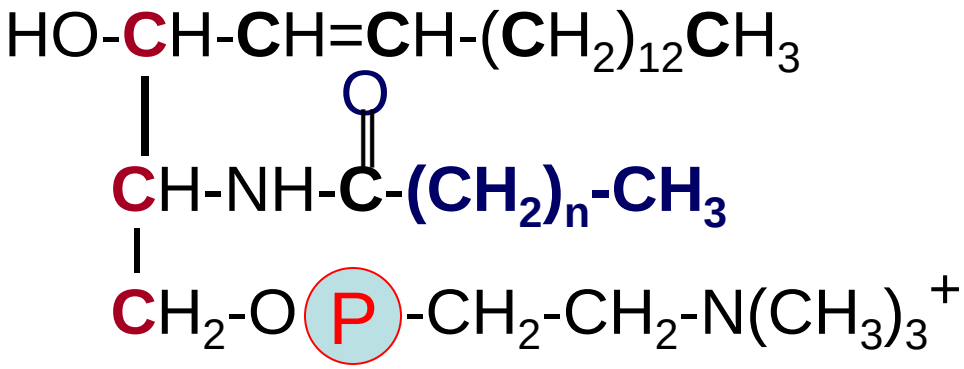
|

CH_2-OH

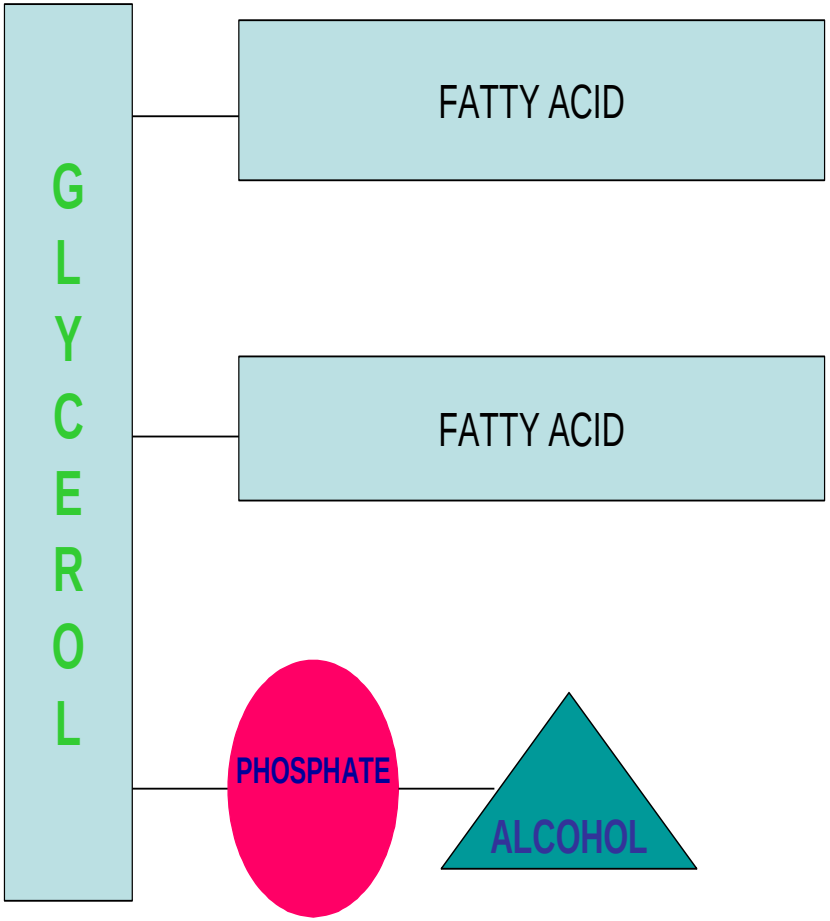
Ceramide: Fatty Acid to joined to Sphingosine



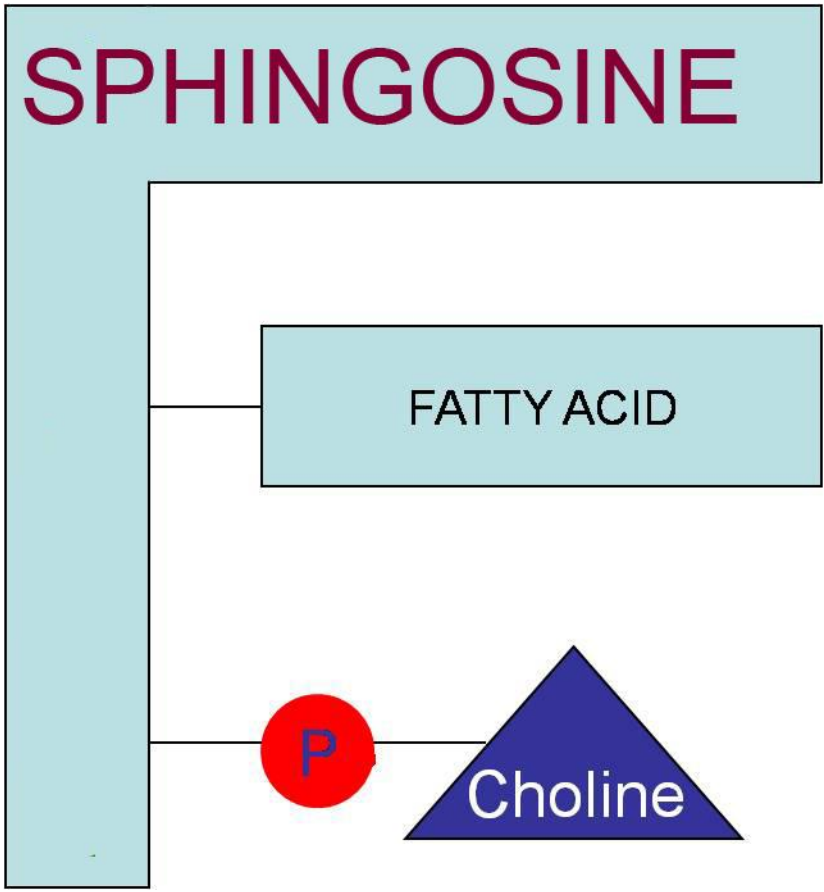
Sphingomyelin is Phosphocholine Ester of Ceramide



Sphingomyelin



PHOSPHOACYLGLYCEROL



Sphingophospholipids

Phosphatidylcholine and Sphingomyelin

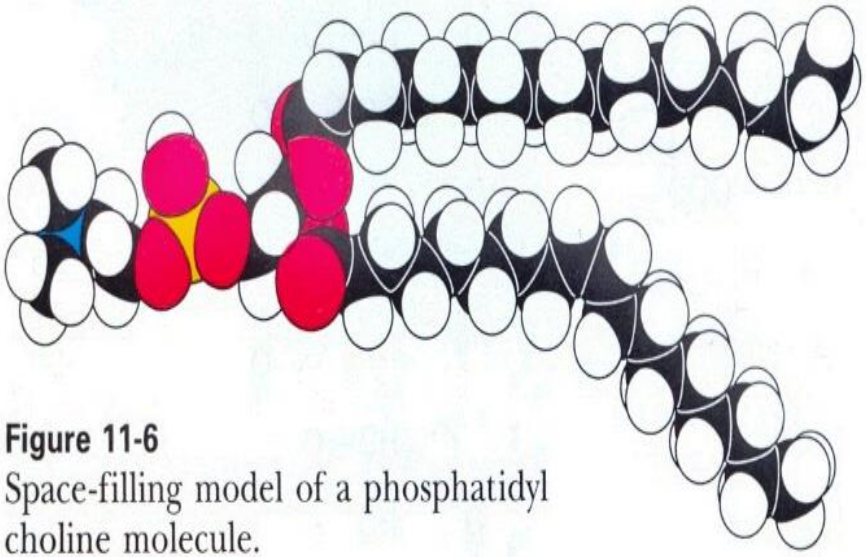


Figure 11-6
Space-filling model of a phosphatidyl choline molecule.

