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Lipid Chemistry

Definition: Lipids are heterogeneous compounds which are insoluble in water but soluble in organic solvents e.g. ether, chloroform, chloroform , alcohols, acetone, etc.

They are widely obtained in nature from plants and animals **OR** they are biologically active molecules that are insoluble in aqueous solutions and soluble in organic solvents.

*- The structure of these molecules determines their function. For example, the very insoluble triacylglycerol are used as the predominant storage form of chemical energy in the body.

Major Biological Roles of Lipids

Lipids are important dietary constituents because of the following reasons:

a- They have a high energy value and they give more energy values than carbohydrates and proteins but the body prefers to get its energy from carbohydrates than that from lipids (9 kcal/mol can be derived from the complete oxidation of fats, in contrast to 4.5 kcal/mol from that of proteins or carbohydrates). (glycogen is highly hydrated. This is because every 1 g of glycogen, 2 grams of water is H-bonded to it. Hence it would take 3 times more weight to store the equivalent amount of energy in carbohydrates as is stored in triacylglycol, which are stored in anhydrous lipid "drops" within the cells.

b- They contain the essential fatty acids which can not synthesized by our bodies.

c- They provide our bodies with fat soluble vitamins (A,D, E and K)

d- They are important constituents of the nervous system.

e- Tissues fat (constant fats) are essential components of cell membrane. This type of lipids is mainly phospholipids that can not affected by starvation.

f- In general, the lipids of physiological importance for humans have the following major functions:

1.They serve as structural components of **biological membranes**.

2.They provide **energy reserves**, **predominantly** in the **form of triacylglycerols.**

3. Both lipids and lipid derivatives **serve as sources of vitamins and hormones.** For example, **cholesterol is used for synthesis of adrenal cortical hormones, vitamins, and bile acids.**

4. Lipophilic bile acids **aid in lipid solubilization.**

5- The deposited fats **(mainly triglycerides)** act as **a pad** for the internal organs to protect them from outside shocks and **an insulator** in the subcutaneous tissue against loss of body heat.

6- Lipoproteins (which are compounds of lipids and proteins) are important cellular constituents occurring both in the cell membrane and in the mitochondria within the cytoplasm.

Classification of lipids

1- Simple lipids : They are esters of fatty acids with alcohol. These type of lipids are further classified into neutral fats (triglycerides or triacylglycerol i.e. fatty acid esters with glycerol) and waxes (esters of fatty acids with long chain alcohols).

2- Conjugated lipids: These types of lipids not only contain fatty acids and alcohols in their structures but also other products.

Therefore, they include:

a- Phospholipids :

They contain phosphoric acid residue and sometimes nitrogen.

b- Glycolipids : They contain sugars.

c- Sulpholipids : They contain sulpher.

d- Lipoproteins : They contain proteins in their structures.

3- Derived lipids: They are substances derived from simple and compound lipids after their hydrolysis. They include, fatty acids, steroids, fat soluble vitamins and hydrocarbons **e.g. squalene** which **gives cholesterol** in the body and **caretenoids** which **are vitamin A precursors**.

Simple lipids

1- Neutral Fats (or triglycerides): They include **fats** (which are **solids** at room temperature) and **oils** (which are **liquids** at room temperature)

Triglycerides

@- Fats and oils are triglycerides with the **same chemical structures** and chemical properties **but differ in their physical states at room temp.**

@-They are formed from one molecule of glycerol and 3 molecules of fatty acids (if similar, they **are called simple** triglycerides (***Tripalmitate)*** but if they are different (***stero-oleo-pamitin***) they **are called mixed** triglycerides) combined with each other through ester linkages.

Physical properties of fats and oils

They are colorless, tasteless and ouderless. They are **insoluble in water but soluble in fat solvents** e.g. ether, chloroform and benzene.

They undergo rancidity, which is the change in the odour and taste of fats produced by bacteria, oxygen and moisture.

The rancidity has 3 types:

Hydrolytic rancidity: The fat is hydrolyzed to fatty acids and glycerol by water or bacterial enzymes.

Oxidative rancidity : The fatty acids are oxidized at the double bonds giving peroxides, fatty aldehyde, ketones and short chains fatty acids.

Ketonic rancidity : In which ketones and aldehydes are produced.

Detection of rancidity: It can be detected by the change in the taste and odour of the fat and quantitatively by the increase in the so called acid number.

Prevention of rancidity: Avoiding exposure to oxygen, moisture, light, and bacteria.

Addition of antioxidants , e,g, vitamin E and hydroquinone are also used.

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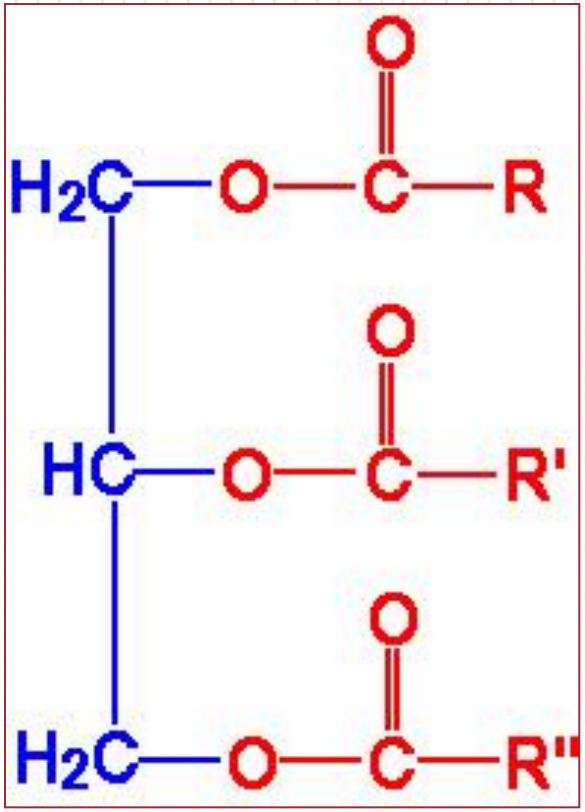
The Basic Structure of Triacylglycerides

Triacylglycerides are composed of a glycerol backbone to which 3 fatty acids are esterified.



Basic composition of a triacylglyceride. The glycerol backbone is in blue.
(Note : R, R*, and R indicate the alkyl groups of 3 different fatty acids)**

When lipids added to water, single chain amphiphiles **form both monolayer** on the surface of the water and **micelles**, while some monomers remain in solution. Double chain amphiphiles form **bilayers** instead of micelles.

The structure of fatty acids and phospholipids show them to amphiphilic - i.e. they have both hydrophobic and hydrophilic domains.

Fatty acids can be represented in "cartoon-form" as single chain amphiphiles with a circular polar head group and a single acyl non-polar tail extending from the head. Likewise, phospholipids can be shown as double chain amphiphiles.

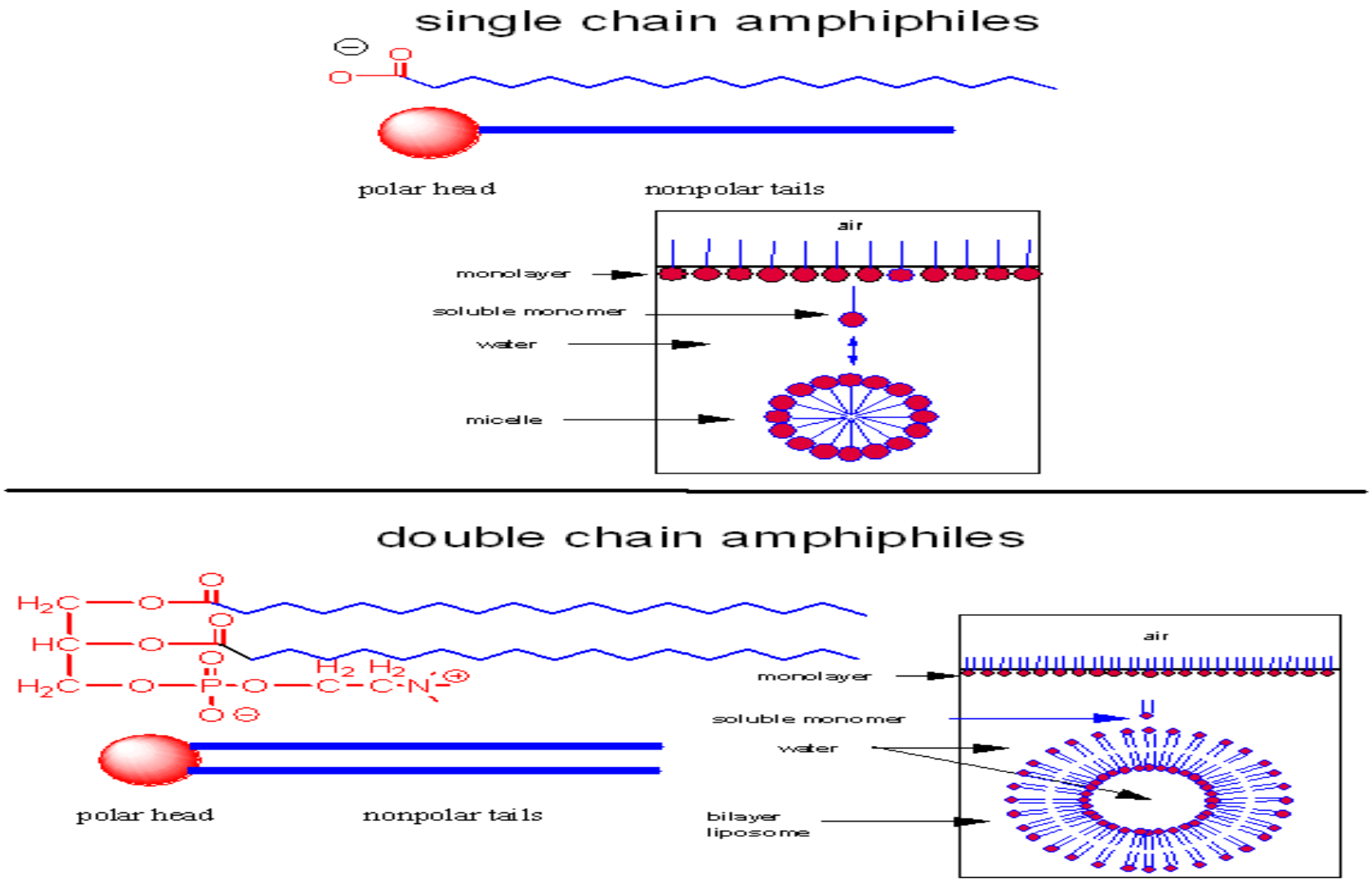


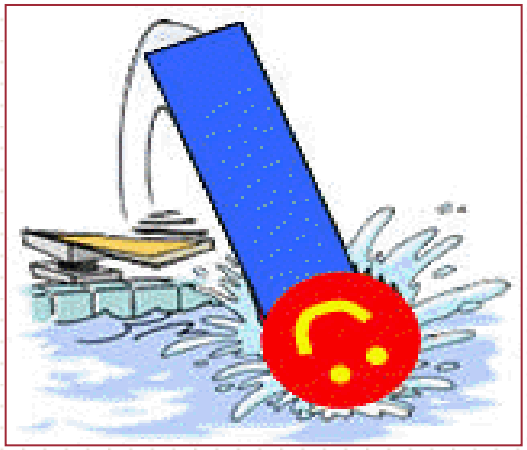
Figure: Structures of single and double chain amphipiles in water - Micelles and Bilayers

Lipids in Water

Micelle and Bilayer Formation:

The figure shows how lipid molecules, specifically single and double chain amphiphiles, interact with each other and solvent when they are added to water.

Now, what would one do if he was a single chain amphiphile and ready to jump into water?



A single chain amphiphile (*Substance with lipotropic action*) jumps into water!

Phospholipids

*- Phospholipids are the primary components of cellular membranes .

*- They are **amphipathic**; that is, **they are both hydrophilic and hydrophobic**.

*- The "head" of a lipid moleule is negatively charged phosphate group and the two "tails" are highly hydrophobic hydrocarbon chains .

*- Phospholipid tails will congregate together to form a local hydrophobic environment.

*- This leaves the charged phosphate groups facing out into the hydrophilic environment. There are three structures that phospholipids can form because of their ampiphatic nature.

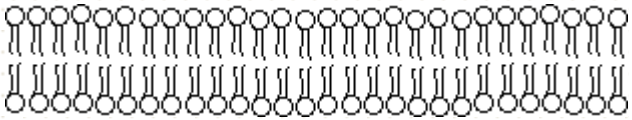
*- Each represents a phospholipid.

*- A phospholipid bilayer is approximately 5 nm thick.

