CHAPTER

3

Chemistry of Lipids

INTRODUCTION

Lipids are a major source of energy for the body besides their various other biochemical function and their role in cellular structure. Lipids are a heterogenous group of water insoluble (hydrophobic) organic molecules. Lipids include fats, oils, steroids, waxes and related compounds.

This chapter introduces the chemistry and functions of lipids.

DEFINITION, CLASSIFICATION AND FUNCTIONS OF LIPIDS

Definition of Lipids

Lipids may be defined as organic substances insoluble in water but soluble in organic solvents like chloroform, ether and benzene. **They are esters of fatty acids with alcohol esters and are utilizable by the living organism.**

Classification of Lipids

There are many different methods of classifying lipids. The most commonly used classification of lipids is modified from Bloor as follows:

1. Simple lipids
2. Complex or compound lipids
3. Derived lipids.

Simple Lipids

These are esters of fatty acids with various alcohols. Depending on the type of alcohols, these are sub-classified as:

1. Neutral fats or triacylglycerol or triglycerides
2. Waxes.

Neutral fats or triacylglycerol or triglycerides

These are esters of fatty acids with alcohol ***glycerol,*** e.g. tripalmitin. Because they are ***uncharged,*** they are termed as ***neutral fat.*** The fat we eat are mostly triglycerides. A fat in liquid state is called an **oil**, e.g. vegetable oils like groundnut oil, mustard oil, corn oil, etc.

Waxes

True waxes

These are esters of fatty acids with higher molecular weight ***monohydric long chain alcohols.*** These compounds have no importance as far as human metabolism is concerned. For example,

- Lanolin (from lamb's wool)
- Bees-wax
- Spermacetic oil (from whales).

These are widely used in pharmaceutical, cosmetic and other industries in the manufacture of lotions, ointments and polishes.

Other waxes

These are esters of fatty acid with alcohol, e.g.
- Cholesterol forms cholesterol ester
- Retinol (vitamin A) forms vitamin A ester
- Cholecalciferol (vitamin D) forms vitamin D ester.

Complex or Compound Lipids

These are esters of fatty acids, with alcohol containing additional (prosthetic) groups. These are subclassified according to the type of prosthetic group present in the lipid as follows:

1. Phospholipids
2. Glycolipids
3. Lipoproteins.

Phospholipids

Lipids containing, in addition to fatty acids and an alcohol, a ***phosphoric acid*** residue. They also have nitrogen containing bases and other substituents. Phospholipids may be classified on the basis of the type of alcohol present in them as:
- Glycerophospholipids
- Sphingophospholipids.

Glycerophospholipids

The alcohol present is ***glycerol.*** Examples of glycerophospholipids are:
- Phosphatidyl choline (lecithin)
- Phosphatidyl ethenolamine (cephalin)
- Phosphatidyl serine
- Phosphatidyl inositol
- Lysophospholipid
- Plasmalogens
- Cardiolipins.

Sphingophospholipids

The alcohol present is **sphingosine**, e.g.
- Sphingomyelins.

Glycolipids

Lipids containing fatty acid, alcohol **sphingosine** and additional residue are ***carbohydrates*** with ***nitrogen base.*** They do not contain phosphate group. These sugar containing sphingolipids are also called ***glycosphingolipids.*** For example:
- Cerebrosides
- Gangliosides.

Lipoproteins

Lipoproteins are formed by combination of lipid with a prosthetic group protein, e.g. serum lipoproteins like:
- Chylomicrons
- Very low density lipoprotein (VLDL)
- Low density lipoprotein (LDL)
- High density lipoprotein (HDL).

Derived Lipids

Derived lipids include the products obtained after the hydrolysis of simple and compound lipids which possess the characteristics of lipids, e.g.
- Fatty acids
- Steroids
- Cholesterol
- Lipid soluble vitamins and hormones
- Ketone bodies.

Functions of Lipids

Lipids serve as:
- **Storage form of energy:** The fats and oils are used almost universally as stored forms of energy in living organisms.
- **Structural Lipids:** Lipids are major structural components of membranes, e.g. phospholipids, glycolipids and sterols.
- **Cholesterol,** a sterol, is a precursor of many **steroid hormones, vitamin D** and is also an important component of plasma membrane.
- Lipid acts as a **thermal insulator** in the subcutaneous tissues and around certain organs.
- Nonpolar lipids act as **electrical insulators** in neurons.
- Lipids are important dietary constituents because of the fat soluble vitamins and essential fatty acids which are present in the fat of natural foods.
- Lipids help in absorption of fat soluble vitamins (A,D,E and K). They act as a solvent for the transport of fat soluble vitamins.

FATTY ACIDS

Fatty acids are carboxylic acids with hydrocarbon chains ($-CH_2-CH_2-CH_2-$) and represented by a chemical formula **R-COOH,** where R stands for hydrocarbon chain. The fatty acids are ***amphipathic*** in nature, i.e. each has hydrophilic (COOH) and hydrophobic (hydrocarbon chain) groups in the structure.

Table 3.1: Some naturally occurring fatty acids

Common name	Carbon atoms	Double bonds	Position of double bond	Unsaturated fatty acid class
Saturated fatty acids				
Acetic acid	1	0		
Propionic acid	3	0		
n-butyric acid	4	0		
Valeric acid	5	0		
Louratic acid	12	0		
Myristic acid	14	0	-	-
Palmitic acid	16	0		
Stearic acid	18	0		
Arachidic acid	20	0		
Behenic acid	22	0		
Lignoceric acid	24	0		
Unsaturated fatty acid				
• **Monoenoic acid** (one double bond)				
Palmitoleic acid	16	1	9	ω-7
Oleic acid	18	1	9	ω-9
Nervonic acid	24	1	15	ω-9
• **Dienoic acids** (two double bonds)				
Linoleic acid	18	2	9, 12	ω-6
• **Trienoic acid** (three double bonds)				
Linolenic acid	18	3	9, 12, 15	ω-3
• **Tetraenoic acid** (four double bonds)				
Arachidonic acid	20	4	5,8,11,14	ω-6
• **Pentaenoic acid** (five double bonds)				
Clupandonic acid	22	5	7, 10,13, 16, 19	ω-3
• **Docosa hexaenoic acid** (DHA)				
Cervonic acid	22	6	4,7,10,13,16,19	ω-3

Some naturally occurring fatty acids are given in **Table 3.1.**

Classification of Fatty Acids

Fatty acids are classified into four major classes **(Figure 3.1).**

1. Straight chain fatty acids
2. Branched chain fatty acids
3. Substituted fatty acids
4. Cyclic fatty acids.

Straight Chain Fatty Acids

Fatty acids, in which the carbons are arranged linearly, are subclassified into two classes:

i. Saturated fatty acids
ii. Unsaturated fatty acids.

Saturated fatty acids

There is no double bond in the hydrocarbon chain of these fatty acids. Saturated fatty acids are subclassified into two classes:

a. **Even carbon acids** carry even number of carbons, e.g. palmitic acid and stearic acid.
b. **Odd carbon acids** carry odd number of carbons, e.g. propionic acid.

Unsaturated fatty acids

These contain double bonds in their hydrocarbon chains.

These are subclassified according to the number of double bonds present in the structure as follows:

a. Monoenoic or monounsaturated fatty acid
b. Polyenoic or polyunsaturated fatty acid.

