

SPHINGOLIPIDS AND MYELIN STRUCTURE

OUTLINES

- Objectives.
- Background.
- Key principles.
- Take home messages.

OBJECTIVES

By the end of this lecture, the students should be able to:

- 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.

BACKGROUND

There are two classes of phospholipids based on the backbone:

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

BACKGROUND (*Cont'd...*)

- Essential component of membranes.
- Abundant in nervous tissue.
- Also exist extra-nervous tissue:

e.g. Receptors for:

Cholera toxins

Diphtheria toxins

Viruses.

BACKGROUND (*Cont'd...*)

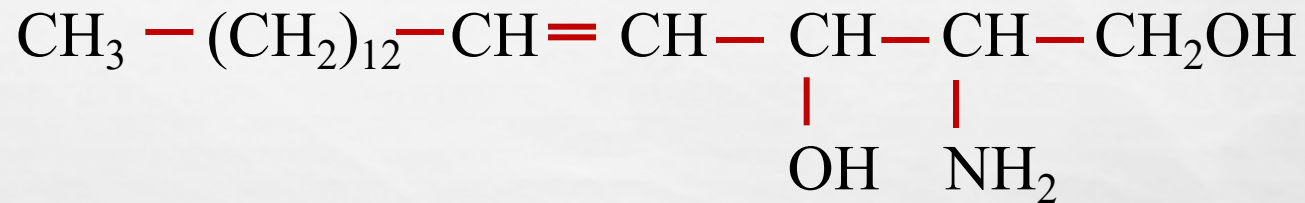
- Regulation of growth and development.
- Very antigenic:
 - Blood group antigen
 - Embryonic antigen
 - Tumor antigen
- Cell transformation.

KEY PRINCIPLES

- Chemical structure of Sphingolipids.
- Types:
 - Glycosphingolipids (Glycolipids).
 - Sphingophospholipids, e.g. Sphingomyelin.
- Myelin structure and function.
- Sphingolipidoses.