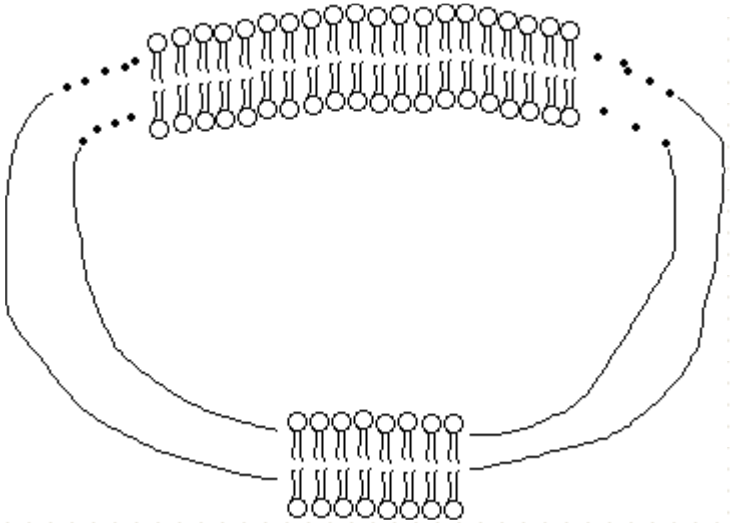
*- This membrane is semipermeable, meaning that most molecules are excluded but some molecules are allowed to pass freely (diffuse) through the membrane.

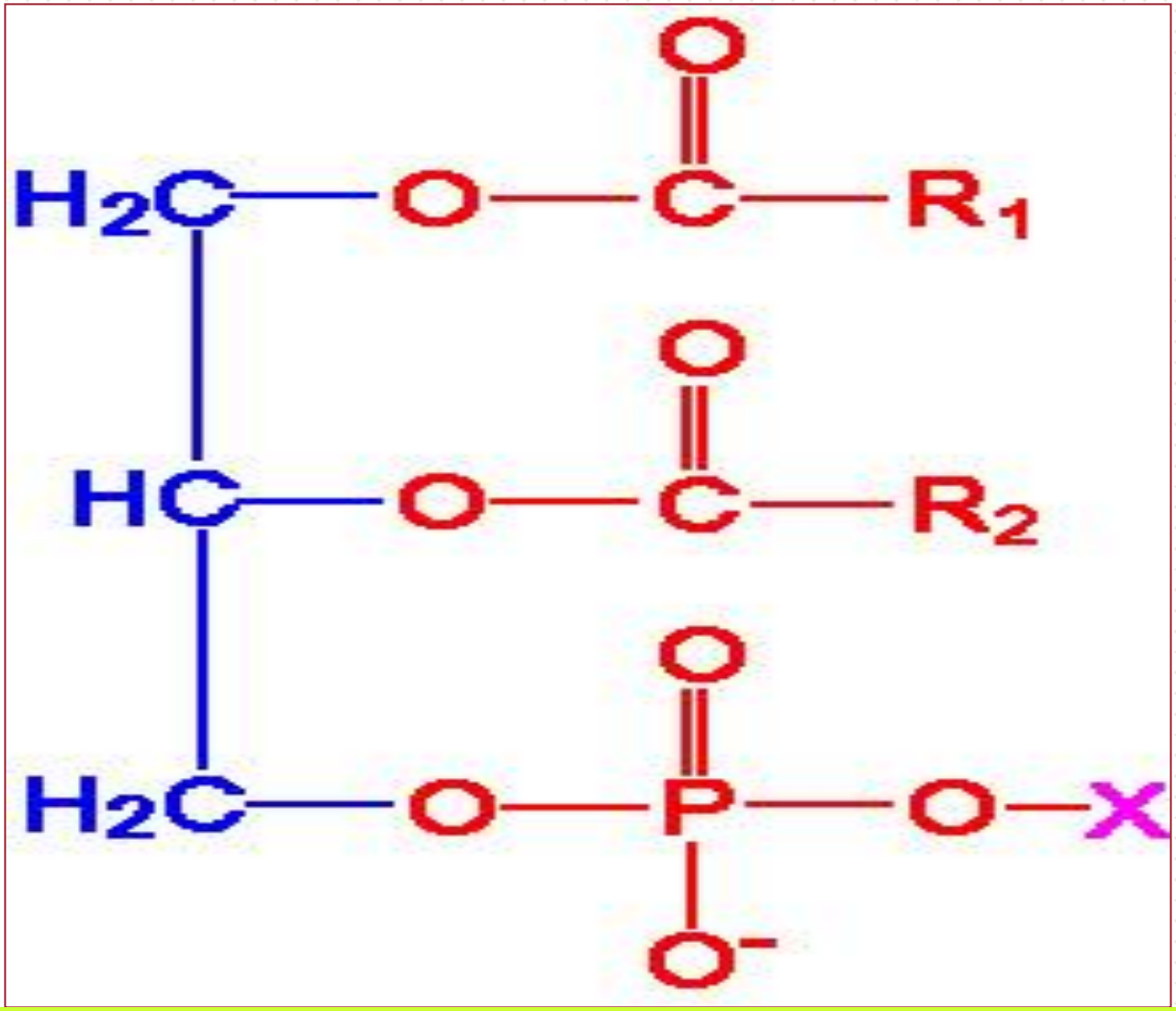
1-Micelles

2-Planar lipid bilayers



3-Spherical lipid bilayers (vesicles)

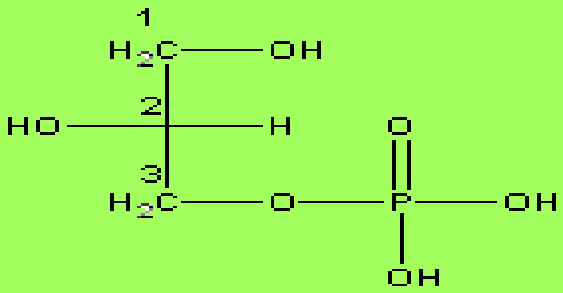




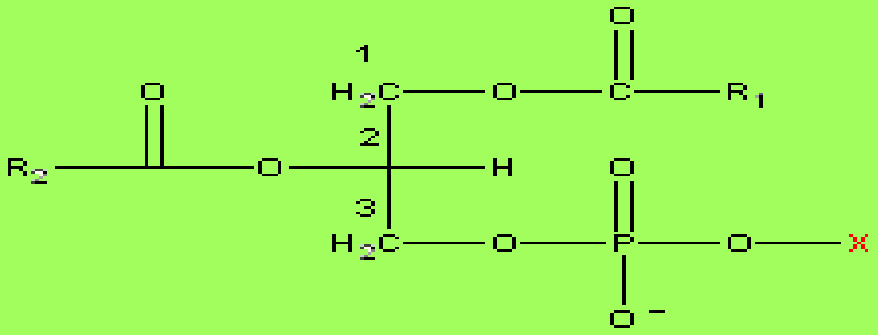
Basic composition of a phospholipid. X can be a number of different substituents.

Structures of common phospholipids

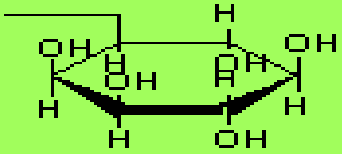
COMMON GLYCEROPHOSPHOLIPIDS



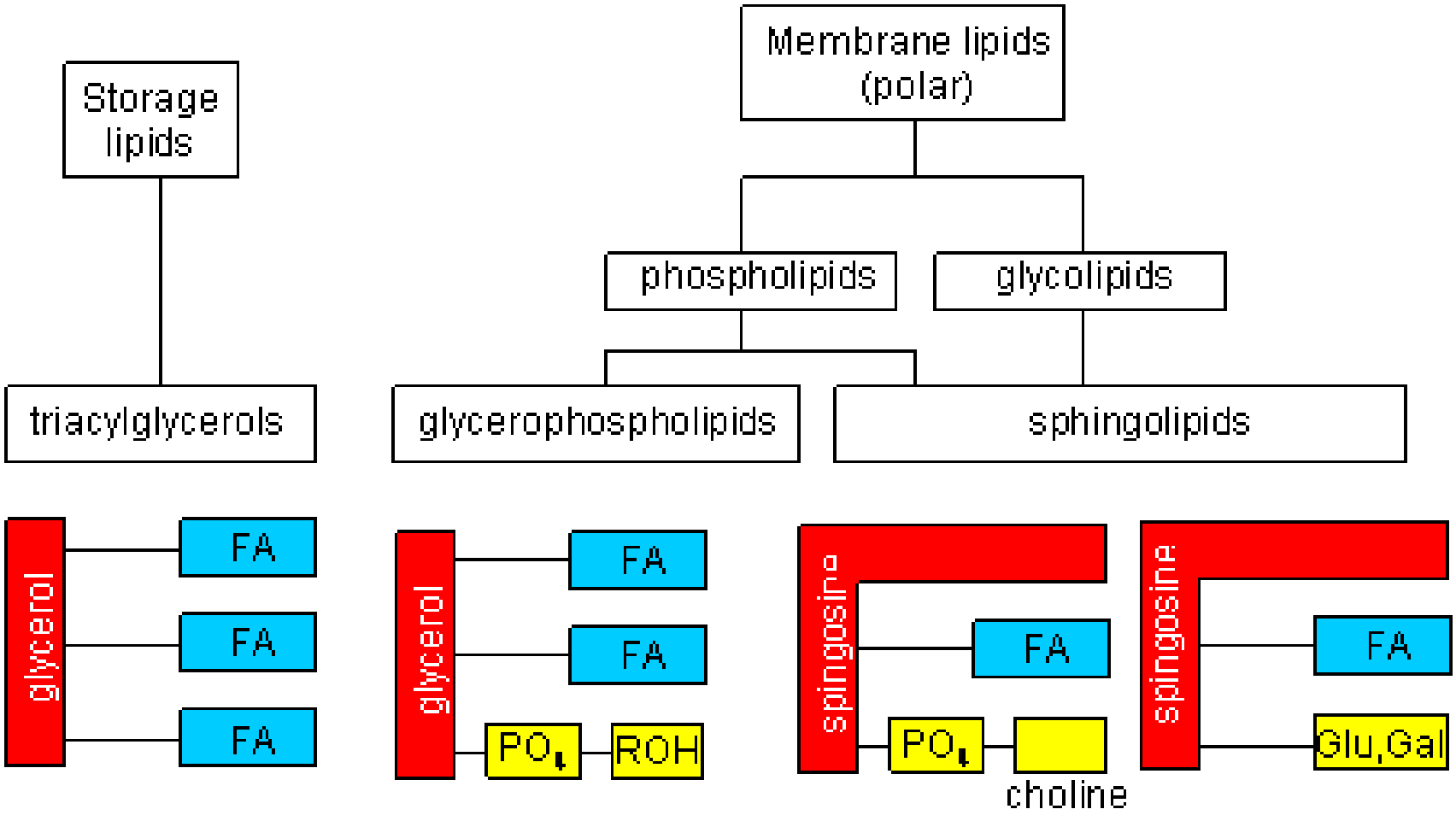
sn-glycerol-3-phosphate



phospholipids

NAME OF X-OH	FORMULA OF X	NAME OF PHOSPHOLIPID
water	—H	phosphatidic acid
ethanolamine	—$CH_2CH_2NH_3^{\oplus}$	phosphatidylethanolamine
choline	—$CH_2CH_2N(CH_3)_3^{\oplus}$	phosphatidylcholine (lecithin)
myoinositol		phosphatidylinositol
glycerol	—$CH_2CH(OH)CH_2OH$	phosphatidylglycerol

Classification of common phosopholipids, glycolipids, and triacylglyerides



after Lehninger et al., Principles of Biochemistry, 2nd ed.

Basic Structure of Phospholipids

- The basic structure of phospolipids is very similar to that of the triacylglycerides except that C-3 of the glycerol backbone is esterified to phosphoric acid.
- The building block of the phospholipids is phosphatidic acid which results when the X substitution in the basic structure shown in the Figure below is a hydrogen atom.
- **Substitutions include:**

a- Lecithin:

- **Choline** (phosphatidyl Choline).

b- Cephalins:

1- **Ethanolamine** (phosphatidyl ethanolamine).

2- **Serine** (phosphatidyl serine),

3- ***Myo*-inositol** (phosphatidyl inositol): **These compounds can have a variety in the numbers of inositol alcohols that are phosphorylated generating polyphosphatidyl inositols.**

c- Cardiolipin:

Both lecithins and cephalins contain one saturated FA and one unsaturated FA.

They are hydrolyzed by the enzyme lecithinase giving what is called lytholecithins and lysocephalins.

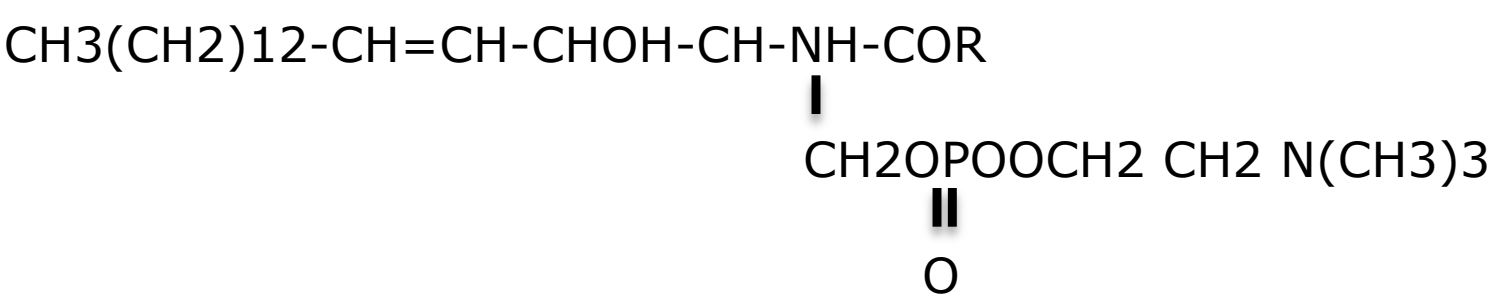
The latter's hydrolyze the RBCs cell membranes leading to Their haemolysis and hyperbilirubinaemia.

