Indira Gandhi National
Open University
School of Sciences

BBCCT-101
MOLECULES OF LIFE

Block

3

LIPIDS

BLOCK 3 : LIPIDS

In Block 2 you have studied the structure and functions ofcarbohydrates.Also, you came acrossthebiological significance of homo and hetero polysaccharides as storage and structural components. The present block presents a detailed discussion on the classification, properties and biological role of different types of lipids.

Lipids are heterogeneous group of compounds which are commonly known as fats and oils. These are generally associated with many of the life style diseases such as obesity and heart diseases. However, these molecules are essential for cellular function and growth. This block on lipids explains structures of different types of lipids and their biological significance. The blockconsists of 3 units (Unit 9 to 11).

In Unit 9 you will learn aboutthe fatty acids and glycerol which acts as building blocks of many lipids. It also explains classification of lipids. Detailed discussion will be based on structure and properties of storage form of lipids; triacylglycerols and waxes.

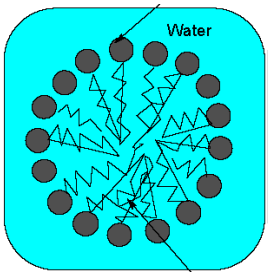
In Unit 10 you will learnaboutmembrane lipids.This unit explainshow glycerophospholipids, sphingolipids and sterols are important for the membrane integrity and function.

In Unit 11 you will study about specialized functions of lipids such as,their role as signaling molecules in both animals and plants. The unit also deals with other significant biological activities of lipidslikecofactors, pigments and plant sterols.

Objectives

After studying this block you will be able to:

- describe the building blocks of lipids;
- describe the structure and biological significance of storage lipids;
- identify the different types ofmembrane lipids present in animals, plants and microbes;
- explain the role membrane lipids;
- write about the general structure of biological membranes and how their composition is related to the functions performed by them;
- appraise the role of lipids in signal transduction; and
- discuss the role oflipids as cofactors and pigments.



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UNIT 9

LIPIDS

Structure

9.1 INTRODUCTION

In this block, we shall discuss about lipids that are important component of our nutrition along with proteins and carbohydrates. Unlike proteins and carbohydrates, lipids are not polymeric. Rather these constitute heterogeneous group of compounds generally termed as fats and oils. Lipids serve as energy reserve like carbohydrates and are the constituent of cell membranes, steroid hormones and some vitamins. Study of lipid biochemistry is important in understanding several health issues such as obesity, high blood pressure and cardiovascular disorders.

In this unit, we shall begin with classification of lipids based on functions they perform. Structure and properties of their common building blocks; fatty acids, glycerol and ceramide will also be discussed. We shall also learn in detail about triglycerides and waxes which are the storage form of lipids. Lipids which play structural role in cell membranes will be dealt with in the next unit.

Objectives

After studying this unit you should be able to:

- describe lipids and their biological importance;
- classify lipids and name some examples from each class;
- write examples and draw structures of saturated and unsaturated fatty acids;
- write structure and functions of triacylglycerides;
- explain different indices of quality of fats; and
- describe waxes and their roles.

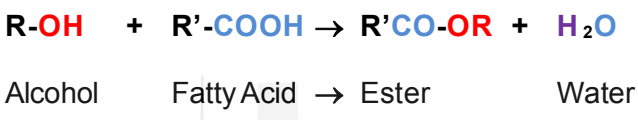
9.2 CLASSIFICATION OF LIPIDS

The term 'Lipid' was coined by a German chemist Bloor in 1943.

Lipids are chemically diverse group of compounds which are relatively insoluble in water. They are generally soluble in organic solvents such as ether and chloroform. Lipids are classified on the basis of chemical structure as well as functions.

Structural classification: On the basis of chemical structure, lipids are divided into three classes: simple lipids, compound lipids and derived lipids.

1) **Simple Lipids:** Simple lipids are esters of carboxylic acids having long unbranched hydrocarbon chain termed as fatty acids.



Based on the type of alcohol molecule, simple lipids are of two types: triglycerides and waxes. Triglycerides contain glycerol, a three carbon alcohol to which three fatty acid chains are esterified whereas waxes contain alcohol of relatively longer chain (generally C_{16} - C_{36}).

2) **Compound lipids:** Compound lipids are formed by modification of simple lipids such as addition of phosphate, sulfate, carbohydrate or protein group. These include phospholipids, glycolipids and lipoproteins.

3) **Derived lipids:** Derived lipids include those derived by modification, condensation or hydrolysis of simple and compound lipids. These include fatty acids derivatives, monoacylglycerols and diacylglycerols, steroid hormones, lipid-soluble vitamins.

Functional classification: Lipids are divided into two major groups on the basis of their functions. They are **storage and membrane lipids**. In addition, lipids also perform **specialized functions** such as signals, cofactors and pigments (Fig. 9.1).

1) **Storage lipids:** Storage lipids serve as the principal form of energy reserves in the animals and plants. These include triglycerides and waxes.

2) **Membrane lipids:** They constitute the major structural components of cell membranes and include phospholipids, galactolipids, sphingolipids and sterols.

3) **Specialized lipids:** This group includes lipids which are present in relatively smaller amounts but play specialized functions such as enzymes, cofactors, electron carriers, light absorbing pigments, hormones and intracellular messengers or signals. These include eicosanoids, steroid hormones, fat soluble vitamins A, D, E, K and conjugated dienes.

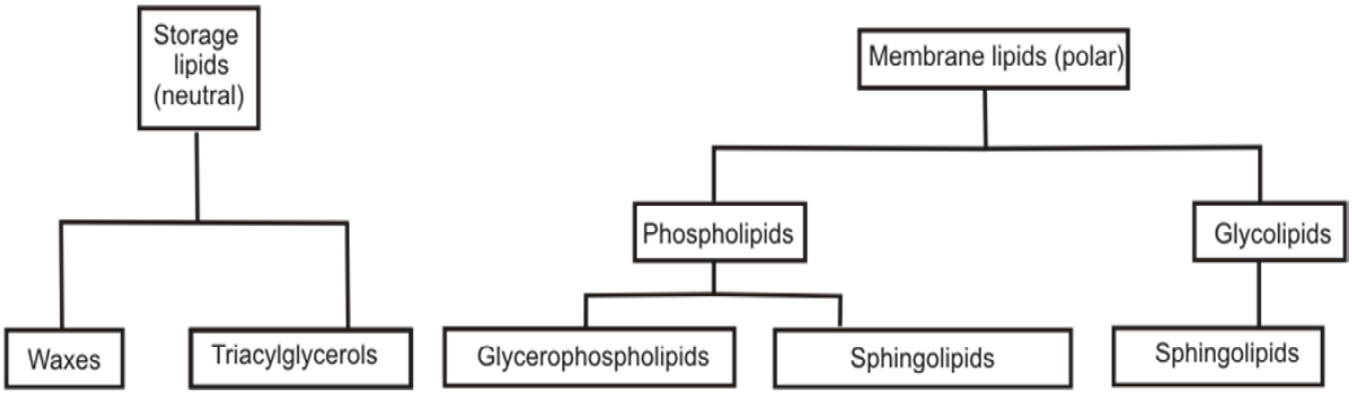


Fig. 9.1: Gives an overview of general classification of lipids.

Classification of lipids based on their functions is a more meaningful way of clubbing structurally diverse classes of lipids. Therefore, units in this block are organized accordingly. In this unit, we begin our discussion on building blocks of most of the lipids with reference to their chemical structure and physical properties. After that we shall learn about lipids which play role in energy storage in living organisms.

9.3 BUILDING BLOCKS OF STORAGE LIPIDS

Lipids are structurally diversified molecules. They are not polymeric unlike other biomolecules such as carbohydrates and proteins. Instead, there are some molecules which are commonly present in different types of lipids. Properties of these building blocks influence the properties of lipid molecules, they constitute. Therefore, it would be helpful to know about these molecules before we learn about complete structures and properties of different types of lipids. We shall learn about fatty acids, glycerol and ceramide in this section.

9.3.1 Fatty Acid

Fatty acids represent the principal component of most lipid classes. They generally have long aliphatic hydrocarbon chains with a carboxylic acid group at one end and methyl group at the other end. Fig. 9.2 shows the general structure of a fatty acid chain and its representation in an extended zig zag form.

Term aliphatic chain refers to non- cyclic hydrocarbon chain.

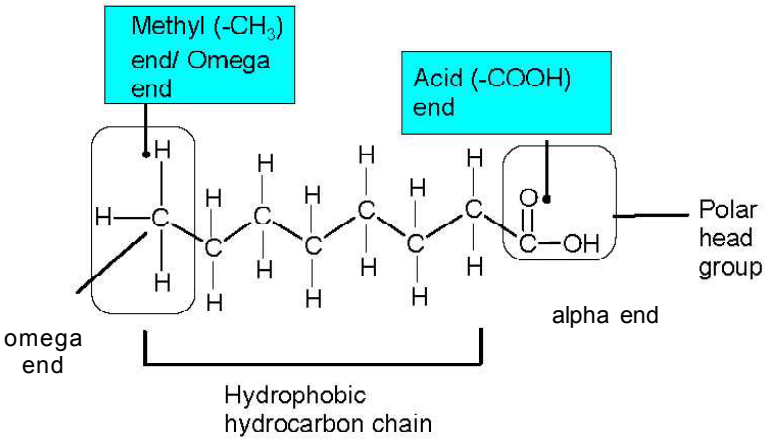


Fig. 9.2: Description of fatty acid chain

Greek letters are sometimes used to denote position of the carbon atoms relative to the Carboxylic acid group. The carbon next to Carboxylic acid is devoted as alpha (α) next to α comes beta (β) and the farthest one is denoted as omega (ω).

Fatty acids are classified on the basis of their chain length, degree of unsaturation or degree of modifications in the aliphatic chain.

Chain length: Most naturally occurring fatty acid chains have **even number** of carbon atoms as they are synthesized in the biological system by addition of two carbon acetate units. In general, the chain length varies from 12-22 carbon atoms although fatty acids with as short as 2 carbons chain and as long as 30 carbons chain also occur in nature. Fatty acids with 2-6 carbon chain are called *short chain fatty acids,* 6-10 carbon chain termed as *medium chain fatty acids* and 12 or more carbons constitute *long chain* fatty acids. They have most often **unbranched** chains though sometimes branched.

Degree of unsaturation: Fatty acids can be **saturated or unsaturated**. Most of unsaturated fatty acids have double bonds although triple bonds have also been found occasionally. Fatty acids with one double bond are called monoenoic or monounsaturated fatty acids (**MUFA**) and those with two or more double bonds are called polyenoic or polyunsaturated fatty acids **(PUFA).** Double bonds of naturally occurring unsaturated fatty acids have two characteristics:

a) The double bonds are generally in **cis** configuration (Fig. 9.3). All the fatty acids found in human body are cis fatty acids, with the exception of retinoic acid present in the eye which is a trans fatty acid.

In general, double bonds in fatty acids are in cis configuration and non-conjugated.

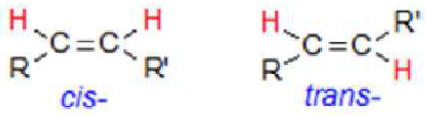


Fig. 9.3: cis and trans-configuration of double bonds. In cis- configuration, hydrogen atoms present on carbon atoms forming double bond are on the same side while in *trans* configuration, these are on opposite sides.

b) When two or more double bonds are present in a fatty acid, they are **non conjugated** as they are separated by a methylene ($-CH_2$). This arrangement is also called a 1**, 4 pentadiene structure.**

$$-CH=CH-CH_2—CH=CH-$$

Degree of modifications: Fatty acid chains with various modifications exist in nature. They are found in certain plants and microorganisms. These include: **acetylenic** (fatty acids with triple bond) and **allenic** (fatty acids with conjugated double bonds), **ring containing** (fatty acids with substituents such as cyclopropane, cyclopropene, cyclopentene and furan rings), **cyclic** fatty acids or fatty acids with substituents such as hydroxyl and epoxy groups.

Nomenclature

Both trivial names and systematic names are prevalent for fatty acids. In addition, shorthand notations have also been designated to fatty acids. Tables 9.1 and 9.2 provide examples of naturally occurring saturated and unsaturated fatty acids, respectively. You may refer to them to understand different examples.

Trivial names: Trivial or common names are generally given based on the most common or abundant source of the compound or from which they are first isolated. These names do not give any information about the structures and one has to learn them. For example, palmitic acid is found in palm oil, oleic acid is a major constituent of olive oil (oleum) and stearic acid (from the Greek word meaning solid) acid is solid at room temperature. Spiders (arachnids) contain arachidonic acid.

Systematic name: A fatty acid chain is assigned systematic name based on the hydrocarbon from which it is derived. Numbering begins from the first carbon at the carboxyl terminal. Saturated fatty acid chain is assigned a suffix 'anoic acid'/ 'anoate' while the unsaturated chain is assigned the suffix 'enoic acid' after the name of the hydrocarbon chain.

Let's consider a fatty acid chain consisting of 18 carbon atoms. It is named as octadec***anoic*** acid, if it is saturated and octadecenoic acid if it is monounsaturated. If there are more than one double bond as in case of polyunsaturated fatty acids, prefix *di*, *tri* etc. are used before the word enoic acid. For example, an 18 carbon fatty acid having unsaturated bonds at positions 9 and 12 is named as 9, 12- octadecadienoic acid. These examples are illustrated by the chemical structures later in this section.

Shorthand notation: Lipid biochemists have developed useful shorthand notation for fatty acids. In order to describe a fatty acid completely, its shorthand name is written in the following sequence:

1) The number of carbon atoms in the fatty acid.
2) The number of double bonds it contains.
3) The position of double bonds. It depends on the end from where numbering is started. It is either **Δ-or ω- numbering** (Fig. 9.4).
4) Type of double bonds (cis or trans) or triple bonds. Double bonds are considered to be cis unless otherwise stated.
5) Other modifications, if present are also to be represented by using appropriate symbols, for instance, **br** for branching.

Let us use the above rules to write a shorthand notation by taking examples of saturated and unsaturated fatty acids:

Stearic acid is an 18 carbon saturated fatty acid and its shorthand notation is 18:0. Oleic acid is an 18 carbon monounsaturated fatty acid and linoleic acid is polyunsaturated with two double bonds. How to write their shorthand notations in Δ-or ω- numbering is shown in Fig. 9.3.

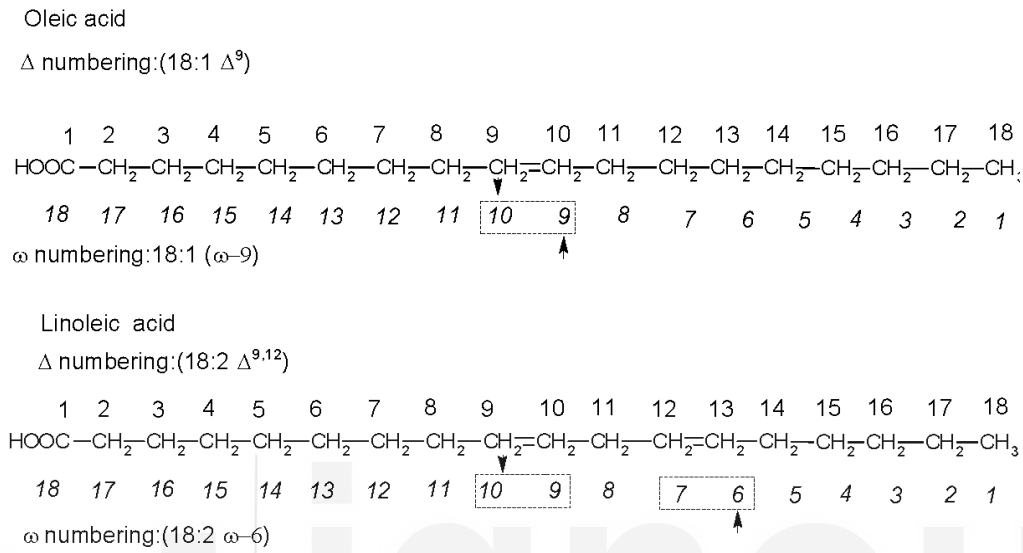


Fig. 9.4: In Δ - numbering of the fatty acid chain, it starts from the carboxyl end as Δ - 1 while in ω - numbering, it begins with methyl end as ω - 1, till it reaches the carbon forming first unsaturated bond.

Let us have a look at the comprehensive list of fatty acids, both saturated (Table 9.1) and unsaturated (Table 9.2) showing their common and systematic names as well as shorthand form. The table also shows common sources and their melting points.