SPHINGOLIPIDS: STRUCTURE AND TYPES

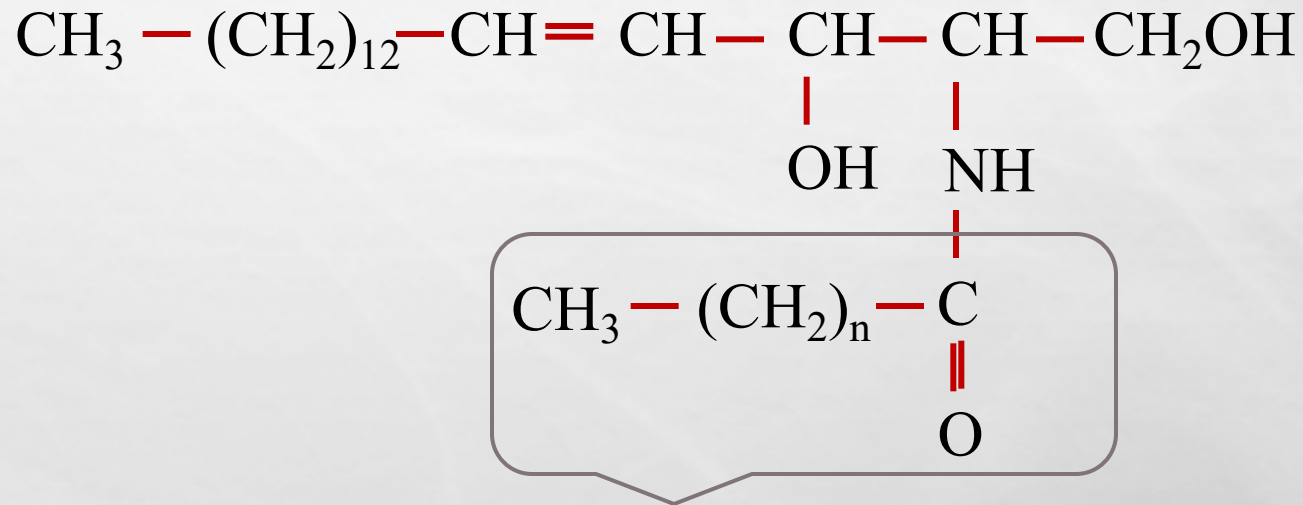
SPHINGOSINE



Long chain, unsaturated amino alcohol

CERAMIDE

Ceramide = Sphingosine + Fatty acid

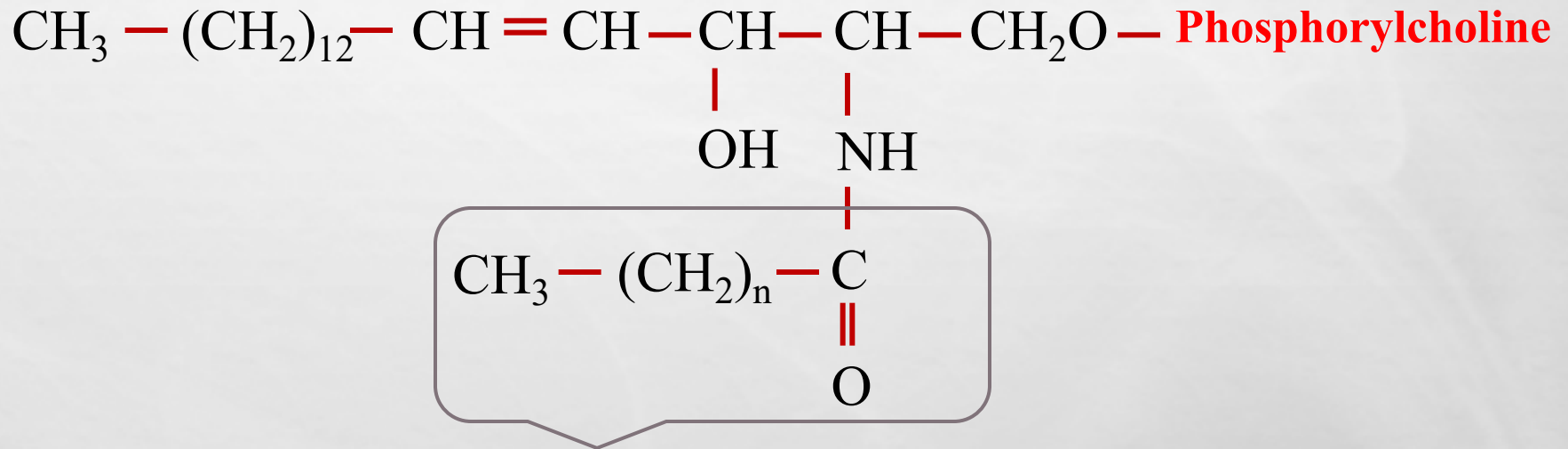


Long chain fatty acid

- *Ceramide play a key role in maintaining the skin's water-permeability barrier.*
- *Decreased ceramide levels are associated with a number of skin diseases.*

SPHINGOMYELIN

Sphingomyelin = Ceramide + Phosphorylcholine



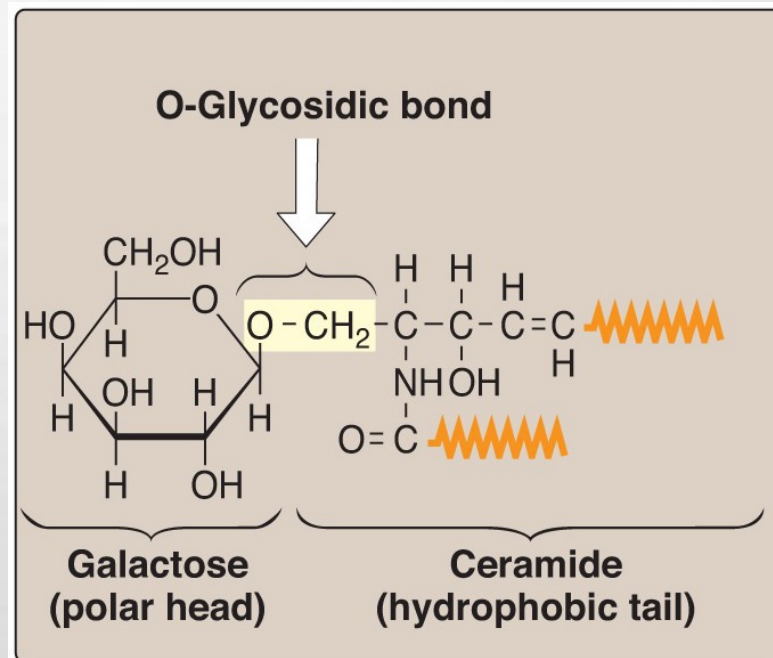
Long chain fatty acid

- Sphingomyelin is the only significant sphingolipid in humans*

CEREBROSIDES

Cerebrosides = Ceramide + Monosaccharides

e.g. Galactocerebroside.