Lecithins also inter in the formation of cell membranes, necessary for fat metabolism. One of these lecithins called dipalmityl lecithin is a very effective surface active agent preventing adherence of the inner surfaces of the lungs due to their surface active properties. Therefore its absence from the lungs of immature infants causes respiratory distress szndrome.

Cephalins also inter in the formation of cell membranes. In addition, phosphatidyl serine and phosphatidyl ethanolamine inter in the formation of thromboplastin which are necessary for blood clotting.

d-Sphingomyleins : There is no glycerol.

It is formed of sphingosine base **(sphingol), one FA, choline** and phosphoric acid.



-They are present in the brain, liver and nervous tissues.

- Absence of sphingomyleinase causes accumulation of sphingomyleins in the liver, spleen and in the brain tissues causing what is called **Niemann, s- Pick's disease.**

- Sphingomyleinase hydrolyses sphingomyleins into choline and ceramides.

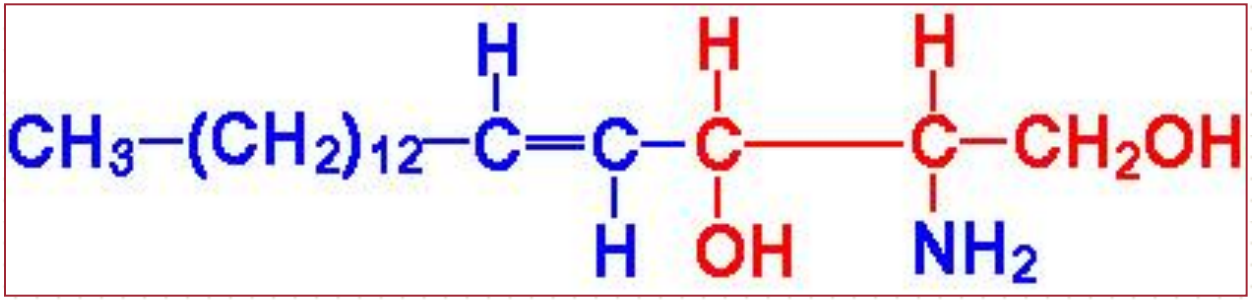
Basic Structure of Sphingolipids

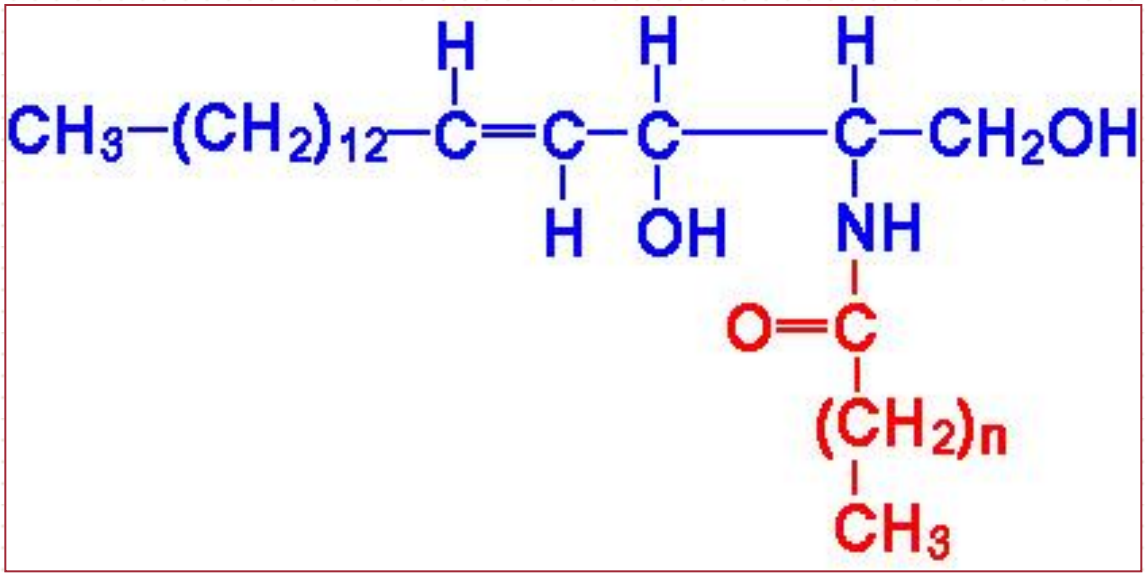
*- Sphingolipids are composed of a backbone of sphingosine which is derived itself from glycerol.

*- Sphingosine is N-acetylated by a variety of fatty acids generating a family of molecules referred to as ceramides.

*- Sphingolipids predominate in the myelin sheath of nerve fibers.

*- Sphingomyelin is an abundant sphingolipid generated by transfer of the phosphocholine moiety of phosphatidylcholine to a ceramide, thus sphingomyelin is a unique form of a phospholipid.





Top: Sphingosine (the atoms in red are derived from glycerol
Bottom: Basic composition of a ceramide and n "indicates any fatty acid may be N-acetylated at this position.

*- **The other major class of sphingolipids (besides the sphingomyelins are the glycosphingolipids generated by substitution of carbohydrates to the *sn1* carbon of the glycerol backbone of a ceramide.**

***- There are 4 major classes of glycosphingolipids:**

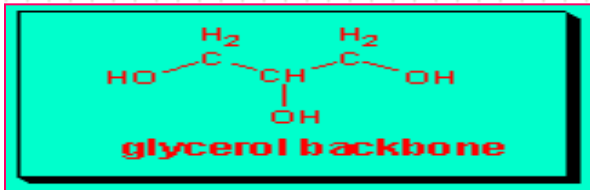
Cerebrosides : They contain a single moiety, principally galactose.

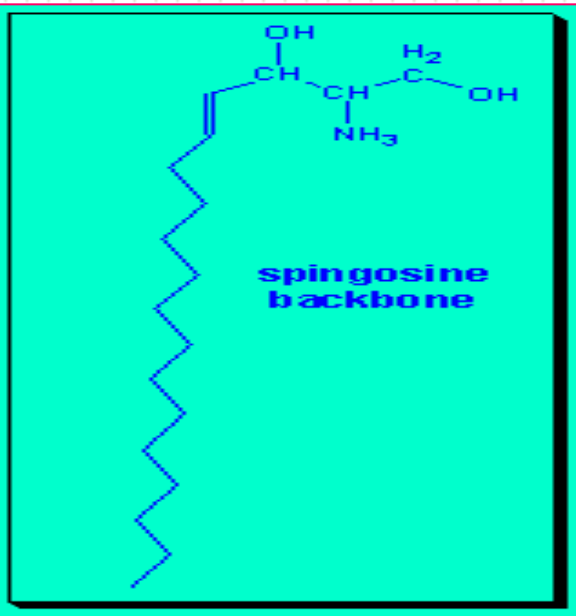
Sulfatides : They are sulfuric acid esters of galactocerebrosides.

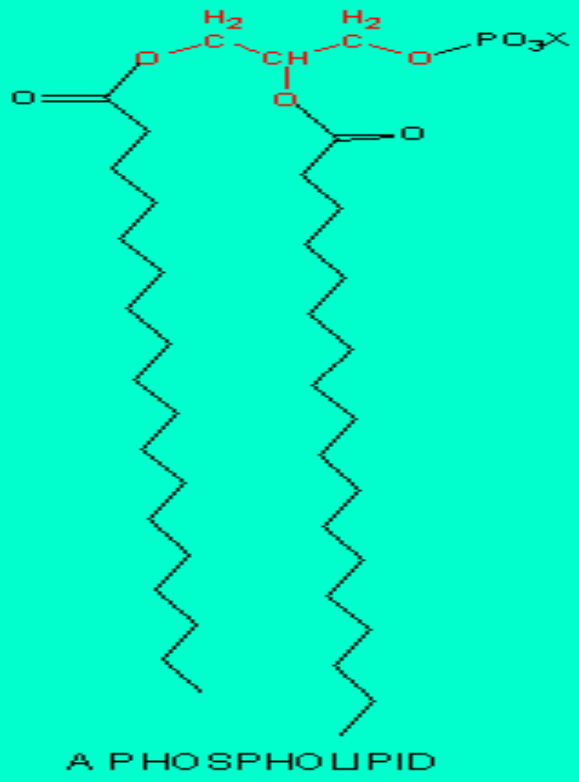
Globosides : They contain 2 or more additional sugars residues than that of galactocerebrosides.

Gangliosides :similar to globosides, gangliosides also contain sialic acid . Some of which are used as **receptors for cholera toxins in the intestine.**

Comparison of lipids with glycerol and sphingosine as backbones

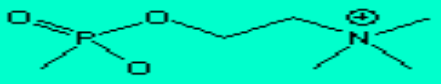


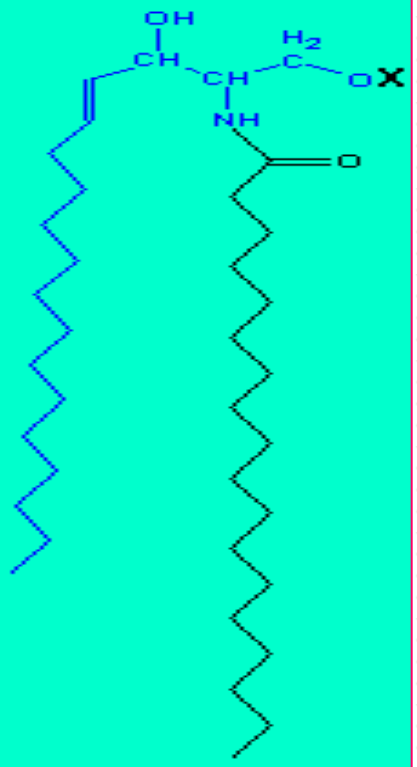


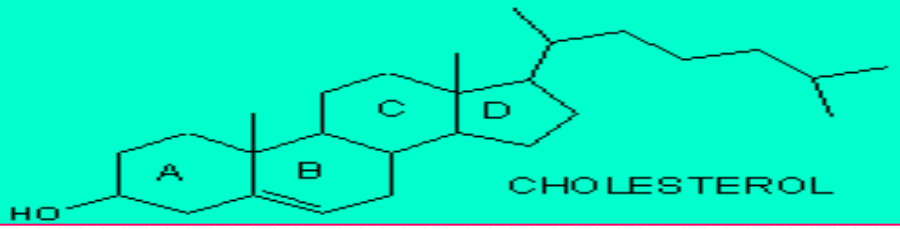


X = H, ceramide

X =







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LIPIDS AS BIOLOGICAL SIGNALS Transducer

#- Lipids are not just used as a passive component of membranes, or as a source of stored energy but they are also involved in the process of **signal transduction** at the cell membrane, a process by which the interior components of the cell respond to an external signal to the cell, allowing the cell to respond to their local environment. Usually a chemical signal on the outside of the cell is the "**primary messengers**" that causes the cell to respond.

#- Usually the chemical transmitter of information **does not get into** the cell. Rather, **it binds to surface receptors** on the cell membrane surface.

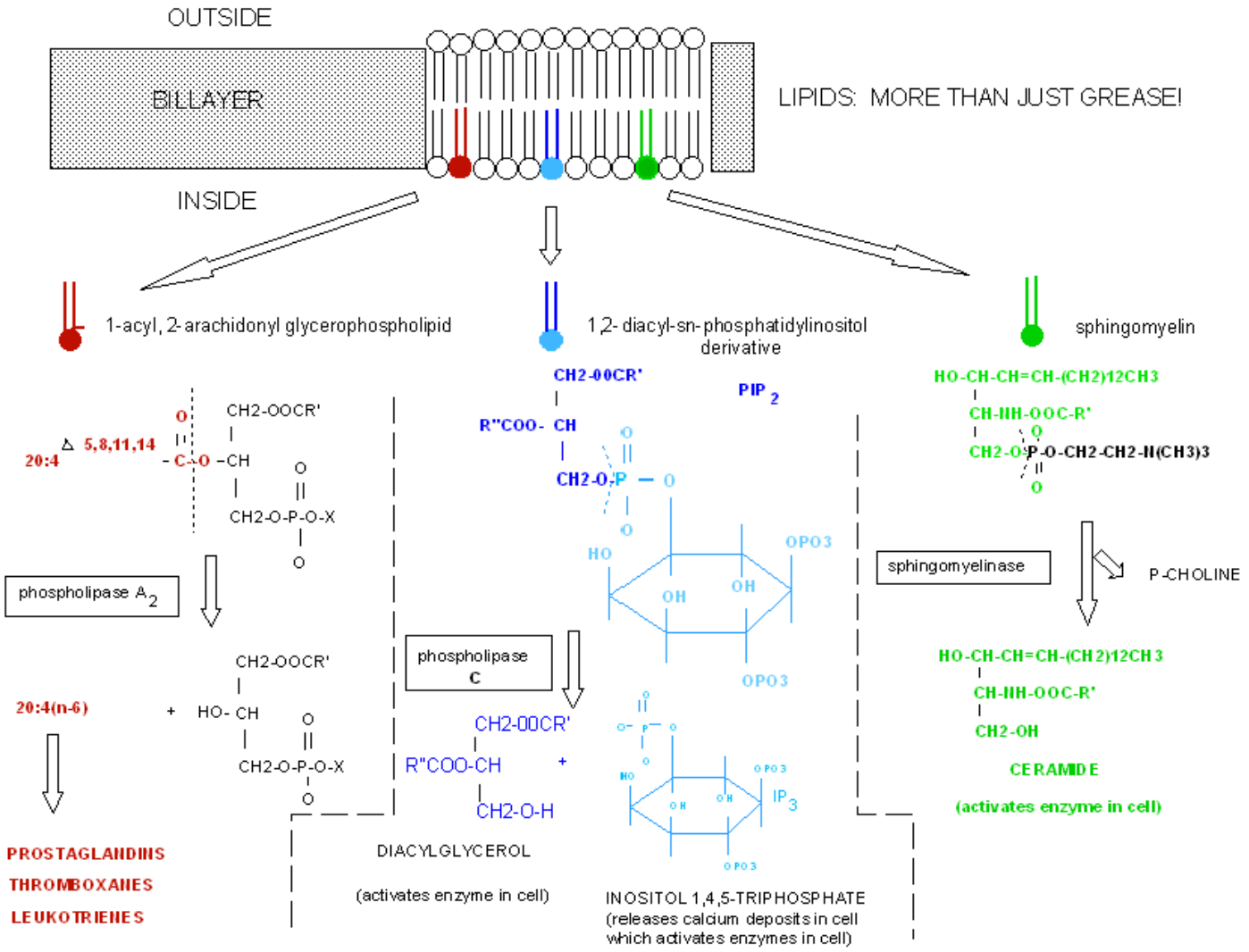
#- Somehow, the cells senses **that a ligand is bound** to the outside.