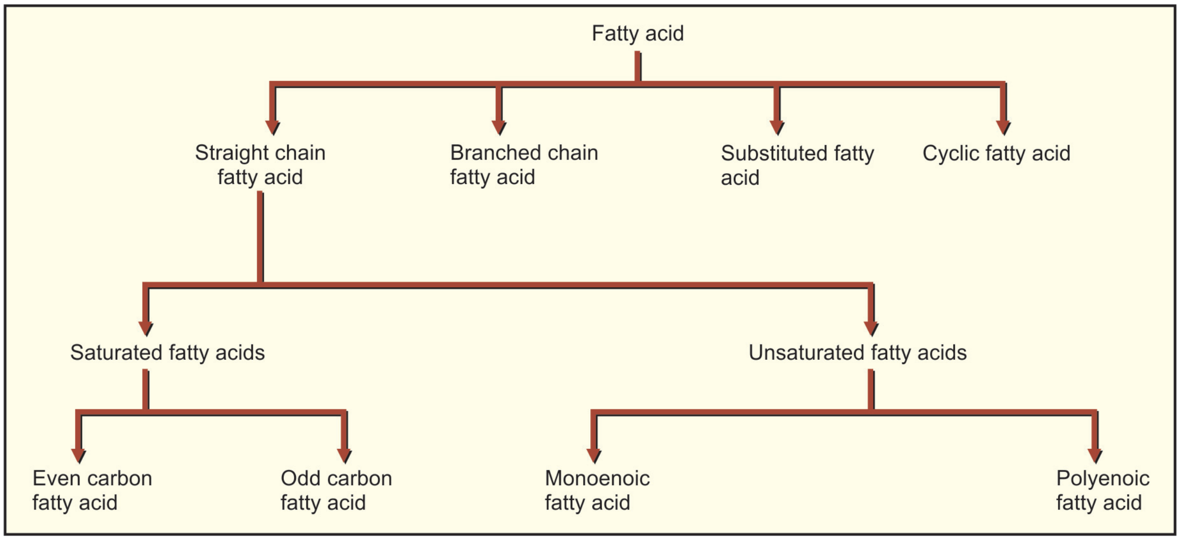


Figure 3.1: Classification of fatty acids

- **Monoenoic** or monounsaturated fatty acids carry a single double bond in the molecule, e.g. oleic acid.
- **Polyenoic** or polyunsaturated fatty acids contain two or more double bonds; for example:
  - **Dienoic acids** have two double bonds, e.g. linoleic acid present in soyabean, sunflower, saffola and groundnut oil.
  - **Trienoic acids** have three double bonds, e.g. Linolenic acid present in poppyseed oil, linseed oil.
  - **Tetraenoic acid** with four double bonds, e.g. arachidonic acid present in groundnuts.

Branched Chain Fatty Acids

These are less abundant than straight chain acids in animals and plants, e.g.

- Isovaleric acid
- Isobutyric acid.

Substituted Fatty Acids

In substituted fatty acids one or more hydrogen atoms have been replaced by another group, e.g.

- Lactic acid of blood
- Cerebronic acid and oxynervonic acids of brain glycolipids
- Ricinoleic acid of castor oil.

Cyclic Fatty Acids

Fatty acids bearing cyclic groups are present in some bacteria and seed lipids, e.g. hydnocarpic acid (Chaulmoogric acid) of chaulmoogra seed.

Functions of Fatty Acids

Fatty acids have three major physiological functions.

1. They serve as building blocks of ***phospholipids*** and ***glycolipids.*** These amphipathic molecules are important components of biological membranes.
2. Fatty acid derivatives serve as ***hormones,*** e.g. ***prostaglandins***.
3. Fatty acids serve as a major fuel for most cells.

Numbering of Fatty Acid Carbon Atoms (Figure 3.2)

- Fatty acid carbon atoms are numbered starting at the carboxyl terminus.

$$\overset{16}{\underset{\omega}{CH_3}}-\overset{15}{CH_2}-\overset{14}{CH_2}-\overset{13}{CH_2}-\overset{12}{CH_2}-\overset{11}{CH_2}-\overset{10}{CH_2}-\overset{9}{CH_2}-\overset{8}{CH_2}-\overset{7}{CH_2}-\overset{6}{CH_2}-\overset{5}{CH_2}-\overset{4}{CH_2}-\overset{3}{\underset{\beta}{CH_2}}-\overset{2}{\underset{\alpha}{CH_2}}-\overset{1}{COOH}$$

Palmitic acid

Figure 3.2: Numbering of fatty acid carbon

- Carbon atoms 2 and 3 are often referred to as α and β respectively.
- The methyl carbon atom at the distal end of the chain is called omega (ω) carbon.

Representation of Double Bonds of Fatty Acids

Two systems are used to designate the position of double bond:
- C-system
- ω- or n-system.

C-System

In C-system (i.e. C_1 being the carboxyl carbon) the position of double bond is represented by the symbol Δ (delta), followed by a superscript number.

For example, oleic acid is a C_{18} fatty acid with one double bond between carbon number 9 and 10 is represented as C: 18:1: Δ^9 **(Figure 3.3).**

ω– or n-System

In this system, '*ω*' or '*n*' refers to the carbon of their terminal methyl group in a fatty acid. In *ω*-system or n-system, the oleic acid is denoted as C: 18:1:ω-9 **(Figure 3.3)** to indicate that:
- *ω*-9 represents the double bond position which is found between 9th and 10th carbon atoms, the first carbon atom being that of the terminal methyl group. This method is widely used by nutritionists.
- Naturally occurring unsaturated fatty acids belong to ***ω-9, ω-6*** and ***ω-3*** series. For example,
  - *ω*-9 : Oleic acid (C:18:1:*ω*-9)
  - *ω*-6 : Linoleic acid (C:18:2:*ω*-6)
    Arachidonic acid (C:20:4:*ω*-6)
  - *ω*-3 : Linolenic acid (C:18:3:*ω*-3)

ESSENTIAL FATTY ACIDS

Fatty acids, that are required for optimal health and cannot be synthesized by the body and should be supplied in the diet are called ***essential fatty acids.***

They are polyunsaturated fatty acids, namely **linoleic acid** and **linolenic acid. Arachidonic acid** can be synthesized from linoleic acid. Therefore, in deficiency of linoleic acid, arachidonic acid also becomes essential fatty acids.

Humans lack the enzymes to introduce double bonds at carbon atoms beyond C_9 in the fatty acid chain. Hence, humans cannot synthesize linoleic acid and linolenic acid having double bonds beyond C_9. And thus, linoleic and linolenic are the essential fatty acids.

Functions of Essential Fatty Acids (EFA)

Synthesis of Eicosanoids

Linoleic acid and linolenic acid supplied by the diet are the precursors for the synthesis of a variety of other unsaturated fatty acids. Arachidonic acid, a fatty acid derived from linoleic acid is an essential precursor of eicosanoids, which include:
- Prostaglandins
- Thromboxanes
- Prostacyclin
- Leukotrienes.

Maintenance of Structural Integrity

EFAs are required for membrane structure and function. These fatty acids are important constituents of phospholipids in cell membrane and help to maintain the structural integrity of the membrane.

Development of Retina and Brain

Docosahexaenoic acid (DHA: ω-3), which is synthesized from linolenic acid is particularly needed for development of the brain and retina during the neonatal period.

Antiatherogenic Effect

Essential fatty acids increase esterification and excretion of cholesterol, thereby lowering the serum cholesterol level. Thus, essential fatty acids help to prevent the atherosclerosis.