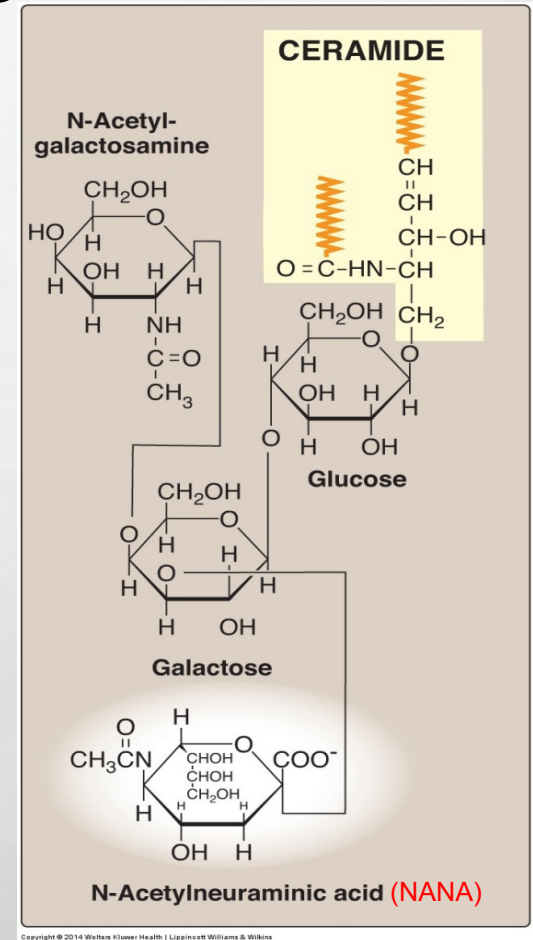
GANGLIOSIDES

Gangliosides = Ceramide oligosaccharides

+

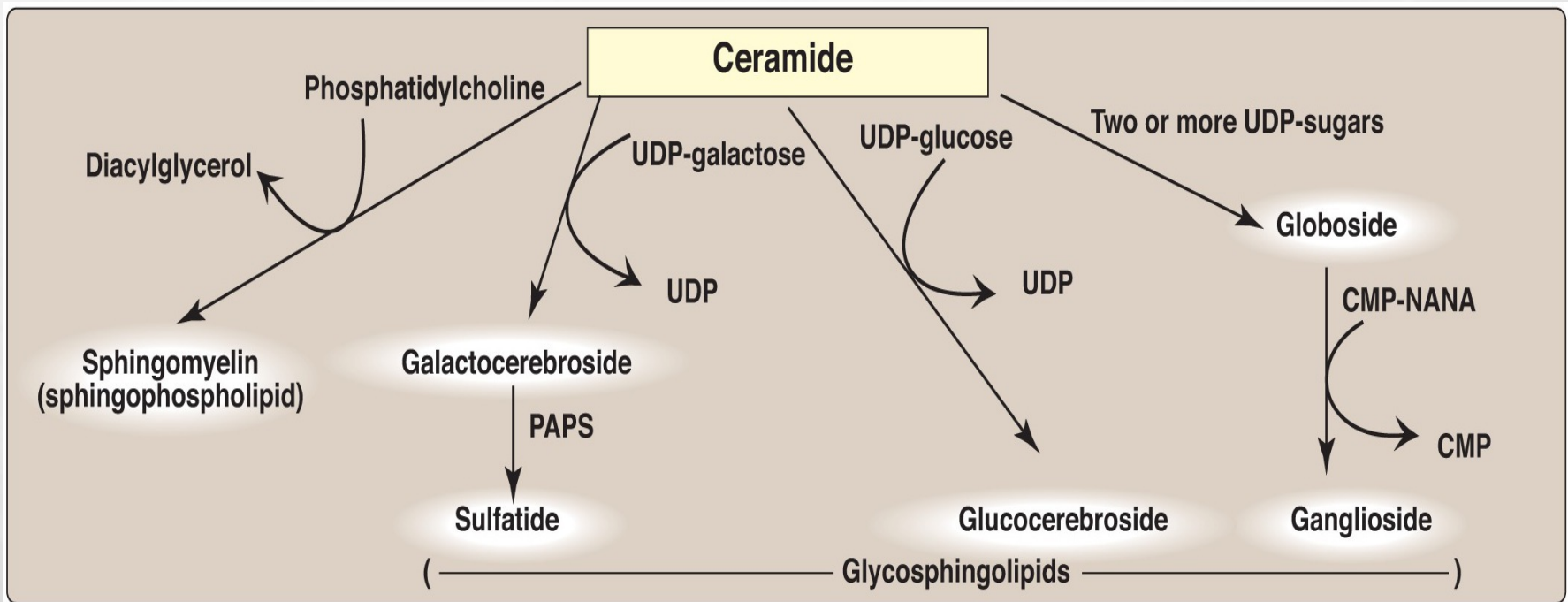
NANA

e.g. G_{M2} .