#- Enzymes (usually in the membrane or at the intracellular surface of the lipid bilayer) are activated. Many of these enzymes cleave lipids in the membrane.

#- The cleaved fragments of the lipid molecules **serve as intracellular signals** or "**secondary messengers**" , which can bind to intracellular enzymes to activate intracellular processes.

#- The following diagram shows some of the lipid mediators which are generated by this process and signal the cell to respond.

Lipids as Mediators in Signal Transduction



2-Glycolipids (Cerebrosides):

They contain no glycerol and phosphoric acid.

They are present in adrenals, liver and spleen.

They are conjugated lipids with carbohydrates.

On their hydrolysis, they give sphingol, FA, galactose and rarely glucose.

CH3(CH2)12-CH=CH-CHOH-CH-NH-COR (Cerebronic acid R=CH3(CH2)21-CHOHCOOH)

CH2 O Galactose (Galactocerebroside

””CH2O-Glucose (Glucocerebroside)

They are classified into:

)

1- Kerasin: (Sphingosine, lignoceric acid = CH3(CH2)22COOH and galactose)

2- Nervons:(Sphingosine, nervonic acid { unsaturated lignoceric acid = CH3(CH2)22COOH) and galactose }

3- Hydroxy Nervons: (Sphingosine,hydroxy nervonic acid and galactose }

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4-CH3(CH2)12CH=CHCHOHCHNHC=ORCH2O (PO4 choline)

(Sphingomyline)

5- N-acetylgalactosamine (Beta-galactose)2 + Sialic acid (Ganglioside or ceramideoligosaccharide)

In Sphingomyline the enzyme ***Sphingomylinase is deficient*** **(*Niemann - Pick,s disease*)** and in Ganglioside or Ceramide oligosaccharide (***Tay-Sachs,s disease***) the enzyme **Hexoaminidase** is deficient.

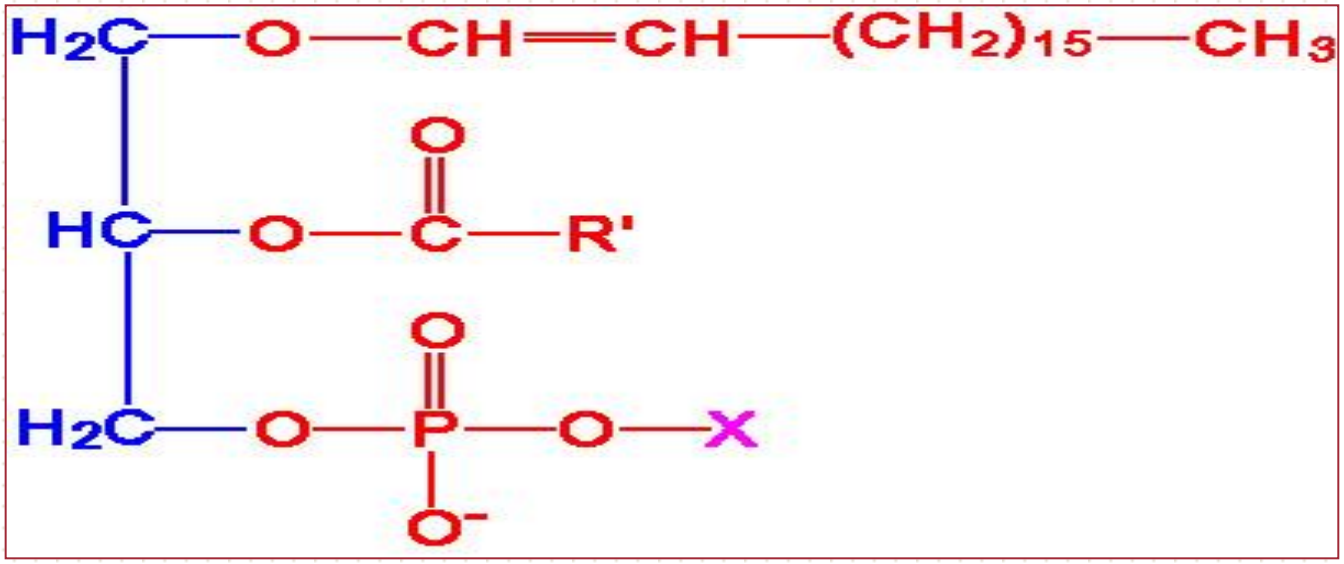
Basic Structure of Plasmalogens

Plasmalogens are complex membrane lipids that resemble phospholipids, principally phosphatidylcholine.

The major difference is that the fatty acid at C-1 (*sn*1) of glycerol contains either an *O*-alkyl (-O-CH2-) or *O*-alkenyl ether (-O-CH=CH-) species.

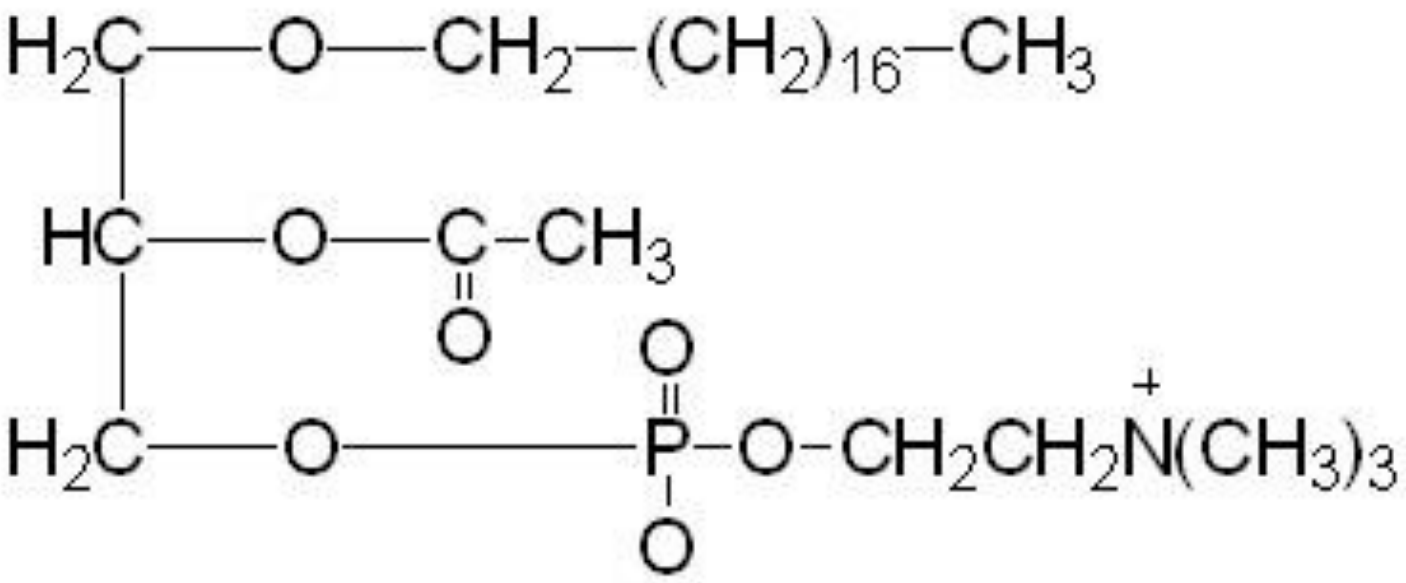
A basic *O*-alkenyl ether species is shown in **the Figure** below.

.



The basic composition of *O*-alkenyl plasmalogens

The structure of PAF



One of the most potent alkyl ether plasmalogens **is platelet activating factor) PAF-1 :***O*-'1-enyl-2-acetyl-*sn*-glycero-3-phosphocholine) which is a choline plasmalogen.

In this type of plasmalogen, the C-2) *sn* (2position of glycerol is esterified with an acetyl group instead of a long chain fatty acid.

PAF functions as a mediator of hypersensitivity, acute inflammatory reactions and anaphylactic shock. PAF is synthesized in response to the formation of antigen-IgE complexes on the surfaces of basophiles, neutrophils, eosinophils, macrophages and monocytes.

The synthesis and release of PAF from cells leads to platelet aggregation and the release of serotonin from platelets.

PAF also produces responses in liver, heart, smooth muscle, and uterine and lung tissues.

Thrombin also binds to and leads to the release of G-protein-coupled protease activated receptors (PARs), specifically PAR-1, -3 and -4. The release of these proteins leads to the activation of numerous signaling cascades that in turn increase release of the interleukins, ILs, IL-1 and IL-6, increases secretion of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1).

The thrombin-induced signaling also leads to increased **platelet activation** and leukocyte adhesion. Thrombin also activates thrombin-activatable fibrinolysis inhibitor (TAFI) thus modulating fibrinolysis (degradation of fibrin clots). TAFI is also known as carboxypeptidase U (CPU) whose activity leads to removal of C-terminal lysines from partially degraded fibrin.

This leads to an impairment of **plasminogen** activation, thereby reducing the rate of fibrin clot dissolution (i.e. fibrinolysis).

Activation of Prothrombin to Thrombin

Two pathways lead to the formation of a fibrin clot: the intrinsic and extrinsic pathway. Although they are initiated by distinct mechanisms, the two converge on a common pathway that leads to clot formation.

The formation of a red thrombus or a clot in response to an abnormal vessel wall in the absence of tissue injury is the result of the intrinsic pathway.

Fibrin clot formation in response to tissue injury is the result of the extrinsic pathway. Both pathways are complex and involve numerous different proteins termed clotting factors.

The common point in both pathways is the activation of factor X to factor Xa. Factor Xa activates prothrombin (factor II) to thrombin (factor IIa).

Thrombin, in turn, converts fibrinogen to fibrin. The activation of thrombin occurs on the surface of activated platelets and requires formation of a prothrombinase complex.

This complex is composed of the platelet phospholipids, **phosphatidylinositol** and **phosphatidylserine**, Ca2+, factors Va and Xa, and prothrombin. Factor V is a cofactor in the formation of the prothrombinase complex, similar to the role of factor VIII in tenase complex formation.

Like factor VIII activation, factor V is activated to factor Va by means of minute amounts and is inactivated by increased levels of thrombin. Factor Va binds to specific receptors on the surfaces of **activated platelets** and forms a complex with prothrombin and factor Xa.

Prothrombin is a 72,000-Dalton, single-chain protein containing ten gla residues in its N-terminal region. Within the prothrombinase complex, prothrombin is cleaved at 2 sites by factor Xa. This cleavage generates a 2-chain active thrombin molecule containing an A and a B chain which are held together by a single disulfide bond.

In addition to its role in activation of fibrin clot formation, thrombin plays an important regulatory role in coagulation. Thrombin combines with thrombomodulin present on endothelial cell surfaces forming a complex that converts protein C to protein Ca. The cofactor protein S and protein Ca degrade factors Va and VIIIa, thereby limiting the activity of these 2 factors in the coagulation cascade.

3-Sulpholipids:

They are present in the testis , liver and muscles

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They are conjugated lipids with carbohydrates.

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CH3(CH2)12-CH=CH-CHOH-CH-NH-COR (Cerebronic acid R=CH3(CH2)21-CHOHCOOH)

CH2 O Galactose-3-Phosphate (Sulpholipids)

4- Lipoproteins:

They are lipids combined with proteins. The lipid component is either phospholipids, cholesterol or triglycerides.

Distribution of lipoproteins in the body:

Tissues: **Cell membrane, muscles, mitochondria and in microsomes.**

In lung tissues: **Thromboplastic protein.**

In the eyes : **Rhodopsin in the rods of retina.**

In the blood : Lipids must bind to proteins to make them water soluble for transport in the blood. This is because lipids are carried in the blood as lipoproteins complexes.