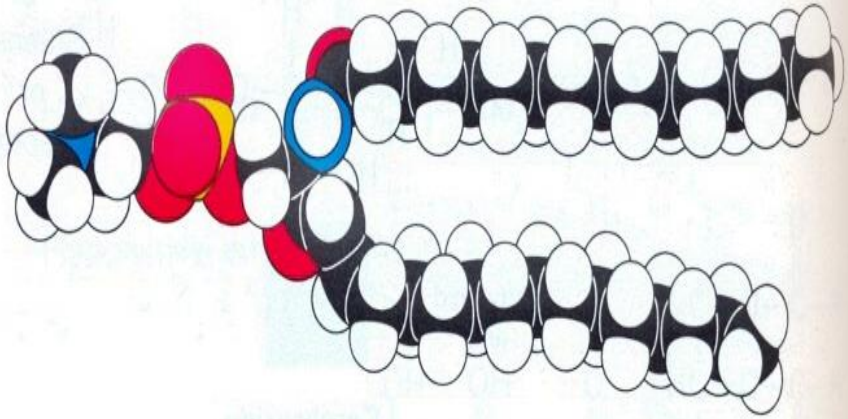
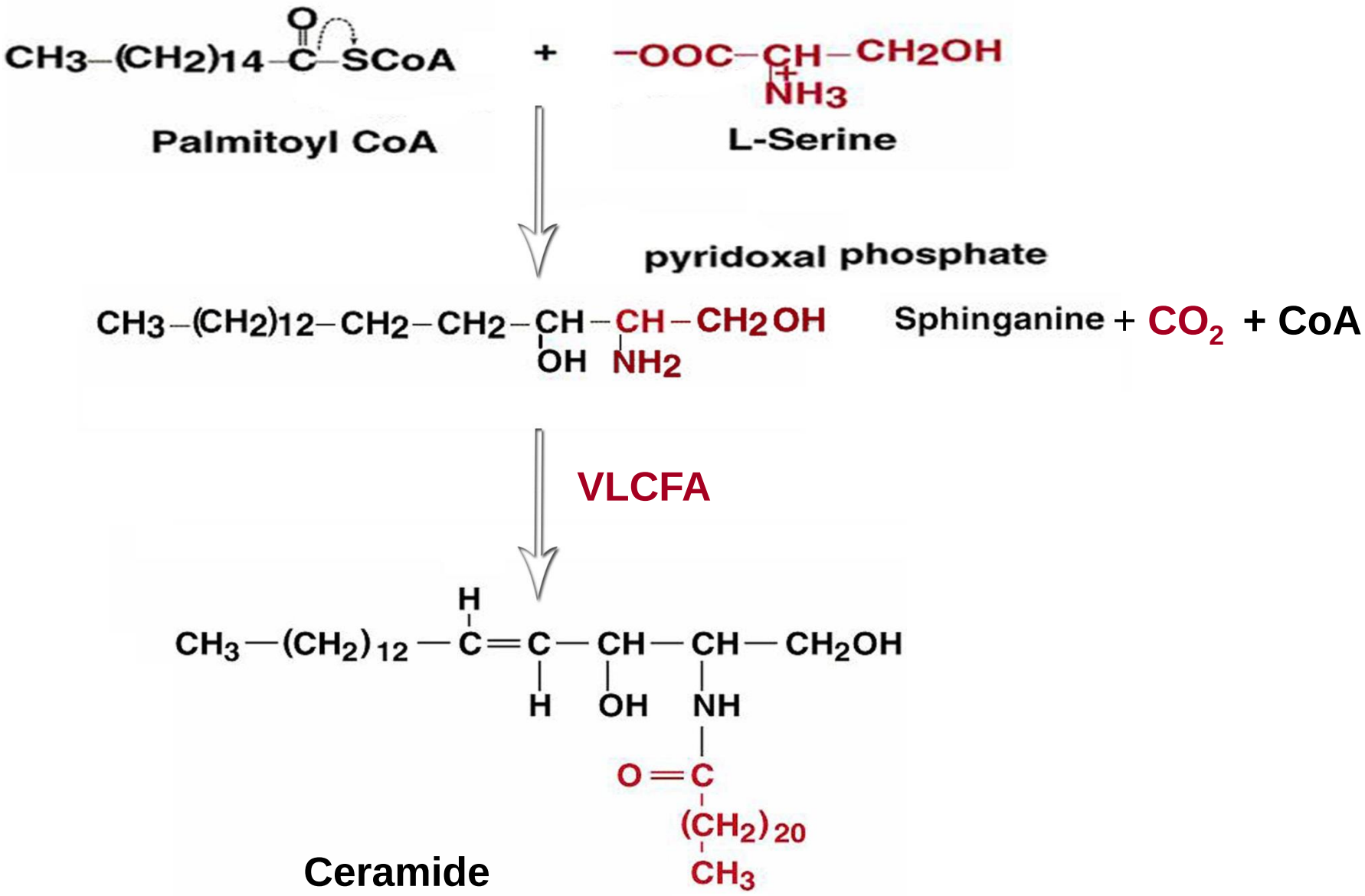
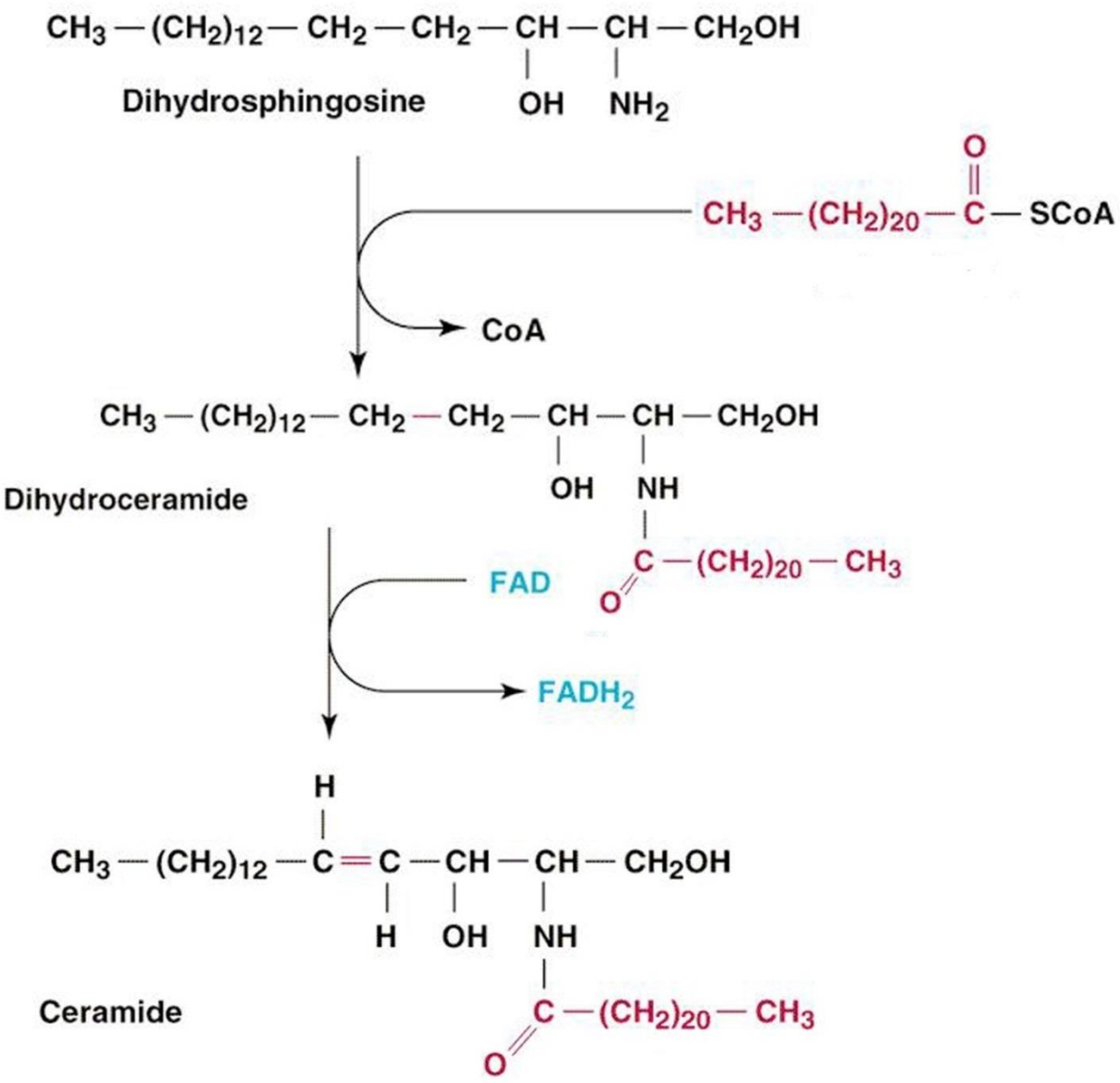


Figure 11-7
Space-filling model of a sphingomyelin molecule.

