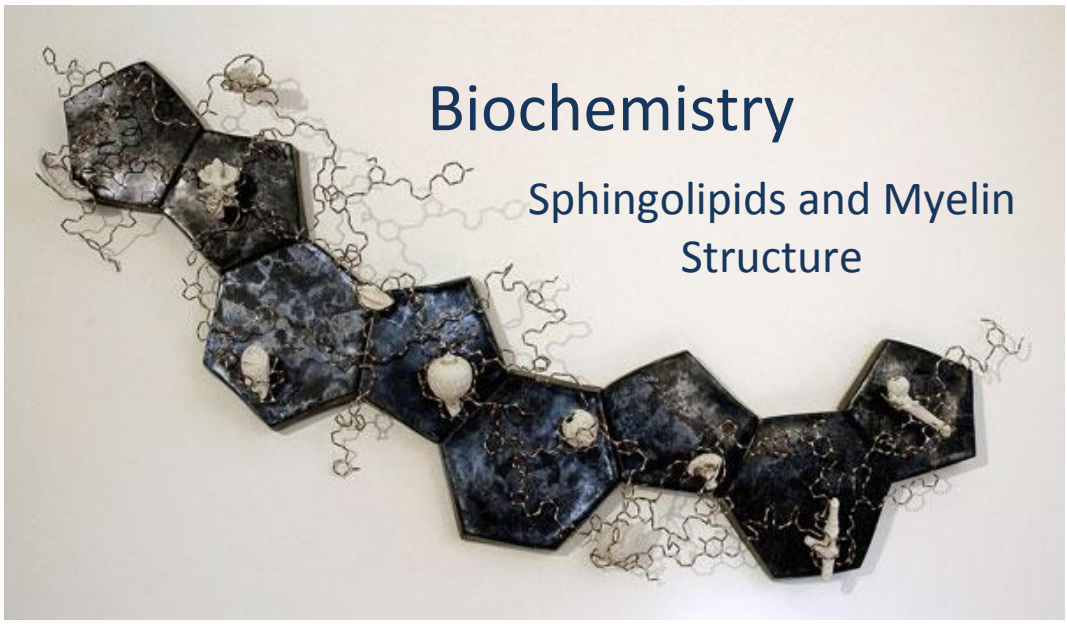

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Sphingolipids

Introduction:

Essential component of membranes

Abundant in nervous tissue

Extra-nervous tissue e.g., receptors for

a. Cholera toxins
b. Diphtheria toxins
c. Viruses

Regulation of growth & development

Cell transformation

The modification of the structure of sphingolipids is greatly related to the transformation of benign cells to malignant cells.

Very antigenic *(the carbohydrates in its structure are what mainly act as antigens)*

a. Blood group antigen
b. Embryonic antigen
c. Tumor antigen

The chemical structure of sphingolipids is sub-divided into two types:

➔ Glycosphingolipids *(Glycolipids)* *contain carbohydrate*

➔ Sphingophospholipids *e.g., Sphigomyelin*

Structure & Types of Sphingolipids:

The backbone of sphingomyelin is the amino alcohol sphingosine, rather than glyserol like in glycolipid

- Ceramide is the precursor of sphingolipids

  Ceramide = sphingosine + fatty acid

  → Ceramide + phosphorylcholine = Sphingomyelin

  → Ceramide + Monosaccharide = Cerebroside

  Note: each cerebroside is given it's name depending on the type of monosaccharide it contains. Ex: glucocerebroside, galactocerebroside..etc

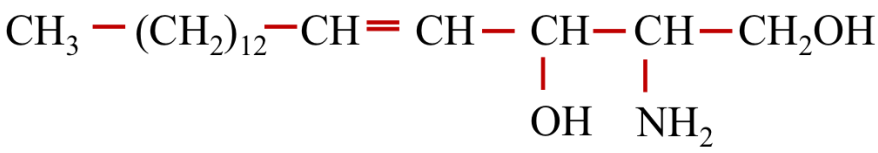
  → Ceramide + Oligosaccharide + 'NANA' or N-Acetylneuraminic acid = Ganglioside

  Note: gangliosides differ in the type of oligosaccharide as well as the number of 'NANA' attached