*The **lipid** fraction in such complexes may be:*

Triglycerides (TG), phospholipids (PL), fat soluble vitamins, steroid hormones, free fatty acids (FFA) or fatty acids esterified with cholesterol.

*The **protein** fraction in such complexes may be:*

*α- globulin and so the lipoprotein formed is **α-lipoprotein.***

*or β- globulin and so the lipoprotein formed is **β-lipoprotein.***

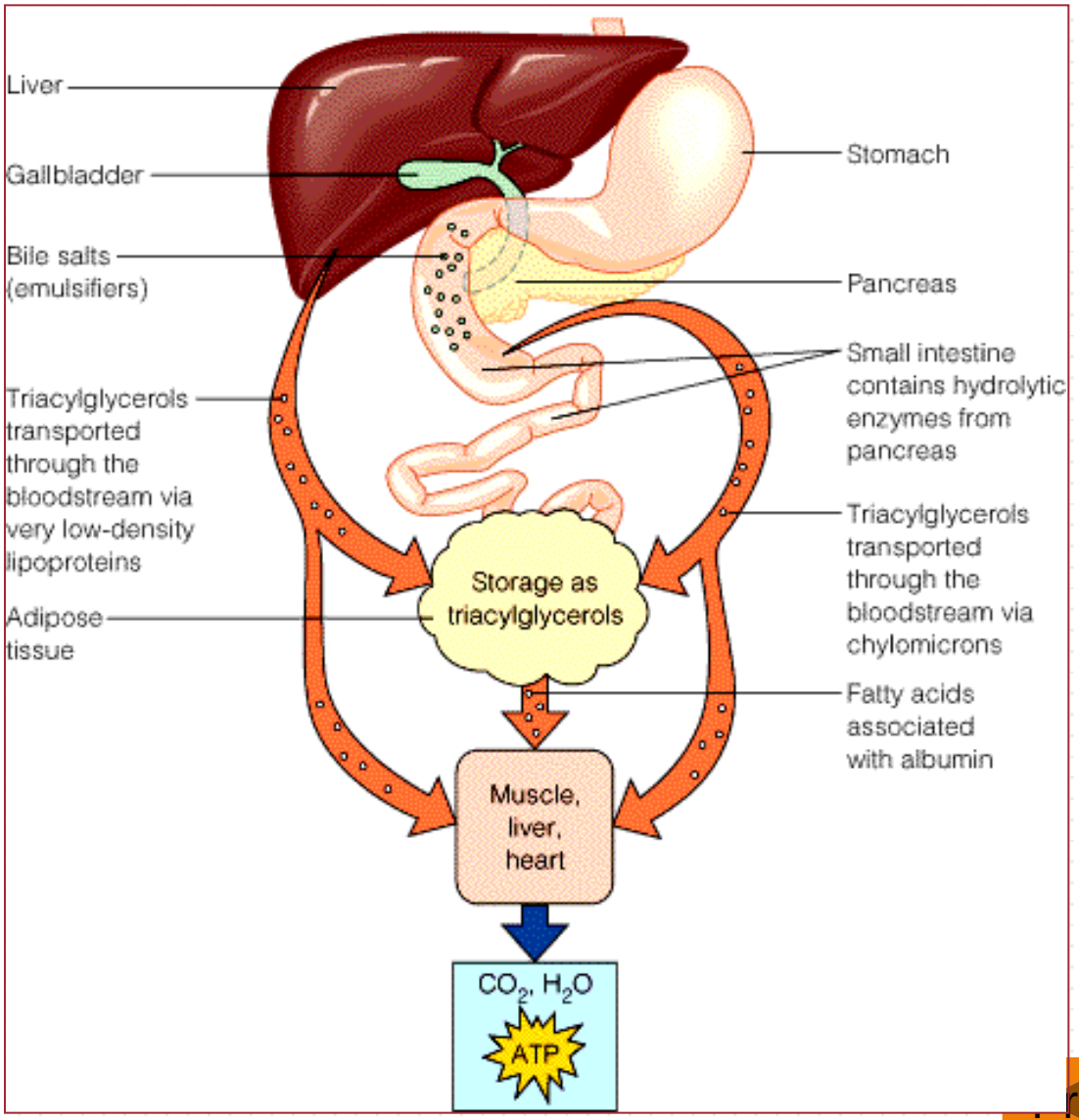
***α-lipoprotein and β-lipoprotein** are the two major types of proteins.*

Lipoproteins can be classified according to the rate of flotation in NaCl solution using ultracentrifugation forces into 5 different types:

*Chylomicrons, very low density lipoproteins (VLDL or pre- **β-lipoproteins**), low density lipoproteins (LDLor **β-lipoproteins**), high density lipoproteins (HDL or*

***α –lipoproteins**) and FFA attached to albumin.*

Overview of **fat** digestion, absorption, storage, and mobilization in the human.



Composition of lipoproteins in human plasma

1- Chylomicrons:

Source (site of synthesis): intestine.

Function: It carries TG, cholesterol ester and phospholipids from the intestine to the peripheral tissues.

Their densities is less than 0.96, protein contents 1 -2 % (**globulin**) , percent of lipids 98 -99% (TG 88 %, phospholipids 8 % , cholesterol ester 3 %, free cholesterol 1 % and no free FAs.

Catabolism: It occurs in the plasma by lipoproteins lipases. These enzymes act on TG converting them into glycerol and FFAs leaving chylomicrons remnant which are taken up by the liver.

2- VLDL (Apo-B, Apo-C and Apo-E):

Source (site of synthesis) : liver

Function: It carries TG from the liver to the extrahepatic tissues.

Their densities is 0.96- 1.006, protein contents 7 -10 % (**globulin**) , percent of lipids 90 -93% (TG 56 %, phospholipids 20 % , cholesterol ester 15 %, free cholesterol 8 % and free FAs 1% .

Catabolism: It occurs in the plasma by lipoproteins lipases. These enzymes act on TG converting them into LDL.

3- LDL (B- lipoproteins, carrier protein Apo-B):

Source : degradation of the VLDL and chylomicrons in the circulation and in the liver.

Function: It carries cholesterol to various tissues.

Their densities is 1.0196- 1.063, protein contents 21% (**globulin**) , percent of lipids 79% (TG 13%, phospholipids 28% , cholesterol ester 48%, free cholesterol 10 % and free FAs 1%

Catabolism: It occurs throught LDL receptors.

LDL has specific receptors in tissues such as liver, adrenal cortex, ovary and testis.

LDL receptors allow the cells to uptake and metabolize plasma LDL.

Defficiency of these receptots lead to severe hypercholesterolaemia.

Oestrogen (female sex hormone) increases the number of LDL-receptors in the liver, so, it decrease blood cholesterol in females.

4- HDL (Alpha-lipoprotein, Apo-A, Apo-C, Apo-D and Apo-E):

Source **: Liver and intestine.**

Function: **It carries cholesterol from tissues to the liver to be catabolised.**

Their densities is 1.125- 1.210, protein contents 57% (**globulin**) , percent of lipids 43% (TG 13%, phospholipids 46% , cholesterol ester 29%, free cholesterol 6% and free FAs 6%..

Deficiency of HDL leads to accumulation of cholesterol in the tissues (**Tanger's disease)**

5- Albumin-free FAs (Plasma albumin):

Sources :

During fasting : Hydrolysis of TG from adipose tissues.

After meal ; Hydrolysis of chylomicrons and VLDL.

Their densities is higher than 1.128, protein contents 99% (**albumin**) , percent of lipids 1% (TG 0%, phospholipids 0% , cholesterol ester 0%, free cholesterol 0% and free FAs 100%.

Fate of FFAs; Oxidation for energy production (**occurs during fasting**)

Esterification'; Formation of phospholipids, TG, glycolipids and cholesterol ester (**occurs after a meal**)

Biosynthesis of prostaglandins (PG)

They are produced by all cells and tissues except red blood cells (RBCs).

The intermediate precursor of PG Is arachidonic acid (C20 , 4 D, 5,8,11 and 14) .

This acid is derived from :

a- Linoleic acid (C18 , 2D) present in the diet

b- Phospholipids present in all cell membranes by the action of phospholipase A2 (See the slide of signal transduction).

The first step in PG synthesis is the oxidation and cyclization of arachidonic acid to give PG2 by prostaglandin endoperoxidase synthetase enzyme complex (which include Fatty acid cyclooxygenase and peroxidase)

Fatty Acids

Fatty acids fill two major roles in the body:

1. They act as components of more complex membrane lipids.
2. They also act **as the major components of stored fat in the form of triacylglycerol.**

*- Fatty acids are long-chain hydrocarbon molecules containing a carboxylic acid moiety at one end.

*- The numbering of carbons in fatty acids begins with the carbon of the carboxylic group.

*- At physiological pH, the carboxyl group is readily ionized, rendering negative charge onto fatty acids in body fluids.

*- Fatty acids that contain no carbon-carbon double bonds are termed **saturated fatty acids**; those that contain double bonds are **unsaturated fatty acids.**

*- The numeric designations used for fatty acids come from the number of carbon atoms, followed by the number of sites of unsaturation (eg, palmitic acid is a 16- carbon fatty acid with no unsaturation and is designated by 16:0).

*- The site of unsaturation in a fatty acid is indicated by the symbol **D** and the number of the first carbon of the double bond (e.g. palmitoleic acid is a 16 carbon

*- Fatty acid with one site of unsaturation between carbons 9 and 10, and is designated by 16:1D9).

Lipids are non-polar (hydrophobic) compounds, soluble in organic solvents.

Most membrane lipids are **amphipathic**,i.e. having a **non-polar** end and a **polar** end.

Fatty acids consist of a hydrocarbon chain with a carboxylic acid at one end.

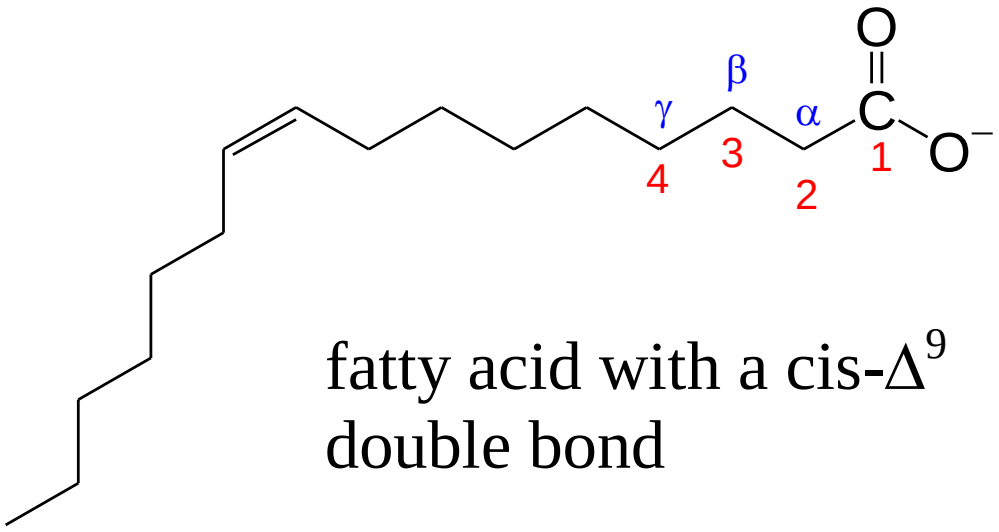
A 16-C fatty acid: $\mathbf{CH_3(CH_2)_{14}\text{-}COO^-}$

Non-polar **polar**

A 16-C fatty acid with one cis double bond between C atoms 9-10 may be represented as **16:1 cis Δ^9**.

Double bonds in fatty acids usually have the **cis** configuration.

Most naturally occurring fatty acids have an **even number** of carbon atoms.



fatty acid with a cis-Δ^9 double bond

Some fatty acids and their common names:

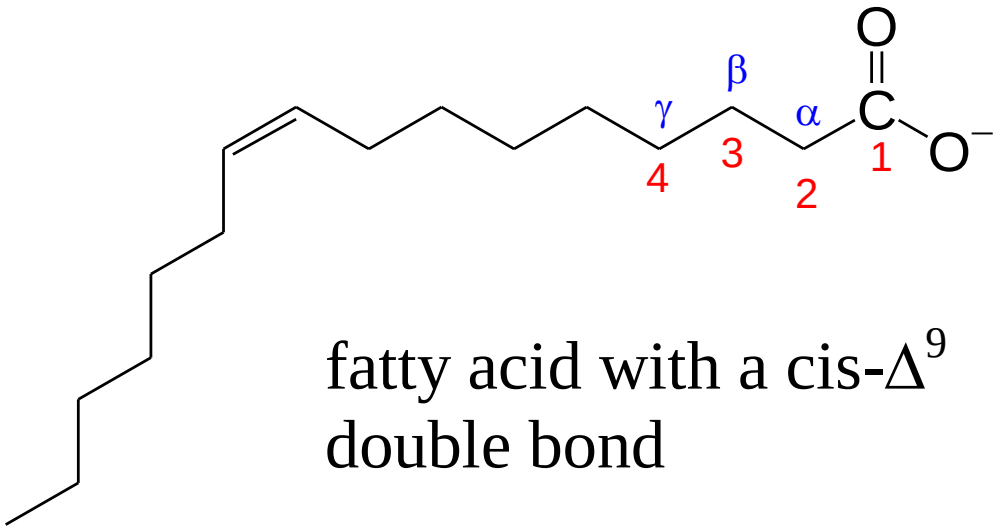
14:0 myristic acid; 16:0 palmitic acid; 18:0 stearic acid; **18:1 cisD*9*** oleic acid

18:2 cisD*9,12* linoleic acid

18:3 cisD*9,12,15* α- Linolenic acid

20:4 cisD*5,8,11,14* **arachidonic acid**

20:5 cisD*5,8,11,14,17* eicosapentaenoic acid (an omega-3)



fatty acid with a cis-Δ^9 double bond

There is a free rotation about **C-C** bonds in the fatty acid hydrocarbon, except where there is a double bond.