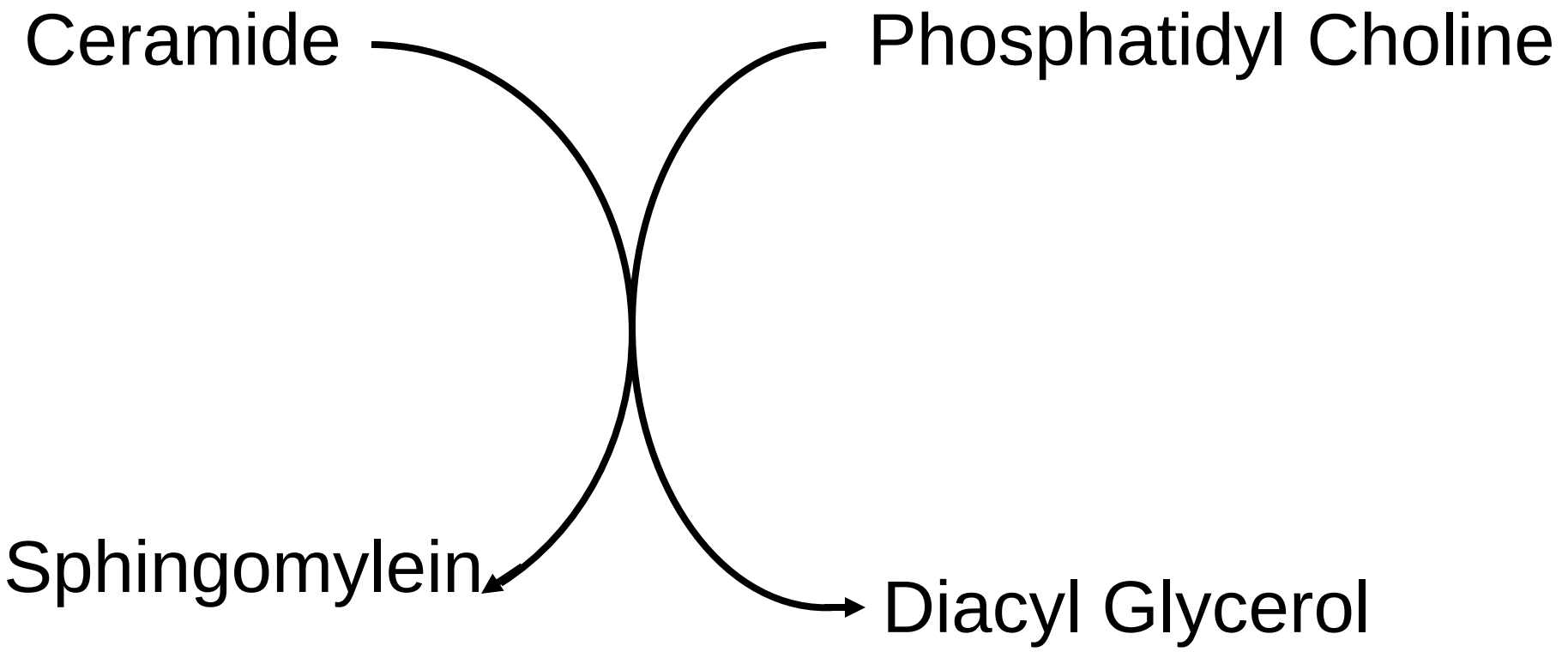
Synthesis of Sphingomyelin



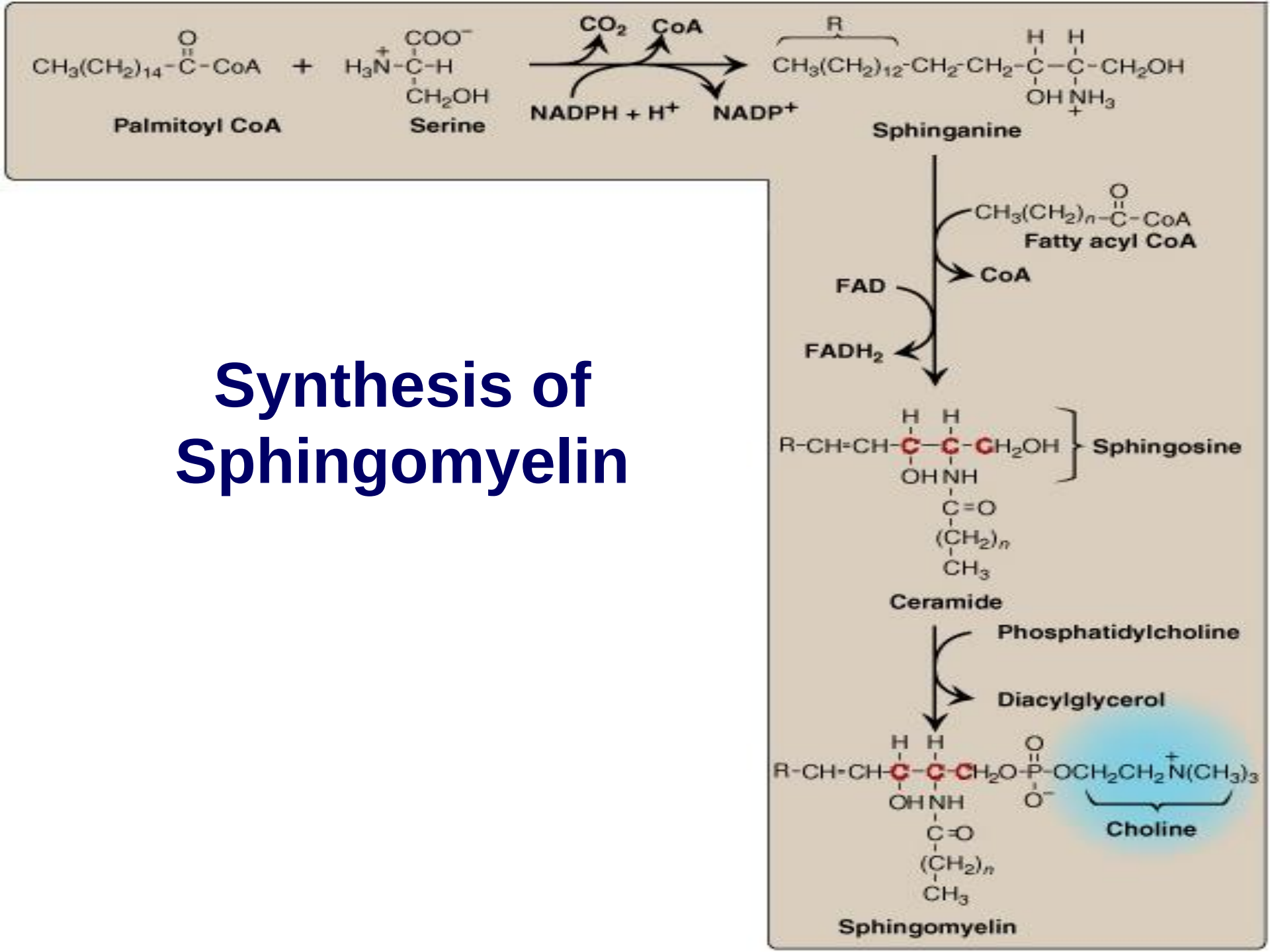
Synthesis of Sphingomyelin



Transfer Of Phosphocholine to Ceramide Produces Sphingomylein



Synthesis of Sphingomyelin



Glycolipids are Formed by Linking one or More Sugars to Ceramide

Ceramide +

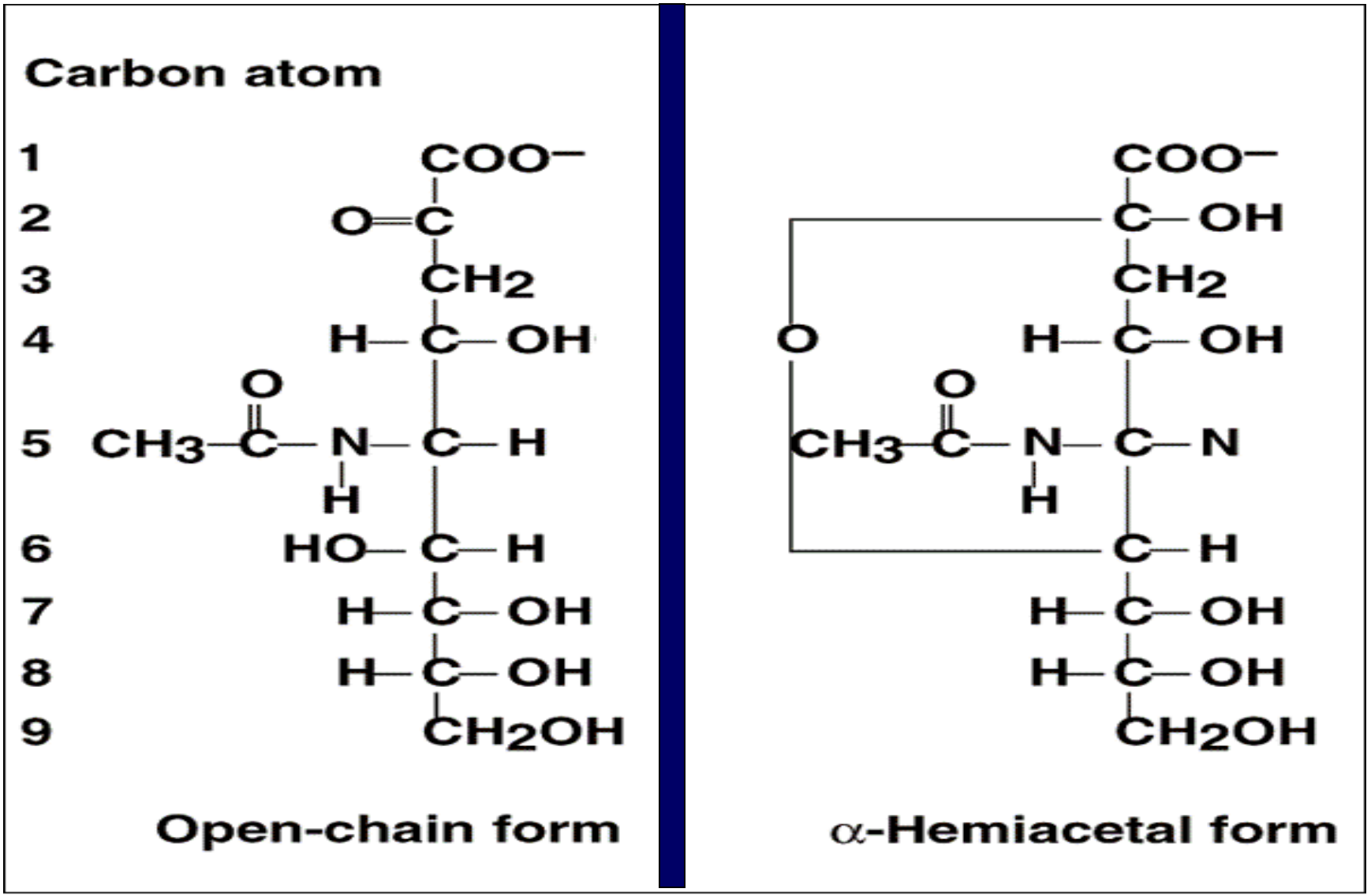