- For G_{M2} : G=ganglioside; M=mono molecule of NANA; 2=the monomeric sequence of the carbohydrate attached to the ceramide

SPHINGOLIPIDS' SYNTHESIS



MYELIN STRUCTURE

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

Myelin is produced by:

Schwann cells: Peripheral nerves.

Oligodendrocytes: CNS.

Myelin composition:

Lipids (80%):

Main component: Cerebrosides

Other component: Sphingomyelin

Proteins (20%):

e.g. Myelin basic protein

MYELIN STRUCTURE

Fatty acid of Sphingomyelin:

Myelin sheath:

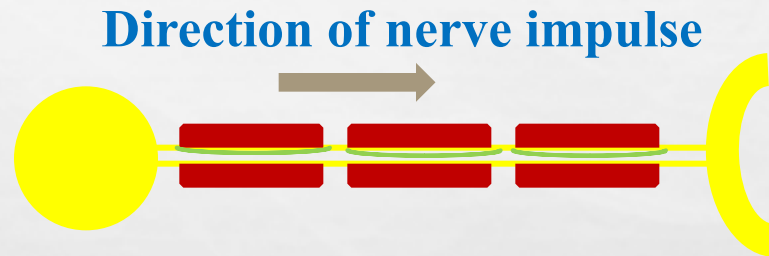
Very long chain fatty acids

Lignoceric 24:0

Nervonic 24:1(15)

MYELIN STRUCTURE AND 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, auto-immune 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**.

SPHINGOLIPIDOSES (*Cont'd...*)

- Synthesis (**Normal**); Degradation (**Defective**).
 - Substrate accumulates in organs..
 - Progressive, early death.
 - Phenotypic and genotypic variability.
 - Autosomal recessive (**mostly**).
 - Rare, **Except in** Ashkenazi Jewish.
- *Usually only a single sphingolipid accumulates in the involved organs in each disease*

SPHINGOLIPIDOSES (*Cont'd...*)

