Biochemistry
2nd stage
Dr.Lamees Majid Al-Janabi

SPHINGOLIPIDS

ILO:K2,S11,A1

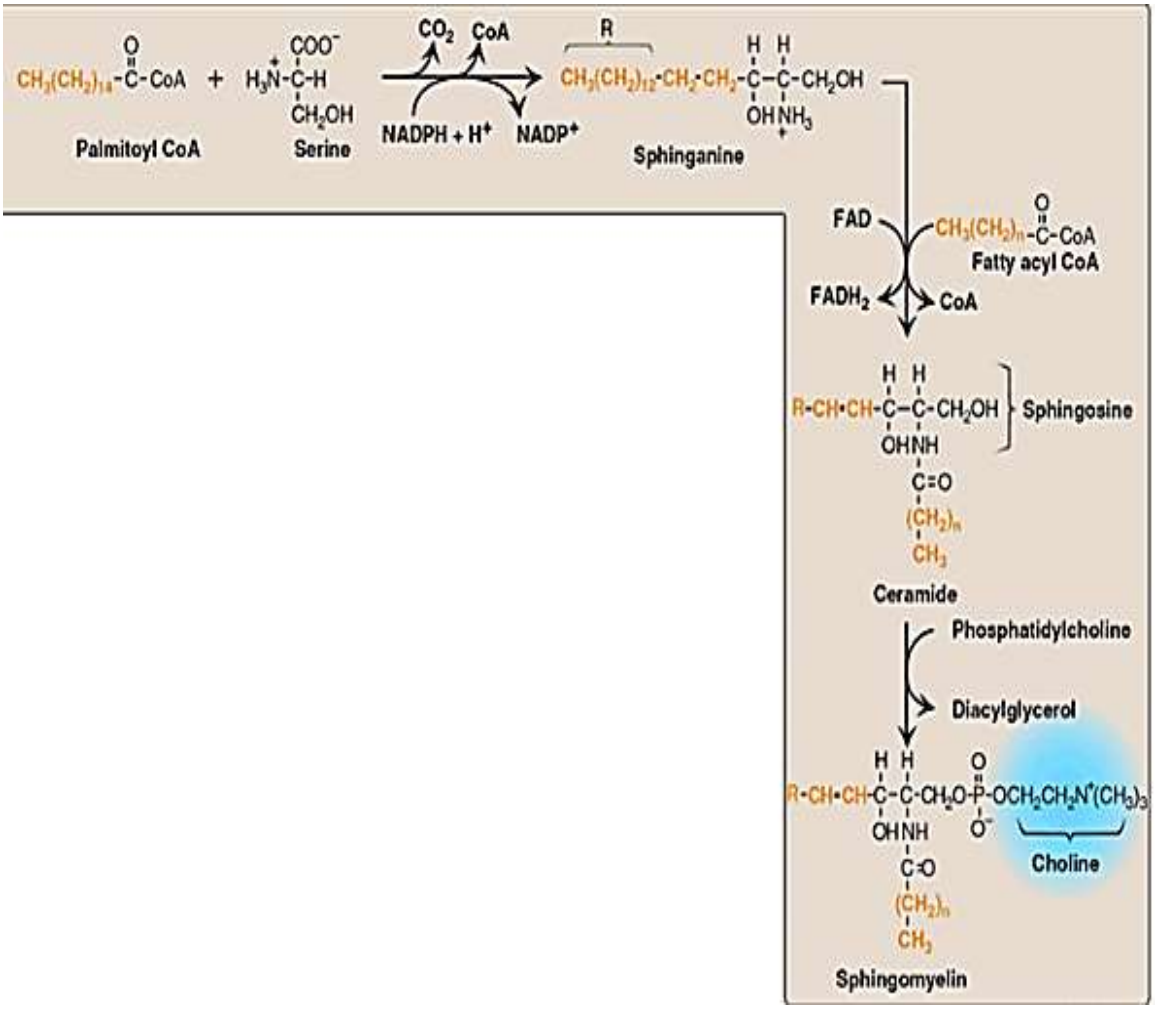
Objectives:

The students are learned to understand the following points:

- **The Synthesis of the Sphingosine**
- **The Type of Sphingolipids**
- **The Synthesis of the Sphingolipids**
- **-The Gangliosides metabolism**

Sphingomyelin:-

Shingomyelin is one of the principal structural lipids of membranes of nerve tissue. This class of phospholipid has sphingosine rather than glycerol as the alcohol. Shingomyelin of the myelin sheath(a structure that insulate and protects neuronal fibers of the central nervous system) contains predominantly longer chain fatty acids such as lignoceric and nervonic acid, wherease gray matter of the brain has sphingomyelin that contains primarily stearic acid.