- Cerebrosides & Gangliosides are types of glycolipids

Sphingosine

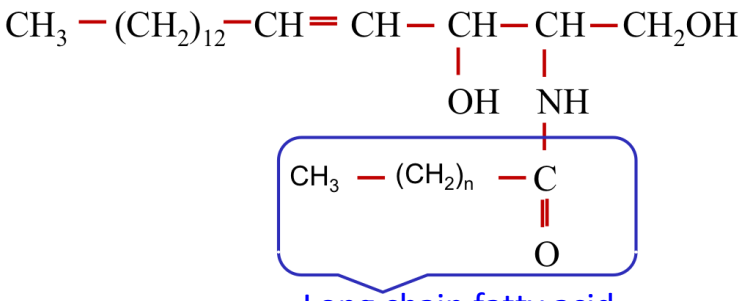
We don't have to memorize the structures



Long chain, unsaturated *(contains a double bond)* amino alcohol

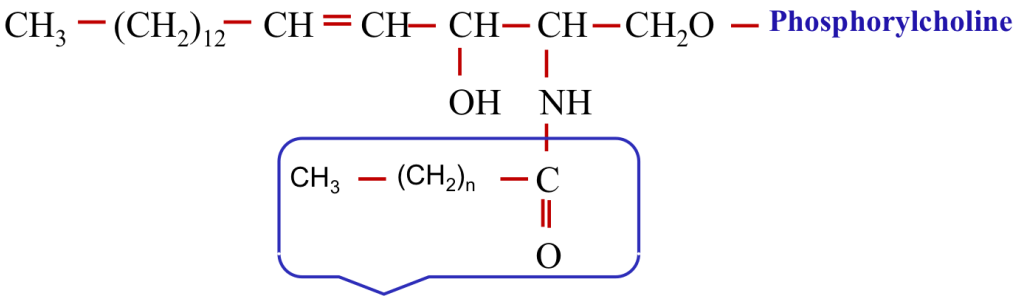
Ceramide

Sphigosine + fatty acid



Sphingomyelin

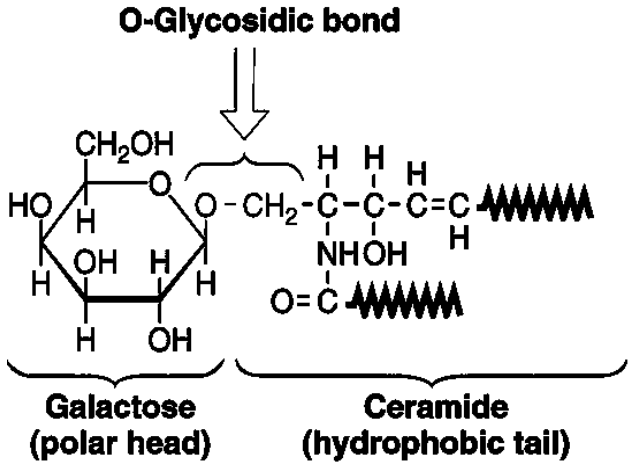
Sphigosine + fatty acid + phosphorylcholine