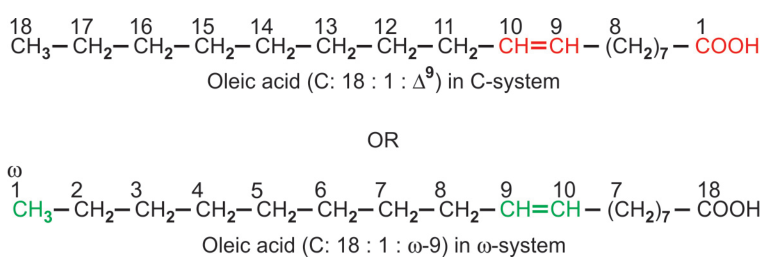


Figure 3.3: Representation of double bonds of unsaturated fatty acid

Essential Fatty Acid Deficiency

- Deficiency of EFAs is characterized by scaly skin, eczema (in children), loss of hair and poor wound healing.
- Impaired lipid transport and fatty liver may occur due to deficiency of EFAs.
- EFAs deficiency decreases efficiency of biological oxidation.

REACTIONS OF LIPIDS

Saponification

Hydrolysis of a fat by ***alkali*** is called ***saponification.*** The products are glycerol and the alkali salts of the fatty acids, which are called **soaps (Figure 3.4).** Acid hydrolysis of a fat yields the free fatty acids and glycerol.

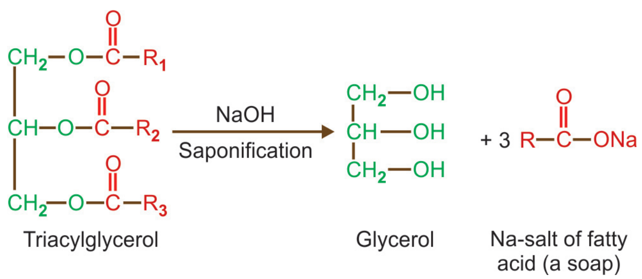


Figure 3.4: Saponification of fat

Hydrogenation

Hydrogenation of unsaturated fats in the presence of a catalyst (nickel) is known as ***"hardening".*** It is commercially valuable as a method of converting these liquid fats, usually of plant origin into solid fats as margarines, vegetable *ghee,* etc.

Peroxidation

Peroxidation (auto-oxidation) of lipids exposed to oxygen is responsible not only for deterioration of foods (rancidity) but also for damage to tissues *in vivo*, where it may be a cause of **cancer.** Lipid peroxidation is a chain reaction generating free radicals that initiate further peroxidation. To control and reduce peroxidation, humans make use of ***antioxidants.*** Naturally occurring antioxidants include vitamin E (tocopherol) and β-carotene (provitamin A), which are lipid soluble and vitamin C, which is water soluble.

Rancidity

The unpleasant odor and taste, developed by natural fats upon aging, is referred to as ***"rancidity".*** Rancidity may be due to ***hydrolysis*** or ***oxidation*** of fat.

- **Rancidity due to hydrolysis:** Naturally occurring fats, particularly those from animal sources, are contaminated with enzyme **lipase.** The action of lipase brings about partial hydrolysis of glycerides of fat.
- **Rancidity may also be caused by various oxidative processes.** For example, oxidation at the double bonds of unsaturated fatty acids of glycerides may form peroxides, which then decompose to form aldehydes of unpleasant odor and taste, this process is increased by exposure to light or heat.

Many natural vegetable fats and oils may contain antioxidants like vitamin E which prevent onset of rancidity. Therefore, vegetable fats can be preserved for a longer time than animal fats.

CHARACTERIZATION OF FAT (TESTS FOR PURITY OF FAT)

Fats are characterized and their purity assayed by the following tests:

Saponification Number

It is defined as, number of mgs of KOH required to saponify one gm of fat. It is inversely proportional to the molecular weight of fat. This value is high in fats containing a short chain fatty acids. For example, the saponification number of:

- Butter = 220
- Coconut oil = 260

Iodine Number

The number of gms of iodine required to saturate 100 gms of a given fat is known as iodine number. Since iodine is taken up by the double bonds, a high iodine number indicates a high degree of unsaturation of the fatty acids in fat, e.g.

- Butter fat = 27
- Coconut oil = 8
- Linseed oil = 200.

Iodine number is important in the identification of the fat or oil as well as is used for identification of adulteration of oils.

Acid Number

Number of mg of KOH required to neutralize the free fatty acids present in one gm of fat is known as acid number. The acid number indicates the degree of rancidity of the given fat. Acid number is directly proportional to the rancidity. The edibility of a fat is inversely proportional to the acid number.

Refined oil should not contain free fatty acids. The presence of free fatty acids in any oil indicates that it is not pure.

Reichert Meissl Number

The number of ml of 0.1 N alkali, required to neutralize the volatile fatty acids distilled from 5 gm of fat, e.g. the Reichert Meissl value for:

- Butter = 26
- Coconut oil = 7.

It is less than one for other edible oils. The admixture of certain fats may be used to prepare synthetic butter which may simulate butter in most of the constants except RM value and hence, can be detected.

TRIACYLGLYCEROLS OR TRIACYLGLYCERIDES OR NEUTRAL FAT

These are esters of fatty acids with glycerol. Triacylglycerol consists of three fatty acids, which are esterified through their carboxyl groups, resulting in a loss of negative charge and formation of neutral fat. **(Figure 3.5).**

- Triacylglycerols containing the same kind of fatty acid in all three positions are called ***simple triacylglycerols.***
- ***Mixed triacylglycerols*** contain two or more different fatty acids. The fatty acid on carbon 1 is usually saturated. That on carbon 2 is usually unsaturated and that on carbon 3 can be either of the two. The stereospecific numbering (sn) of the glycerol carbon atom is shown in **Figure 3.5**.
- As the polar hydroxyl groups of glycerol and polar carboxyl groups of the fatty acids are bound in ester linkages, triacylglycerols are nonpolar, hydrophobic and neutral (in charges) molecules, essentially insoluble in water.
- The presence of the unsaturated fatty acid(s) in triacylglycerol decreases the melting temperature of the lipid and remains in liquid form (oil).
- Vegetable oils such as corn and olive oil are composed largely of triacylglycerols with unsaturated fatty acids and thus are liquids at room temperature.
- Triacylglycerols containing only saturated fatty acids, such as beef fat, are white greasy solids at room temperature.
- Triacylglycerols are highly concentrated storage form of metabolic energy.

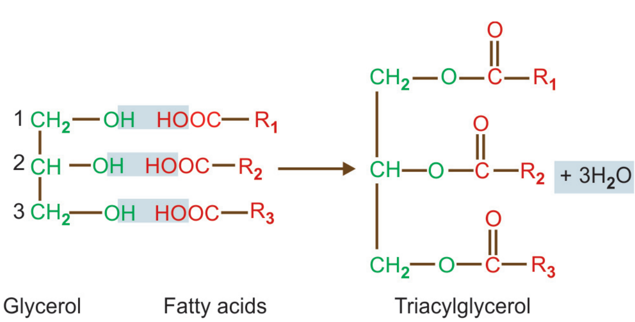


Figure 3.5: Glycerol and triacylglycerol

PHOSPHOLIPIDS

- These are made up of ***fatty acid, glycerol*** or other alcohol, ***phosphoric acid*** and ***nitrogenous base.***
- Phospholipids are the major lipid constituents of cell membranes.
- Like fatty acids, phospholipids are ***amphipathic*** in nature, i.e. each has a hydrophilic or polar head (phosphate group) and a long hydrophobic tail (containing two fatty acid chains) **(Figure 3.6).**

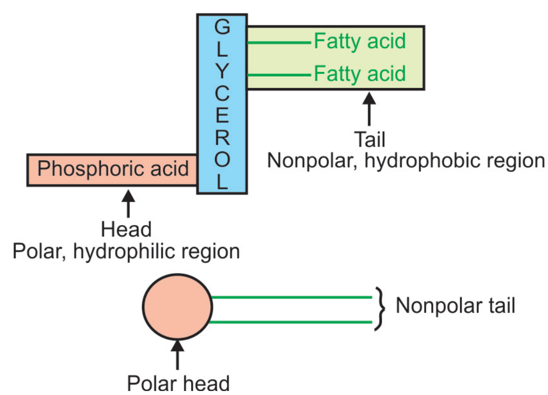


Figure 3.6: Diagrammatic representation of amphipathic phospholipid

Classification of Phospholipids

There are two classes of phospholipids **(Figure 3.7):**

1. Glycerophospholipids or phosphoglycerides, that contain glycerol as the alcohol.
2. Sphingophospholipids that contain sphingosine as the alcohol.