Table 9.1: Structure, name and common sources of saturated fatty acids

Structure	Short-hand form	Syste-matic name	Common name	Occurrence	Melting point (°C)
$COOH(CH_2)_6CH_3$	8:0	Octanoic acid	Caprylic Acid	Milk fat	12.7
$COOH(CH_2)_8CH_3$	10:0	Decanoic acid	Capric Acid	Many milk and some seeds	29.6
$COOH(CH_2)_{10}CH_3$	12:0	Dodecanoic acid	Lauric acid	Most milk fats, Cinnamon, palm kernel, coconut oils	42.2
$COOH(CH_2)_{12}CH_3$	14:0	Tetrade-canoic acid	Myristic acid	Cow's milk, Nutmeg, palm kernel, coconut oils, Butter	52.1
$COOH(CH_2)_{14}CH_3$	16:0	Hexade-canoic acid	Palmitic acid	Most abundant saturated fatty acid in plants, animals and micro-organisms, highest concent-ration in palm oil	60.7

$COOH(CH_2)_{16}CH_3$	18:0	Octade - canoic acid	Stearic acid	Second most abundant, highest in ruminant fats, vegetable oils such as, cocoa butter, meat, hydro-genated fats	69.6
$COOH(CH_2)_{18}CH_3$	20:0	Eicosanoic acid	Arachidic acid	Peanut and fish oil	75.4

Table 9.2: Structure, name and common sources of unsaturated fatty acids

Structure	Short-hand form	Syste-matic name	Common name	Type of (ω) fatty acid	Occurr-ence	Melting point (^oC)
Monoenoic Acid (Fatty acids with one double bond. Also called monounsaturated)						
$COOH(CH_2)_7HC=CH(CH_2)_5CH_3$	16:1(Δ^9)	cis-9-Hexa decenoic acid	Palmitoleic acid	ω -7 acid	In nearly all animal fats.	1-0.5
$COOH(CH_2)_7HC=CH(CH_2)_7CH_3$	18:1(Δ^9)	cis-9-Octa decenoic acid	Oleic acid	ω- 9	Olive oil, possibly the most abundant monoun-saturated fatty acid in plants and animals.	16
$COOH(CH_2)_7HC=CH(CH_2)_7CH_3$	18:1(Δ^9)	trans-9-O cta decenoic acid	Elaidic Acid	ω- 9	Hydro-genated and ruminant fats.	44
Polyenoic Fatty acids (fatty acids with two or more double bonds. Also known as polyunsaturated)						
Dienoic Acid (Fatty acids with two double bonds)						
$COOH(CH_2)_7HC=CHCH_2CH=CH(CH_2)_4CH_3$	18:2 ($\Delta^{9, 12}$)	all-cis-9, 12-Octa-decadie-noic acid	*Linoleic acid	ω- 6	Corn, peanut, cottonseed, soybean, grape seed oil	-5
Trienoic acid (Fatty acids with three double bonds)						
$COOH(CH_2)_7HC=CHCH_2CH=CHCH_2CH=CHCH_2CH_3$	18:3 ($\Delta^{9, 12, 15}$)	all-cis-9, 12, 15-Octadeca trienoic acid	*α-Linolenic acid	ω- 3	Linseed (flaxseed) oil.	-11
$COOH(CH_2)_4HC=CHCH_2CH=CHCH_2CH=CH(CH_2)_4CH_3$	18:3 ($\Delta^{6,9,12}$)	all-cis-6,9,12 Octadeca trienoic acid	*γ-Linolenic acid	ω- 6	oil of evening primrose, borage oil; minor fatty acid in animals	

Tetraenoic acid (Fatty acids with four double bonds)						
$COOH(CH_2)_3HC=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_4CH_3$	20:4 ($\Delta^{5,8,11,14}$)	all-cis-5, 8,11,14-Eicosa tetraenoic acid	Arachi-donic acid	ω- 6	animal fats and peanut oil, liver fat	-49.5

*Essential fatty acids

As we already mentioned that structure and nature of fatty acids greatly influences the properties of lipids they constitute. Therefore, we shall discuss some important properties of fatty acids.

Geometric isomerism of Fatty acids

Saturated fatty acids are flexible molecules because of the freedom of rotation about the C-C single bonds and therefore, capable of assuming a wide range of conformations. However, they exclusively occur in the fully extended (zig zag) conformation as it results in the least steric interference between neighboring methylene groups making them quite stable. Fig. 9.5 shows structure of stearic acid.

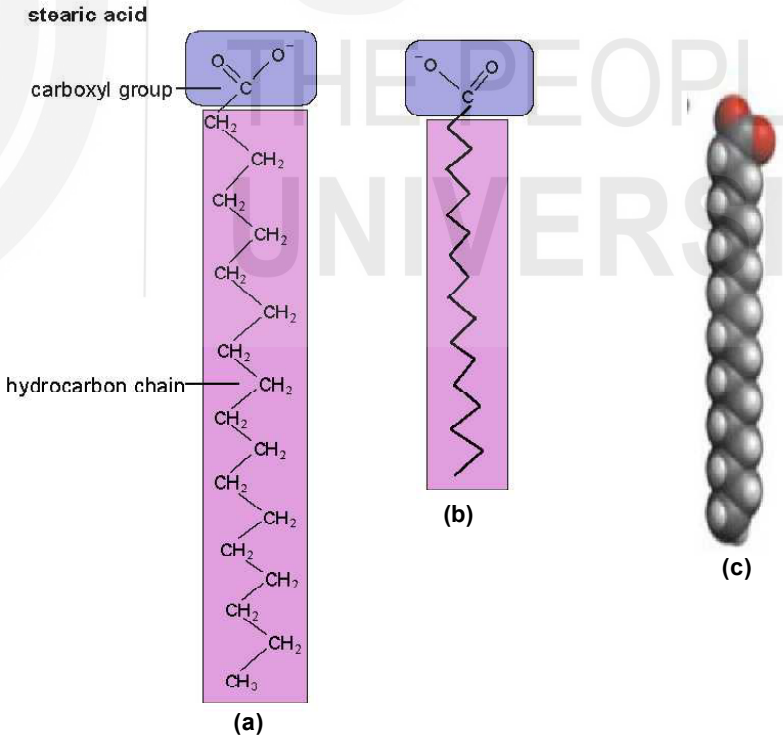


Fig. 9.5: Chemical structure of stearic acid, a saturated fatty acid with 18 carbon chain: (A) shows arrangement of all the atoms in the zig zag conformation. (B) represents graphical presentation of the zig zag from of stearic acid- lines represent the single bonds between the carbon atoms which are present at end of each line and hydrogens are explicit and not shown. (C) shows spacefilling model of stearic acid, where oxygen atoms of carboxylic acid group are shown in red color.

In case of unsaturated fatty acids, presence of a double bond causes restriction in rotation around the C=C bond. This results in two geometrical isomers; *cis* and *trans* which differ in arrangement of substituents at carbons forming double bond. In a *cis* double bond the side chains or groups on carbons forming double bond are on the same side, therefore experience more steric hindrance. Presence of a *cis* double bond introduces a bend/ kink in the otherwise fully extended structure of a saturated fatty acid.

Cis and trans fatty acids are geometric isomers.

On the other hand, in *trans (means far) isomers,* side chains or groups are on the opposite sides of the carbon atoms forming double bond and have more or less extended structure. Thus, ***trans* fatty acids are thermodynamically more stable than *cis* fatty acids.** Surprisingly, in spite of having less stability, *cis* fatty acids are more common in nature as compared to *trans* fatty acids.

Difference between cis and trans fatty acids can be understood by taking examples of oleic acid and elaidic acid. Both are 18 carbon fatty acids with one double bond at position 9. However, oleic acid is *cis* isomer while elaidic acid is *trans*. This difference results in different shapes of these fatty acids. Oleic acid assumes L- shape whereas elaidic acid remains straight (Fig. 9.6).

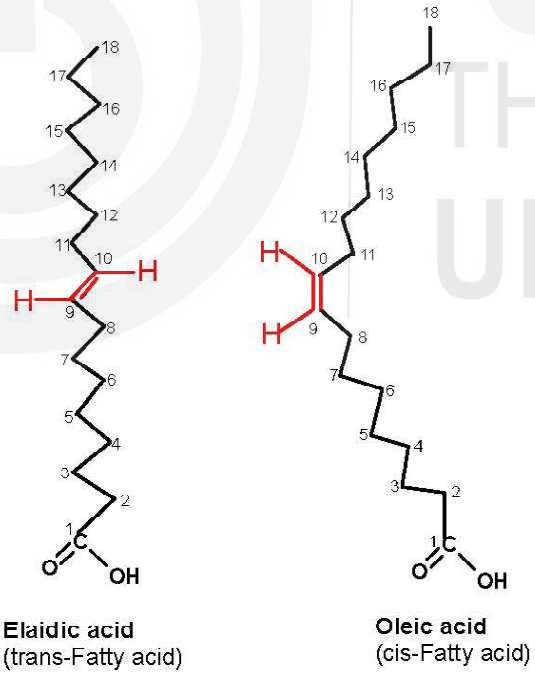


Fig. 9.6: Geometric isomerism of 18:1(Δ^9) **fatty acid; oleic acid and elaidic acid.** Oleic acid is ***cis* isomer having bent L- shape, while elaidic acid is *trans* isomer having extended structure.**

Essential Fatty acids: Most of the fatty acids can be synthesized in our body. However, there are some which cannot be synthesized by the mammals and therefore, need to be taken in the diet to fulfill their daily requirement.

So, such fatty acids are considered as essential fatty acids. Example of essential fatty acids are Linoleic, Linolenic and arachidonic acids. It is because mammals lack enzymes that can introduce double bonds beyond 9th position.

Fatty acids which can be synthesized in the body and need not necessarily to be taken in the diet are called **non-essential fatty acids**, for example, oleic acid. However, these terms in no way imply that non essential fatty acids are less important than essential fatty acids. Both types of fatty acids are required for normal functioning of the body.

SAQ 1

a) Fill in the blanks with appropriate words:

i) Lipids are generally soluble in..... and insoluble in .....

ii) The term 'Lipid' was coined by a German chemist ..... in the year .....

iii) Shorthand notation for arachidonic acid is ..... .

iv) Unsaturated fatty acids exist in *cis* and *trans* forms, this type of isomers are known as ..... isomers.

v) ..... and ..... are essential fatty acids

b) Answer in brief:

i) What are different ways to classify lipids? Give suitable examples.

ii) Write one example, each of ω-3, ω-6 and ω-9 fatty acids.

iii) What are the two characteristic features of unsaturated bonds found in fatty acid chains?

c) Identify the following fatty acids with trivial and systematic names. Also write shorthand notation and indicate the type of ω fatty acid.

i) $COOH(CH_2)_7HC=CH(CH_2)_5CH_3$

ii) $COOH(CH_2)_{14}CH_3$

iii) $COOH(CH_2)_7HC=CHCH_2CH=CHCH_2CH=CHCH_2CH_3$

Physical Properties of Fatty acids

Let us discuss some physical properties of fatty acids in correlation to their structures.

1) **Solubility**: Fatty acids are made up of long aliphatic hydrocarbon chains which make them **non polar**; however carboxylic acid group at one end of the chain makes it slightly polar. In general, fatty acids are more soluble in

organic/ non polar solvents such as chloroform and ether. Solubility in water and other polar solvents decreases with increase in chain length, e.g. butyric acid, a short chain fatty acid of four carbons is soluble in water in all proportions. Caproic acid with six carbon chain length is slightly soluble in water and higher fatty acids are practically insoluble in water.

2) **Melting Point**: Melting point of a fatty acid depends on two factors:

a) Degree of unsaturation: Saturated fatty acids have fully extended chains in zigzag form, which can fit very well with other chains; however unsaturated fatty acid chains are bent wherever there is a *cis* double bond. Higher the number of double bonds, higher is the number of bends; which makes it difficult for the chains to pack compactly (Figure 9.7). Also they have fewer Vander Waal's interactions. For example stearic acid (69.6°C) has higher melting point than oleic acid (16°C), although both are of same length (Tables 9.1 and 9.2)

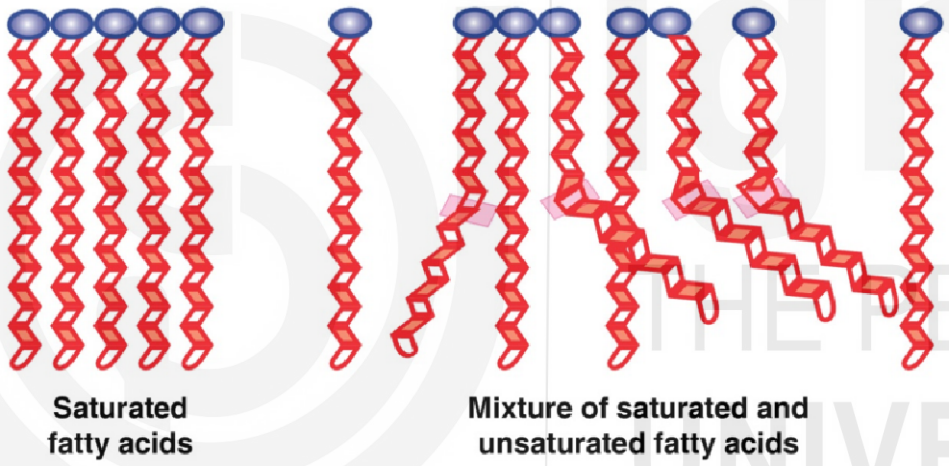


Fig. 9.7: Packing arrangement of unsaturated and saturated fatty acids

It is because of this arrangement, lipids that are rich in saturated fatty acids have higher melting point and exist as solids at room temperature (e.g. coconut oil) whereas those containing unsaturated fatty acids have lower melting point and exist as liquid at room temperature (e.g. olive oil). To observe the effect of increase in number of double bonds on decreasing melting points, you may compare the melting points of oleic (13.4°C), linoleic (1°C)and linolenic (-11°C) acids from the Tables 9.2 and 9.3. Further note that *cis* isomer of a fatty acid has lower melting point than the *trans* isomer. The melting point of oleic acid is 16°C and that of elaidic acid is 44°C.

b) Length of chain: Fatty acids with longer chains have higher melting point than the ones having shorter chain length, for example, saturated fatty acids of eight carbon atoms are liquids at room temperature while those containing more than ten carbons are solids at room temperature.

3) **Ionization:** Fatty acids are weak acids; therefore do not undergo complete ionization of the carboxylic group. Their pKa value is approximately 4.5. In general, fatty acids are neutral below pH 4.5 and charged above pH 4.5 (Fig. 9.8).

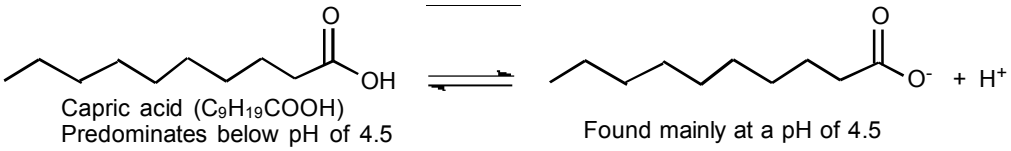


Fig. 9.8: Ionization of fatty acids at pH 4.5

Hence at physiological pH, the carboxyl group is readily ionized, rendering a negative charge onto the fatty acids.

Chemical reaction of fatty acids

Esterification of fatty acids: Fatty acids rarely occur as free fatty acids and undergo esterification reaction typical of carboxylic acids. They react with alcohols to form esters and water (Fig. 9.9).

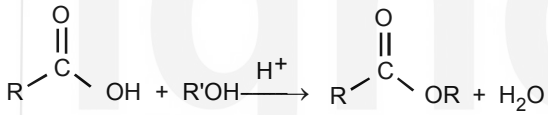


Fig. 9.9: Formation of esterified fatty acid.

It is the esterified form of fatty acids which constitute major component of various lipids.

SAQ 2

Answer True / False

i) Solubility of fatty acids in water/ polar solvents increases with increase in chain length. ( )

ii) Saturated fatty acids have higher melting point as compared to unsaturated fatty acids. ( )

iii) Fatty acids are negatively charged at physiological pH. ( )

Enzymes readily distinguish between C1 and C3 of glycerol and are nearly always specific for one or the other carbon. For example, glycerol kinase always phosphorylates glycerol on *sn*-3 to produce glycerol-3-phosophate and not glycerol-1-phosphate.

9.3.2 Glycerol

Glycerol is a trihydric molecule. It has three carbon atoms with one hydroxyl group at each carbon (Fig. 9.10). Presence of three hydroxyl groups makes it polar in nature. Hence it is miscible with water and alcohol in all proportions, but insoluble in ether, chloroform and benzene. Fig. 9.10 shows the structure of glycerol. It is important to note that C1 and C3 in glycerol are not identical when viewed in three dimensions. This is done by numbering the carbon atoms of glycerol unambiguously by the stereochemical numbering (-*sn*) system.

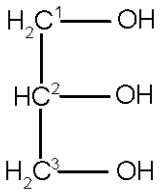


Fig. 9.10: Structure of glycerol

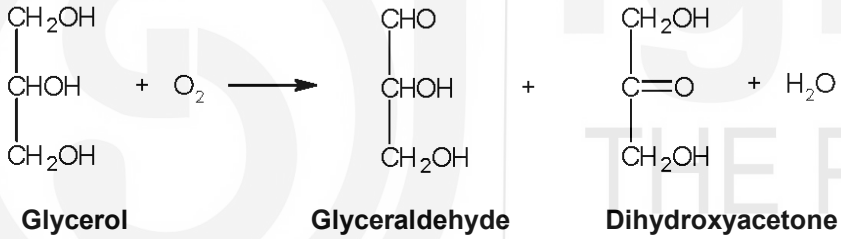
Glycerol forms backbone of most of storage and membrane lipids. Let us study some of the reactions of glycerol.

Reactions of glycerol

Glycerol has lot of industrial applications. It is used in medical, pharmaceutical and personal care industry such as cough syrups, tooth paste, mouth wash, soaps and hair care products.

Esterification- One or more hydroxyl groups of glycerol may react with carboxylic acids to form esters. As mentioned earlier, esterification reaction of glycerol and fatty acids is important in formation of storage and membrane lipids.

Oxidation- Glycerol can be oxidized with bromine water or hydrogen peroxide (H_2O_2) in slightly alkaline solutions in the presence of an iron salt to give a mixture of glyceraldehyde and dihydroxyacetone (Fig. 9.11).