-Glucose or Galactose => Cerebroside

-Sulfated Galactose => Sulfoglycosphingolipids

-Oligosaccharide => Globoside

-Oligosaccharide with NANA => Gangliosides

N-AcetylNeuraminic Acid (NANA)



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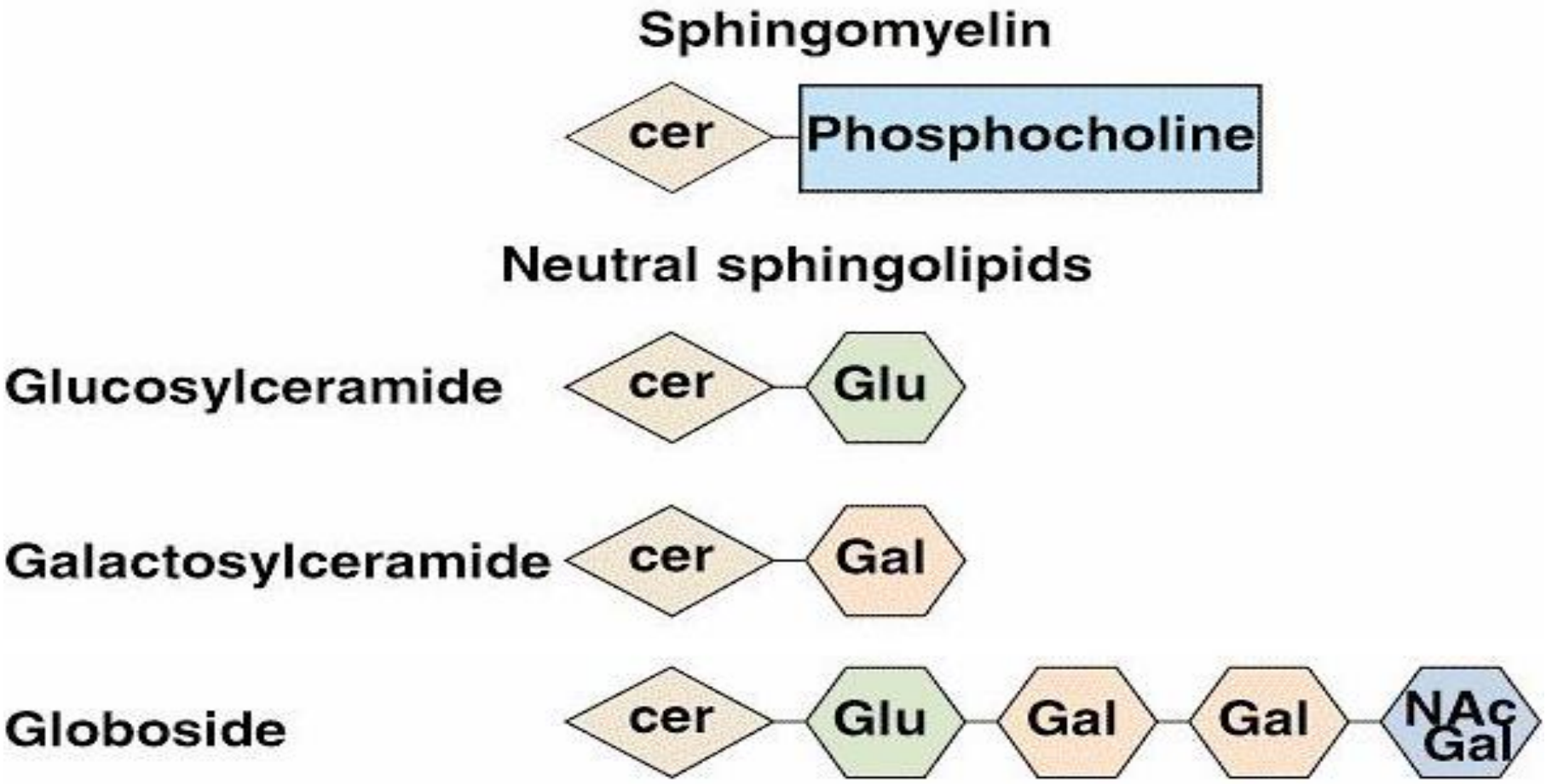
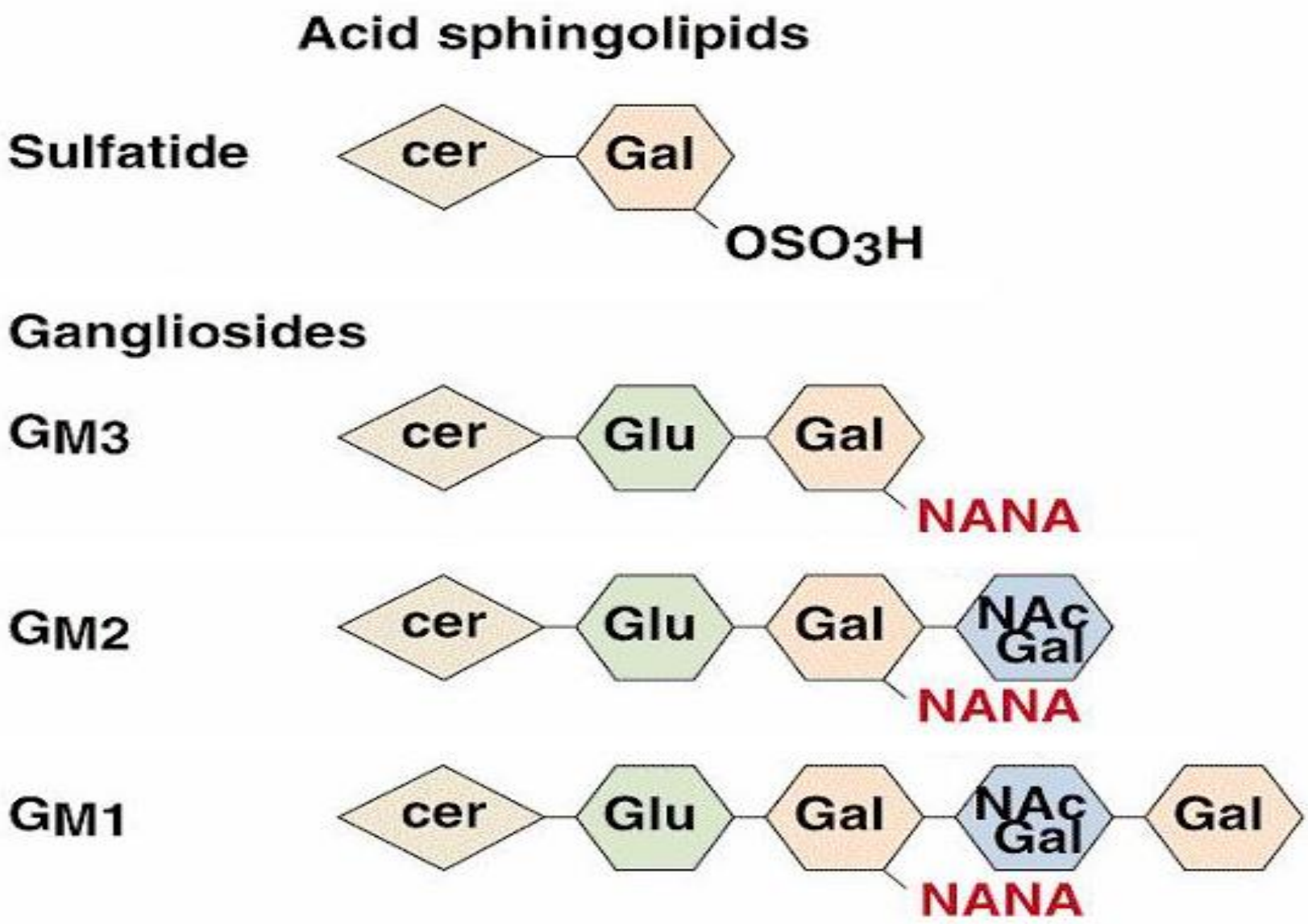
Types of Sphingolipids