Glycerophospholipids or Phosphoglycerides

- Phospholipids derived from glycerol are called **phosphoglycerides** or **glycerophospholipids.**

Phospholipid

- Glycerophospholipid or phosphoglyceride, e.g.
  - Phosphatidylcholine (lecithin)
  - Phosphatidylethanolamine (Cephalin)
  - Phosphatidylserine
  - Phosphatidylinositol
  - Plasmalogens
  - Lysophospholipids
  - Cardiolipin
- Sphingophospholipid, e.g.
  - Sphingomyelins

Figure 3.7: Classification of phospholipids

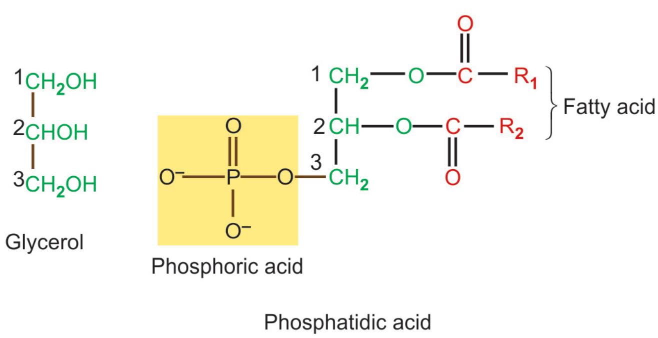


Figure 3.8: Structure of glycerol and phosphatidic acid

- In glycerophospholipid, the hydroxyl groups at C_1 and C_2 of glycerol are esterified with two fatty acids. The C_3 hydroxyl group of the glycerol is esterified to phosphoric acid and resulting compound called, ***phosphatidic acid*** **(Figure 3.8).**
- Phosphatidic acid is a key intermediate in the biosynthesis of other glycerophospholipids.
- In glycerophospholipid, phosphate group of phosphatidic acid becomes esterified with the hydroxyl group of one of the several nitrogen base or other groups. Different types of glycerophospholipids are discussed below.

Phosphatidylcholine (lecithin)

- These are glycerophospholipids containing choline **(Figure 3.9).** These are most abundant phospholipids of the cell membrane having both structural and metabolic functions.
- Dipalmitoyl lecithin is an important phosphatidylcholine found in lungs, secreted by **pulmonary type II epithelial** cell. It acts as a *lung surfactant* and is necessary for normal lung function. It reduces surface tension in the alveoli, thereby prevents alveolar collapse (adherence of the inner surfaces of the lungs).

Acute Pulmonary Respiratory Distress Syndrome (RDS)
- RDS in infants is associated with insufficient ***surfactant dipalmitoyl phosphatidylcholine*** production.
- The lungs of immature infants do not have enough type II epithelial cells to synthesize sufficient amounts of dipalmitoyl phosphatidylcholine (DPPC).
- In its absence, the lungs tend to collapse and this condition is known as ***respiratory distress syndrome.***

Phosphatidylethanolanine (Cephalin)

- They differ from lecithin in having nitrogenous base ethanolamine in place of choline **(Figure 3.9).**
- ***Thromboplastin*** (coagulation factor III), which is needed to initiate the clotting process, is composed mainly of cephalins.

Phosphatidylserine

It contains the amino acid serine rather than ethanolamine and is found in most tissues **(Figure 3.9).**

Phosphatidylinositol

- In phosphatidylinositol, inositol is present as the stereoisomer ***myoinositol*** **(Figure 3.9).**
- Phosphatidylinositol is a **second messenger** for the action of hormones like oxytocine and vasopressin.

Plasmalogens

- Plasmalogens are generally similar to other phospholipids but the fatty acid at C_1 of glycerol is linked through an **ether**, rather than an ester bond **(Figure 3.9).**