Galatocerebroside

Sphigosine + fatty acid + galactose

Galactocerebroside is from the cerebroside group



Ganglioside

Sphigosine + fatty acid + oligosaccharide + NANA

Gangliosides are found in the ganglion mainly

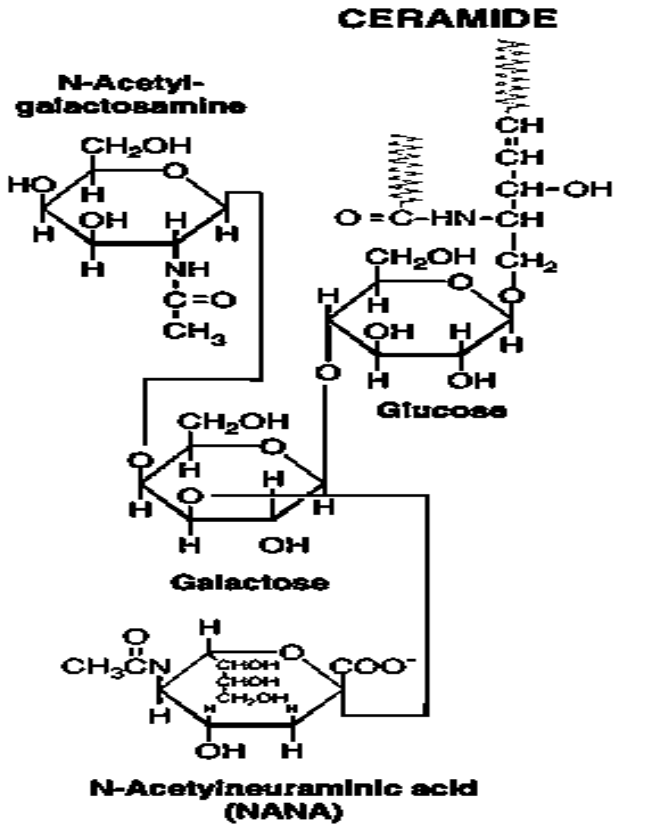


Figure 17.15
Structure of the ganglioside G_{M2}.

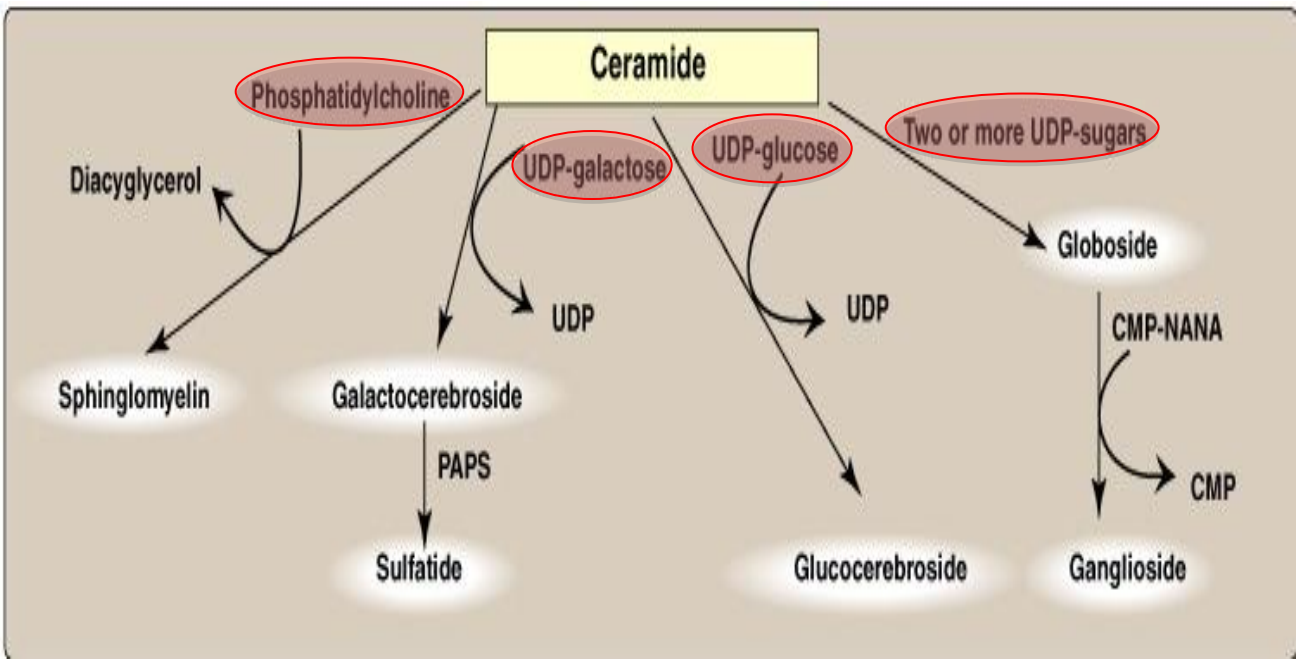
Sphingolipid Synthesis

the enzymes involved are important

Ceramide is the precursor of all sphingolipids.