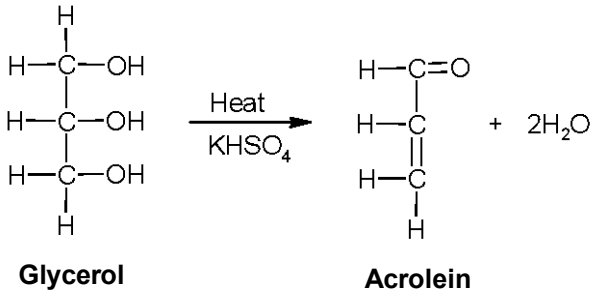


Glycerol **Glyceraldehyde** **Dihydroxyacetone**

Fig. 9.11: Oxidation of glycerol

You know that both glyceraldehyde and dihydroxyacetone are triose sugars and the mixture produced in this reaction reduces alkaline copper reagents giving positive Fehling and Benedict tests. The reaction is important in metabolic pathways as glycerol is oxidized in the presence of enzymes and used to generate energy via glycolysis.

2. Dehydration: Glycerol when is heated with a dehydrating agent such as potassium bisulphate ($KHSO_4$) produces an unsaturated aldehyde, acrolein. Pungent vapours of acrolein turn ammonical $AgNO_3$ paper black. It forms the basis of acrolein test of glycerol. (Fig. 9.12).



Glycerol **Acrolein**

Fig. 9.12: Formation of acrolein by removal of water from glycerol.

9.3.3 Ceramides

Ceramides are group of molecules with wax like properties. These form building block of sphingomyelins, one of the major lipid constituents of cell membranes. We shall discuss about these lipids in Unit 10. A ceramide consists of an amino base, sphingosine linked to a fatty acid by amide linkage. Fig. 9.13 shows general structure of a ceramide.

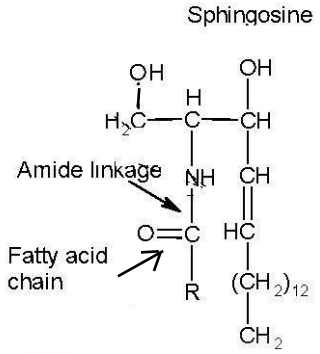


Fig. 9.13: General structure of a ceramide

As we go further with detailed description of different types of lipids, you would come across these building blocks. You would be able to appreciate how these building blocks have been used by nature to create diversity in structures of lipids which is suited to their functions. Let's begin with examples of storage lipids.

9.4 STORAGE LIPIDS

Storage lipids are deposited in animals and plants as energy reserve so that they are mobilized to provide energy in case of starvation or absence of food. Lipids are highly reduced and hydrophobic molecules therefore they are stored as long term energy resources and are utilized after carbohydrates reserves are consumed. **Triacylglycerol** (TAG) and **waxes** come in this category.

9.4.1 Triacylglycerides

The utility of triacylglycerols as an energy source is illustrated by the abilities of migratory birds which can fly great distances without eating.

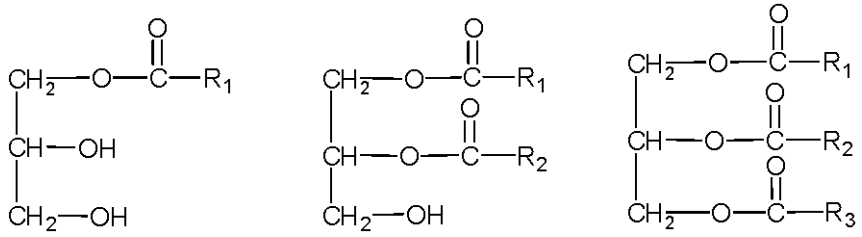
The utility of triacylglycerols as an energy source is illustrated by the abilities of migratory birds which can fly great distances without eating.

Triacylglycerols (TAG) also known as triglycerides are the ester derivatives of glycerol which constitute the storage form of fatty acids in animals and plants. In the previous section, you have learnt about properties of fatty acids. You also learnt that these form esters with glycerol. Recall from the Fig. 9.7 that glycerol has three hydroxyl groups; one or more of these may be esterified to fatty acid chains. Based on the number of esterified hydroxyl groups in glycerol, following nomenclature is used:

Monoacylglycerol (MAG) - If only one hydroxyl group of glycerol is esterified to a fatty acid; it is called monoacylglycerol or monoglyceride.

Diacylglycerol (DAG) - If two hydroxyl groups of a glycerol are esterified to two fatty acids; it is termed as diacylglycerol or diglyceride.

Triacylglycerol (TAG) - When all the three hydroxyl groups of a glycerol are esterified, it is termed as triacylglycerol (TAG) or triglyceride (TG). General structures of glycerides are shown in Figure 9.14.

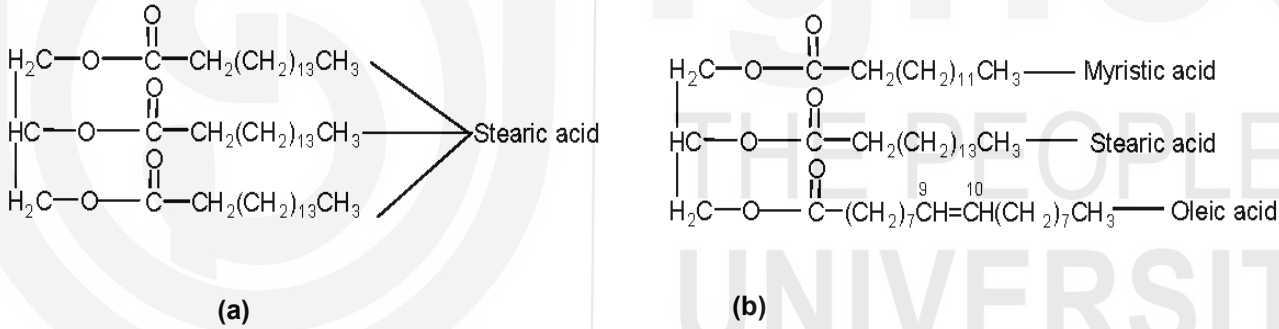


(a) (b) (c)

Fig. 9.14: General chemical structures of (a) monoacylglycerol, (b) diacylglycerol and (c) triacylglycerol. R - a fatty acid chain; R1, R2 and R3 can be same or different fatty acids.

The glycogen and glucose stores provide enough energy to sustain biological function for about 24 hours, whereas the triacylglycerol stores allow survival for several weeks.

TAGs having same fatty acid at all the three positions are known as **simple triacylglycerol,** for example, tristearoylglycerol (common name tristearin) and trioleoylglycerol (triolein). The term **mixed triacylglycerol** is used, if two or three different fatty acids are esterified to the hydroxyl groups of glycerol. Fig. 9.15 shows examples of simple and mixed TAG.



(a) (b)

Fig. 9.15: a) Tristearin is a simple TAG as it has stearic acid esterified to glycerol at all the three hydroxyl groups. b) An example of mixed TAG, as three fatty acids attached to glycerol are different.

Most of the natural fats, such as vegetable oils, dairy products and animal fats are complex mixtures of simple and mixed TAGs. TAG is also the form in which our body stores excess of fatty acids in the adipocytes of adipose tissue. In plants, such reserves are present in germinating seeds.

The lipid reserves are utilized with the help of enzyme; lipase present in these tissues. Lipase breaks TAG into its contituents; glycerol and fatty acids which are subsequently exported to the needy tissue to provide energy. TAGs are highly concentrated stores of metabolic energy as complete oxidation of fatty acids yields about 9 kcal g^{-1} (38 kJ g^{-1}), as compared to 4 kcal g^{-1} (17 kJ g^{-1}) for carbohydrates or proteins. The difference is because fatty acids are more ***reduced*** than carbohydrates. Moreover, they are stored as ***anhydrous molecules*** due to their non polar nature, whereas more polar carbohydrates and proteins are hydrated, occupying more space for storage. ***One gram of anhydrous fat stores more than six times as much energy as a gram of***

Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils.

hydrated glycogen, which could probably be the reason that TAGs rather than glycogen were selected as the major energy reservoir during evolution.

Physical properties of TAGs: Physical properties of TAGs depend on the nature of constituent fatty acids. Based on whether they exist as liquid or solids at 25^0C, TAGs are known as oils or fats, respectively. These differences in melting points reflect differences in the degree of unsaturation and number of carbon atoms in the constituent fatty acids. Table 9.3 shows composition of some common fats and oils.

Table 9.3: Average Fatty Acid Composition of Some Common Fats and Oils (%)*

	Lauric	Myristic	Palmitic	Stoaric	Oleic	Linoletic	Linolenic
Fats							
butter (cow)	3	11	27	12	29	2	1
lard		2	26	14	44	10	
Oils							
canola oil			4	2	62	22	10
coconut oil$	47	18	9	3	6	2	
corn oil			11	2	28	58	1
olive oil			13	3	71	10	1
peanut oil			11	2	48	32	
soybean oil			11	4	24	54	7

* Totals less than 100% indicate the presence of fatty acids with fever than 12 carbon atorms or more than 18 carbon atorms.

$ Coconut oil is highly saturated. It contains an unusually high percentage of the low-melting C_8, C_{10}, and C_{12} saturated fatty acids.

Pure fats and oils are tasteless, colourless and odourless. The characteristic odour or colour of some fats and oils is because of the foreign substances which are fat soluble and have been absorbed by these lipids. For example, yellow colour of the butter is due to addition of pigment carotene.

The taste of butter comes from two compounds—diacetyl and 3-hydroxy-2-butanone—produced by bacteria in the ripening cream from which the butter is made.

TAGs are lighter than water, having densities of about 0.8 g/cm^3. They are poor conductors of heat and electricity and therefore serve as excellent insulators for the body, slowing the loss of heat through the skin.

Chemical reactions of TAGs: TAGs undergo three major reactions-hydrolysis, hydrogenation and oxidation. These reactions produce products, which are useful for the analysis of a quality index of TAGs.

1) **Hydrolysis -** TAGs undergo hydrolysis in the presence of an acid, a base or specific enzymes called lipases. The hydrolysis yields their constituent

fatty acids and glycerol. Free fatty acids react with alkalies (NaOH/KOH) and produce the salts. These salts are considered as soaps and having a cleansing properties (Fig. 9.16). These salts are called soaps having excellent cleansing properties. This process of formation of soap is known as saponification.

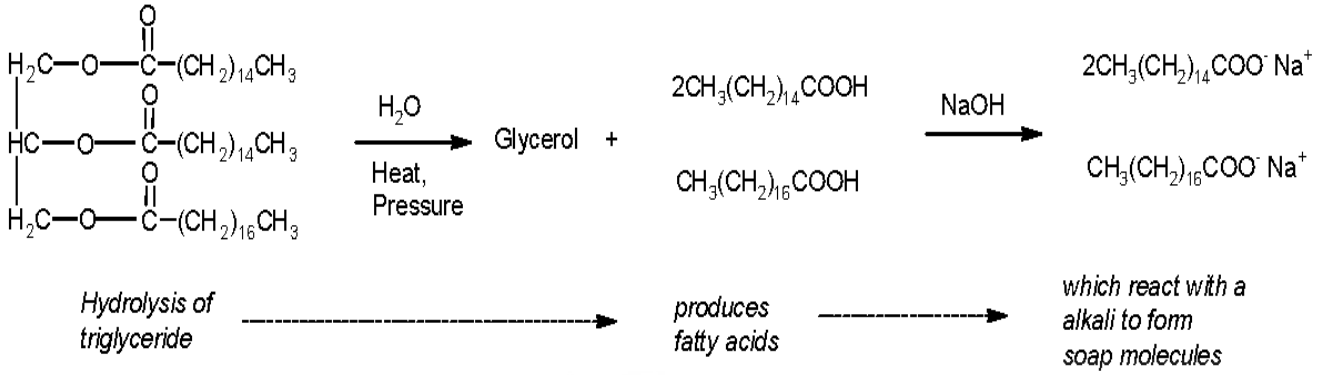


Fig. 9.16: Saponification reaction: TAGs when hydrolyzed in the presence of a alkali release fatty acids which react with the alkali to form soap

Lipids are sometimes classified as **sponifiable** and **non- sponifiable** based on their ability to release salts of long fatty acids on alkaline hydrolysis. Thus, MAG, DAG and TAG are sponifiable lipids.

Based on this property, TAGs are assigned **saponification number** which is **the number of milligrams of KOH required to neutralize the fatty acids resulting from the complete hydrolysis of 1g of fat**.

The saponification number, thus, provides information about the average chain length and molecular weight of the fatty acids in a fat. It varies inversely with the chain length of the fatty acids. The shorter the average chain length of the fatty acids, the higher is the saponification number (Wonder why!!!). It is so because more number of short chain fatty acids are present in 1 gram of fat compared to that of long chain fatty acids. This results in availability of more acid groups for saponification in a fat containing short chain fatty acids as compared to fat with longer chain length for the same weight i.e. 1 gram.

Hydrophilic (*hydro*- water; *philic*- loving) molecules loves to be in water or other polar solvents. Hydrophobic (*hydro*- water; *phobic*- hate) molecule shies away from water and interacts only with molecules of its own kind.

Mechanism of action of soap- TAGs are non polar molecules as polar groups of both glycerol (OH) and fatty acid chains (COOH) are occupied in making ester bonds. However, soap is amphipathic molecule which means that it has both polar and non polar ends (fatty acid chain). Polar head is constituted by the ionizable carboxylic group (COO^+Na^-). This part is hydrophilic. Non polar end is the hydrocarbon chain of the fatty acid which is hydrophobic (Fig. 9.17).

When such molecules are present in water or other such polar solvent, they form micelles. They arrange themselves in such a way so that nonpolar chains are close together with least contact with water and polar heads are exposed to water.

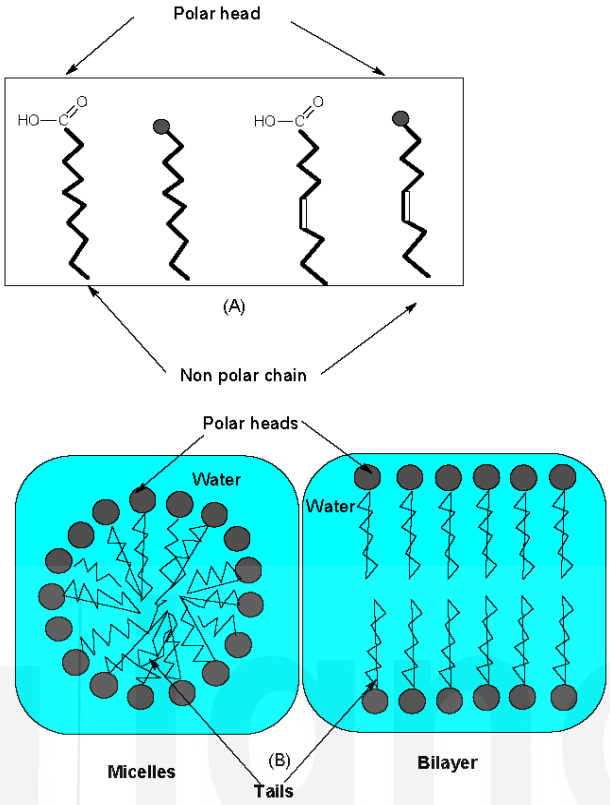


Fig. 9.17: a) Polar and non-polar part of soap; b) Micelle formation by amphipathic molecules of soap in contact with water

Cleansing action of soap involves entrapment of grease and dirt in the non-polar part of micelles which are then washed away with water as the polar part is in contact with water. The phenomenon of entrapping grease or oily substances into micelle formed by soap is known as *emulsification*.

2) **Hydrogenation-** Hydrogenation means addition of hydrogen. Unsaturated fatty acids get hydrogenated across the double bonds in the presence of catalyst such as nickel to yield saturated fatty acids (Fig. 9.18). The phenomenon has been used in a controlled manner for preparation of margarine and processed cheese by conversion of unsaturated fatty acids of oils to the saturated ones resulting in solidification.

$$HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\mathbf{CH{=}CH}\text{-}CH_2\text{-}CH_3 \rightarrow HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\mathbf{CH_2\text{-}CH_2}\text{-}CH_2\text{-}CH_3$$

Fig. 9.18: Hydrogenation of unsaturated fatty acid results in addition of H atoms across the double bonds.

In nature, partial hydrogenation of some of the unsaturated fats ingested by ruminants takes place by bacteria in the rumen. Therefore, milk fat, diary products, beef and mutton fat also contain cis and trans fatty acids such as vaccenic acid.

Just like addition of hydrogen across unsaturated double bonds, halogens such as iodine can add across the double bonds to form dihalogenated fatty acid. The reaction in Fig. 9.19 shows the addition of iodine across the unsaturated bond. The process is known as iodination.

Catalysts used during hydrogenation of oils containing unsaturated fatty acids convert some of the *cis* fatty acids to *trans*. Elaidic acid is generally formed. *Trans* fatty acids are harmful and have been associated with the cardiovascular diseases.

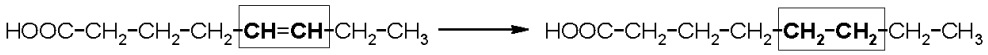


Fig. 9.18: Hydrogenation of unsaturated fatty acid results in addition of H atoms across the double bonds.

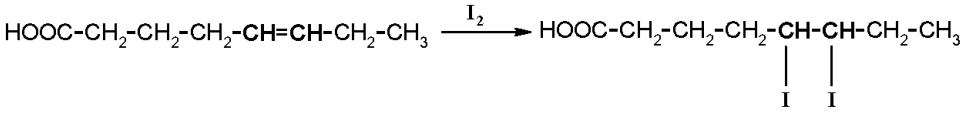


Fig. 9.19: Addition of iodine across the double bond of a fatty acid chain.

This property of fatty acids has been used to assess the extent of unsaturation in the lipids. Higher the number of unsaturated fatty acids chains, higher will be amount of iodine consumed by it for addition across the unsaturated bonds. This parameter is known as **iodine number** and is defined **as number of grams of iodine required to saturate 100 grams of the lipid.**

In nature, partial hydrogenation of some of the unsaturated fats ingested by ruminants takes place by bacteria in the rumen. Therefore, milk fat, diary products, beef and mutton fat also contain cis and trans fatty acids such as vaccenic acid.