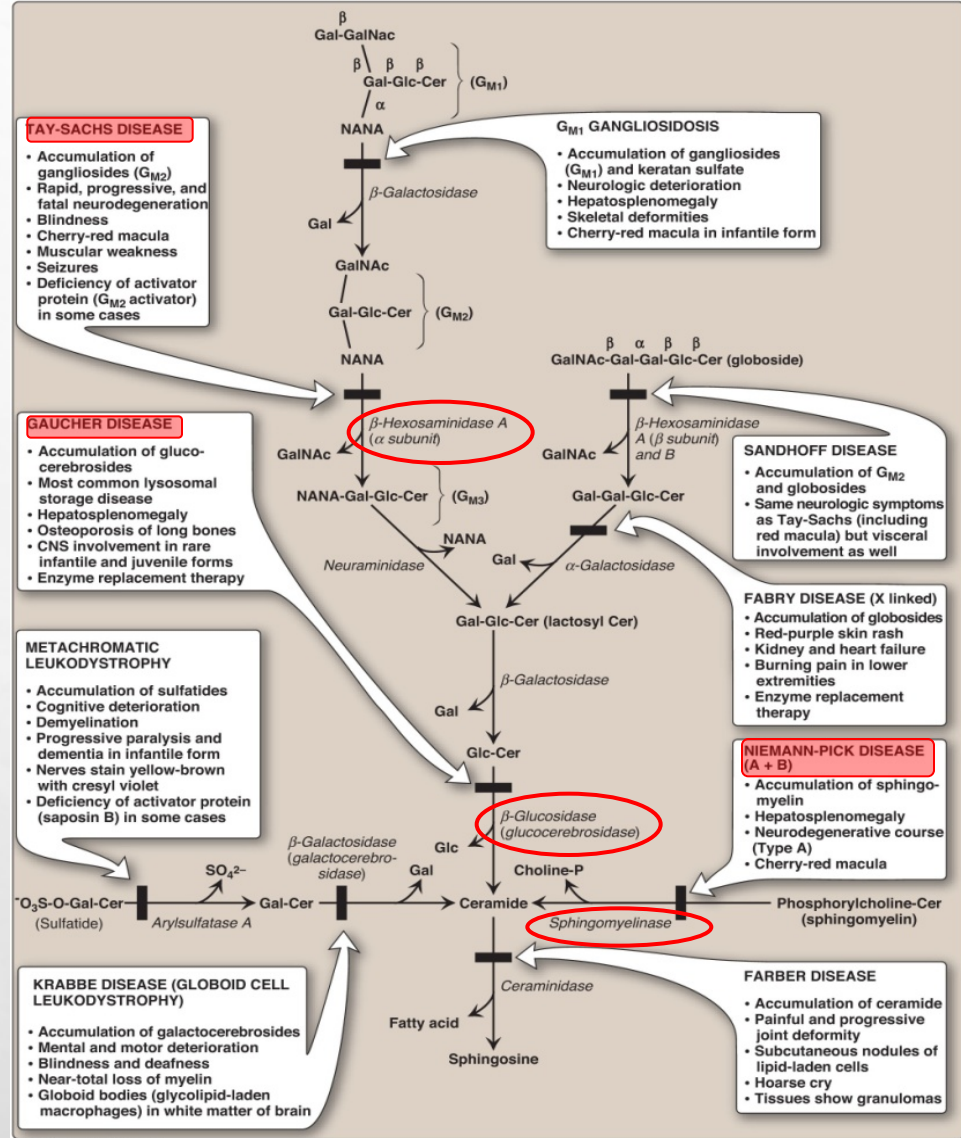
- **Diagnosis:**

- Measure enzyme activity:
 - Cultured fibroblasts or peripheral leukocytes.
 - Cultured amniocytes or chorionic villi (prenatal).
- Histologic examination.
- DNA analysis.

- **Treatment: e.g. for Gaucher disease:**

- Replacement Therapy (e.g. recombinant human enzyme).
- Bone marrow transplantation.

SPHINGOLIPIDOSES

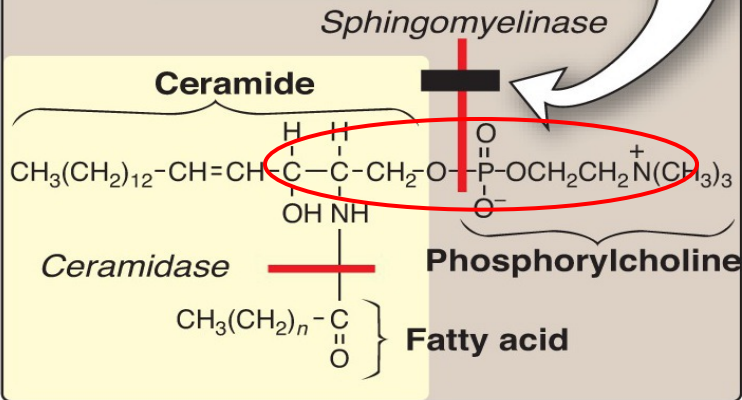


Copyright © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins

NIEMANN-PICK DISEASE

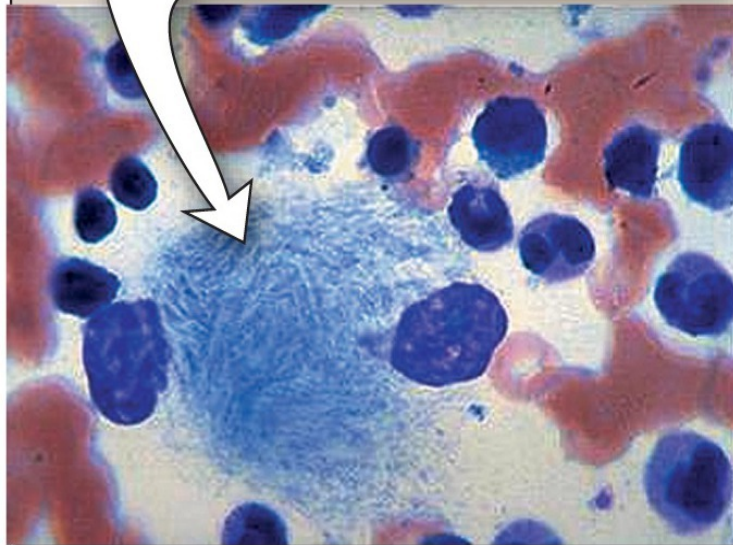
NIEMANN-PICK DISEASE

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



GAUCHER DISEASE

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



TAKE HOME MESSAGES

- Sphingolipids are complex lipids that includes sphingophospholipids 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.

REFERENCE

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014,
Unit 3, Chapter 17, Pages 201-218.