PAPS → Source of sulfate

Globoside → Ceramide + Oligosaccharide



Myelin Structure

- Myelin is a specialized cell membrane that ensheathes an axon to form a myelinated nerve fiber.
- Myelin is produced by either:
  - Schwann cells in the Peripheral nerves
  - Oligodendrocyte in the Central nervous system
- Myelin composition:
  - (80%) Lipid:
    - Main component: Cerebroside
      Sphigosine + fatty acid + monosaccharide = Cerebroside
    - Other component: Sphingomyelin
      Sphigosine + fatty acid + phosphorylcholine = Sphingomyelin
  - (20%) Protein: e.g., Myelin basic protein
- Fatty acid of Sphingomyelin: differs depending on the location in the body
  - Myelin sheath (white matter): *very long chain fatty acids*
    - Lignoceric 24:0
    - Nervonic 24:1
  - Gray matter: *long chain fatty acid*
    - *Stearic* *18:0*
- Function: Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speed up the transmission of impulses along axons.

- The first number indicates the number of carbons and the second indicates the number of double bonds.
- Sphingomyelin (meaning lipid not the myelin sheath) is in the gray matter.

Multiple sclerosis:

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

Sphingolipidosis

- Are a group of inborn errors of metabolism diseases defined by disrupted turnover of sphingolipids. The synthesis of substrate is normal, while the degradation pathway is defected. This leads to accumulation of that substrate in the body.
- The defect of enzymes cause stoppage of substrate degradation → accumulation of substrate.
- Are progressive diseases often resulting in early death.
- This group of diseases are mostly* autosomal recessive and therefore rare, mainly seen in communities with high consanguinity rates (only marry one another, with no outside exposure) as Ashkenazi Jews.

* all are autosomal recessive EXCEPT Fabryl disease which is X-linked

- Have high phenotypic and genotypic variability *(➔ phenotypic in that the manifestations of each disease are not consistent among all patients. Genotypic meaning that not all patients have the exact same gene mutation. Any of the many genes contributing to that enzyme can be affected.)*
- This group of diseases are also called lysosomal lipid storage disease because the substrate will accumulate in the lysosomes of the cells. (seen histologically)

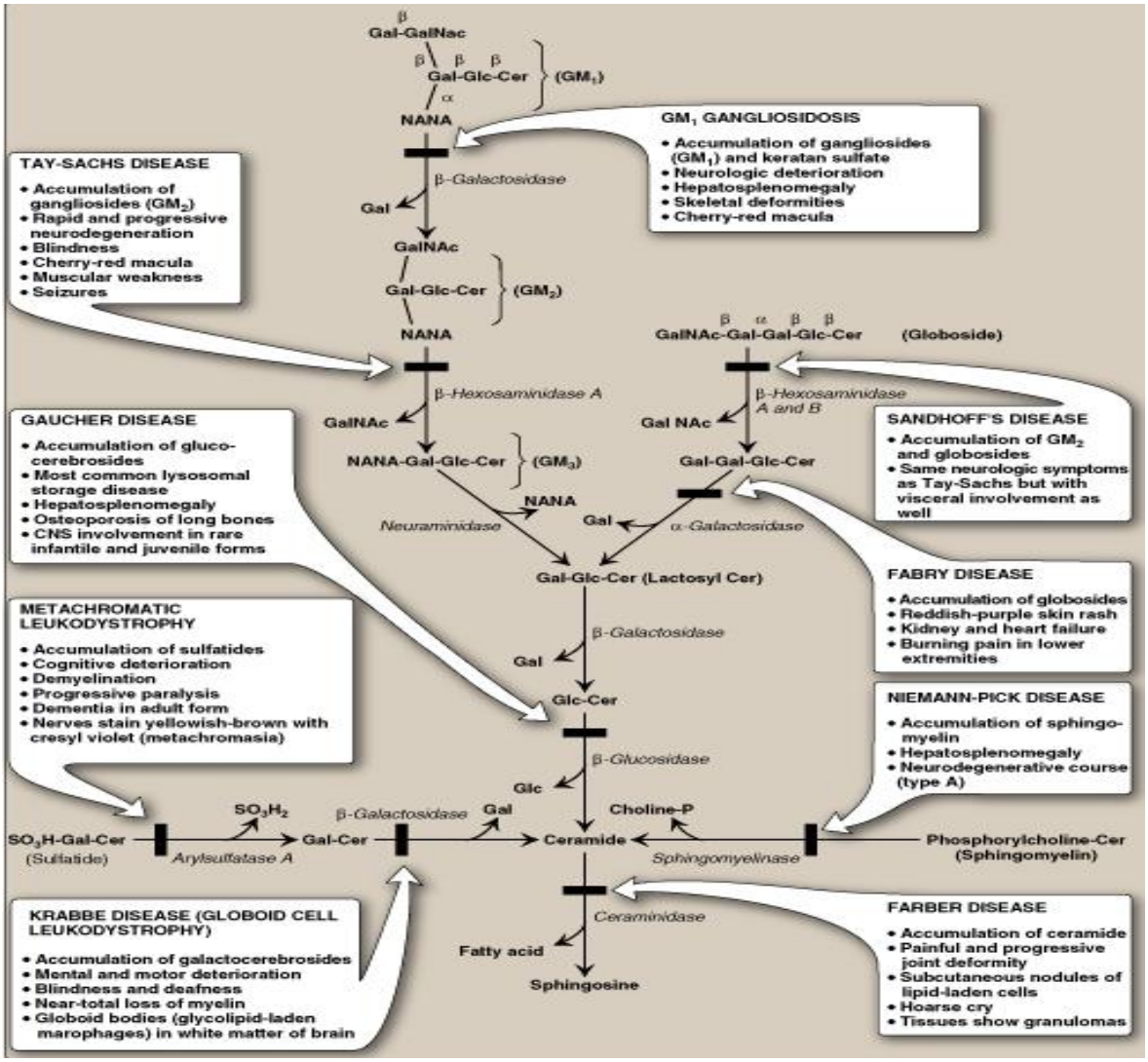
Diagnosis:

- Clinical picture
- Measure enzyme activity via:
  - Cultured fibroblasts (from skin scrape) or peripheral leukocytes (from blood test)
  - Cultured amniocytes (prenatal testing)
- Histologic examination will view lysosomes engorged with substrate *(used more post-natally)*
- DNA analysis *(used more pre-natally)*

Treatment:

- Replacement Therapy:
  - Recombinant human enzyme
- Bone marrow transplantation:
  - mostly used for Gaucher disease patients

Sphingolipidosis Types:



TAY-SACHS Disease:

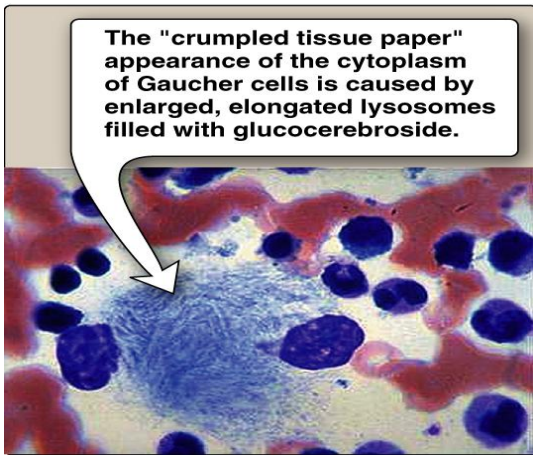
enzyme involved Beta-Hexosaminidase A

- Accumulation of gangliosides (GM_2)
- Rapid, progressive, and fatal neurodegeneration
- Blindness
- Cherry-red macula
- Muscular weakness
- Seizures

GAUCHER Disease:

enzyme involved Beta-Glucosidase (glucocerebrosidase)

- Accumulation of glucocerebrosides
- Most common lysosomal storage disease
- Hepatosplenomegaly
- Osteoporosis of long bones causing severe bone aches
- CNS involvement in rare infantile & juvenile forms



NIEMANN-PICK disease:

enzyme involved Sphingomyelinase

- Subdivided into (A+B) types which refer to the degree of severity
- Accumulation of sphingomyelin
- Hepatosplenomegaly
- Neurodegenerative course (type A)
- Type A
    - Acute disease
    - Sever deficiency of enzyme.
    - Which comes with neurodegernative effect (severe mental retardation)
- Type B
    - Chronic disease.
    - Mild deficiency of enzyme.
    - Little or no neurological defect.

Take home message:

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

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