3) **Oxidation:** Unsaturated fatty acids can spontaneously react with atmospheric oxygen and gets oxidized. The process of oxidation results in formation of fatty acid peroxides, epoxides or aldehydes which give unpleasant smell and taste to lipids. Such lipids are said to be rancid and are toxic and unsuitable for consumption. Degree of rancidity can be assessed by ***acid number*** **which is defined as** ***the number of milligrams of KOH required to neutralize free fatty acids in a gram of fat.*** It is different from saponification number as it takes into account both free fatty acids as well as those present as esters in a fat. For a lipid which is properly processed and stored has low acid number. Rancidity can be prevented with the help of antioxidants such as vitamin E.

SAQ 3

Define the following terms and what type of information do we get from these?

a) *Saponification value*

b) *Acid number*

c) *Iodine number*

9.4.2 Waxes

Glycerol is absent in waxes.

Waxes are also esters of long chain saturated or unsaturated fatty acid chains (C_{14}-C_{36}). However, instead of glycerol, they contain long chain (C_{16}-C_{30}) alcohols. They have higher melting point than TAGs. Waxes are the major energy storage form in planktons, which serve as food for marine organisms such as whale, herring, salmon .

In vertebrates, waxes secreted by cutaneous glands provide a protective coating on the skin and hair to keep them lubricated and waterproof. Birds, particularly waterfowl, secrete waxes to make their feathers water-repellent. The leaves of many plants such as rhododendron and calotropis are shiny because of the deposition of protective waxy coating.

Waxes find important use in pharmaceutical and cosmetic industry. Lanolin from lamb's wool, beeswax, carnauba wax from a Brazilian palm tree is used in lotions, ointments and polishes. Fig. 9.20 gives the structure of myricyl cerotate present in beeswax and carnauba wax.

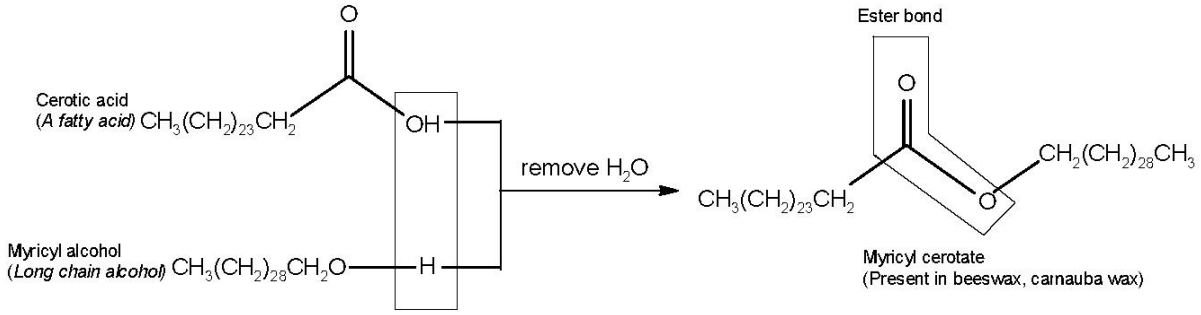


Fig. 9.20: Synthesis of Beeswax

Let's summarize the biological roles of TAGs and waxes, we have discussed so far.

Biological Importance of lipids

1) Excess of energy obtained from food is converted to storage form of lipids called triglycerides and deposited in the adipose tissue. It is used to provide energy for the body activities during long periods of starvation.
2) They insulate the body to maintain normal body temperature and cushion the internal organs for protection.
3) They protect surfaces of animal and plants by forming a waxy coating and making the surface water proof.

9.5 SUMMARY

1) Lipids constitute a diverse class of molecules which are sparingly soluble in water and polar solvents. They are generally soluble in organic solvents such as ether and chloroform.
2) They are not only structurally diverse, but also play diverse functions. They play roles such as energy reserves, constituent of cell membranes, steroid hormones, fat soluble vitamins and signaling molecules.
3) Lipids are classified on the basis of similarity in chemical structure and the functions they perform. Structurally they are classified as simple, compound and derived lipids.
4) Functionally, lipids are classified as storage lipids, membrane lipids and lipids with specialized functions such as signals, cofactors and pigments.
5) Storage lipids serve as the principal form of energy reserves in the animals and plants. These include triglycerides and waxes.
6) Membrane lipids constitute the major structural components of cell membranes and include phospholipids, galactolipids, sphingolipids and sterols.
7) Specialized lipids such as eicosanoids, steroid hormones, fat soluble vitamins A, D, E, K and conjugated dienes are present in relatively smaller

amounts. They perform specialized functions such as enzymes, cofactors, electron carriers, light absorbing pigments, hormones and intracellular messengers or signals.

8) Fatty acids, glycerol and ceramide are the building blocks which are found in different types of lipids.

9) Fatty acids are long aliphatic chains (acyclic/non-cyclic) with carboxylic acid group at one end and methyl group at the other end. They are the structural component of most of the simple and compound lipids. Most naturally occurring fatty acid chains have even number of carbon atoms (usually 12-24) and can be saturated or unsaturated with double bonds almost always in *cis* configuration.

10) Fatty acids are reactive molecules due to presence of carboxylic group. Length of the hydrocarbon chain and degree of unsaturation in fatty acids determine their physical properties, such as melting temperature and solubility.

11) Triacylglycerols (TAGs) constitute the storage form of fatty acids in animals and plants. Glycerol is at the backbone of these molecules and three fatty acid molecules are esterified to its three hydroxyl groups. These are of two types; simple and mixed.

12) Simple TAGs are made of only one type of fatty acid at all the three positions, while mixed contain two or three different types of fatty acid chains. Most natural fats, such as vegetable oils, dairy products and animal fat contain TAGs.

13) Fats and oils are the nomenclature given to TAGs based on their physical state. Fats are those TAGs which are solid at room temperature and oils are liquid.

14) Chemical reactions of TAGs include hydrolysis in presence of acid, enzyme or alkali, saponification, addition of hydrogen or halogens across double bonds and oxidation reactions. Saponification value, iodine number and acid numbers are important parameters to determine the quality of fatty acids present in a lipid.

15) Waxes are the esters of long chain saturated or unsaturated fatty acid chains (C_{14}-C_{36}). However instead of glycerol, they contain long chain (C_{16}-C_{30}) alcohols.

16) Waxes are the major energy storage form in planktons, which serve as food for marine organisms such as whale, herring, and salmon. They also provide water proof, protective coating on skin, hair and feathers of many animals, birds and plants.

9.6 TERMINAL QUESTIONS

1) What are the major biological functions of lipids?

2) Explain different physical and chemical properties of fatty acids.

3) Give one example each of ω-6 and ω-9 fatty acid.

4) What are soaps and explain their cleaning action.

5) Which different parameters are used to determine the quality of lipids?

6) What are waxes and how are they different from TAGs?

9.7 ANSWERS

Self-Assessment Questions

1. a) i) Organic solvents; water ii) Bloor; 1943 iii) 20:4($\Delta^{5,8,11,14}$)

iv) Geometric v) Linoleic acid and linolenic acid

b) i) According to Bloor, lipids can be classified into three categories: simple, compound and derived.

Simple lipids :

a) Fats and oils are esters of long chain saturated or unsaturated fatty acids with glycerol, e. g. Butter and olive oil respectively.

b) Waxes are the ester of long chain saturated or unsaturated fatty acid chains (C14-C36) and longer chain alcohol (generally C16- C36) instead of glycerol, eg. Beeswax.

Compound Lipids : These are made up by further modification of simple lipids such as addition of phosphate, sulfate, carbohydrate or protein group. This class of lipids includes phospholipids, glycolipids and lipoproteins and plasmalogens.

Derived Lipids : These are compounds derived which are derived from hydrolysis of simple and compound lipids. They include fatty acids, glycerol and other alcohols, mono- and diglycerides, steroids such as cholesterol, lipid-soluble vitamins such as carotenoids, and hormones.

ii) ω3- α-Linolenic acid; ω6- Arachidonic acid; ω9- Oleic acid

iii) a) Double bonds exist in *cis* conformation except some ruminants (e.g. cow) which contain *trans* fatty acids.

b) Double bonds in polyunsaturated fatty acids are conjugated, i.e. two consecutive double bonds are separated by a (-CH_2) group.

c) i) Palmitoleic acid, cis-9-Hexadecenoic acid, 16:1(Δ^9), ω7

ii) Palmitic acid, Hexadecanoic acid,16:0, saturated fatty acid, so not ω fatty acid

iii) α-Linolenic acid, all-cis-9, 12, 15-Octadeca trienoic acid, 18:3 ($\Delta^{9, 12, 15}$), ω3

2. i) False ii) True iii) True

3. a) Saponification value- It is the number of milligrams of KOH required to saponify 1 gm of fat. The saponification number, thus, provides information about the average chain length of the fatty acids in the fat. It varies inversely with the chain length of the fatty acids.

   b) Acid number- It is the number of milligrams of KOH required to neutralize free fatty acids in a gram of fat. Thus this number gives an idea about the number of free fatty acids present in a lipid sample. For a lipid which is properly processed and stored has a low acid number.

   c) Iodine number- It is the number of gram iodine required to saturate 100 grams of the lipid. Higher the number of unsaturated fatty acids in a lipid, higher is its iodine number.

Terminal Questions

1) Refer to the section 9.2, Storage lipids, membrabe lipids and specialized functions such as signal or chemical messenger, hormones, enzymes, cofactors and pigments.

2) Solubility, melting temperature, ionization and esterification reaction. Please refer to the section 9.3.1 of unit for the physical and chemical properties of fatty acids.

3) Oleic acid is ω-9, linoleic acid and arachidonic acid are ω-6.

4) Under basic conditions, fatty acids produced by hydrolysis react with base to form salt of the fatty acid. These salts are called soaps having excellent cleansing properties. This process of formation of soap is known as saponification. Soap is amphipathic molecule which means that it has both polar ($COONa^+$) and non polar ends (fatty acid chain). When such molecules are present in water or other such polar solvent, they form micelles. Cleansing action of soap involves entrapment of grease and dirt in the nonpolar part of micelles which are then washed away with water as the polar part is in contact with water. The phenomenon of entrapping grease or oily substances into micelle formed by soap is known as *emulsification*.

5) Saponification number, iodine number and acid number. Please refer to section 9.4.1.

6) Waxes are the esters of long chain saturated or unsaturated fatty acid chains (C_{14}-C_{36}). However instead of glycerol, they contain long chain (C_{16}-C_{30}) alcohols.

9.8 FURTHER READINGS

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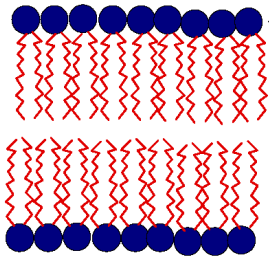


Lipid bilayer

UNIT 10

MEMBRANE LIPIDS

Structure

10.1 INTRODUCTION

In the previous unit, you learnt that lipids are heterogeneous group of compounds which perform diverse functions. We discussed about their classification, common building blocks and their properties with suitable examples. We explained classification of lipids based on their functions such as storage lipids, membrane lipids and others with specialized functions. Among the energy storage lipids, we described the structure and important reactions of triacylglycerols and wares in the previous unit.

In this unit, we shall discuss about another class of lipids; membrane lipids. As evident from their name, these serve as structural component of biological membranes. Lipids in this class include phospholipids, galactolipids and sulpholipids, sphingolipids and cholesterol. These lipids along with proteins not only provide structural support to the biological membrane but also help it to maintain fluidity. Let us learn about structure and specific functions of membrane lipids in detail.

Objectives

After studying this unit you should be able to:

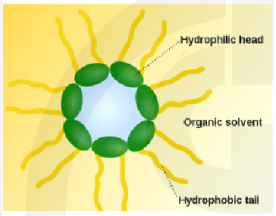
- identify structural features of different types of phospholipids and their derivatives;
- discuss importance of galactolipids and sulpholipids;
- classify sphingolipids and explain their biological importance;
- dxplain structure and importance of cholesterol; and
- write about structure and composition of biological membranes.

10.2 STRUCTURAL LIPIDS IN MEMBRANES

You know from your school biology that all living cells are bound by a membrane. In addition to the outer cell membrane, cell organelles such as mitochondria, chloroplast, nucleus, golgi bodies and endoplasmic reticulum present in eukaryotic cells are also bound by their own membranes. All biological membranes are composed of a lipid bilayer and proteins and serve as barrier for polar molecules and ions.

Lipids present in the biological membranes are amphipathic in nature. You learnt about the amphipathic nature of soaps in the last unit, which are salts of fatty acid under alkaline conditions. Hydrocarbon chain is the hydrophobic part while the carboxylic group forms the hydrophilic or polar part. When exposed to aqueous environment, hydrophobic chains of the amphipathic lipids tend to stay together excluding water and their hydrophilic ends are oriented towards polar environment. Such ordered arrangements result in formation of micelles or sheets (Fig. 10.1). In case of soap, polar head and single fatty acid chain form wedge like structure which is more stable by forming micelles. However, most of the membrane lipids have one polar head and two fatty acid chains giving rise to cylindrical shape. Such shape is more stable to make sheet like structure as observed in the biological membranes.

Amphipathic means a molecule has both polar/ hydrophilic and non polar/ hydrophobic ends.



This is the arrangement you will see if a drop of water is added to oil.

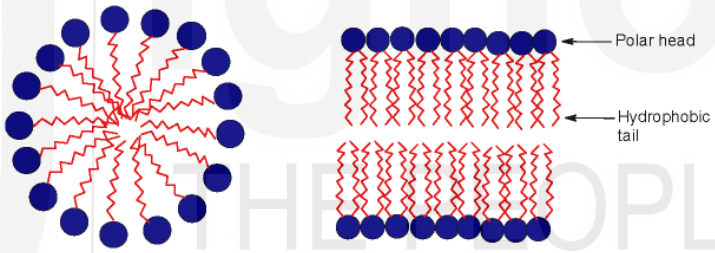


Fig. 10.1: Micelles and lipid bilayers arrangements of amphipathic lipids when exposed to aqueous environment.

In this section, we shall discuss about five different types of membrane lipids: **Glycerophospholipids, galactolipids, sulfolipids, sphingolipids and sterols**. Except for sterols, all membrane lipids are sponifiable because of the presence of fatty acid chains.

10.2.1 Glycerophospholipids

Glycerophospholipids are also known as phosphoglycerides. These lipids constitute the most abundant class of membrane lipids throughout animal, plant and bacterial kingdom and are derivatives of phosphatidic acid. Phosphatidic acid is composed of a glycerol backbone (Fig. 10.2) with fatty acids esterified at positions 1 and 2 and phosphoric acid at position 3.

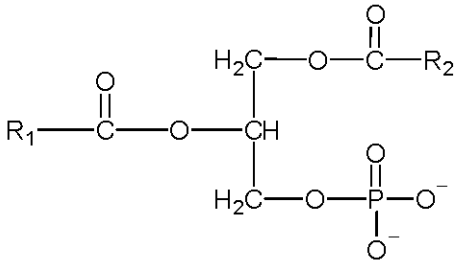


Fig. 10.2: Chemical structure of phosphatidic acid, the parent compound of glycerophospholipids. R1 and R2 are fatty acids.

Different substituents are esterified to phosphoric acid giving rise to different glycerophospholipids. These substituents are highly polar or charged groups which are attached to glycerol via phosphoric acid. As phosphoric acid makes two ester bonds; one with glycerol and second with the substituent, it is known as phosphodiester bond. Thus, we can say that **glycerophospholipids are membrane lipids in which two fatty acids are attached in ester linkage to the first and second carbons of glycerol and a highly polar or charged group is attached through a phosphodiester linkage to the third carbon** (Fig. 10.3a).

Note in Fig. 10.3b that each glycerophospholipid is an amphipathic molecule having: (i) **polar region** constituted by phosphate group with attached polar head group **(X),** and (ii) **non polar region** consisting of hydrocarbon tails of fatty acids **R1 and R2.** In most cases, R1 is a C16 or C18 saturated fatty acid and R2 is an unsaturated fatty acid with chain length of C18 or C20. These features are depicted by a cartoon showing polar head group and non polar tails (Fig. 10.3b).

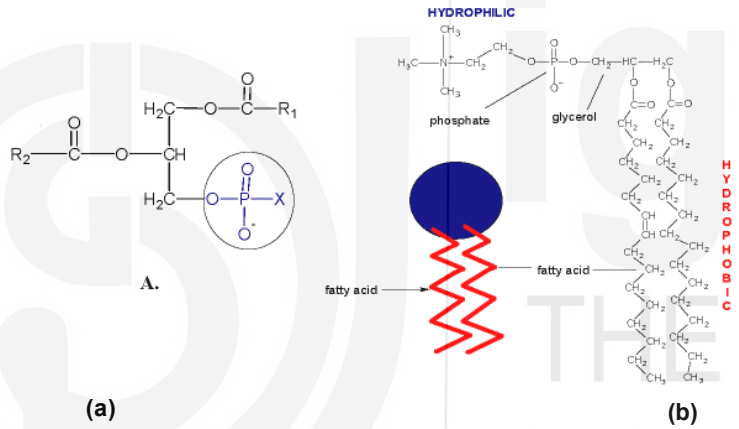
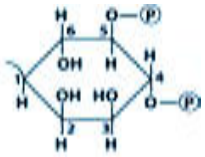
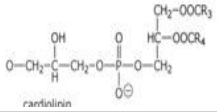


Fig. 10.3: (a) General structure of a glycerophospholipids, where R1 and R2 are hydrophobic fatty acid chains and X is the polar substituent, generally an alcohol. (b) Cartoon depicting amphipathic nature of a glycerophospholipid molecule.