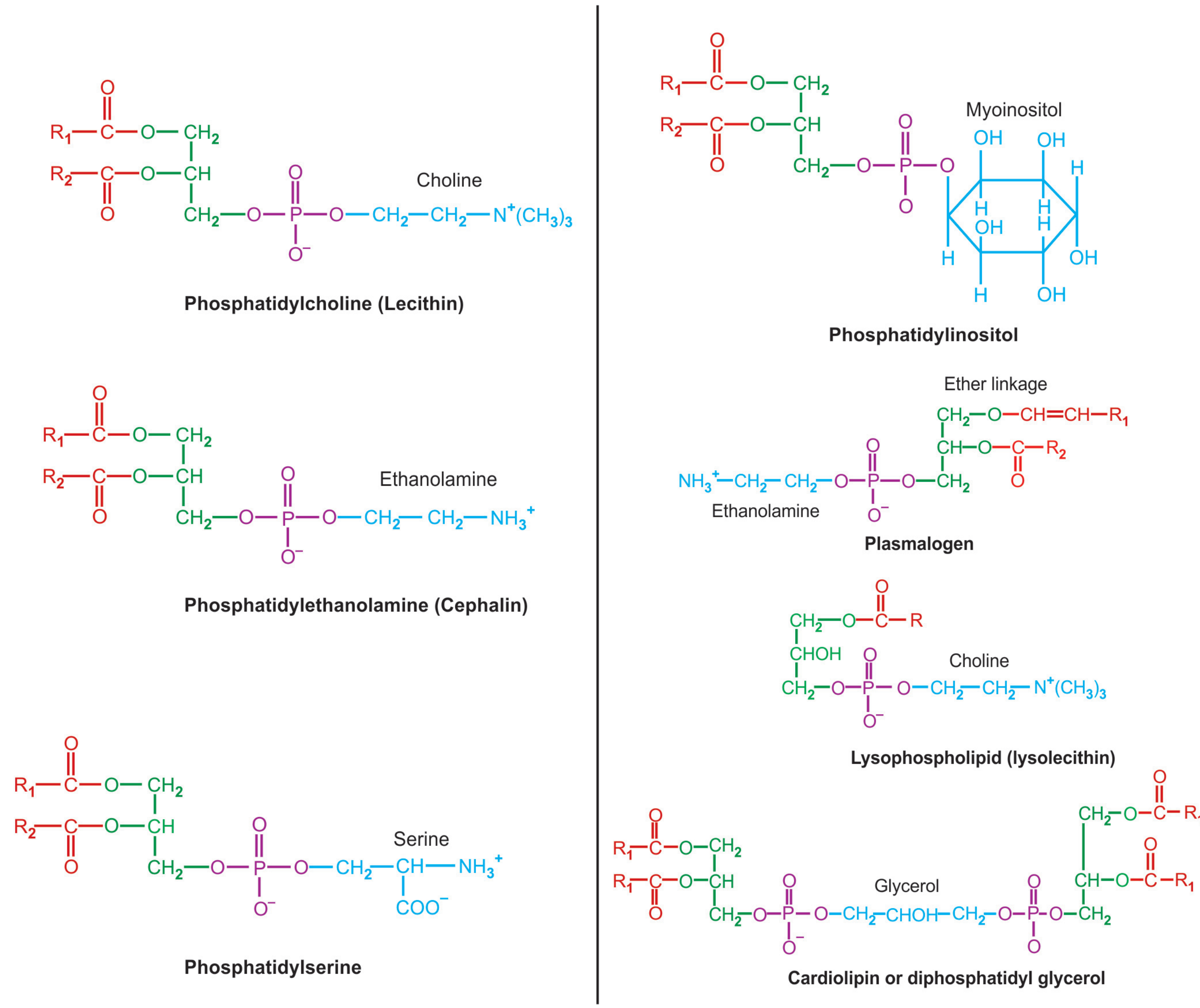


Figure 3.9: Structure of different phospholipids

- There are three major classes of plasmalogens:
  - i. Phosphatidylcholines
  - ii. Phosphatidylethanolamines
  - iii. Phosphatidylserines.
- These are found in myelin and in cardiac muscle.
- Plasmalogen is a platelet activating factor (PAF) and involved in platelet aggregation and degranulation.

Lysophospholipids

Lysophospholipids are produced when one of the two fatty acid is removed from glycerophospholipid. The most common of these are lysophosphatidylcholine (lysolecithin) **(Figure 3.9)** and lysophosphatidylethanolamine.

Cardiolipin (Diphosphatidylglycerol)

- Cardiolipin is composed of two molecules of phosphatidic acid connected by a molecule of glycerol.
- Two molecules of phosphatidic acid esterified through their phosphate groups with a molecule of glycerol are called cardiolipin **(Figure 3.9).**
- Cardiolipin is a major lipid of mitochondrial membrane and is necessary for optimum function of the electron transport process.

- This is only human glycerophospholipid that possess ***antigenic properties.***

Sphingophospholipids

Phospholipids derived from alcohol ***sphingosine*** instead of glycerol are called sphingophospholipids, e.g. sphingomyelin.

Sphingomyelin

- Sphingomyelin is the only phospholipid in membranes that is not derived from glycerol. Instead, the alcohol in sphingomyelin is ***sphingosine,*** an amino alcohol.
- In sphingomyelin, the amino group of the sphingosine is linked to a fatty acid to yield ***ceramide*** (sphingosine-fatty acid complex).
- In addition, the primary hydroxy group of sphingosine is esterified with phosphorylcholine **(Figure 3.10).**
- Sphingomyelin is one of the principal structural lipids of membranes of nerve tissue.

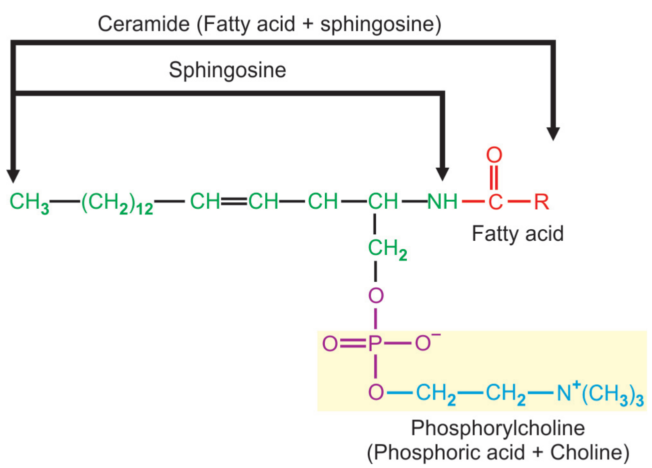


Figure 3.10: Structure of sphingomyelin

Functions of Phospholipids

- Phospholipids are the major lipid constituents of cell membranes.
- They regulate ***permeability of membranes*** as well as activation of some membrane bound enzymes.
- Phospholipids are of importance in ***insulating the nerve impulse*** (like the plastic or rubber covering around an electric wire) from the surrounding structures, e.g. sphingomyelins act as eletrical insulators in the myelin sheath around nerve fibers.
- Phospholipids are important constituents of lipoproteins.
- Phospholipids act as a ***lipotropic factor.*** Lipotropic factor is the component that prevents ***fatty liver,*** i.e. accumulation of fat in the liver.
- These are good ***emulsifying agents*** that help in intestinal absorption of lipids.
- ***Thromboplastin*** (coagulation factor III), which is needed to initiate the clotting process, is composed mainly of ***cephalins.***
- Phospholipid (lecithin) acts as ***lung surfactant,*** which prevents alveolar collapse.
- Lecithin represents a storage form of lipotropic factor **choline.**
- Phosphatidylinositol acts as a **second messenger** for the activity of certain hormones.
- In mitochondria, cardiolipin is necessary for optimum fuctions of the **electron transport process.**
- Plasmalogens (platelet activating factor) involved in **platelet aggregation** and **degranulation.**

GLYCOLIPIDS (GLYCOSPHINGOLIPIDS)

- Glycolipids as their name implies, are sugar containing lipids. Glycolipids consist of alcohol **sphingosine.**
- The amino group of sphingosine is esterified by a fatty acid and one or more sugar units are attached to the hydroxyl group of sphingosine.
- Glycolipids are widely distributed in every tissue of the body, particularly in nervous tissue such as brain.

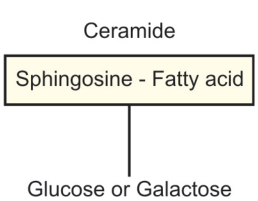
Classification of Glycolipids

Four classes of glycolipids have been distinguished:

1. Cerebrosides
2. Sulfatides
3. Globosides
4. Gangliosides.

Cerebrosides (Ceramide + Monosaccharides)

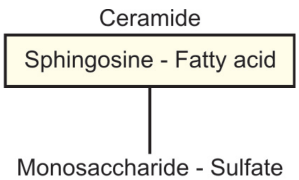
- Cerebroside is the simplest glycolipid in which there is only one sugar residue, either ***glucose*** or ***galactose*** linked to ceramide and named as ***glucocerebroside*** and ***galactocerebroside*** respectively.
- Galactocerebroside is found in nerve tissue membrane. whereas glucocerebroside is the predominant glycolipid of extraneural (non-neural) tissues, where it acts as a precursor for the synthesis of more complex glycolipids, e.g. gangliosides.



Cerebroside

Sulfatides (Ceramide + Monosaccharide + Sulfate)

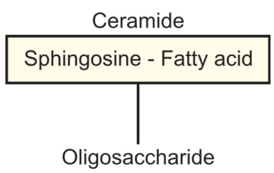
- Sulfatides are cerebrosides in which the monosaccharide contains a sulfate ester.