Each cis double bond causes a **kink** in the chain.

Rotation about other **C-C** bonds would permit a more linear structure than shown, but there would be a kink.

*- Saturated fatty acids **of less than eight carbon atoms are liquid** at physiological temperature, whereas those containing **more than ten are solid**

*- The **presence of double bonds** in fatty acids **significantly lowers** the **melting point** relative to a saturated fatty acid.

*- The majority of body fatty acids are acquired in the diet.

*- However, the lipid biosynthetic capacity of the body (fatty acid synthase and other fatty acid modifying enzymes) can supply the body with all the various fatty acid structures needed.

*- Two key exceptions to this are the highly unsaturated fatty acids know as linoleic acid and linolenic acid, containing **unsaturation** sites beyond carbons 9 and 10.

*- These two fatty acids cannot be synthesized from precursors in the body, and are thus considered the **essential fatty acids**; **essential in the sense that they must be provided in the diet.**

*- Since plants are capable of synthesizing linoleic and linolenic acid **humans can acquire these fats by consuming a variety of plants or else** by eating the meat of animals that have consumed these plant fats.

In general, the general formula of the fatty acids are RCOOH and they are classified into:

A- Saturated fatty acids (F.As.): Such F.As. contain no double bounds in their structures and they are further classified into :

i-Short chain F.As.: They contain 2 - 10 carbon atoms. This subtype also are further classified into :

a-Volatile saturated short chain F.As.: *They are liquid in nature and contain 2 – 6 carbon atoms and they are volatile at room temp. (acetic, propionic, butyric, valeric and caproic acid)*

b-Non-volatile short chain saturated FAs : They are solids, non-volatile, and contains 7 – 10 carbon atoms in their skeletons (e.g. C8 = octanoic acid or caprylic acid).

ii- Long chain FAs : Contains more than 10 carbon atoms, non-volatile and solids at room temp. and they are not soluble in water (even number of carbon atoms, mostly) eg palmitic C16 , stearic C18 and lignoceric C24.

B- Unsaturated FAs : contains double bond(s).

One = Oleic (Unsaturated stearic) C18 at C9-C10 and nervonic acid C24 (C15-16)

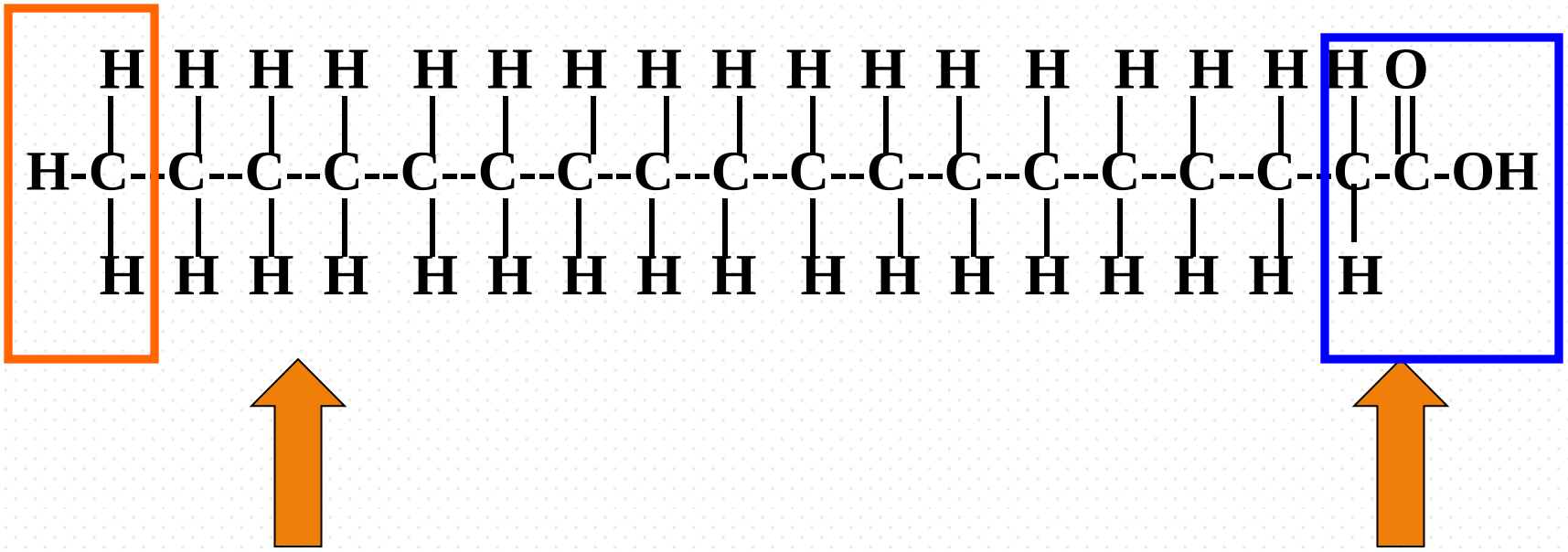
Two = Linoleic acid (C18, at C9 and C12)

Three = Linolenic acid (C18, at C9, C12 and 15)

Four = Arachidonic acid (C20, at C5, C8, C11 and 14) **and five** (clupandonic acid).

Essential FAs: They are polyunsaturated FAs containing more than one double bond. They are also not synthesized in our bodies and, therefore, must be supplied in food. They include linoleic, linolenic, arachidonic and clupandonic acid. One of them is arachidonic acid is the precursor of prostaglandins.