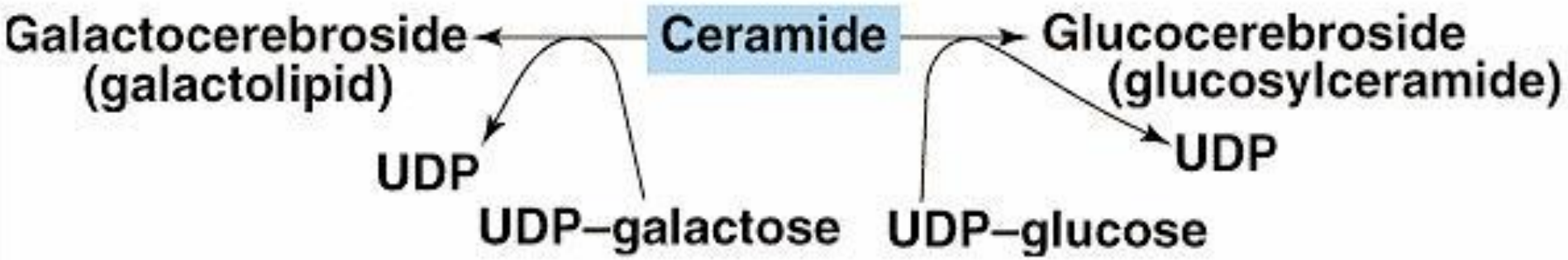
Types of Sphingolipids



Activated Donors in Glycolipids Synthesis

- UDP-**Glucose**
- UDP-**Galactose**
- UDP-**N-Acetylgalctoseamine**
- CMP- **N-Acetylneuraminic Acid**

Glycolipid synthesis



Glycosyltransferases

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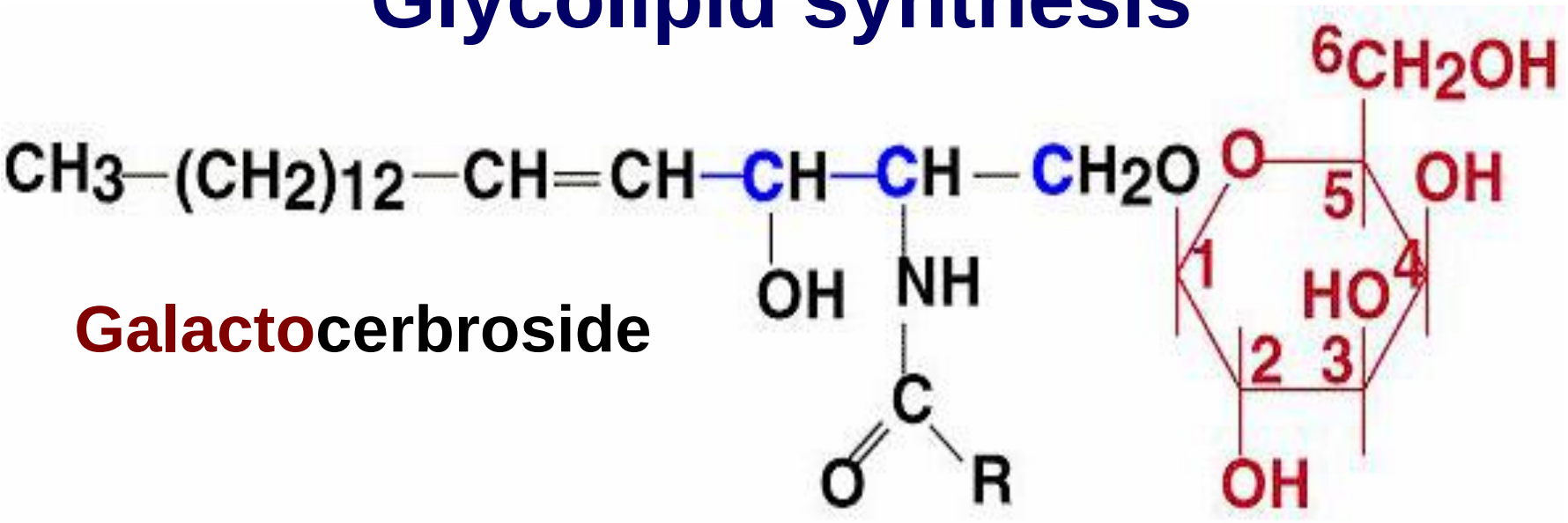
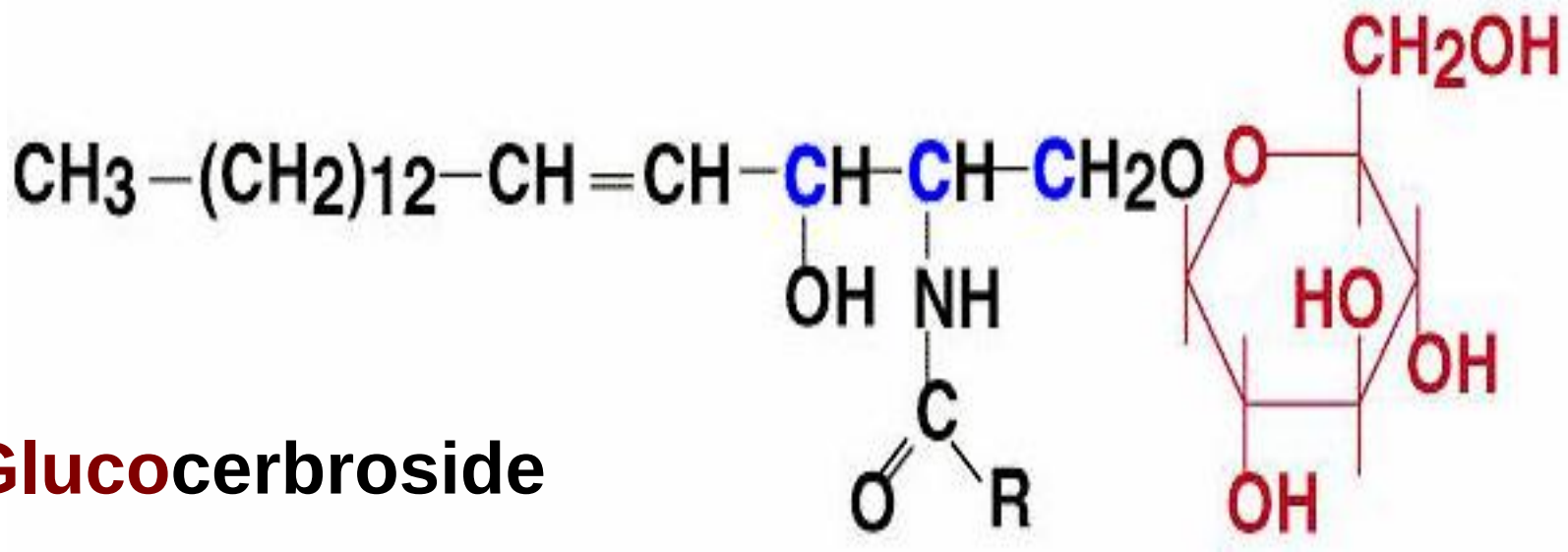
Glycolipid synthesis