Sulfatide

Globosides (Ceramide + Oligosaccharide)

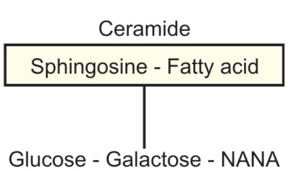
- Globosides contain two or more sugar molecules attached to ceramide.
- These glycolipids are important constituents of the RBC-membrane and are the determinants of the A,B,O blood group system



Globoside

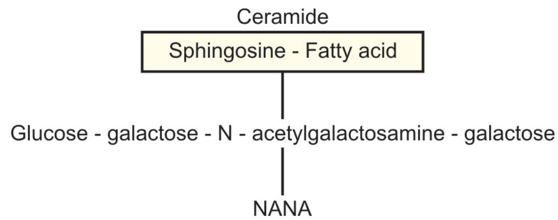
Gangliosides: (Cerebroside + Oligosaccharides + N-acetylneuraminic acid, NANA)

- Gangliosides are complex glycolipids, derived from glucocerebroside.
- Ganglioside contains oligosaccharides and one or more molecules of ***sialic acid,*** which is usually ***N-acetylneuraminic acid (NANA)*** attached to ceramide.
- Several types of gangliosides such as **GM_1, GM_2, GM_3,** etc. have been isoloted from brain and other tissues. The simplest ganglioside found in tissues is GM_3. G represents Ganglioside, M represents mono which indicate presence of one residue of NANA and subscript number assigned on the basis of chromatographic migration of ganglioside.



GM_3 - Ganglioside

- GM_1 is a more complex ganglioside derived from GM_3.



GM_1 - Ganglioside

Functions of Glycolipids

- Glycolipids are important constituents of the nervous tissue, such as brain and outer leaflet of all cell membrane.
- They play a role in the regulation of cellular interactions, growth and development.
- Glycolipids serve as cell **surface receptors** for certain hormones and a number of drugs. They also serve as receptors for cholera and tetanus toxins.
- Glycolipids are antigenic and they have been identified as a source of blood group antigens.

CHOLESTEROL (ANIMAL STEROL)

- Cholesterol is the major sterol in animal tissues. Sterols are a class of steroids containing hydroxyl group.
- It consists of steroid nucleus namely ***phenanthrene*** containing 19-carbon atoms **(Figure 3.11)**.
- It consists of methyl side chains at position C_{10} and C_{13} which are shown as single bonds.
- Cholesterol, a 27-carbon compound, has an 8-carbon side chain attached to the D ring at C_{17} and a hydroxyl group attached to C_3 of the A ring, with one double bond between carbon atoms 5 and 6 **(Figure 3.12).**

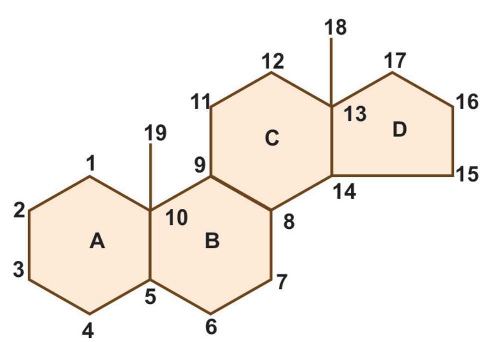


Figure 3.11: The steroid nucleus, phenanthrene (ring A, B and C), to which cyclopentane D ring is attached

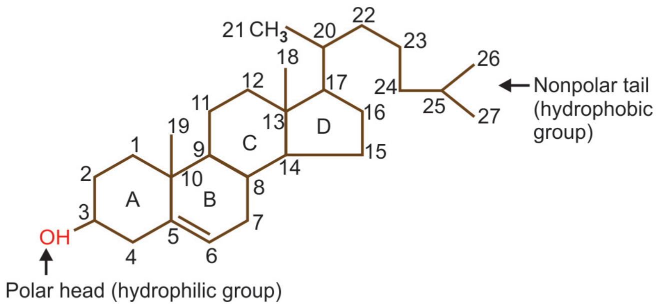


Figure 3.12: The structure of cholesterol

- Cholesterol is ***amphipathic,*** with a ***polar*** head the hydroxyl group at C_3 and a ***nonpolar,*** the steroid nucleus and hydrocarbon side chain at C_{17}.
- Most of the cholesterol in the body exists as a cholesterol ester, with a fatty acid attached to the hydroxyl group at C_3.
- Cholesterol is widely distributed in all the cells of the body but particularly in nervous tissue.
- ***It occurs in animal fats but not in the plant fats.***

Functions of Cholesterol

- It is a major structural constituent of the cell membranes and plasma lipoproteins.
- Cholesterol serves as the precursor for a variety of biologically important products, including:
  1. **Steroid hormones:** Cholesterol is the precursor of the five steroid hormones, e.g.
     - i. Progesterones
     - ii. Glucocorticoids
     - iii. Mineralocorticoids
     - iv. Androgens (male sex hormones)
     - vi. Estrogen (female sex hormones).
  2. **Bile acids:** Bile acids, derived from cholesterol, act as a detergent in the intestine, emulsifying dietary fats to make them readily accessible to digestive enzyme lipase.
  3. **Vitamin D:** It is derived from cholesterol and is essential in calcium and phosphate metabolism.

LIPOPROTEINS

- Lipoproteins are large water soluble complexes formed by a combination of lipid and protein that transport insoluble lipids through the blood between different organs and tissues.
- Lipoproteins consist of a lipid core containing nonpolar ***triacylglycerol*** and ***cholesterol ester*** surrounded by a single layer of ***amphipathic phospholipids*** and ***free cholesterol*** molecules with some ***proteins***, (apoprotein) **(Figure 3.13)**.
- The protein components are referred to as an ***apoprotein*** or ***apolipoprotein.*** There are four major types of apolipoproteins designated by letters A, B, C and E with subgroups given in Roman numerals I, II, III, etc.

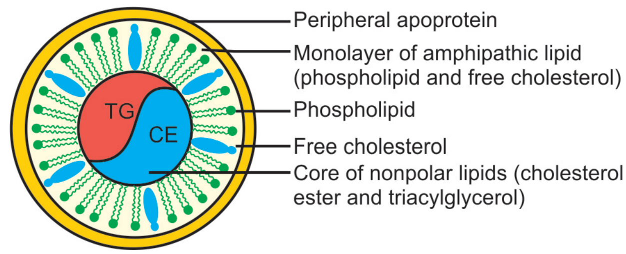


Figure 3.13: Structure of lipoprotein
where, TG: triacylglycerol, CE: cholesterol ester

Classes of Lipoproteins

Lipoproteins have been categorized into four major classes according to their physical and chemical properties **(Table 3.2).** These are :

1. Chylomicrons
2. Very low density lipoproteins (VLDL)
3. Low density lipoprotein (LDL)
4. High density lipoprotein (HDL).

- These lipoprotein complexes contain different proportions of lipids and proteins **(Table 3.2)**. The density of these lipoproteins is inversely proportional to triacylglycerol content. As the density increases, the diameter of the particle decreases as shown in **Figure 3.14.**
- Chylomicrons containing about 1 percent protein and 99 percent triacylglycerol have the lowest density.
- While HDL containing 50 percent of protein and 50 percent of lipid have the highest density.
- Triacylglycerol is the predominant lipid in chylomicrons and VLDL. Cholesterol is the predominant lipid in LDL, whereas phospholipid is the predominant lipid in HDL.
- Percentage of three major lipid classes, i.e. triacylglycerol, cholesterol and phospholipids present in lipoproteins are shown in **Table 3.2**.