Fatty Acid Structure

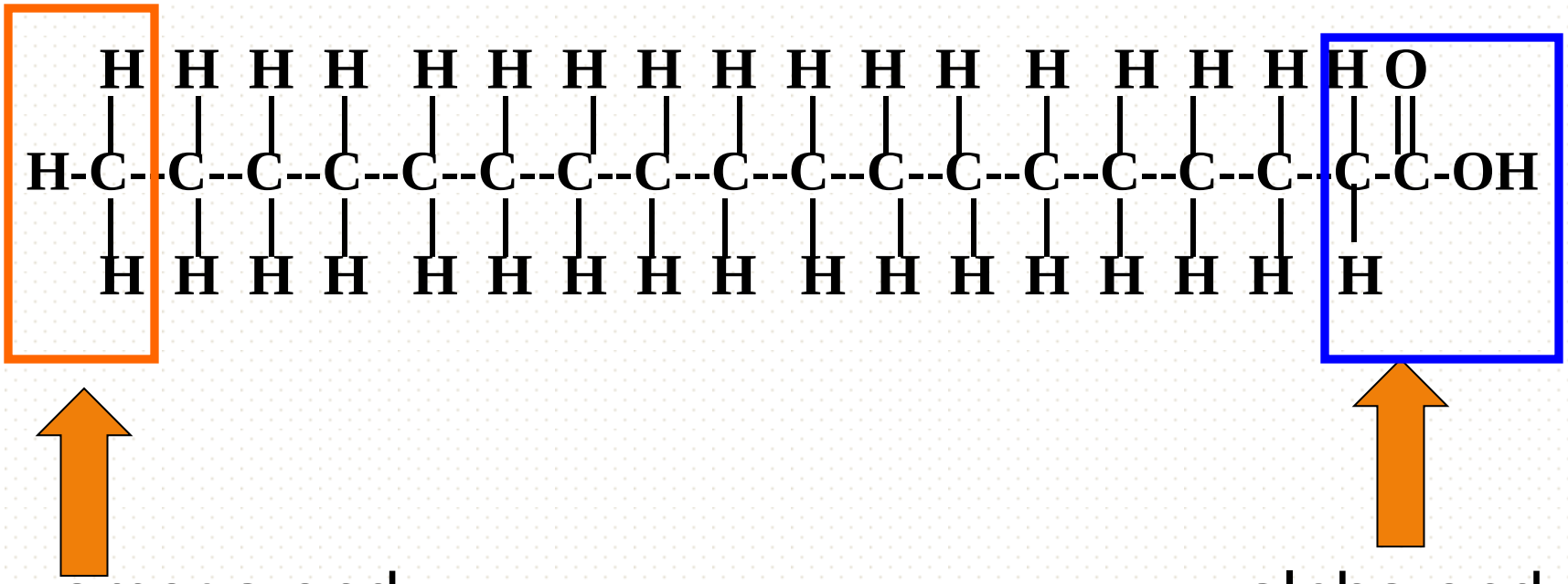


Omega end

Alpha end

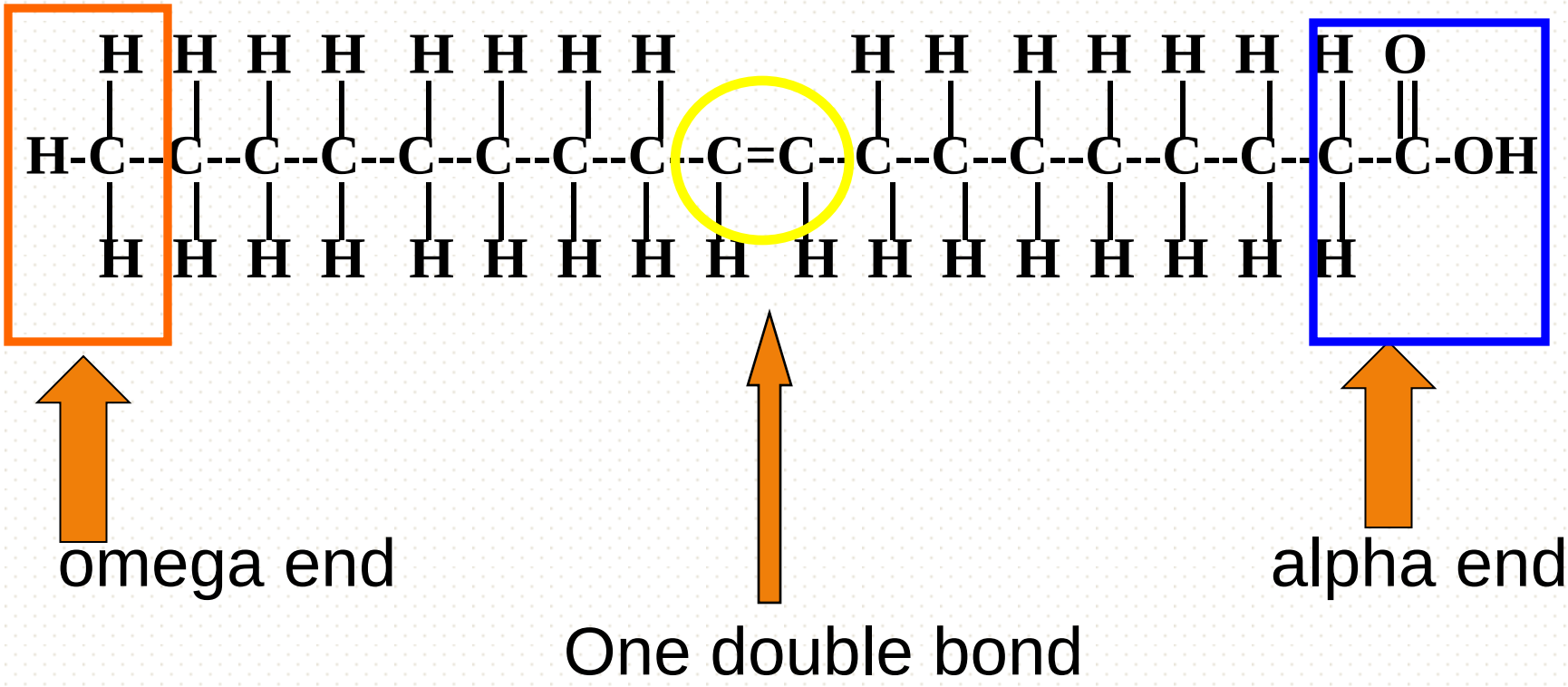
Degree of saturation

Saturated Fatty Acid Structure

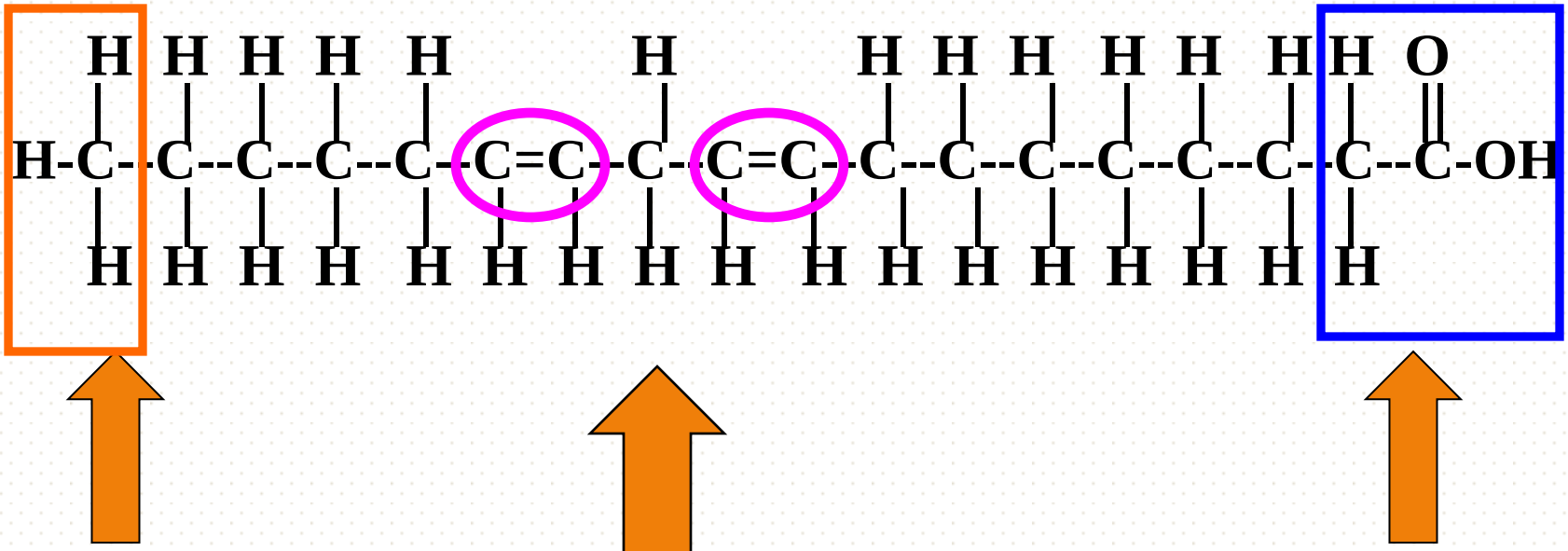


degree of saturation: single carbon bond

Monounsaturated Fatty Acid Structure



Polyunsaturated Fatty Acid Structure



Chain Length of Fatty Acids

- Long chain FA
  - ≥ 12 Carbons
- Medium chain FA
  - 6 - 10 Carbons
- Short chain FA
  - < 6 Carbons

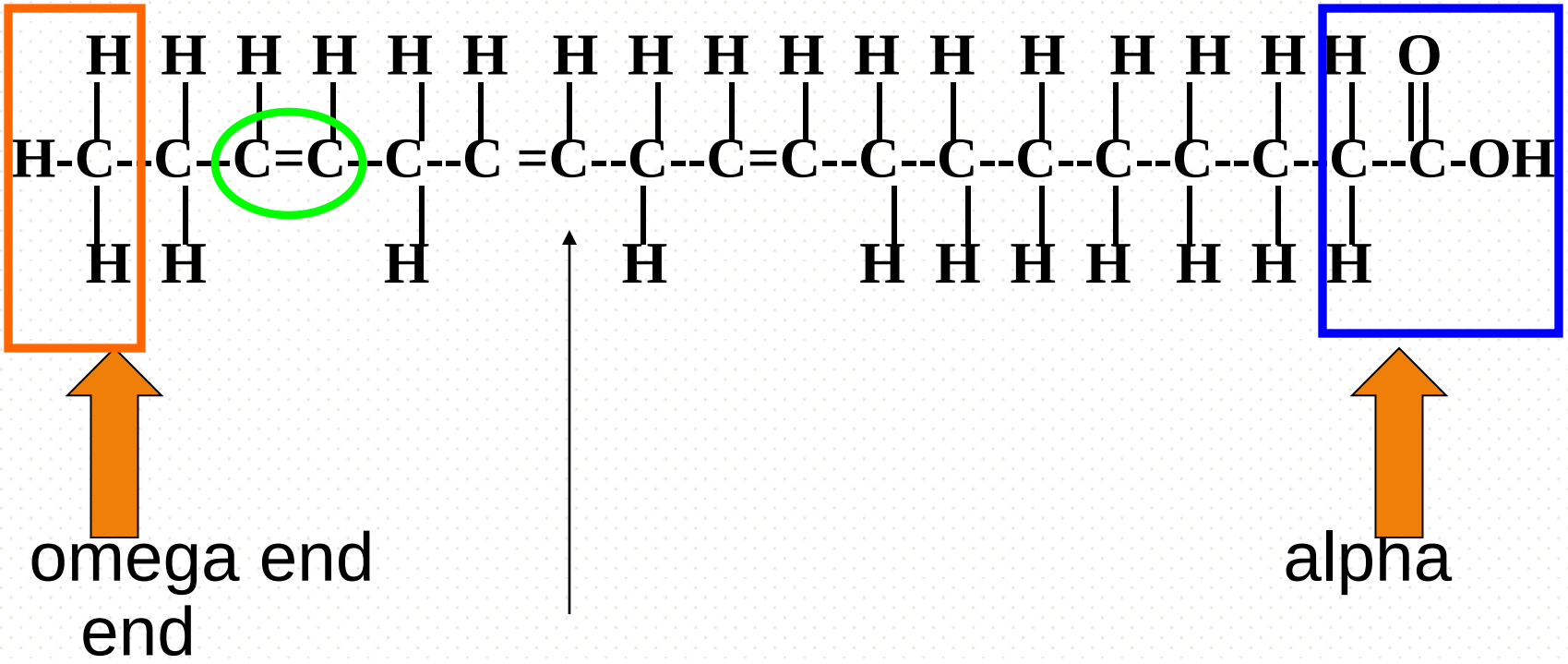
Physiologically Relevant Fatty Acids

Numerical Symbol	Common Name	Structure	Comments
14:0	Myristic acid	**CH3 (CH2)12 COOH**	Often found attached to the N-term. of plasma membrane-associated cytoplasmic proteins
16:0	Palmitic acid	**CH3 (CH2)14 COOH**	End product of mammalian fatty acid synthesis
16:1D9	Palmitoleic acid	**CH3 (CH2)5 HC=CH (CH2)7 COOH**	
18:0	Stearic acid	**CH3(CH2)16COOH**	
18:1D9	Oleic acid	**CH3 (CH2)7 HC=CH (CH2)7COOH**	
18:2D9,12	Linoleic acid	**CH3(CH2)5C=CCH$_2$C=C9(CH2)7COOH**	Essential fatty acid
18:3D9,12,15	Linolenic acid	**CH3 (CH2)5 C=CCH2 C=CCH2C=C9 (CH2)7COOH**	Essential fatty acid
20:4D5,8,11,14	Arachidonic acid	**CH3 (CH2)4 C=C14 CH2 C=C CH2 C=C8 CH2C=C5 (CH2)3COOH**	Precursor for prostaglandins

Essential Fatty Acids

- Must be eaten
- Body can only make double bonds after the 9th carbon from the omega end
- Needed for immune function, vision, cell membrane, and production of hormone-like compounds

Essential Fatty Acid- Omega-3 (alpha-linolenic acid)

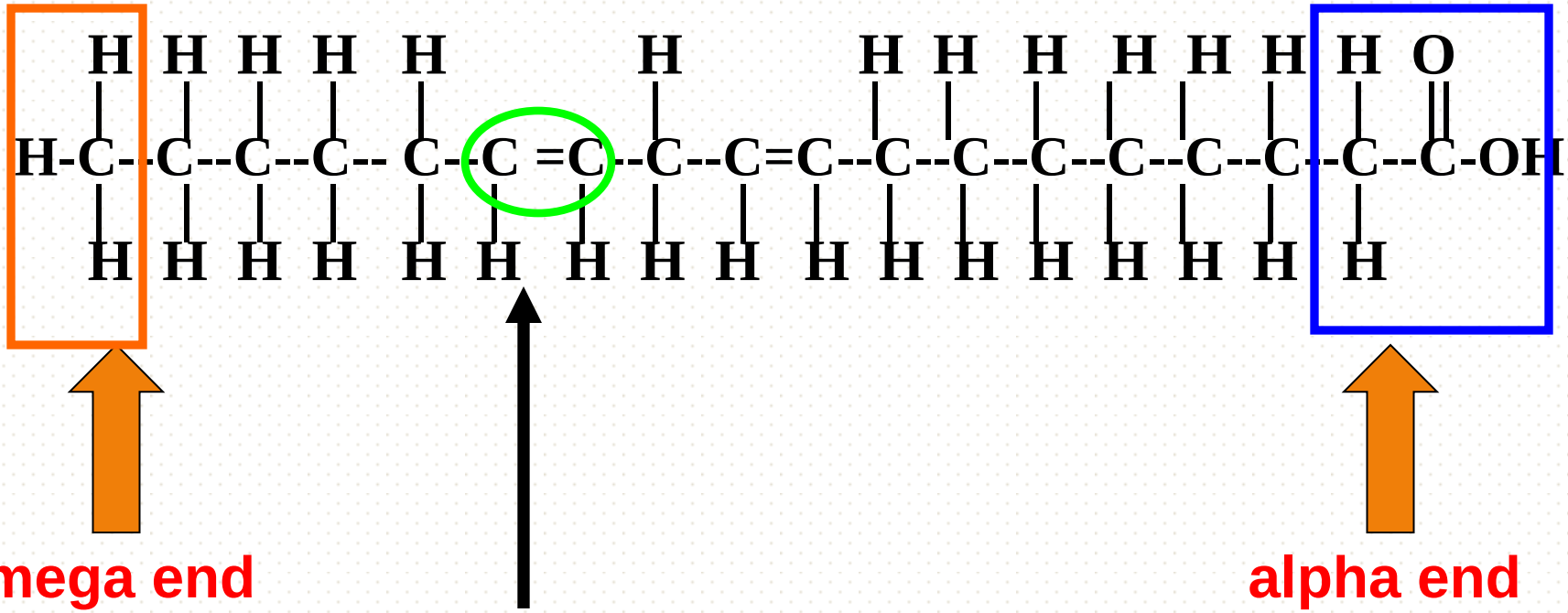


Omega-3: 1st double bond is located on the 3rd carbon from the omega end

Omega-3 Fatty Acid

- Primarily from fish oil
- Also found in canola or soybean oil
- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are related
- Metabolized to form eicosanoids
- Recommend intake of ~2 servings of fish per week

Essential Fatty Acid- Omega-6 (linoleic acid)



Omega-6: means that the 1st double bond is located on the 6th carbon atom from the omega end

Omega-6 Fatty Acid

- Found in vegetable oils
- Only need ~ 1 tablespoon a day
- Arachidonic acid can be made from omega-6
- Metabolized to form eicosanoids

Omega-6 Fatty Acid

Omega-6

Linoleic Acid (C18:2)

2C

2H

Dihomo-gama-linolenic acid (C20:3)

2H

Arachidonic acid (C20:4)

Omega-3 Fatty Acids

Omega-3 (C18:3)

Alpha-linolenic Acid (C18:3)

2C

4H

Eicosapentaenoic Acid (C20:5)

(EPA)

2C

4H

Docosahexaenoic Acid (C22:6)

(DHA)

Eicosanoids

- A group of hormone-like compounds
- Regulates blood pressure, childbirth, clotting, immune responses, inflammatory responses, & stomach secretions
- By-pass the blood stream and work in the area of origin

Eicosanoids Have Different Effects

- Omega-6 eicosanoids; Archidonic acid
  - increase blood clotting
  - increase inflammatory responses
- Omega-3 eicosanoids, DHA, EPA
  - decrease blood clotting
  - reduce heart attack
  - excess may cause hemorrhagic stroke
- Eicosanoid has different effect on different tissues

Signs and Symptoms of Essential Fatty Acids Deficiency

- Flaky, itchy skin
- Diarrhea
- Infections
- Retarded growth and wound healing
- Anemia

Calculations of energy gain by palmitic acid:

B- oxidation of palmetic acid (C16) will be repeated 7 times giving 8 molecules of acetyl CoA . In each time, FADH2 and NADH+H (FADH2 give 3 ATP and NADH+H give 3ATP so 7 times = 7 X5 ATP = 35 ATP

Citric acid cycle; Each acetyl CoA oxidized in citric acid cycle gives 12 ATP

8 X 12 ATP = 96 ATP.

Also, 2 ATP were used in the activation of Palmitic acid to active CoA ;

Thus the energy gain= Energy produced – Energy utilized

= 35 ATP + 96 ATP – 2 ATP

= 131 ATP – 2 ATP

= 129 ATP

Saponifiable and Nonsaponifiable Lipids

*- Lipids can be considered to be biological molecules which are soluble in organic solvents, such as chloroform/methanol, and are sparingly soluble in aqueous solutions.

*- There are two major classes, **saponifiable** and **nonsaponifiable**, based on their reactivity with strong bases.

*- The nonsaponifiable classes include the "fat-soluble" vitamins (A, E) and cholesterol. .

Saponification

*- Is the process that produces soaps from the reaction of lipids and a strong base (sodium soap or calcium soap depending on the type of the base used).

*- The saponifiable lipids contain long chain carboxylic acids, or **fatty acids**.