These phosphoglycerides are not only important component of cell membranes but also participate in other cell functions. Table 10.1 lists some common glycerophospholipids, the polar substituents (X) that are attached to phosphatidic acid and their chemical formula and biological roles these play in the cell.

Table 10.1: Polar substituent groups present in different phosphoglycerides and their biological roles.

Name of the phospho-glyceride	Polar Substituent group (X)	Formula of the substituent group (X)	Significance
Phosphatidyl choline (Lecithin)	Choline	$HO\text{-}CH_2\text{-}CH_2\text{-}N^+(CH_3)_3$	Major component of cell membranes, source of choline, a form of vitamin B, important for brain and liver function, precursor of acetylcholine, a neurotrans-mitter, component of bile which helps in fat digestion

Phosphatidyl Ethanolamine (Cepahlin)	Ethanolamine	$HO\text{-}CH_2\text{-}CH_2\text{-}N^+H_3$	Important component of cell membranes in plants, animals as well as microbes, helps in assembly of proteins and orientation of enzymes in membranes
Phosphatidyl serine	Serine	$HO\text{-}CH_2\text{-}CH(COOH)\text{-}N^+H_3$	Important component of cell membranes; important for brain and nerve function
Phosphatidyl inositol-4,5-bisphosphate	*myo*-inositol-4,5-bisphosphate		Relatively less in cell membranes compared to other phosphoglycerides, important in signal transduction, source of arachidonic acid
Cardiolipin	Phosphatidyl glycerol		Major component of mitochondrial inner membrane

Let us look at the structure of phosphatidyl choline (Fig. 10.4) to get an idea how this group is linked to phosphoric acid in a phosphoglyceride.

Phospholipids are important for proper functioning of cell membranes as well as optimal brain health.

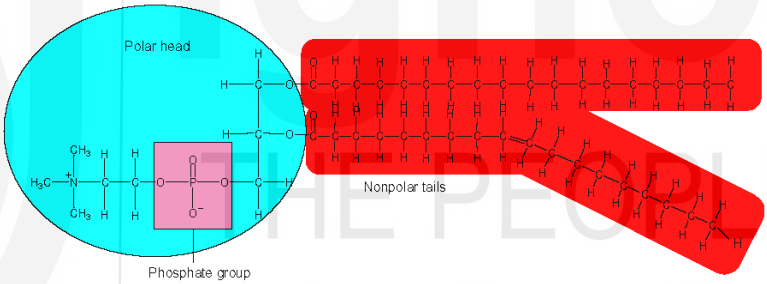


Fig. 10.4: Structure of phosphatidyl choline

Ether glycerophospholipids: Some animal tissues and unicellular organisms are rich in ether lipids. In such lipids one of the two acyl chains is linked to glycerol by ether instead of ester linkage. Ether linked chain can be saturated or unsaturated. Two important examples in this category are platelet activating factor (PAF) and plasmalogens.

Platelet activating factor (PAF), a mediator in inflammation and allergic reactions, is released from basophils and causes platelet aggregation and dilation of blood vessels. It consists of a long alkyl chain which is ether linked at C1 of glycerol. C2 of glycerol is ester linked to acetic acid. This acetic acid group makes PAF more water soluble than other lipids. C3 is linked to the polar head choline by phosphodiester bond (Fig. 10.5).

Plasmalogens contain unsaturated chain with double bond between its C1 and C2. It is ether linked to C1 of glycerol, C2 is esterified to a fatty acid and C3 is linked to a polar group (X) by phosphodiester bond. Based on the type of X, plasmalogens are referred to as phosphatidyl choline (Fig. 10.5), Phosphatidyl ethanolamine and Phosphatidyl serine. Vertebrate heart tissue is rich in ether lipids with more than 50% constituted by plasmalogens. Their function is however unknown.

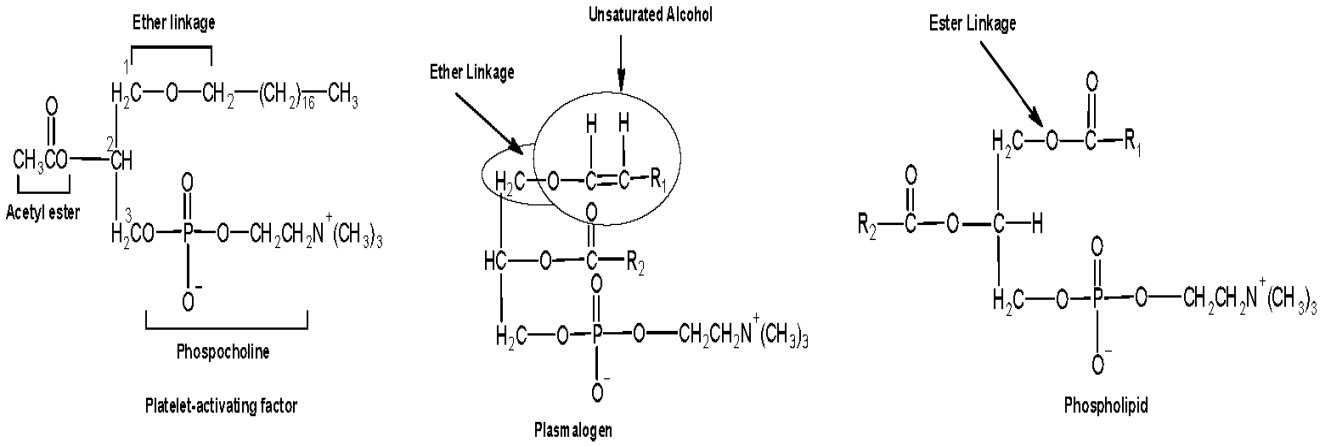


Fig. 10.5: Structures of PAF and phosphatidyl choline, a plasmalogen with reference to the phospholipid.

10.2.2 Galactolipids and Sulpholipids

Galactolipids are the membrane lipids found mainly in plant cells. They have one or two galactose residues linked to C3 of diacylglycerols by a glycosidic linkage (Fig. 10.6 a, b). They are present in thylakoid membranes of chloroplasts and make up 70-80% of the total membrane lipids in vascular plants. Thus galactolipids are probably the most abundant membrane lipids in biosphere.

Phosphate is a limiting nutrient on soil. Therefore probably during evolution, plants preferred to make phosphate free lipids and conserving it for more important roles.

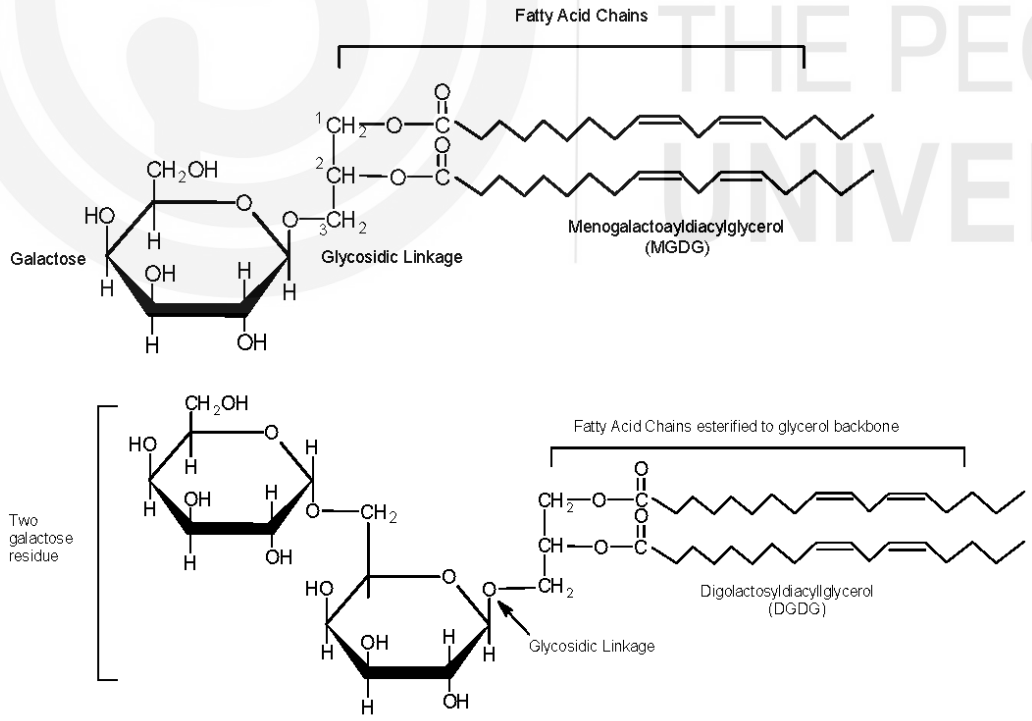


Fig. 10.6: Structures of galactolipids –(a) monogalactosyldiacylglycerol; (b) digalactosyldiacylglycerol

Sulfolipids contain a sulfonated glucose residue attached to diacylglycerol by a glycosidic linkage. The sulfonate group carries negative charge (Fig. 10.7).

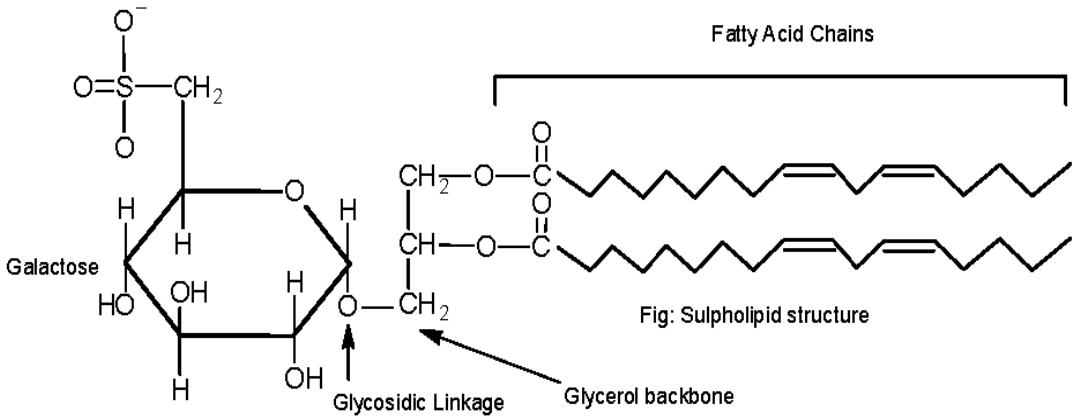


Fig: Sulpholipid structure

Fig. 10.7: Structure of sulfolipid

SAQ 1

a) Match the followings:

i)	Lecithin	a)	Ethanolamine
ii)	Galactolipids	b)	Ether lipid
iii)	Plasmalogen	c)	choline
iv)	Cardiolipin	d)	phosphatidyl glycerol
v)	Cephalin	e)	plant lipids

b) Name the structural conponents of the following:

i) Phosphatidyl choline

ii) Phosphatidyl serine

iii) Phosphatidyl ethanolamine

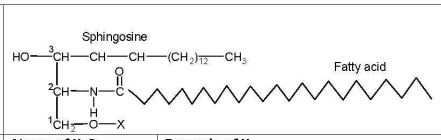
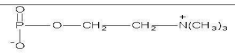
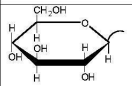
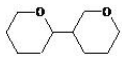
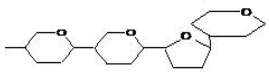
10.2.3 Sphingolipids

The structure of sphingosine includes a long hydrophobic tail so it requires addition of only one fatty acid chain to make it suitable as membrane lipid.

Sphingolipids are also important constituent of some biological membranes. Like glycerophospholipids, they also have a polar head and non polar tails. However, they differ from glycerophospholipids and galactolipids as they do not have glycerol. Instead, they contain a long chain amino alcohol, sphingosine. Sphingosine is part of ceramide, which is the parent molecule of sphingolipids. We mentioned about ceramides in the last unit in section 9.3.3.

Different derivatives of ceramide are formed by reaction with hydroxyl group present at C1resulting in three subclasses: **sphingomyelins, glycosphingolipids and gangliosides**. Table 10.2 shows the general structure of a sphingolipid and different chemical groups present in different sub classes of sphingolipids.

Table 10.2: The general structure of a sphingolipid and different chemical groups.

Sphingolipid (general structure)		
Name of Sphingolipid	**Name of X-O**	**Formula of X**
Ceramide	——	H
Spingomyelin	Phosphocholine	
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di - tri - or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	

Sphingomyelin: Sphingomyelins contain a phosphocholine or phosphoethanolamine group esterified to C1 group of ceramide. They are important component of nervous tissue in higher animals and are predominantly found in the myelin sheath of neurons. They are clinically important molecules as their deposition in brain leads to *Niemann Pick disease* which results in brain damage and early death.

Glycosphingolipids: They consist of one or more sugar residues attached by glycosidic linkage at C1 of ceramide. These are of two types- cerebrosides and globosides.

Cerebrosides contain a single glucose or galactose residue attached to ceramide. Galactosyl cerebrosides are generally found in neural membranes while glucosyl cerebrosides are present in membranes of non neural tissues. Globosides contain two or more sugar residues; which usually include D-glucose, D- galactose or N- acetyl- D- galactosamine. Cerebrosides and globosides are sometimes known as neutral glycolipids as they are uncharged at pH 7.

Glycosphingolipids are largely found at the outer surface of plasma membrane where they act as recognition sites. Carbohydrates of certain glycosphingolipids define blood groups and therefore determine the type of blood that individuals can receive in blood transfusions.

Gangliosides: They are the most complex sphingolipids that contain an oligosaccharide and one or more residues of N- acetyl neuraminic acid, a sialic acid (refer to section 5.4.3 of Unit 5 in block 2). Presence of sialic acid gives gangliosides negative charge at pH 7 that distinguishes them from neutral glycolipids.

Based on the number of sialic acid residues, gangliosides are assigned different series. Gangliosides with one, two, three and four sialic acid residues belong to GM (M- mono), GD (D- di), GT (T-tri) and GQ (Q-quadra) series, respectively. They are concentrated on the cell surface where they act as point of recognition for neighboring cells or extracellular molecules. However,

specific functions of many sphingolipids are not known and they are the topic of current research by many researchers. Fig. 10.8 shows different members of GM series.

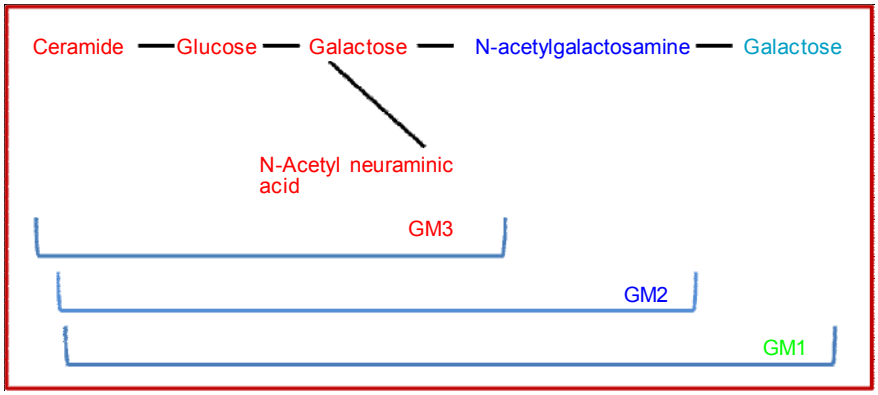


Fig. 10. 8 : Structures of members of GM gangliosides: G_{M1}, G_{M2} and G_{M3} where G denotes ganglioside, M is a single sialic acid; and the subscript 3 is a number assigned on the basis of chromatographic migration. The simplest of these is G_{M3}, which contains ceramide, one molecule each of glucose, galactose, and NANA. G_{M1}, the more complex ganglioside derived from G_{M3}, is of considerable biologic interest, as it is known to be the receptor in human intestine for cholera toxin.

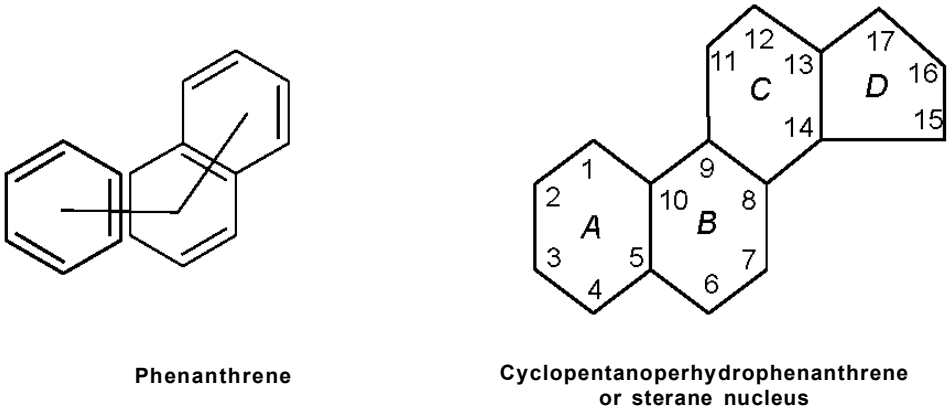
SAQ 2

Name three classes of sphingolipids and their polar head groups.

10.2.4 Sterols

These are the cyclic lipids which lack fatty acid chain and therefore, are *nonsaponifiable*, *i.e.*, cannot be hydrolyzed by heating with alkali to yield soaps. (Recall section 9.4.1). They are derived from **four** fused and fully saturated rings called **cyclopentanoperhydrophenanthrene** or **sterane**. This system consists of 3 cyclohexane rings (A, B and C) fused in nonlinear or phenanthrene manner and a terminal cyclopentane ring (D). The sterane nucleus along with the conventional numbering of the carbon atoms is shown in the Fig. 10.9. Molecules containing sterane ring are known as steroids.

Cholesterol literally means 'solid alcohol from bile'; *chole*-bile and *stereos*-solid. It was first isolated in 1784 from human gallstones which consist almost entirely of cholesterol and hence its name.