Table 3.2: Characteristics of human plasma lipoproteins

Variable	*Chylomicron*	*VLDL*	*LDL*	*HDL*
Diameter (nm)	70 to 1200	25 to 70	20 to 25	5 to 10
Density (g/ml)	< 0.95	0.95 to 1.006	1.019 to 1.063	1.063 to 1.210
Lipid-Protein ratio	99:1	90:10	80:20	50:50
Major lipids	Triacylglycerol	Triacylglycerol	Cholesterol	Phospholipids
Apolipoproteins	B-48	B-100	B-100	A, C and E
Lipid components (%)				
Triacylglycerol	86	55	6	5
Cholesterol (free and ester)	5	20	50	20
Phospholipid	7	18	22	25

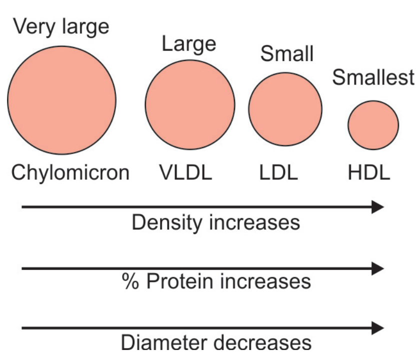


Figure 3.14: Diagrammatic representation of lipoprotein with increasing densities

Site of Synthesis and Functions of Lipoproteins

The site of synthesis of the four main lipoproteins and their functions are summarized in **Table 3.3.**

EICOSANOIDS

- **Prostaglandins** and the related compounds **thromboxanes** and **leukotriens,** are collectively known as **eicosanoids.**
- Eicosanoids are synthesized from **arachidonic acid.** A polyunsaturated fatty acid containing 20-carbon atoms from which they take their general name (Greek: eikosi means twenty).

Prostaglandins

- Prostaglandins are a group of 20-carbon compounds derived from **arachidonic acid (Figure 3.15)**.
- They derive their name from the tissue in which they were first recognized (the prostate gland) but they are now known to be present in almost all tissues.
- Chemically, the prostaglandins are derivatives of the hypothetical parent compound **prostanoic acid**, having cyclopentane (5 carbon) ring and two aliphatic side chains R_1 and R_2 **(Figure 3.15)**.
- Prostanoic acid does not occur naturally but is regarded as the parent compound of the prostaglandins and thromboxanes for the purpose of classification and carbon numbering.
- In addition to cyclopentane ring, each of the biologically active prostaglandin has a hydroxyl group at carbon 15, a double bond between carbons 13 and 14, and various substituents on the ring.

Table 3.3: The four main lipoproteins and their site of synthesis and function

Lipoprotein	*Site of synthesis*	*Function*
Chylomicrons	Intestine	Transport of dietary lipids from intestine to peripheral tissues
VLDL	Liver	Transport of triacylglycerol from liver to peripheral tissues
LDL	Plasma VLDL	Transport of cholesterol from liver to peripheral tissues
HDL	Liver and intestine	Transport of free cholesterol from peripheral tissues to the liver (Reverse cholesterol transport)

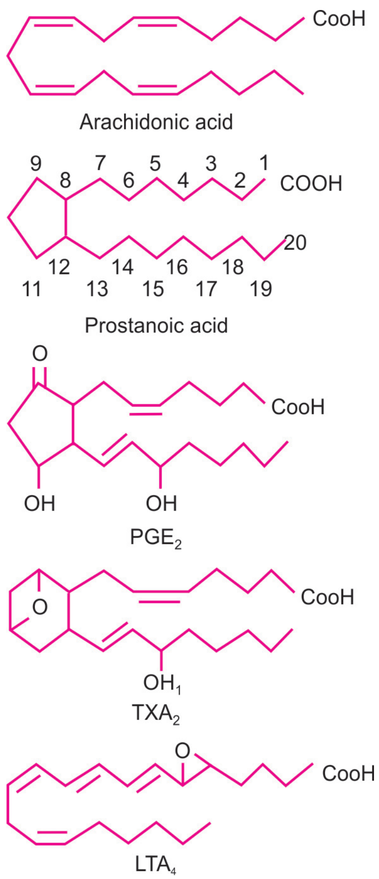


Figure 3.15: The structure of arachidonic acid, prostanoic acid, common prostaglandin (PGE_2), thromboxane (TXA_2) and leukotrienes (LTA_4)

Classification of prostaglandins

- By convention, prostaglandins are abbreviated as PG.
- They are classified into groups designated by a capital letter (A, B, C, D, E, F, G, H and I) depending on the substituents on the cyclopentane ring.
- These are subclassified by a subscript number 1, 2, or 3 corresponding to the number of double bonds in the side chains but not in the cyclopentane ring.
- Sixteen naturally occurring prostaglandins have been described but only seven are found commonly throughout the body. These are PGE_1, PGE_2, $PGF_1\alpha$, $PGF_2\alpha$, PGG_2, PGH_2, PGI_2.
- Prostaglandins are not stored, instead the precursor C_{20} arochidonic acids are stored in tissues.

Functions of prostaglandins

- Prostaglandins and other eicosanoids have hormone like actions.
- Prostaglandins in many tissues act by regulating the synthesis of cyclic AMP (cAMP). As cAMP mediates the action of many hormones, the prostaglandins affect a wide range of cellular and tissue functions. Some of these are:
  – **Smooth muscle contraction and relaxation:** For example, in pregnancy $PGF_{2\alpha}$ are produced in response to oxytocin and act to promote uterine contraction. Because of this effect, they have been used to terminate unwanted pregnancies. PGE_2 are involved in relaxation of bronchial smooth muscle.
  – **Inflammatory response:** PGs are involved in inflammatory response causing pain, edema, swelling and prolonged erythema (abnormal flushing of skin) by increasing capillary permeability.
  – **Platelet aggregation:** Prostaglandins have an effect on platelet aggregation. PGE_2 promote aggregation and are thus, involved in the blood clotting.
  – **Regulation of Blood pressure:** PGE_2 decrease blood pressure. It can lower systemic arterial pressure through their vasodilator effect.
  – **Body temperature:** Prostaglandins elevate body temperature producing fever and cause inflammation, resulting in pain.
  – **Gastric secretion:** PGE_2 suppress gastric secretion.
  – PGs are involved in $\mathbf{Na^+}$ and ***water retention*** by kidney tubules.

Thromboxanes

Thromboxanes were first isolated from blood platelets, thrombocytes—hence the name. They have six membered oxane ring **(Figure 3.15)** that includes an oxygen atom.

Nomenclature of thromboxanes

- Thromboxanes are abbreviated as TX.
  Different capital letters are used to designate different substituents of the ring (like prostaglandins).
- A subscript, if present, denotes the number of unsaturated bonds (double bonds), e.g. the most common thromboxane TXA_2 having two double bonds.

Functions of thromboxanes

- TXA_2 is produced by platelets, promotes platelets aggregation. Platelet aggregation initiates thrombus formation at sites of vascular injury.
- TXA_2 causes contractions of the smooth muscles of the arterial wall and therefore, raises blood pressure.

Leukotrienes (LT)

Leukotrienes were so named because they were initially described in leucocytes and are characterized by a conjugated **triene** system but no such ring structure that is found in prostaglandins and thromboxanes.

Nomenclature of leukotrienes

- All leukotrienes are abbreviated as LT.
- These are grouped into five classes (A to E) based on the type of substituents attached to the parent compound.
- The LTs found in humans have a subscript four to denote that they contain four double bonds **(Figure 3.15).**

Functions of leukotrienes

- The LTs facilitate chemotaxis, inflammation and allergic reactions.
- LTC_4, LTD_4 induce contraction of muscle of the lung and constrict pulmonary airways. Overproduction of LT causes asthmatic attacks.
- LTD_4 has been identified as the ***slow reacting substance of anaphylaxis (SRS-A)*** which causes smooth muscle contraction.
- LTB_4 attracts neutrophils and eosinophils to sites of inflammation.