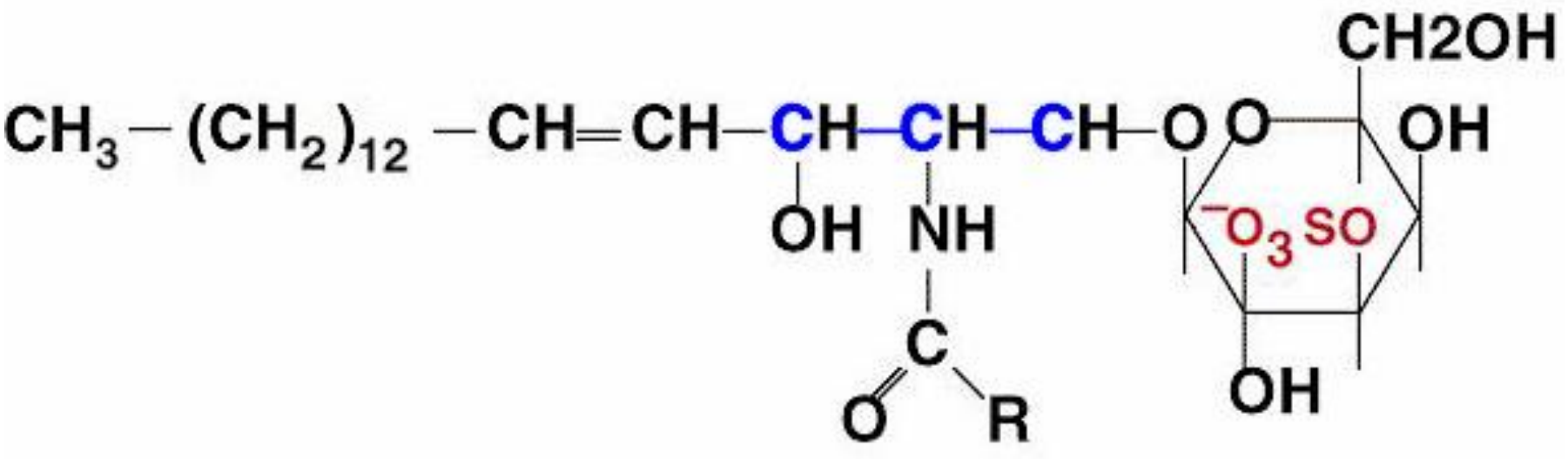
Galactocerbroside



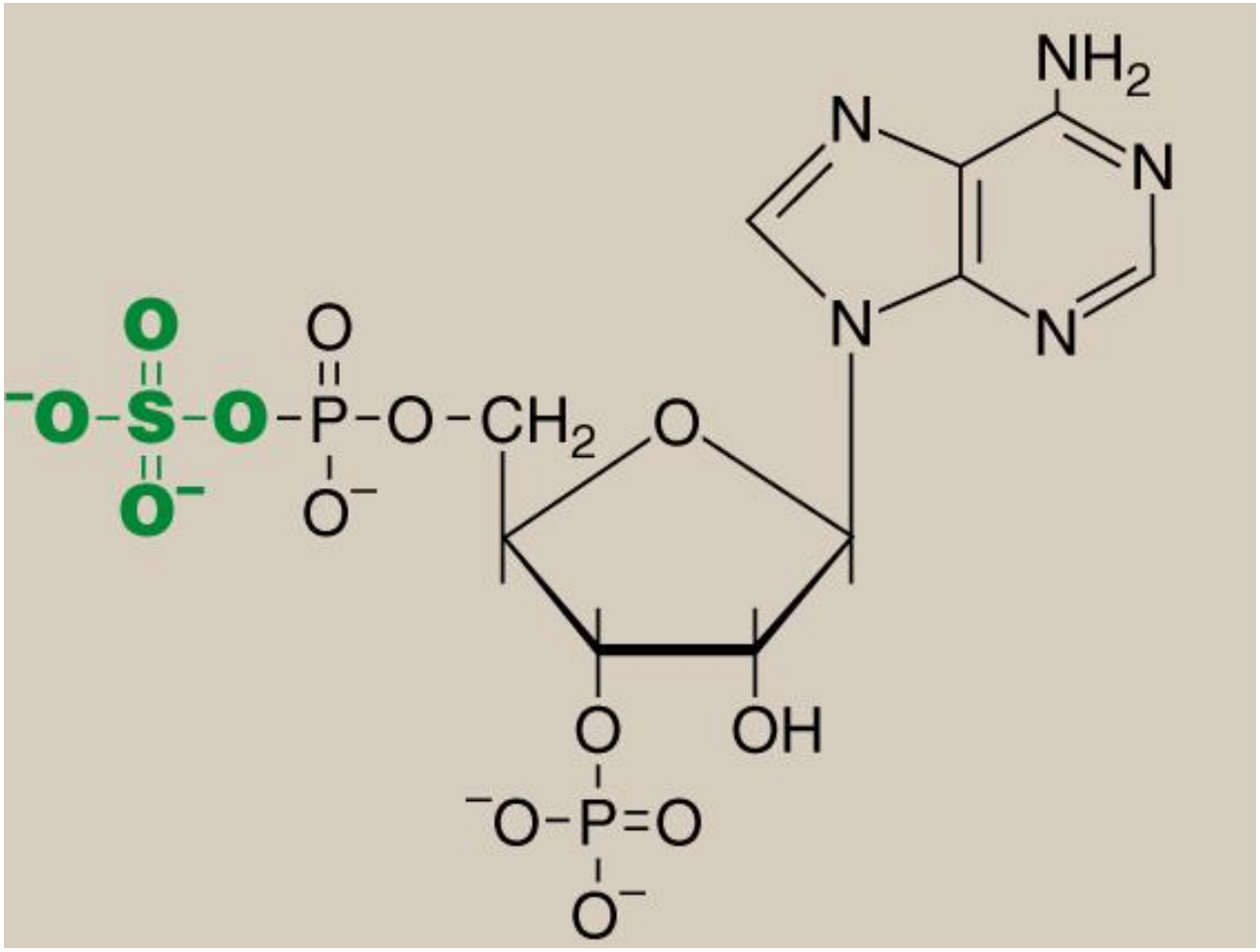
Glucocerbroside

Glycolipid synthesis

Transfer of Sulfate Group to Galactocerbroside by sulfotransferases Produces **Sulfogalatocerbroside** (Sulfatide)