Degradation of sphingomyelin:-

Sphingomyelin is degraded by sphingomyelinase, a lysosomal enzyme that hydrolytically removes phosphorylcholine, leaving a ceramide. The ceramide is, in turn, cleaved by ceramidase into sphingosine and a free fatty acid.

Glycolipids:-

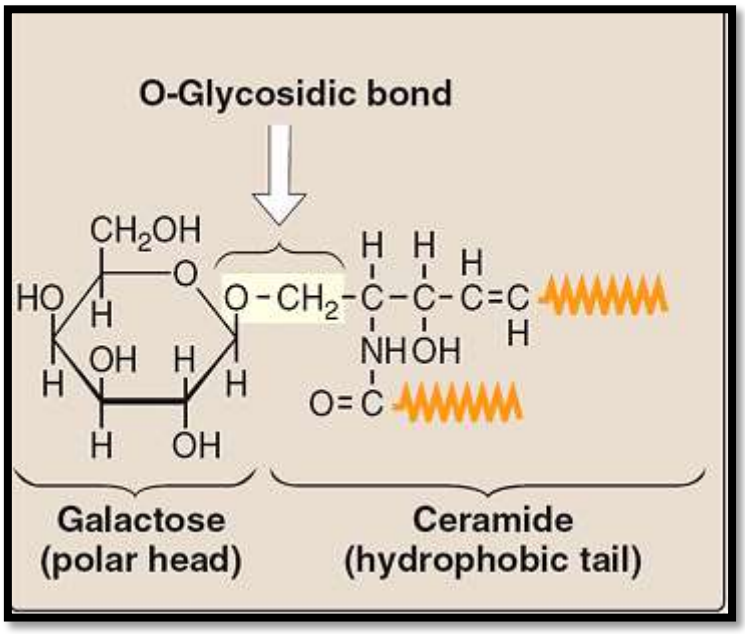
Glycolipids are molecules that contain both carbohydrate and lipid components. Like the phospholipid sphingomyelin, glycolipids are derivatives of ceramides in which a long-chain fatty acid is attached to the amino alcohol sphingosine. They are, therefore, called glycosphingolipids.

-Functions:-

1. They are essential components of all membranes in the body, but they are found in greatest amounts in nerve tissue. They are located in the outer leaflet of the plasma membrane, where they interact with the extracellular environment. As such, they play a role in the regulation of cellular interactions, growth, and development.
2. Glycosphingolipids are antigenic, and they have been identified as a source of blood group antigens, various embryonic antigens specific for particular stages of fetal development, and some tumor antigens.
3. They also serve as cell surface receptors for cholera and tetanus toxins, as well as for certain viruses and microbes.

-Types of glycolipid:-

A. Neutral glycosphingolipids:-The simplest neutral (uncharged) glycosphingolipids are the cerebrosides. These are ceramidemonosaccharides that contain either a molecule of galactose (galactocerebroside—the most common cerebroside found in membranes) or glucose (glucocerebroside, which serves primarily as an intermediate in the synthesis and degradation of the more complex glycosphingolipids).Cerebrosides are found predominantly in the brain and peripheral nervous tissue, with high concentrations in the myelin sheath.