MICELLES, LIPID BILAYER AND LIPOSOMES

Micelles

The polar lipid like phospholipid is amphipathic in nature. It has a hydrophilic or polar head (phosphate group attached to choline, ethanolamine, inositol, etc.) and a long hydrophobic tail containing two fatty acid chains **(Figure 3.16).** In aqueous systems the polar phospholipid spontaneously disperse to form micelles, in which the hydrocarbon tails of the phospholipid are hidden from the aqueous environment and electrically charged hydrophilic heads are exposed on the surface facing the aqueous medium **(Figure 3.16)**.

Lipid Bilayer

Phospholipids also readily and spontaneously form a very thin bilayer separating two aqueous compartments. In these structures, the hydrocarbon tails of the phospholipid molecules extend inward from the two surfaces to form a continuous inner hydrocarbon core and the hydrophilic heads face outwards extending into the aqueous phase **(Figure 3.16).**

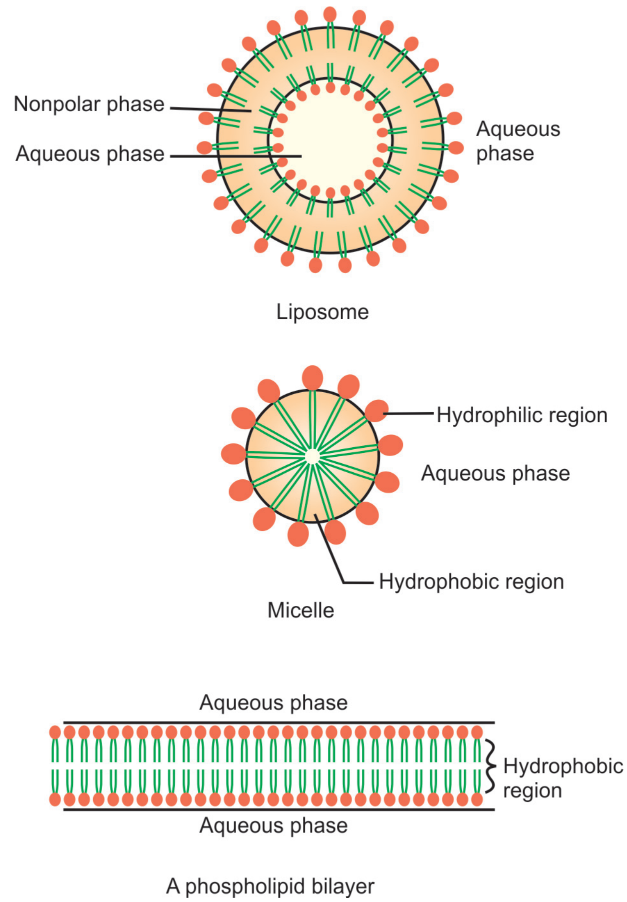


Figure 3.16: Formation of micelle, a phospholipid bilayer and liposome

Liposome (Artificially Formed Phospholipid Vesicles)

- Liposomes are artificially formed aqueous vesicles enclosed by a lipid bilayer.
- In the laboratory, liposomes (lipid bilayer) are formed by suspending phospholipid in an aqueous medium and then sonicating, i.e. agitating by high frequency sound waves to give a dispersed closed vesicles. Vesicles formed by these methods are nearly spherical in shape **(Figure 3.16)** and have a diameter of about 5 nm.
- Liposomes can be used to study membrane permeability or to deliver drugs to cells.

DETERGENTS

- Detergents are amphipathic molecules and are not natural membrane constituents. In aqueous solutions, they form micelles, with the hydrophilic regions on the outside, interacting with the water, and the hydrophobic regions inside.

- The bile acids and bile salts are powerful naturally occurring detergents which emulsify fats in the digestive tract; they can also be used to solubilize membrane proteins.
- Lysophospholipids also have detergent like action.

SUMMARY

- Lipids are water insoluble components of cells.
- Some lipids serve as structural component of membrane and others as storage form of fuel.
- Triacylglycerols contain three fatty acid molecules esterified to the three hydroxyl groups of the glycerol and are storage fats.
- The polar lipids (phospholipids, glycolipids and cholesterol), which have polar heads and nonpolar tails, are amphipathic and major components of membranes.
- Sphingolipids, i.e. sphingomyelins, cerebrosides and gangliosides are also membrane components and contain sphingosine but no glycerol.
- Cerebrosides and gangliosides are glycolipids which contain various sugar components.
- Cholesterol, a sterol is a precursor of many steroids and is also an important constituent of plasma membranes of the cell.
- Lipoproteins are macromolecular complexes that transport insoluble lipids in the blood. The proteins of the lipoprotein are referred to as apoprotein or apolipoprotein.
- Prostaglandins, thromboxanes and leukotrienes are derived from PUFA arachidonic acid.
- Liposomes are artificially formed phospholipid vesicles.
- Detergents are amphipathic molecules, and are not natural membrane constituents.

EXERCISE

Multiple Choice Questions (MCQs)

1. The precursor for vitamin D is:
a) Cholesterol b) Arachidonic acid
c) Triacylglycerol d) Phospholipids

2. Which of the following lipids is deficient in infants with respiratory distress syndrome?
a) Sphingomyelins
b) Cardiolipins
c) Leukotrienes
d) Dipalmitoyl phosphatidylcholine

3. Which of the following carbohydrates distinguishes a ganglioside from a globoside?
a) Glucose
b) N-acetylneuraminic acid
c) N-acetylgalactosamine
d) Galactose

4. Methylated form of phosphatidyl ethanolamine is known as:
a) Phosphatidylinositol
b) Phosphatidylserine
c) Phosphatidylcholine
d) Lysophosphatidylcholine

5. Which ring of the cholesterol molecule contains a double bond?
a) A-ring b) B-ring
c) C- ring d) D-ring

6. All of the following statements are true for phosphoglycerides, *except*:
a) They are major storage of metabolic energy
b) They are found in cell membrane
c) They are amphipathic
d) They are derived from glycerol

7. All of the following are sphingolipids, *except*:
a) Sphingomyelin
b) Cerebroside
c) Phosphatidylinositol
d) Ganglioside

8. The lipoprotein particles that have the highest concentration of triacylglycerol are:
a) VLDL b) HDL
c) LDL d) Chylomicrons

9. All of the following statements about prostaglandins are true, *except*:
a) They are cyclic fatty acids
b) They are potent biologic effectors
c) They were first observed to cause uterine contraction
d) They are synthesized only in prostate gland

10. Glycerol is the backbone of:
a) Glycerophospholipid
b) Sphingophospholipid
c) Glycolipids
d) Cholesterol esters

11. All of the following statements about lipids are true, *except*:
a) They are esters of fatty acids
b) They have poor solubility in water
c) They are a source of energy
d) They are polyhydroxy aldehydes

12. Which of the following statements about cholesterol is true?
a) It is saturated
b) It contains 27-carbon atom
c) It is a major sterol of plants
d) It contains four hexane rings fused together

13. Which of the following phospholipids has an antigenic activity?
a) Lecithin
b) Cardiolipin
c) Sphingomyelin
d) Cephalin

14. Which of the following glycolipids is known to be the receptor in human intestine for cholera toxin?
a) GM1
b) GM3
c) Globoside
d) Cerebroside

15. Which of the following is the major storage and transport form of fatty acids?
a) Cholesterol
b) Triacylglycerol
c) Albumin
d) Phospholipid

Correct Answers for MCQs

1-a	2-d	3-b	4-c
5-b	6-a	7-c	8-d
9-d	10-a	11-d	12-b
13-b	14-a	15-b	