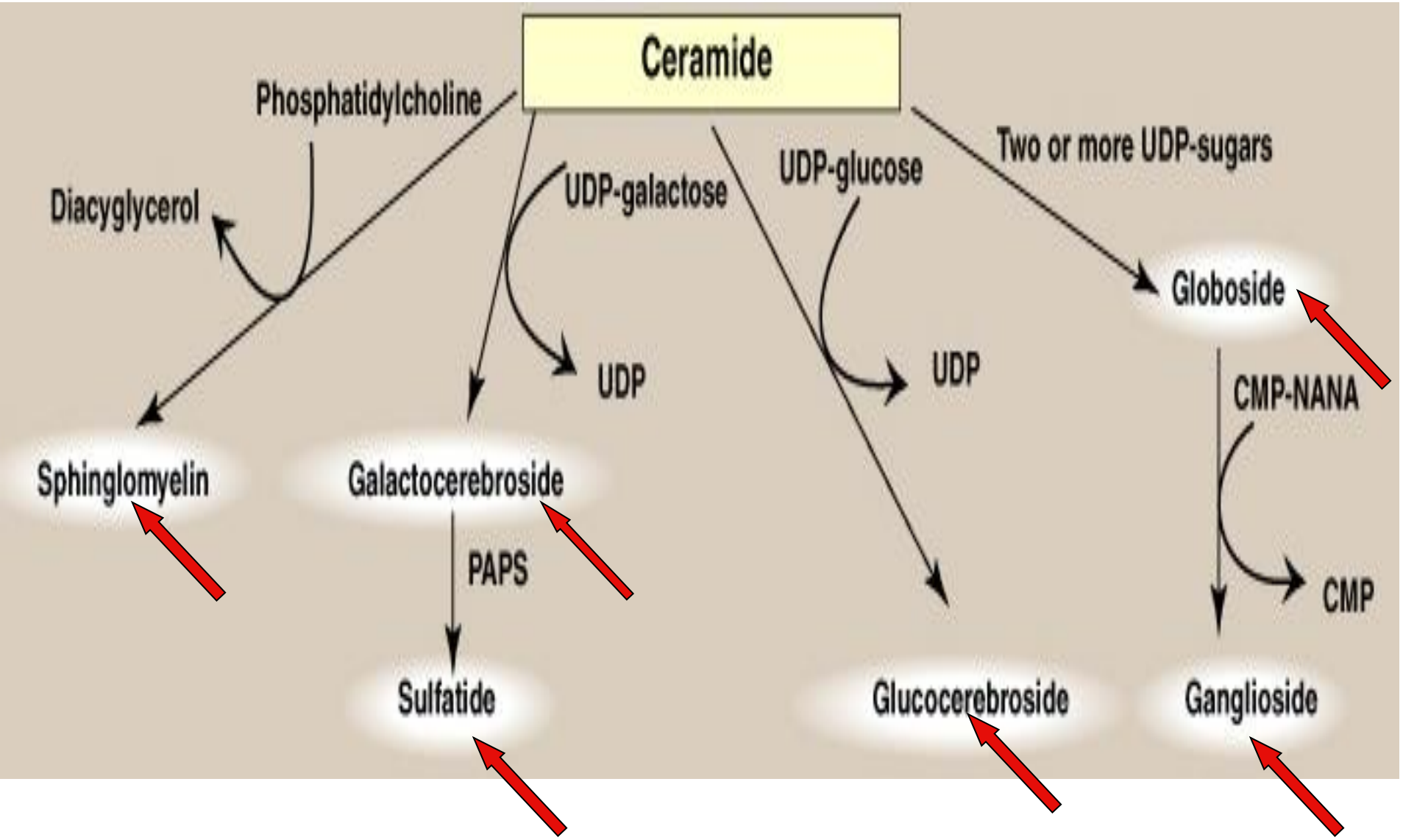


Sulfate Group Donor



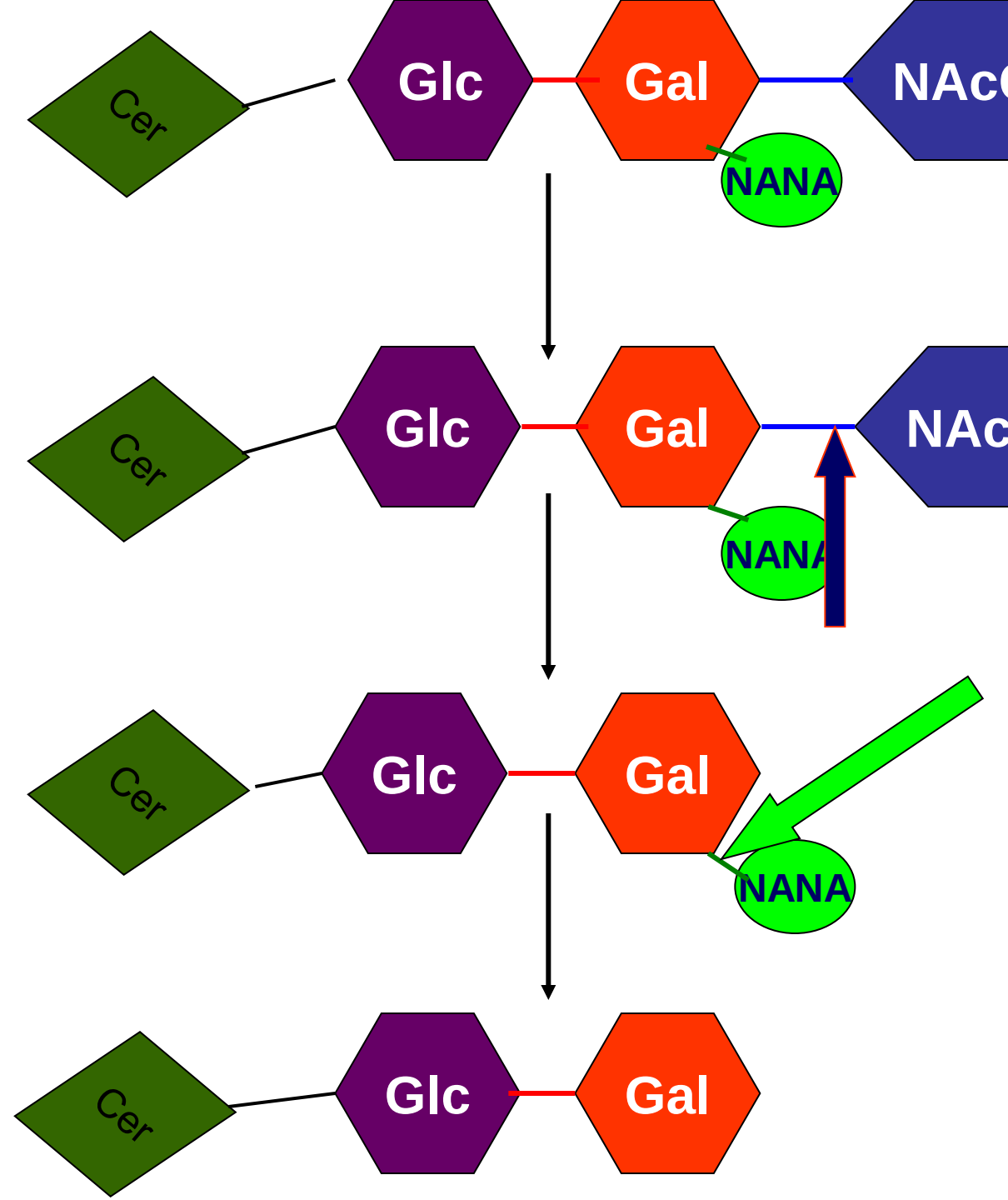
3 Phosphoadenosine 5 Phosphosulfate PAPS

Glycolipid synthesis



Degradation of Sphingolipids

- ✓ Hydrolytic Enzymes, Specific for the Sugar
- ✓ - **α Galactosidase**
  - ✓ **β Galactosidase**
  - ✓ **Neuraminidase**
  - ✓ **Hexoaminidase**
- ✓ In Lysosomes
- ✓ Enzymes are firmly Bound to Lysosomal Membrane.
- ✓ The pH Optimum 3.5-5.5
- ✓ Stepwise Sequential Process
- ✓ “Last on, First off”