Phenanthrene

Cyclopentanoperhydrophenanthrene or sterane nucleus

Fig. 10.9: Parent compounds of steroids- A: Phenanthrene B: Sterane

Steroids containing hydroxyl groups (hydroxy steroids) are often referred to as **sterols**. One of the commonly known sterol is cholesterol, which is an important constituent of many biological membranes.

Cholesterol is a 27 carbon compound derived from sterane with molecular formula $C_{27}H_{45}OH$. You may be quite familiar with this name as high levels of cholesterol in blood are widely associated with the cardiovascular disease. The hydroxyl group of cholesterol constitutes its polar head; the rest of the molecule is hydrophobic making it weakly amphipathic. Structure of cholesterol is shown in Fig. 10.10.

The structure of cholesterol was determined by the German chemist, Adolph Windaus who received Nobel Prize in Chemistry in 1928. Since its discovery it has occupied a central stage in the area of biology. As many as thirteen Nobel Prizes have been awarded to the scientists who devoted most of their career working on cholesterol.

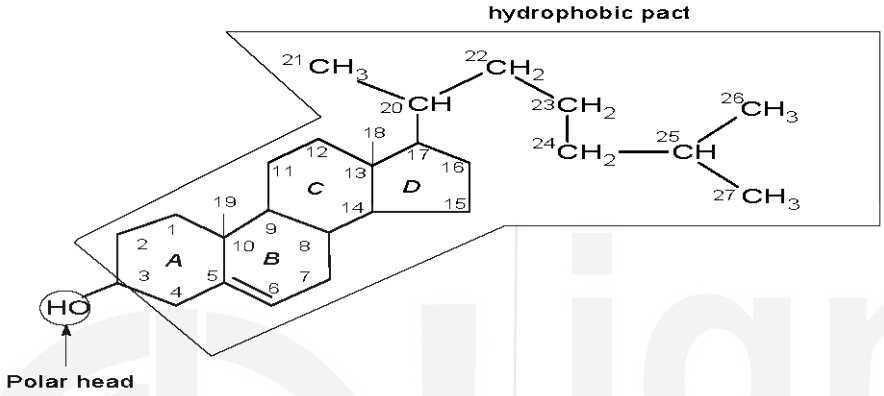


Fig. 10.10: Structure of cholesterol (mark polar and non polar parts)

It is quite evident from the Fig. 10.10 that cholesterol is a bulky rigid structure as compared to other hydrophobic membrane lipids. Therefore, it tends to disrupt the regular packing of fatty acid tails in the membrane structure. This property of cholesterol has quite an impact on the membrane fluidity as cholesterol constitutes 25% or more of the total lipid content in some of the membranes.

It is primarily an animal fat as it is absent in plants. It is not only an important component of some cell membranes and plasma lipoproteins but also the precursor of many other biologically important steroids, such as bile acids and various steroid hormones. It is the major sterol of higher animals and is especially abundant in nerve tissues and gallstones. It occurs either free or as fatty esters in all animal cells. Similar sterols exist in other eukaryotes, for example; stigmasterol in plants and ergosterol in fungi. We shall discuss about some of these sterols in the next unit.

SAQ 3

State whether the following statements about cholesterol are true or false?

i) Cholesterol is a sponifiable lipid.

ii) Cholesterol lack fatty acid chains.

iii) Cholesterol is also present in plants.

iv) Parent compound of cholesterol is sterane.

v) Cholesterol has no effect on membrane fluidity as it has a rigid structure.

So far we discussed the structures and roles of different types of membrane lipids. We observed that they all share a common feature; amphipathic nature. Due to this feature, when they come in contact with aqueous environment, they arrange themselves to form variety of structures. Moreover, their distribution also varies depending on the localization and function of the membrane. In the next section, you will learn about these aspects.

10.3 COMPOSITION AND ROLE OF BIOLOGICAL MEMBRANES

Amphipathic membrane lipids form various types of aggregated structures in contact with aqueous environment. All these structures expose hydrophilic polar head towards aqueous medium and maximize the contact among hydrophobic lipid chains, for example, soaps. Lets us look at these arrangements.

10.3.1 Ordered Structures of Lipids in Water

Membrane lipids arrange themselves into monolayers, micelles, liposomes or bilayers when exposed to an aqueous environment. Fig. 10.11 shows these arrangements.

Monolayers are formed when few lipid molecules are added to aqueous solution. This single layer formed at water- air interface exposes polar head towards water and hydrophobic tails towards air.

Micelles are spherical structures that contain anywhere from a few dozen to a few thousand amphipathic molecules. These molecules are arranged with their hydrophobic tails aggregated in the interior, where water is excluded, and their hydrophilic/polar head groups are at the surface, in contact with water (Fig. 10.11a). Amphipathic molecules form micelles at or above a specific concentration. This concentration is known as **critical micelle concentration** (CMC). Below CMC, these molecules exist as individual molecules.

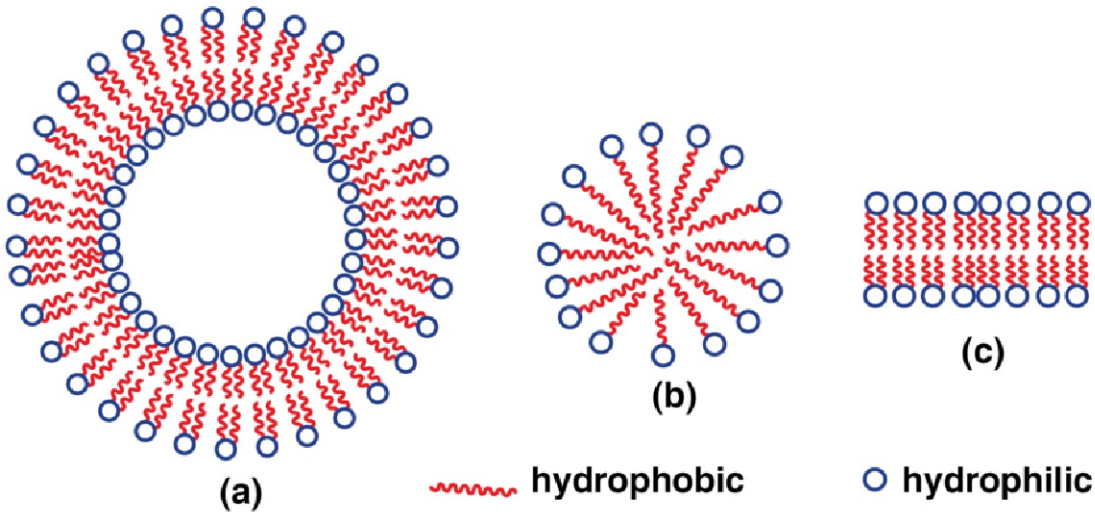


Fig. 10.11: Aggregation of lipids as a. Micelles, b. Bilayer c. Liposome

Bilayer is another type of lipid aggregate in water in which two lipid monolayers are arranged back to back to form a two-dimensional sheet. The hydrophobic portions in each monolayer interact with each other (Fig. 10.11b). The hydrophilic head groups interact with water at each surface of the bilayer. Because the hydrophobic regions at its edges are transiently in contact with water, the bilayer sheet is relatively unstable and spontaneously forms a third type of aggregate: it folds back on itself to form a hollow sphere, a vesicle or liposome.

It is likely that the precursors to the first living cells resembled liposomes, their aqueous contents segregated from the rest of the world by a hydrophobic shell.

Liposomes are the closed self sealing solvent filled vesicles bound by a single bilayer (Fig. 10.11c). By forming liposomes, bilayers lose their hydrophobic edge regions, achieving maximal stability in the aqueous environment. These bilayer vesicles enclose water, creating a separate aqueous compartment. Liposomes have been widely used as models to study properties and functions of biological membranes. They are also used a vehicle for drug delivery since they are absorbed by many cells through fusion with the plasma membrane.

Liposomes can be prepared artificially by using a suspension of phospholipids and different solvents on the inner side

10.3.2 Biological Membranes

Biological membranes exist as lipid bilayers and play active role in the life of a cell. Their basic functions include:

1) Separation: Membranes provide a closed compartment around the cells as well as within the cell. This permits separation of one cell from the other so that they can maintain their individuality. Compartmentalization within the cell helps to shape many of the morphologically distinguishable organelles, such as mitochondria, endoplasmic reticulum, golgi complexes, secretory granules, lysosomes and the nucleus.

2) Exchange: Membranes are characterized by providing cells with selective permeability which means they allow entry and exit of specific substances across them. This helps in maintaining differences in composition between the inside and outside of the cell. They enable the transport and translocation of cellular metabolites and macromolecules.

3) Metabolism: Cell membranes are integral part of metabolic pathway organization. They contain many enzymes involved in energy harvesting pathways such as photosynthesis and respiration.

4) Communication: Cell membranes also mediate cell to cell communication, recognition and interaction between cells and propagation of electrical and chemical signals

Many different models have been proposed to explain the structure and functions of the membranes. The most widely accepted model is by S.J. Singer and G.L. Nicolson in 1972which is known as **Fluid mosaic model of biological membranes**. The model emphasizes two basic characteristics of all cell membranes: mosaic sheet of lipids and proteins and their dynamic fluid properties. This models can very well explain most of the structural and functional features of biological membranes. Let us discuss some of the characteristic features of this model:

1) Biological membranes are formed of a bilayer of lipids constituted mainly by phospholipids. The lipid bilayer is organized in such a way that the hydrophilic part of phospholipids is on the exterior of the lipid bilayer in contact with the water, while their hydrophobic tails face inward.

2) Importance of transverse asymmetry can be understood from the example that appearance of phosphatidyl serine in the outer monolayer of plasma membrane triggers cell death and is seen in aging erythrocytes so that they are removed from the blood circulation.

   Proteins embedded in this bilayer are of two types: integral and peripheral. An **integral membrane protein** (IMP) or **intrinsic protein** is a protein molecule or assembly of proteins permanently attached to the biological membrane. **Peripheral membrane proteins or extrinsic proteins** adhere only temporarily to the biological membrane. These molecules attach to integral membrane proteins or penetrate the peripheral regions of the lipid bilayer (Fig. 10.12).

3) Integral membrane proteins span the membrane; they are involved in forming pores that transport many molecules, such as ions and polar molecules, across the membrane.

4) Peripheral proteins perform diverse function as enzymes, membrane-targeting domains, structural domains, carriers of hydrophobic molecules.

5) Many integral membrane proteins and some lipids are attached to oligosaccharides; these are known as glycoproteins and glycolipids respectively. These oligosaccharides are important for cell recognition; these allow cells to recognize other cells and interact with each other.

6) Lipids and some proteins in the lipid bilayer are not stationary. They frequently move laterally (side-to-side, about 10^7 times per second) and transversely (flip-flopping, only about once per month). This fluid bilayer of membrane lipids containing milieu of proteins and carbohydrates constitutes the “fluid mosaic model”.

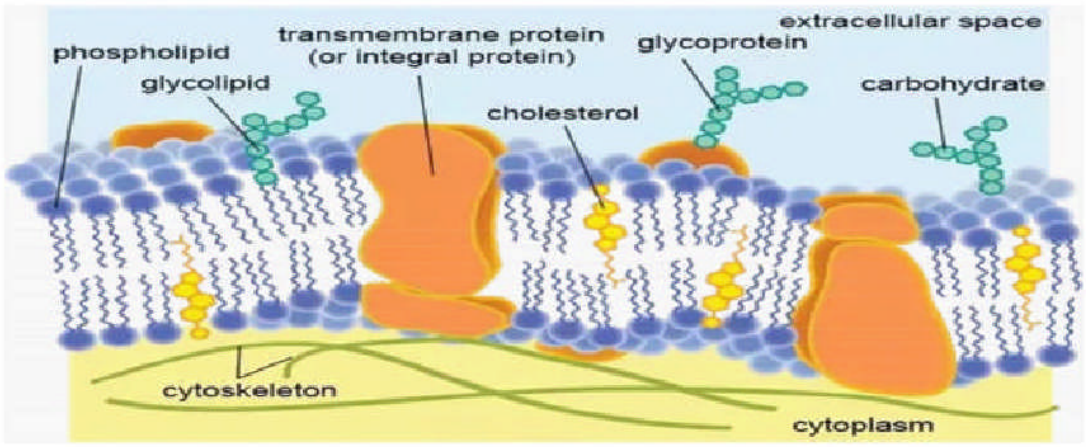


Fig. 10.12: Structure of a typical membrane.

Role of biological membranes depend on their composition. Type and distribution of different types of lipids influences their properties which are more suited to perform specific functions. Therefore, it is important to study their composition.

Composition of biological membranes: An important feature of biological membranes is their modular structure. Proteins and lipids in membranes interact through non covalent bonding, therefore, can be inserted, extracted and rearranged independently and in unlimited variations. They can fine tune their composition and redistribution of their components. It allows rapid adjustment in the structure and composition in response to changing demands of the cell or influences of the environment.

Membranes vary in their composition; some of these may have as much as 75- 80% of proteins and only 20-25% of lipids while others may contain 80-85% lipids and 15-20% proteins (Table 10.3). This variation in structural composition is reflected in their functions. Generally the membranes which carry out enzyme catalyzed reactions and transport activities such as mitochondrial and chloroplast membranes are rich in proteins. The membranes which carry out less protein based activities are rich in lipids such as myelin sheath in neurons.

Membranes have an interesting feature: self renewal. Just as cells come from cells, cell membranes also come only from the cell membranes. They stay intact throughout the life of a cell.

Biological membranes are **asymmetric** as the monolayers of a lipid bilayer do not have same composition. This variation in lipid and protein composition in the two monolayers of a bilayer membrane is termed as **transverse asymmetry**. For example, phosphatidyl choline comprises 29% of the total phospholipid in erythrocyte membrane. Of this amount, 76% is found in the outer monolayer and only 24% is present in the inner monolayer. Transverse asymmetry gives sidedness or direction to the membrane structure and is important for its functions that occur in a particular direction such as transport of different ions and molecules across membrane, action of hormones at the surface and recognition of a cell by signals present at the surface. Fig. 10.13 shows distribution of membrane lipids in a typical erythrocyte membrane.

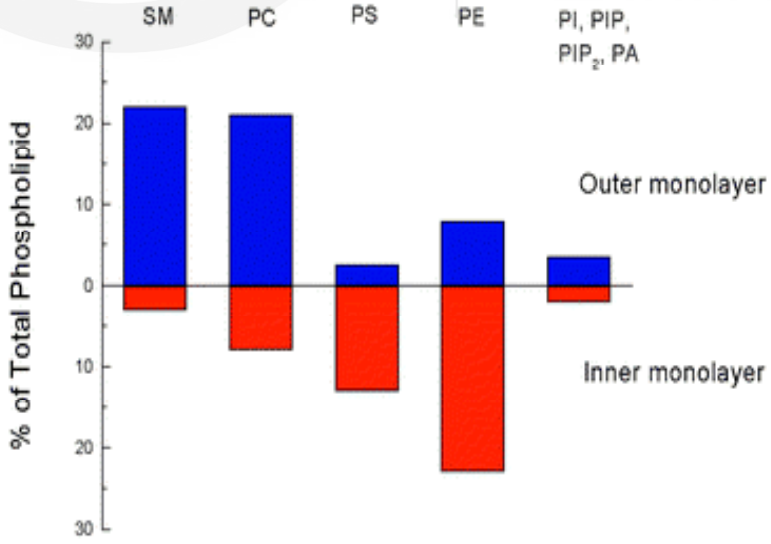


Fig. 10.13: Distribution of membrance lipids in a typical erythrocyte membrane

10.4 SUMMARY

1) Five different types of membrane lipids: Glycerophospholipids, galactolipids, sulfolipids, sphingolipids and sterols.

2) Glycerophospholipids are the compound lipids which constitute the most abundant component of cell membrane and are derivatives of phosphatidic acid. They are made up of glycerol, phosphoric acid and fatty acids. They are amphipathic molecules and are named after the type of polar group these are attached to: phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol and cardiolipin.

3) Phospholipids are important for proper functioning of cell membranes as well as optimal brain health.

4) Some animal tissues and unicellular organisms are rich in ether glycerophospholipids. In such lipids one of the two acyl chains is linked to glycerol by ether instead of ester linkage. Platelet activating factor (PAF) and plasmalogens belong to this group.

5) Galactolipids and sulfolipids are the membrane lipids found mainly in plant cells. These are phosphate free lipids and contain galactose or sulfonated glucose, respectively which attach t diacylglycerol chain through glycosidic bonds.

6) Sphingolipids are also important constituent of some biological membranes and are derived from ceramide. They do not have glycerol, instead, they contain a long chain amino alcohol, sphingosine which is part of ceramide.

7) Different derivatives of ceramide result in three subclasses: **sphingomyelins, glycosphingolipids and gangliosides**.

8) Sphingomyelins contain a phosphocholine or phosphoethanolamine group esterified to ceramide. They are important component of nervous tissue in higher animals and are predominantly found in the myelin sheath of neurons. Their deposition in brain leads to *Niemann Pick disease* which results in brain damage and early death.

9) Glycosphingolipids consist of one or more sugar residues attached by glycosidic linkage to ceramide. These are of two types- cerebrosides and globosides.

10) Gangliosides are the most complex sphingolipids that contain an oligosaccharide and one or more residues of N-acetyl neuraminic acid, a sialic acid.

11) Steroids are the cyclic lipids which lack fatty acid chain and therefore, are nonsaponifiable. They are derived from fused and fully saturated ring system called cyclopentanoperhydrophenanthrene or sterane. Steroids containing hydroxyl groups are often referred to as sterols. One of the commonly known sterol is cholesterol. It is a 27 carbon compound derived from sterane with molecular formula $C_{27}H_{45}OH$.