Galactocerebroside

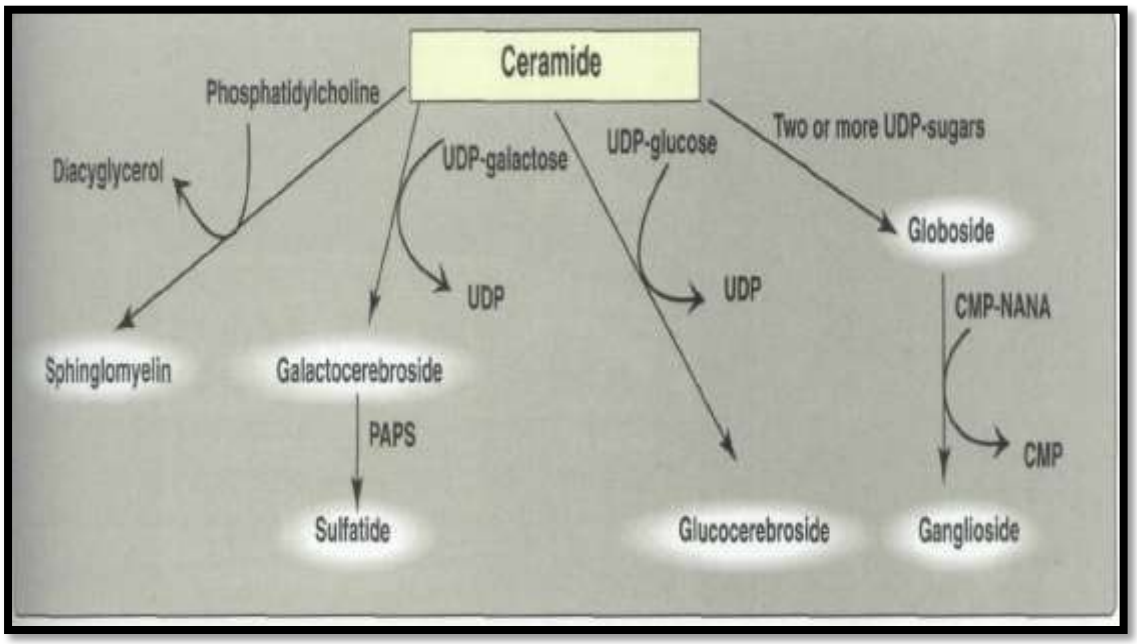
B. Acidic glycosphingolipids:-

-**Gangliosides:** These are the most complex glycosphingolipids, and are found primarily in the ganglion cells of the central nervous system, particularly at the nerve endings. They are derivatives of ceramide oligosaccharides, and contain one or more molecules of NANA(N-acetylneuraminic acid).

-Synthesis of Glycosphingolipids:-

Synthesis of glycosphingolipids occurs primarily in the Golgi by sequential addition of glycosyl monomers transferred from UDP–sugar donors to the acceptor molecule. The mechanism is similar to that used in glycoprotein synthesis .

The enzymes involved in the synthesis of glycosphingolipids are glycosyltransferases, each specific for a particular sugar nucleotide and acceptor.



— **UDP-GAL = uridine diphosphate galactose.**

— **UDP-GLU = uridine diphosphate glucose.**

— **PAPS = phosphoadenosine phospho sulfate**

-Degradation of glycosphingolipids:-

All of the enzymes required for the degradative process are present in lysosomes, which fuse with the endocytotic vesicles. The lysosomal enzymes hydrolytically and irreversibly cleave specific bonds in the glycosphingolipid. As seen with the glycosaminoglycans and glycoproteins, degradation is a sequential process following the rule "last on, first off," in which the last group added during synthesis is the first group removed in degradation.

-Sphingolipidoses (lipid storage diseases) :-

Group of inherited lipid storage disorders due to gene mutations leading to defective synthesis of specific lysosomal hydrolytic enzymes responsible for breakdown of lipids

i. They are otherwise called as Sphingolipidoses. They form a group of lysosomal storage diseases.
ii. The diseases result from failure of breakdown of a particular sphingolipid due to deficiency of a single enzyme.
iii. The children afflicted by these diseases are severely retarded mentally and seldom survive for long.
iv. All these diseases can be diagnosed prenatally by amniocentesis and culture of amniotic fluid cells. Since the children born with these diseases will have serious mental deficits, the pregnancy may be terminated. Replacement of deficient enzyme has been tried in Gaucher's disease, with limited success.
v. The common features of lipid storage diseases include:
a.Only one type of sphingolipid accumulates.
b. Rate of synthesis of the lipid is normal, only degradation is affected.
c. The extent of the enzyme deficiency is the same in all tissues.

The syndrome	Enzymes	accumulation
Tays-sachs disease	β-hexosaminidase	GM2
Gaucher disease	β-glucosidase	glucocerebroside
Niemann-pick disease	sphingomylinase	shingomyelin

Multiple Sclerosis

It is a demyelinating disease. Phospholipids (ethanol amine plasmalogen and sphingolipids) are lost from white matter of the central nervous system. Cerebrospinal fluid contains increased quantity of phospholipids.