Degradation of Sphingolipids

βGalactosidase

βHexoseaminidase

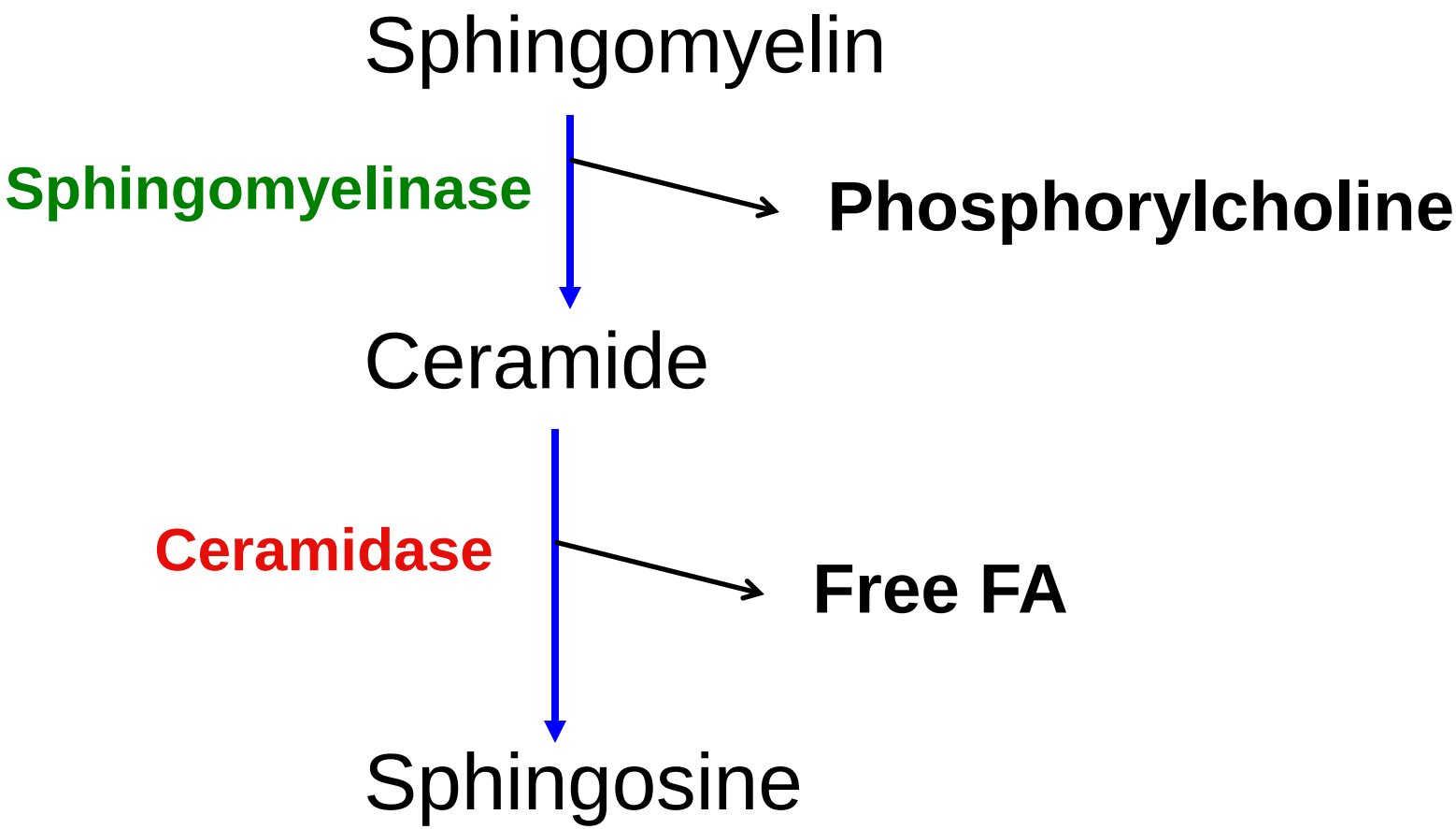
Neuraminidase

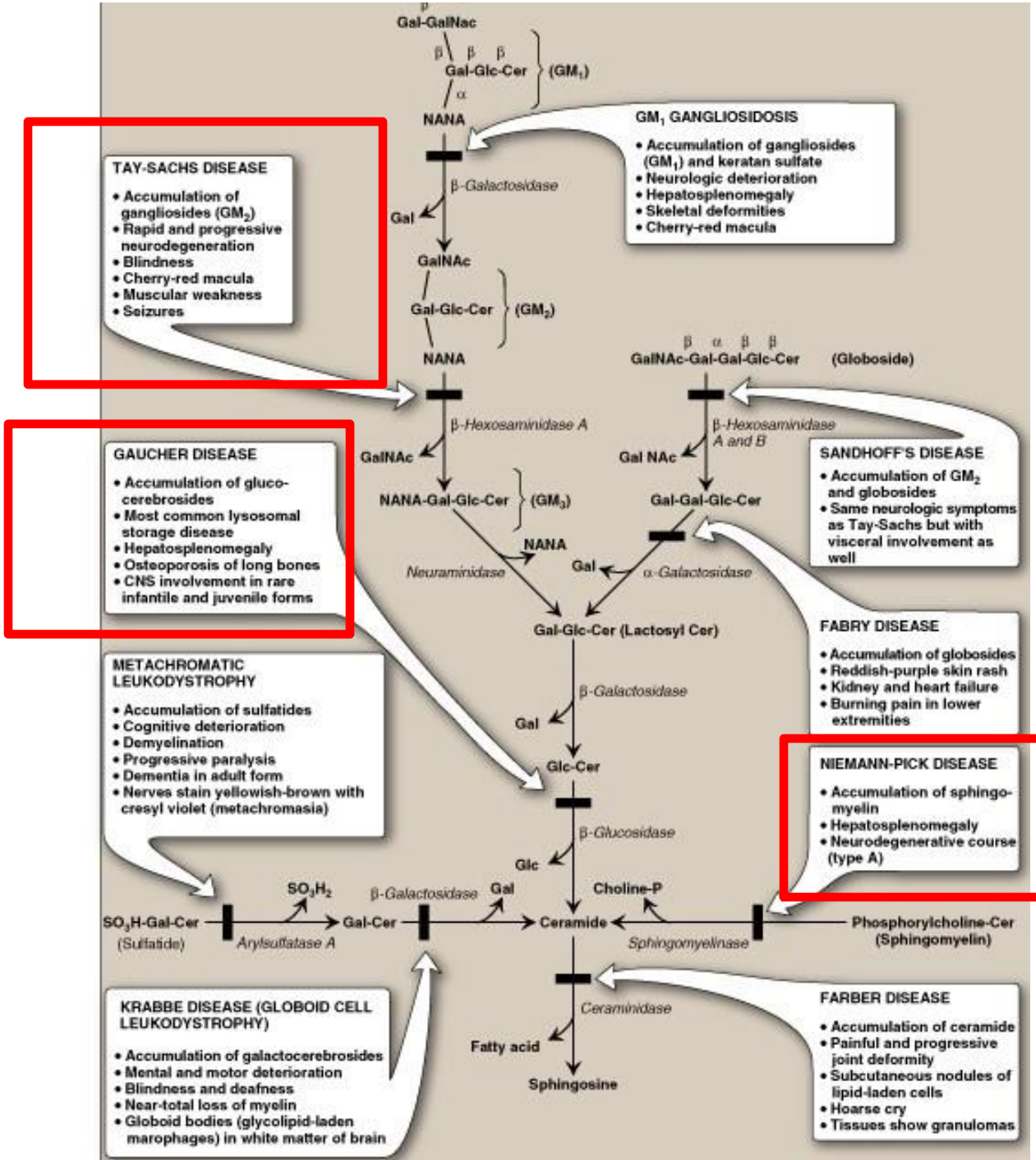
Sphingolipidoses

- **Lipid Storage Diseases**
- **Defect in one of the Enzymes (acid hydrolasase)**
- **Inherited as Autosomal RecessiveDisease**
- **Accumulation of Specific Lipid**

  Substrate of the Defective Enzyme
- **Brain is Mostly Affected.**
- **Extent of Enzyme deficiency is the same in Different Tissues**.

Degradation of Sphingomyelin




Gal-GalNac
Gal-Glc-Cer
(GM1)
NANA
GM1 GANGLIOSIDOSIS
• Accumulation of gangliosides (GM1) and keratan sulfate
• Neurologic deterioration
• Hepatosplenomegaly
• Skeletal deformities
• Cherry-red macula
TAY-SACHS DISEASE
• Accumulation of gangliosides (GM2)
• Rapid and progressive neurodegeneration
• Blindness
• Cherry-red macula
• Muscular weakness
• Seizures
β-Galactosidase
Gal
GalNAc
Gal-Glc-Cer
(GM2)
NANA
GalNAc-Gal-Gal-Glc-Cer
(Globoside)
β-Hexosaminidase A
β-Hexosaminidase A and B
GAUCHER DISEASE
• Accumulation of gluco-cerebrosides
• Most common lysosomal storage disease
• Hepatosplenomegaly
• Osteoporosis of long bones
• CNS involvement in rare infantile and juvenile forms
GalNAc
Gal NAc
SANDHOFF'S DISEASE
• Accumulation of GM2 and globosides
• Same neurologic symptoms as Tay-Sachs but with visceral involvement as well
NANA-Gal-Glc-Cer
(GM3)
Gal-Gal-Glc-Cer
NANA
Neuraminidase
Gal
α-Galactosidase
Gal-Glc-Cer (Lactosyl Cer)
FABRY DISEASE
• Accumulation of globosides
• Reddish-purple skin rash
• Kidney and heart failure
• Burning pain in lower extremities
METACHROMATIC LEUKODYSTROPHY
• Accumulation of sulfatides
• Cognitive deterioration
• Demyelination
• Progressive paralysis
• Dementia in adult form
• Nerves stain yellowish-brown with cresyl violet (metachromasia)
β-Galactosidase
Gal
Glc-Cer
NIEMANN-PICK DISEASE
• Accumulation of sphingo-myelin
• Hepatosplenomegaly
• Neurodegenerative course (type A)
β-Glucosidase
Glc
SO3H
β-Galactosidase
Gal
Choline-P
SO3H-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 marophages) in white matter of brain
Ceraminidase
FARBER DISEASE
• Accumulation of ceramide
• Painful and progressive joint deformity
• Subcutaneous nodules of lipid-laden cells
• Hoarse cry
• Tissues show granulomas
Fatty acid
Sphingosine