12) Membrane lipids are amphipathic molecules. Except for cholesterol, all have a polar head group and two hydrophobic chains which prefer to aggregate as bilayers when exposed to the aqueous environment.

13) Bilogical membranes have been found to have a bilayers structure in which two lipid monolayers are arranged back to back to form a two-dimensional sheet. The hydrophobic portions in each monolayer interact with each other. The lipid bilayers has proteins associated with it.

14) Cholesterol is a bulky rigid structure tends to disrupt the regular packing of fatty acid tails in the membrane structure. This property of cholesterol has quite an impact on the membrane fluidity.

15) A bilayer model for biomembranes called Fluid mosaic model was put forward by S.J. Singer and G.L. Nicolson (1972) and is so far the most widely accepted model as it can very well explain most of the structural and functional features of biomembranes.

10.5 TERMINAL QUESTIONS

1) What are phospholipds? Explain structural components of phospholipids and their derivatives.

2) Draw structure of cholesterol and discuss its biological significance.

3) Draw a neat diagram of Fluid Mosaic Model of a biological membrane and explain its important features.

10.6 ANSWERS

Self-Assessment Questions

1) a) (i) (c); (ii) (e); (iii) (b); (iv) (d); (v) (a)

   b) Structural components of:

      i) Phosphatidylcholine-Glycerol, two fatty acid chains, phosphoric acid and choline

      ii) Phosphatidylserine-Glycerol, two fatty acid chains, phosphoric acid and serine

      iii) Phosphatidylethanolamine-Glycerol, two fatty acid chains, phosphoric acid and ethanolamine.

2) Sphingomyelins- phosphocholine or phosphoethanolamine

   Glycosphingolipids- one or more monosaccharides such as glucose, galactose, N-acetyl glucosamine and

   Gangliosides-complex oligosaccharides and N-acetyl neuraminic acid

3) (i) False; (ii) True; (iii) False; (iv) True; (v) False.

Terminal Questions

1) Glycerophospholipids are membrane lipids in which two fatty acids are attached in ester linkage to the first and second carbons of glycerol and a highly polar or charged group is attached through a phosphodiester linkage to the third carbon. Please refer to section 10.2.1 for the detailed information their derivatives.

2) Cholesterol is a 27 carbon compound derived from sterane with molecular formula $C_{27}H_{45}OH$. It is primarily an animal fat as it is absent in plants. It is not only an important component of some cell membranes and plasma lipoproteins but also the precursor of many other biologically important steroids, such as bile acids and various steroid hormones. It is the major sterol of higher animals and is especially abundant in nerve tissues and gallstones.

3) Please refer to the section 10.12.

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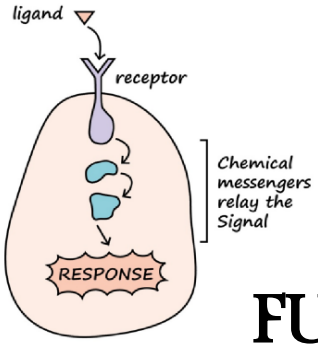


UNIT 11

SPECIALIZED FUNCTIONS OF LIPIDS

Structure

11.1 INTRODUCTION

In the previous units we discussed about lipids which play role in storage of energy and cell membrane composition. These two functional classes of lipids constitute major cellular components; membrane lipids make upabout 5-10% of the dry mass of most cells and storage lipids more than 80% of the adipocytes, the cells which store fat. In addition to these two classes, there are lipids which are present in much smaller amounts and play active role in the cell. Theseinclude lipids acting as chemical messengers or signals mediating communication of a cell with other cells or environment, cofactors for enzymes or pigments that contribute in metabolic pathways. Any aberration or disruption metabolism of these lipids disrupts the cell communication or physiological pathways resulting in many diseases. That's why these lipids are tightly regulated. In this unit we shall describe some of the representatives of these biological active lipids.

Objectives

After going through this unit, you should be able to:

- define the terms; signal transduction, primary and secondary messenger;
- explain different types of signaling;
- discuss about lipids which act as signaling molecules;
- explain role of different lipid derivatives which act as pigments cofactors; and
- mention about plant steroids and their importance.

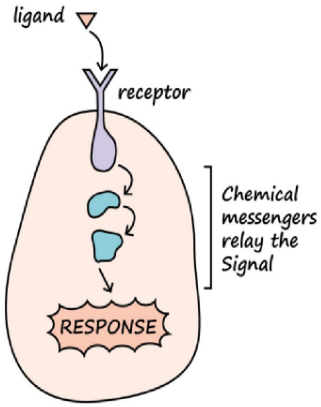


Fig. 11.1: Process of signal transduction

11.2 LIPIDS AS SIGNALING MOLECULES

Role of lipids is not limited to being a passive component of membranes, or source of stored energy. They are also involved in the dynamic process of signal transduction at cell membrane. Signal transduction is the process by which the internal components of the cells respond to an external signal, allowing cells to respond to their local environment. It is important to understand that signaling may take place between cells of different organisms or those in the same organism. Unicellular organisms such as bacteria, for example, release signal molecules in environment to sense bacterial population in environment and modulate their behavior. However, in multicellular organisms (such as humans), cell-cell signaling allows cells to coordinate their activities, ensuring proper functioning at tissues, organs as well as at the system level.

Cell signals are, in most cases,chemical in nature and referred to as “primary messenger”. Hormones, neurotransmittersand growth factors are some examples of primary messengers. The primary messenger binds to the specific proteins called receptors present on the cell membrane. These receptors are generally transmembrane in nature and interact with internal cell components. When bound to a signal, these receptors are activated and trigger synthesis of intracellular signal molecules called second messengers. Second messengers initiate series of biochemical reactions known as signal transduction cascades which amplify the message (Fig. 11.1).

Not all receptors are present on the cell surface; some are also present in cytosol or nucleus. These intracellular receptors bind to signal molecules that can cross the cell membrane barrier.

SAQ 1

Match the following:

i)	Signal transduction	a)	Specific binding to primary messenger
ii)	Primary messenger	b)	Hormones
iii)	Secondary messenger	c)	Cell response to external signal
iv)	Receptor	d)	Amplification of signal

Based on the distancebetween the cells releasing signal molecule and the one on which the signal acts, signaling is divided into three types:

1) **Endocrine** - When signaling molecules produced act on cells located far from their location of origin; it is known as endocrine signaling (Fig. 11.2). Most of the hormones act by endocrine signaling. These are secreted by specialized endocrine cells,carried through the circulation to act on target cells located far away in the body.For example, hormone insulin is released by pancreas and regulates the uptake of glucose in cells all over the body.

2) **Paracrine** - When signaling molecule released by a cell acts on neighboring target cells, it is known as paracrine signaling, for example, neurotransmitters (Fig. 11.2). These are the chemical signal molecules released by a sensory neuron which affects the neighbouring receptor neuron.

3) **Autocrine** - In this type of signaling, cells respond to the signaling molecules that they themselves produce (Fig. 11.2). An example for this type of signaling is seen during immune response when T-helper cells are activated in response to an antigen and secrete a cytokine which binds to the cell surface receptors present on the same cells resulting in their proliferation.

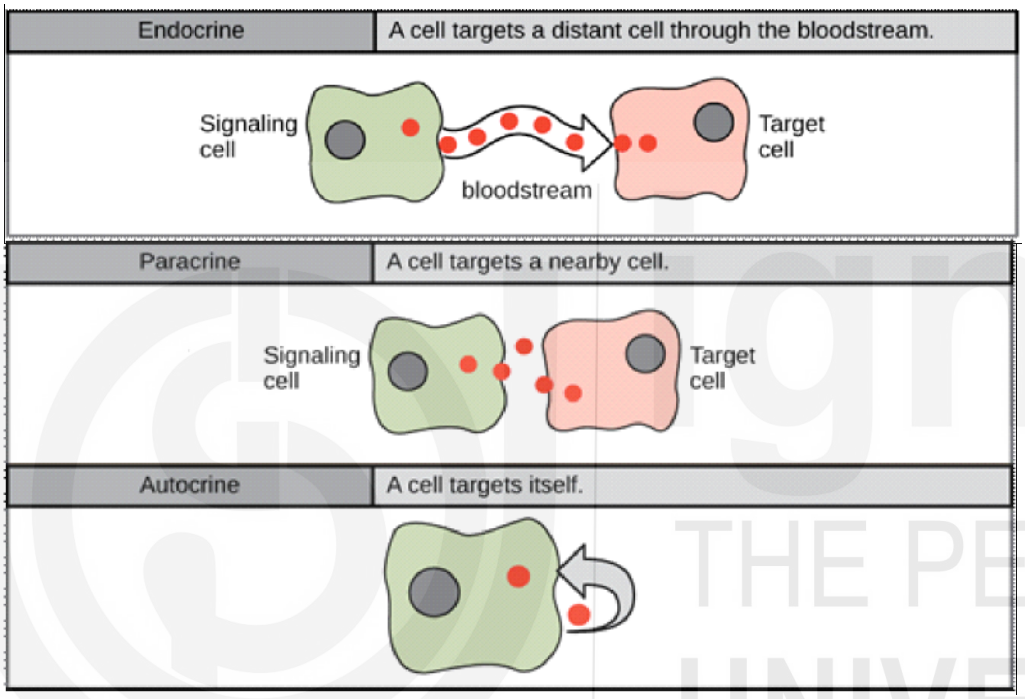


Fig. 11.2 : Types of cell signaling

Abnormal autocrine signaling is shown to be associated with unregulated growth of cancer cells. Cancer cell produces a growth factor to which it also responds, thereby leading to its own unregulated division.

A variety of signaling molecules are derived from phospholipids, sphingolipids and sterols and involved in signaling through these three modes.

Phospholipases, the enzymes that catalyze splitting of phospholipids play an important role in formation of signal molecules from phospholipids. Four different types of phospholipases hydrolyze the ester bond of phospholipids. yielding different products. Fig. 11.3 shows the site of action of different phospholipases.

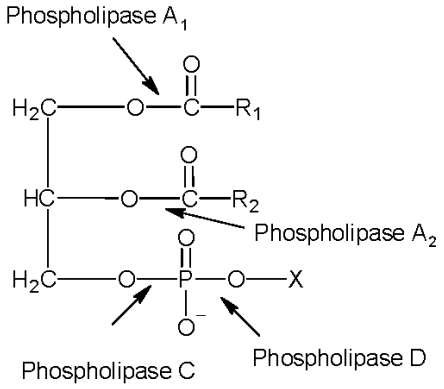


Fig. 11.3: Site of action of different phospholipases

Non steroidal inflammatory drugs (NSAIDS) like aspirin and ibuprofen inhibit synthesis of prostaglandins and thromboxanes from arachidonic acid.

11.2.1 Intracellular Signals

Phosphatidylinositol (PI)and its phosphorylated derivatives serve as reservoir of many intracellular signal molecules which are released in response to the interaction between an external signal and its cell surface receptor. Fig. 11.4 demonstrates the formation of intracellular signal molecules IP3 (inositol triphosphate) and DAG (diacylglycerol) fromphosphatidyl inositol 4,5-bisphosphate (PIBP) by action of enzyme phospholipase C . IP3 is soluble and releases Ca^{2+}. DAG which stays membrane bound and along with Ca^{2+} regulates different cellular processes mediated phosphorylation reactions by enzyme protein kinase C and (Fig. 11.4).

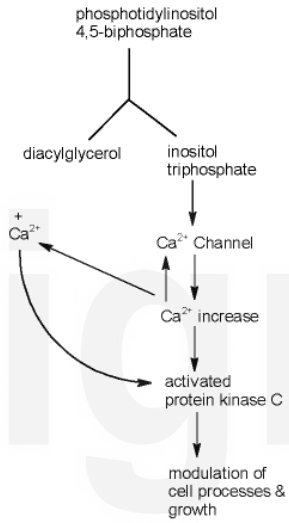


Fig. 11.4: Formation of IP3 and DAG from PIP2 by action of PLC. Both act as intracellular signaling molecules.

Similarly,ceramide and sphingomyelin which are derivatives of membranesphingolipidsalso act as intracellular signaling molecules. These also activate protein kinases andregulate processes like cell division, differentiation, migration and programmed cell death.

11.2.2 Paracrine

Eicosanoids are the signaling molecules in animals that carry the signal to nearby cells within a tissue, therefore, act as paracrine signals. These are derived from arachidonic acid (C20:4Δ5,8,11,14; n-6), a twenty carbon unsaturated fatty acid, formed from degradation of phospholipids by action of phospholipase A_2.

Methyl ester of jasmonate is responsible for the characteristic fragrance to jasmine oil and is used in perfume industry.

There are three classes of eicosanoids: prostaglandins, thromboxanes and leukotrienes (Fig. 11. 5). These are mainly involved in inflammatory responses in different tissues.

Prostaglandins: Prostaglandins get their name from prostate gland, the tissue from which they were first isolated. These are involved in contraction of smooth muscles of uterus during menstruation and labor pain, regulation of blood flow to specific organs, wake sleep cycle and response of certain tissues to epinephrine and glucagon hormones.These also mediate increase in body temperature (fever), pain and inflammation.

Thromboxanes: These are produced by platelets (thrombocytes) and regulate formation of blood clot by reducing the flow of blood to the site of clot formation.

Leukotrienes: Found in leukocytes, leukotrienes are the signals for contraction of smooth musclesin lungs. Their overproduction causes asthmatic attack,that's why pathways of leukotrienes synthesis are one of the targets for development of antiasthamatic drugs.

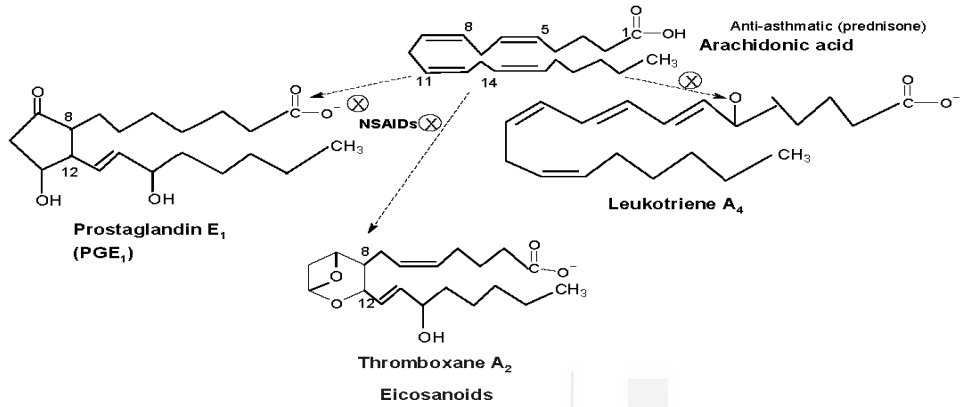


Fig. 11.5: Structures of different types of eicosanoids.

11.2.3 Endocrine Hormones

Steroid hormones represent endocrine mode of signaling carrying the information between tissues. They are derived from cholesterol by side chain removal, demethylation and oxygenation reactions. They resemble cholestero in having the four-ring steroid nucleus and differ in being more polar than cholesterol. These are carried in blood from the site of synthesis to the target tissue, where they diffuse through plasma membrane and bind their intracellular receptor on nucleus to affect growth and development (Fig. 11. 6).

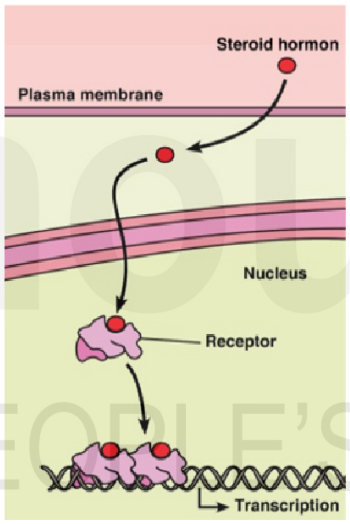


Fig. 11.6: Intracellular signaling by steroid hormones

Sex hormones and corticosteroids come in this category. Testosterone, estrogen, progesterone are the sex hormones produced by the gonads. The corticosteroids are produced by the adrenal gland and include the **glucocorticoids** and the **mineralocorticoids.** Glucocorticoids regulate glucose levels in blood plasma independently of food intake. Mineralocorticoids act on the kidney to regulate salt and water balance (Fig. 11.7).

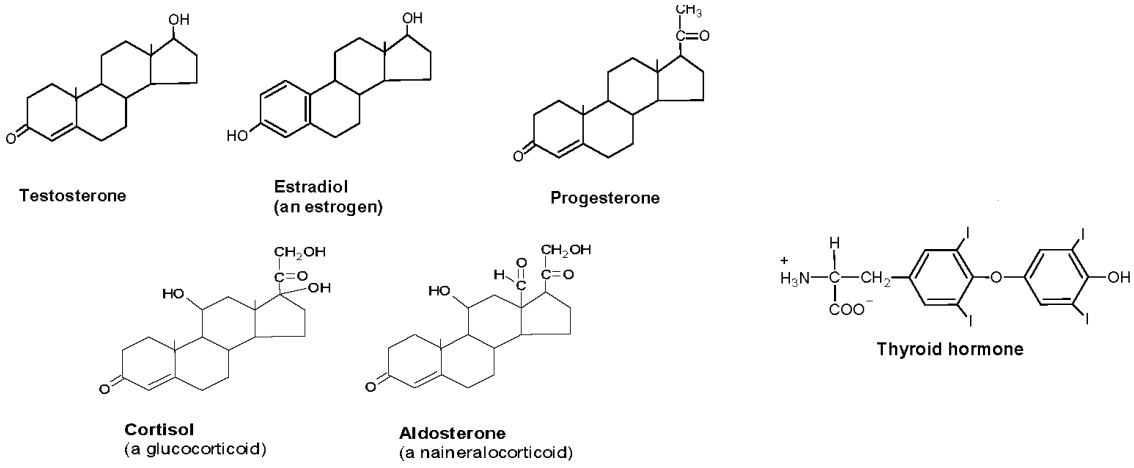


Fig. 11.7: Structures of steroid hormones

In addition to steroid hormones, cholesterol is also the precursor of vitamin D, which plays an essential role in the control of calcium and phosphorus

metabolism. Vitamin D_3 (cholecalciferol) is formed from 7-dehydrocholesterol (provitamin D_3) in the presence of ultraviolet light of sunlight. Vitamin D_3 is converted into calcitriol (1,25-dihydroxy cholecalciferol), the active hormone in the liver and kidneys. Although not a steroid, vitamin D acts in similar fashion. It binds to a receptor which is structurally similar to the steroid receptors and regulates uptake of calcium in intestine and calcium levels in kidney and bone.