Prostaglandins and Related Compounds

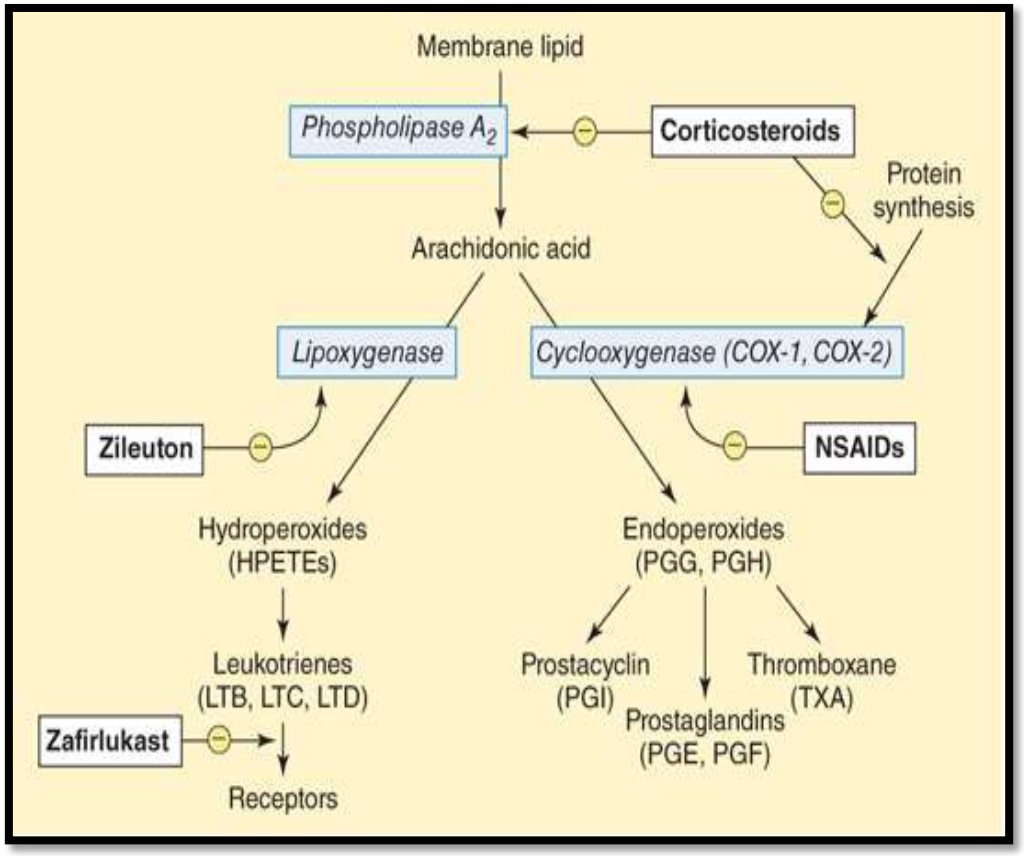
Prostaglandins, and the related compounds thromboxanes and leukotrienes, are collectively known as eicosanoids to reflect their origin from polyunsaturated fatty acids with 20 carbons. They are extremely potent compounds that elicit a wide range of responses, both physiologic and pathologic. These compounds have been very difficult to study because they have an extremely short half-life and are produced in very small amounts.

Although they have been compared to hormones in terms of their actions but they differ from the true hormones in that:-

1. they are produced in very small amounts in almost all tissues rather than in specialized glands.
2. They also act locally rather than after transport in the blood to distant sites, as occurs with true hormones such as insulin.
3. They are not stored, and they have an extremely short half-life, being rapidly metabolized to inactive products. Their biologic actions are mediated by plasma membrane G protein–coupled receptors, which are different in different organ systems.

Synthesis of prostaglandins:-

The dietary precursor of the prostaglandins is the essential fatty acid, linoleic acid. It is elongated and desaturated to arachidonic acid, the immediate precursor of the predominant class of prostaglandins (those with two double bonds) in humans.



Inhibition of prostaglandin synthesis:

The synthesis of prostaglandins can be inhibited by a number of unrelated compounds. For example, cortisol (a steroidal anti-inflammatory agent) inhibits phospholipase A_2 activity and, therefore, the precursor of the prostaglandins, arachidonic acid, is not available. Aspirin, indomethacin, and phenylbutazone (all nonsteroidal anti-inflammatory agents [NSAIDS]) inhibit both COX-1 and COX-2 and, therefore, prevent the synthesis of the parent prostaglandin, PGH_2.