Retinoic acid, a derivative of vitamin A (retinol) is a hormone which binds to its receptor in nucleus and regulates gene expression for development of epithelial cells such as skin.

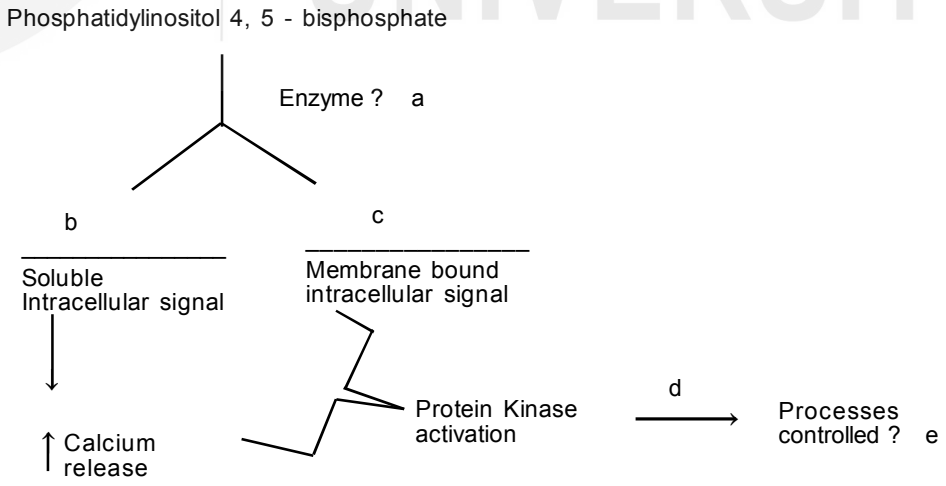
Another derivative of retinol is retinal which is a visual pigment and initiates response of rod and cone cells to light producing a neuronal signal to the brain.

11.2.4 Plant Signaling Molecules

Plants also produce many signaling molecules which are volatile in nature and help to attract pollinators, repel herbivores or communicate with other plants. For example, jasmonates, the volatile signaling molecules in plants are derived from α-linolenic acid (C18:2). These play role in plant development such as seed germination, growth of root, flowering tuber as well as triggering of immune responses to wound and pathogen invasion. Other plant signaling molecules with characteristic fragrance are limolene in limes and â - pinene in pine trees.

SAQ 2

A) Complete the given signaling cascade:



B) Active hormone form of vitamin D is..... which is formed in liver and ..... from its precursor ..... .

C) Steroid hormones are more polar than cholesterol. (True/ False)

D) Match the following:

i)	Retinal	a)	Plant development
ii)	Retinoic acid	b)	Glucose levels
iii)	Calcitriol	c)	Salt and water balance
iv)	Glucocorticoids	d)	Visual pigment
v)	Mineralocorticoids	e)	Calcium levels
vi)	Jasmonates	f)	development of epithelial cells

11.3 LIPIDS AS COFACTORS AND PIGMENTS

A group of lipids known as isoprenoids contain two or more isoprene units (Fig. 11. 8).These are hydrophobic in nature, therefore, cantraverse the lipid membrane and act as donor or acceptor of electrons in oxidation- reduction (redox) reactions.

Isoprene $CH_2 = \underset{\displaystyle CH_3}{\overset{|}{C}} - CH = CH_2$

Fig. 11.8: Structure of isoprene

Isoprene is a five carbon unsaturated hydrocarbon unit. Isoprenoids are also known as terpenoids or prenol lipids

Isoprenoids include organic compounds with functions ranging from fragrance to precursors of vitamins and sex hormones. In this section we shall learn about fat soluble vitamins (A, D, E, K) and lipids quinones which form pigments and play role as cofactors in metabolic reactions.

1) Vitamin A (retinol) is a visual pigment which helps to see in low light. That's why deficiency of vitamin A leads to night blindness. You can get vitamin A from food sources such as carrots, eggs, fish oil, whole milk and butter. Carrots contain α-carotene, a pigment which is converted to vitamin A.

2) Vitamin E,also known as, tocopherols include group of lipids that contain a substituted aromatic ring with a long isoprenoid side chain (Fig. 11.9). Tocopherols due to their hydrophobic nature associate with cell membranes, lipid deposits and lipoproteins in blood. They are biological antioxidants; destroy most reactive species of oxygen or other free radicals. This prevents oxidation of polyunsaturated lipids and damage to cell membranes and cell integrity. Eggs, vegetable oils and wheat germ are rich sources of vitamin E.

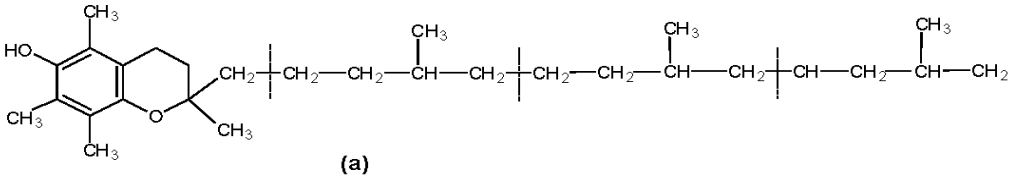
3) Vitamin K undergoes a cycle of oxidation and reduction during formation of active prothrombin, a protein which converts soluble blood protein to insoluble fibrous protein that helps in clot formation.

4) Ubiquinone (Coenzyme Q) and plastoquinone are the isoprenoids which act as cofactor in redox reactions involved in ATP synthesis in mitochondria and chloroplast, respectively. ATP is the energy currency of the cell.

5) Assembly of bacterial cell wallsand formation of eukayoticglycoproteins and glycolipids require sugars in activated state. The activation is done by

attaching these sugars to isoprenoid alcohols known as dolichols. Dolichols interact strongly with hydrophobic membrane lipids and transfer attached activated sugars. Structures of these biologically active isoprenoids are shown in the Fig. 11.9.

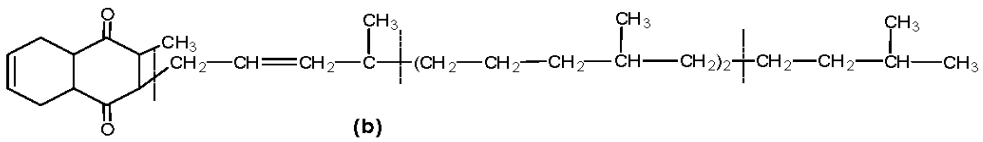
Vitamin E
Associate with cell membranes Destroy oxygen radicals
Found in eggs, oils, wheat germ
Deficiency- scaly skin, muscle weakness



(a)

Vitamin E: an antioxidant

Vitamin K
Undergoes redox during formation of prothrombin
Vitamin K deficiency slows blood clotting
Newborns given a 1 mg injection of vitamin K
K_1 found in green plant leaves



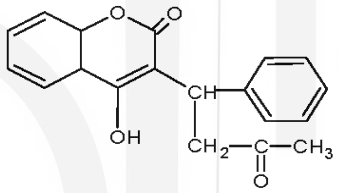
(b)

Vitamin K_1: a blood-clotting cofactor (phylloquinone)

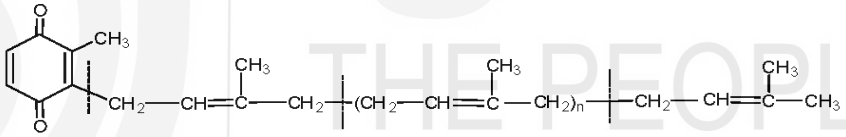
(c)

Warfarin: a blood anticoagulatn

Warfarin (cumadin)
Rat poison- causes internal bleeding
Anticoagulant drug to treat those at risk of blood clotting



ubiquinone
electron carriers in the redox reactions that drive ATP synthesis in mitochondria and chloroplasts



(d)

Ubiquinone: a mitochondrial electron carrier (coenzyme Q) (n=4 to 8)

Fig. 11.9: Structures of different isoprenoids and their roles as pigments

Warfarin inhibits formation of active prothrombin, therefore, it is useful as an anticoagulant in surgical patients at risk of excessive bleeding and those with blocks in coronary artery.

6. Many lipids with conjugated dienes have alternating single and double bonds which allows delocalization of electrons. Such compounds when exposed to low energy get excited and give colors visible to human eye. One such pigment is carotene which is orange yellow colored pigment is found in carrots. Similar compounds give colors to bird feathers.

11.4 PLANT STEROIDS

Stanols
are saturated sterols.

You must have seen advertisements of vegetable refined oils such as soybean, cotton seed and sunflower that say that these oils are cholesterol free and help reduce cholesterol. It is true that cholesterol is an animal fat and is not present in plants. But you would be surprised to know that plants also synthesize similar compounds known as phytosterols. These vary from cholesterol only in carbon side chains and/or presence or absence of a double bond. Phytosterols are of two types: sterols and stanols. Fig. 11.10 presents structures of some plant sterols and stanols in comparison to cholesterol.

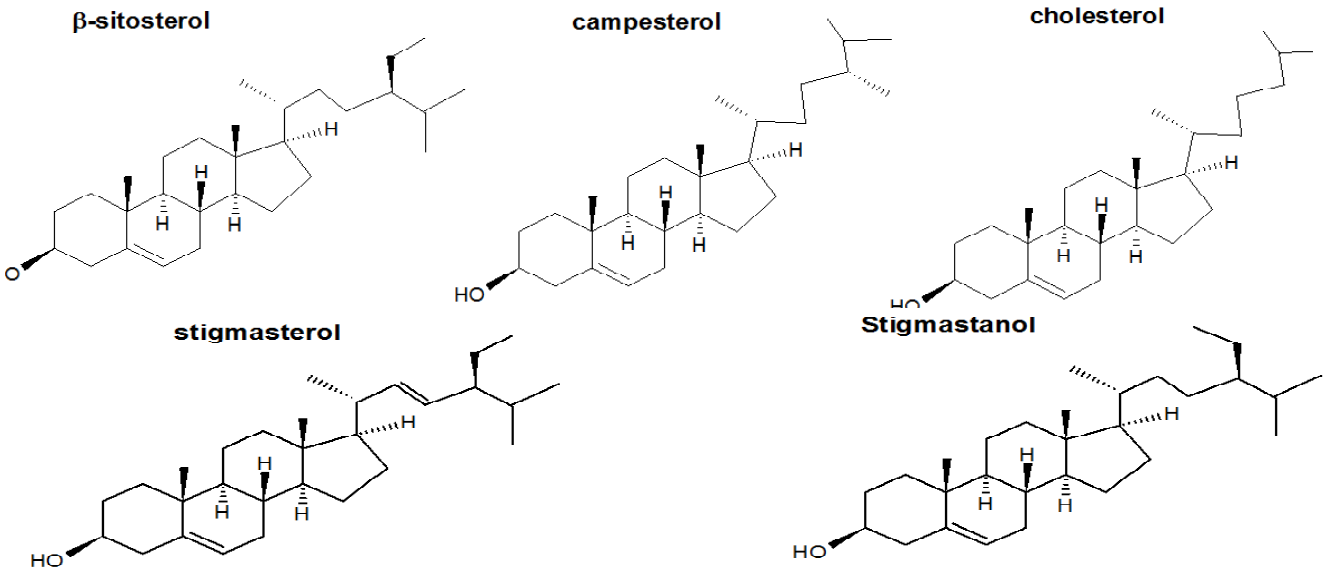


Fig. 11.10: Structures of phytosterols and comparison to cholesterol.

Phytosterols are generally produced as secondary metabolites in plants. These are being increasingly studied due to their economic and medicinal importance. Many studies indicate that phytosterols lower LDL-cholesterol; however, their direct role in cardiovascular diseases is not proved yet.

SAQ 3

Match the followings:

i)	Vitamin A	a)	lower LDL
ii)	Vitamin K	b)	Night blindness
iii)	Phytosterols	c)	Activated sugars
iv)	Tocopherols	d)	Anti coagulant
v)	Warfarin	e)	Anti oxidant
vi)	Ubiquinone	f)	Blood clotting
vii)	Dolichols	g)	ATP synthesis

11.5 SUMMARY

Let us summarize what we have learnt so far.

1) Lipids play many important roles in living organisms Fat deposits provide energy and heat when required. Lipids are also one of the major constituents of cell membranes. These are considered as passive roles of lipids for which these are required in bulk amounts.

2) Lipids also participate actively in dynamic process of signal transduction; a process in which internal components of a cell respond to an external signal allowing it to interact with local environment.

3) Signal molecule is generally chemical in nature and is known as primary messenger. Depending on the distance between the cells producing the signal and the cells on which it acts, it is of three types: autocrine, paracrine and endocrine signaling.

4) A variety of signaling molecules are derived from phospholipids, sphingolipids and sterols and involved in signaling through these three modes.

5) Phosphatidylinositol (PI) and its phosphorylated derivatives serve as precursor of intracellular signal molecules IP3 and DAG which regulate calcium levels and different cellular processes mediated phosphorylation reactions by enzyme protein kinase C.

6) Similarly, ceramide and sphingomyelin which are derivatives of membrane sphingolipids also act as intracellular signaling molecules. These also activate protein kinases and regulate processes like cell division, differentiation, migration and programmed cell death.

7) Arachidonic acid is precursor of eicosanoids which are paracrine signaling molecues.

8) There are three classes of eicosanoids: prostaglandins, thromboxanes and leukotrienes. These are mainly involved in inflammatory responses in different tissues.

9) Prostaglandins are involved in contraction of smooth muscles of uterus during menstruation and labor pain, regulation of blood flow to specific organs, wake sleep cycle and response of certain tissues to epinephrine and glucagon hormones. These also mediate increase in body temperature (fever), pain and inflammation.

10) Thromboxanes regulate formation of blood clot by reducing the flow of blood to the site of clot formation.

11) Leukotrienes are the signals for contraction of smooth muscles in lungs. Their overproduction causes asthmatic attack

12) Steroid hormones represent endocrine mode of signaling carrying the information between tissues. These are carried in blood from the site of synthesis to the target tissue, where they diffuse through plasma membrane and bind their intracellular receptor on nucleus to affect growth and development.

13) Steroid hormones include sex hormones and corticosteroids. Testosterone, estrogen, progesterone are the sex hormones produced by the gonads. The corticosteroids are produced by the adrenal gland and include the glucocorticoids and the mineralocorticoids.

14) Glucocorticoids regulate glucose levels in blood plasma independently of food intake. Mineralocorticoids act on the kidney to regulate salt and water balance.

15) Plants produce many signaling molecules which are lipid in nature. Jasmonates for example are derived from α-linolenic acid (C18:2 and play role in plant development such as seed germination, growth of root and flowering tuber as well as triggering of immune responses to wound and pathogen invasion.

16) A group of lipids known as isoprenoids gives rise to diverse molecules which act as pigments and perform many important functions. Isoprenoids

include fat soluble vitamins such as vitamins A, D, E and K. These are involved in diverse processes such as generation of ATP, oxidation-reduction reactions and visual cycle to name a few.

11.6 TERMINAL QUESTIONS

1) Explain different types of signaling.
2) Write briefly about different classes of eicosanoids and their roles.
3) What are isoprenoids? Discuss their roles as pigments.
4) Draw structures of the followings:

   (i) Isoprene unit (ii) vitamin E (iii) cholesterol

11.7 ANSWERS

Self-Assessment Questions

1. (i)-c; (ii)- b; (iii)- d; (iv)- a.
2. A) a- Phospholipase C; b- IP3; c- DAG; d- phosphorylation of cell proteins; e- cellular growth and processes

   B) Calcitriol (1,25-dihydroxy cholecalciferol); kidneys; Vitamin D_3 (cholecalciferol)

   C) True

   D) (i)-(d); (ii)- (f); (iii)- (e); (iv)- (b); (v)-(c); (vi)- (a)
3. (i)- (b); (ii)- (f); (iii)- (a); (iv)- (e); (v)- (d); (vi)- (g); (vii)- (c)

Terminal Questions

1) There are three types of signaling:

   Endocrine - When signal acts on the cells distant from its point of origin, for example insulin hormone.

   Paracrine - When the signal cats on the neighboring cells, for example, neurotransmitters

   Autocrine - When the signal acts on the same cells which generate it, for example, antigen mediated activation of T helper cells.

   For more details refer to section 11.2.

2) There are three classes of eicosanoids: prostaglandins, thromboxanes and leukotrienes. These are mainly involved in inflammatory responses in different tissues. Refer section 11.2.2 for more details

3) Isoprenoids are a group of lipids that contain two or more isoprene units. These are hydrophobic in nature, therefore, can traverse the lipid membrane and act as donor or acceptor of electrons in oxidation-reduction (redox) reactions.

4)i) Isoprene $CH_2 = \overset{CH_3}{\overset{|}{C}} - CH = CH_2$

Vitamin E Associate with Destroy oxygen Found in eggs.

ii) **Vitamin E : an antioxidant refer Fig. 11.9**

iii) **Cholesterol refer Fig. 11.10**

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