*- These **fatty acids are esterified** to a "backbone" molecule, **or alcohols.**

*- The **alcohols** are either **glycerol** or **spingosine**. **Also**, cholesterol as an stroidal alcohol is included.

*- **The major saponifiable lipids** are triacylglycerides, glycerophospholipids, and the sphingolipids. The first two use glycerol as the backbone.

*- Triacylglycerides have three fatty acids esterified to the three OHs on glycerol.

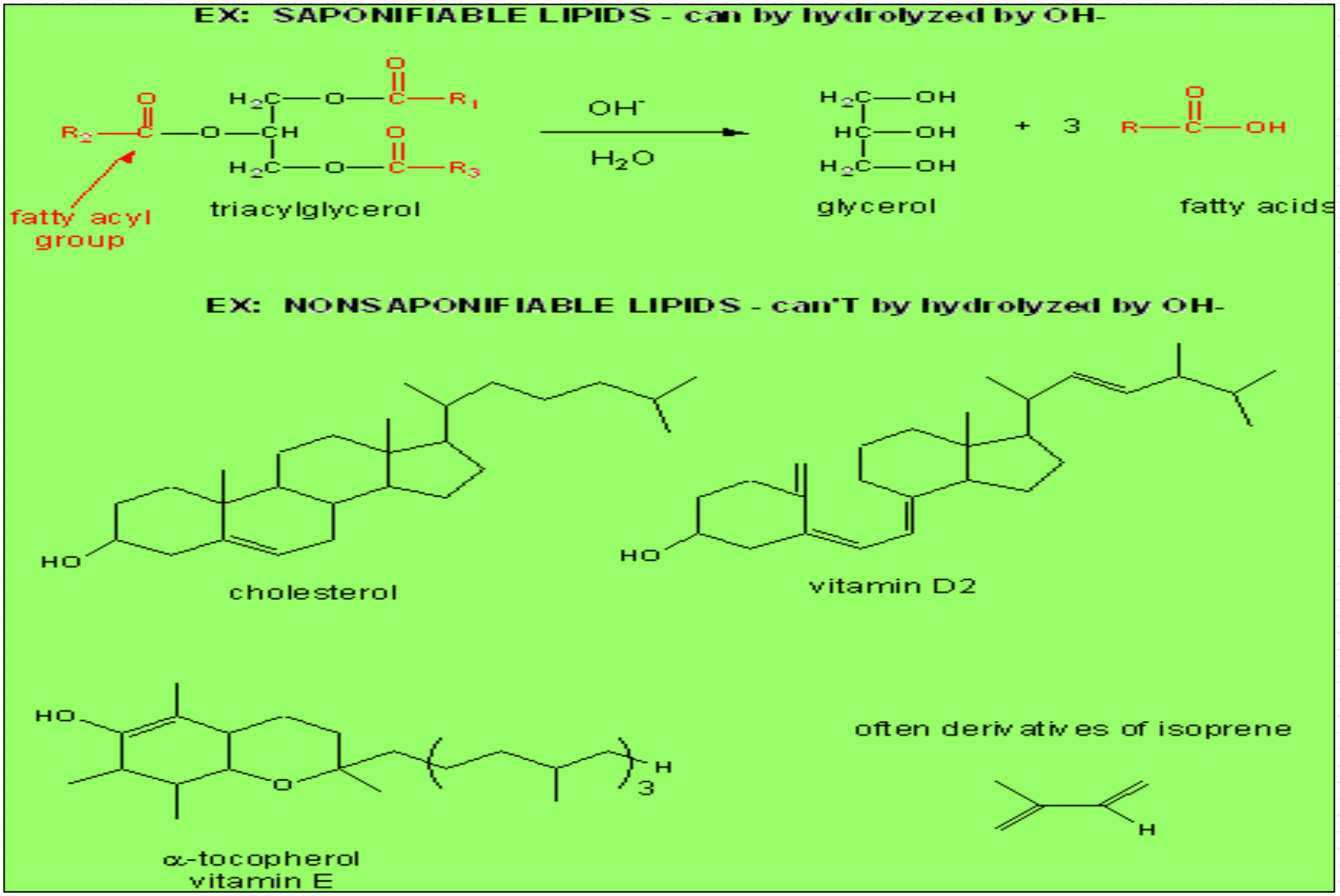
Glycerophospholipids have two fatty acids esterified at carbons 1 and 2, and phospho-X groups esterifed at C3.

*- Spingosine, the backbone for spingolipids, has a long alkyl group connected at C1 and a free amine at C2, as a backbone.

*- In spingolipids, a fatty acid is attached through an amide link at C2, and a H or esterified phospho-X group is found at C3.

*- A general diagrams showing the difference in these structures is shown below.

Figure: Examples saponifiable and nonsaponifiable lipids



Fat constants

1-Saponification value: It is the number of mgs of KOH necessary to combine with all fatty acids present in one gm of fat (after their hydrolysis, marker of M Wt)

2- Reichert-Meissel number: It is the number of ml of 0.1 N alkali needed to neutralize the volatile short chain FAs present in one gm of fat (Markers of quality= M wt).

3- Acid value: It is the number of mgs of KOH necessary to neutralize theFree fatty acids present in one gm of fat (Before hydrolysis, marker of rancidity)

4- Iodine number : It is the number of gm of iodine absorbed by 100 gm of fat or oil (Marker of unsaturation)

Introduction to Cholesterol Metabolism

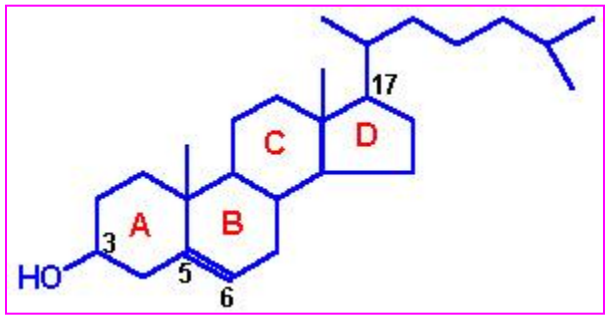
Cholesterol is an extremely important biological molecule that has roles in membrane structure as well as being a precursor for the synthesis of the steroid hormones and bile acids.

Both dietary cholesterol and that synthesized *de novo* are transported through the circulation in lipoprotein particles. The same is true of cholesteryl esters, the form in which cholesterol is stored in cells.

The synthesis and utilization of cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body.

Of particular importance clinically is the abnormal deposition of cholesterol and cholesterol-rich lipoproteins in the coronary arteries.

Such deposition, eventually leading to atherosclerosis, a disease is the leading contributory factor in diseases of the coronary arteries.



Biosynthesis of Cholesterol

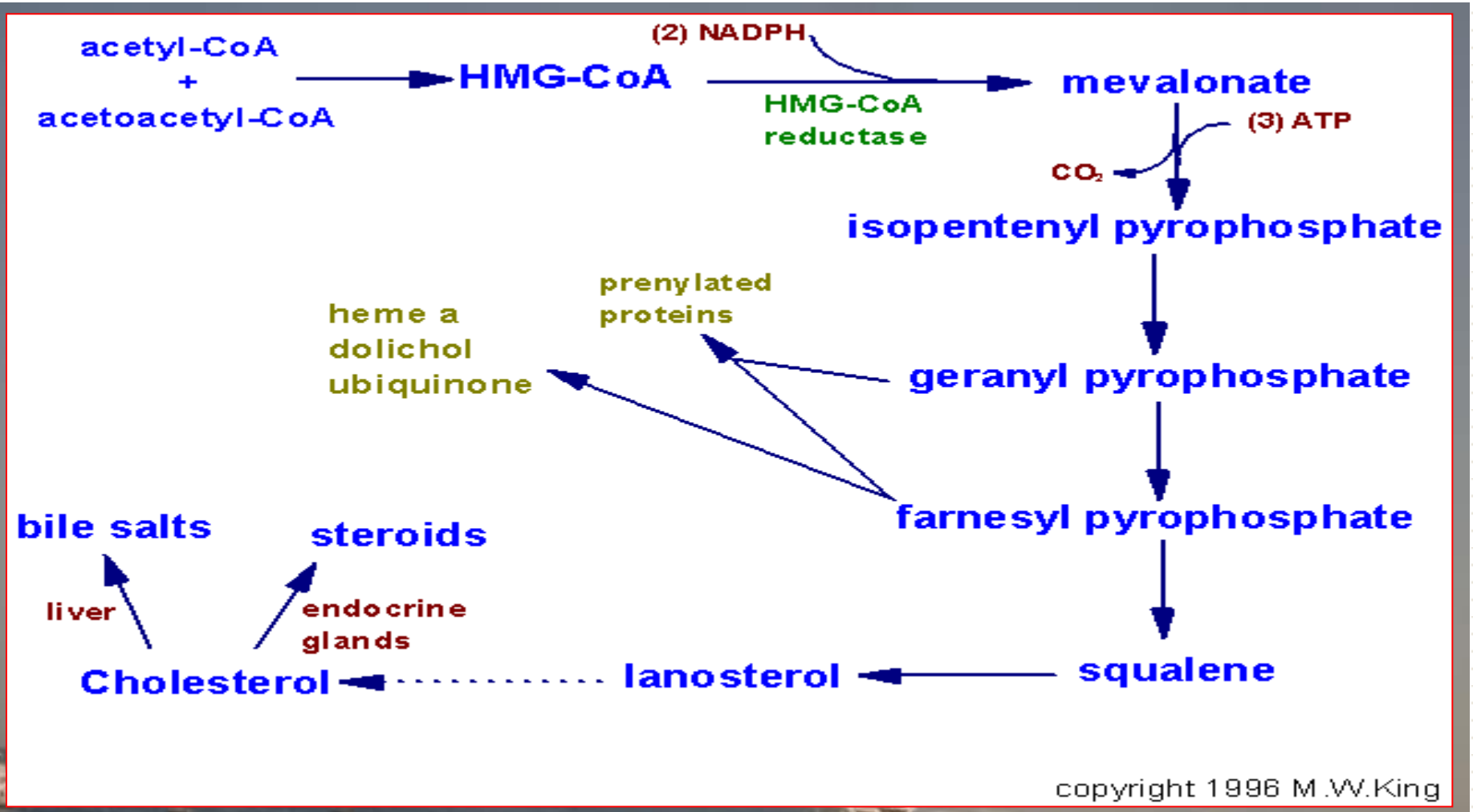
Slightly less than half of the cholesterol in the body derives from biosynthesis *de novo*.

Biosynthesis in the liver accounts for approximately 10%, and in the intestine approximately 15%, of the amount produced each day.

Cholesterol synthesis occurs in the cytoplasm and microsomes from the two-carbonacetate group of acetyl-CoA.

The process has five major steps:

1. Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
2. HMG-CoA is converted to mevalonate
3. Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO2.
4. IPP is converted to squalene
5. Squalene is converted to cholesterol.



Pathway of cholesterol biosynthesis. Synthesis begins with the transport of acetyl-CoA ffrom the mitochondrion to the cytosol. The rate limiting step occurs at the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reducatase, HMGR catalyzed step. The phosphorylation reactions are required to solubilize the isoprenoid intermediates in the pathway. Intermediates in the pathway are used for the synthesis of prenylated proteins, dolichol, coenzyme Q and the side chain of heme *a*.

Acetyl-CoA units are converted to mevalonate by a series of reactions that begins with the formation of HMG-CoA. Unlike the HMG-CoA formed during ketone body synthesis in the mitochondria, this form is synthesized in the cytoplasm.
However, the pathway and the necessary enzymes are the same as those in the mitochondria. Two moles of acetyl-CoA are condensed in a reversal of the thiolase reaction, forming acetoacetyl-CoA.

Acetoacetyl-CoA and a third mole of acetyl-CoA are converted to HMG-CoA by the action of HMG-CoA synthase. HMG-CoA is converted to mevalonate by HMG-CoA reductase, HMGR (this enzyme is bound in the endoplasmic reticulum, ER).

HMGR absolutely requires NADPH as a cofactor and two moles of NADPH are consumed during the conversion of HMG-CoA to mevalonate. The reaction catalyzed by HMGR is the rate limiting step of cholesterol biosynthesis, and this enzyme is subject to complex regulatory controls.

Mevalonate is then activated by three successive phosphorylations, yielding 5-pyrophosphomevalonate. In addition to activating mevalonate, the phosphorylations maintain its solubility, since otherwise it is insoluble in water.

After phosphorylation, an ATP-dependent decarboxylation yields isopentenyl pyrophosphate, IPP, an activated isoprenoid molecule. Isopentenyl pyrophosphate is in equilibrium with its isomer, dimethylallyl pyrophosphate, DMPP.

One molecule of IPP condenses with one molecule of DMPP to generate geranyl pyrophosphate, GPP. GPP further condenses with another IPP molecule to yield farnesyl pyrophosphate, FPP.

Finally, the NADPH-requiring enzyme, squalene synthase catalyzes the head-to-tail condensation of two molecules of FPP, yielding squalene (squalene synthase also is tightly associated with the endoplasmic reticulum).

Squalene undergoes a two step cyclization to yield lanosterol. The first reaction is catalyzed by squalene monooxygenase.
This enzyme uses NADPH as a cofactor to introduce molecular oxygen as an epoxide at the 2,3 position of

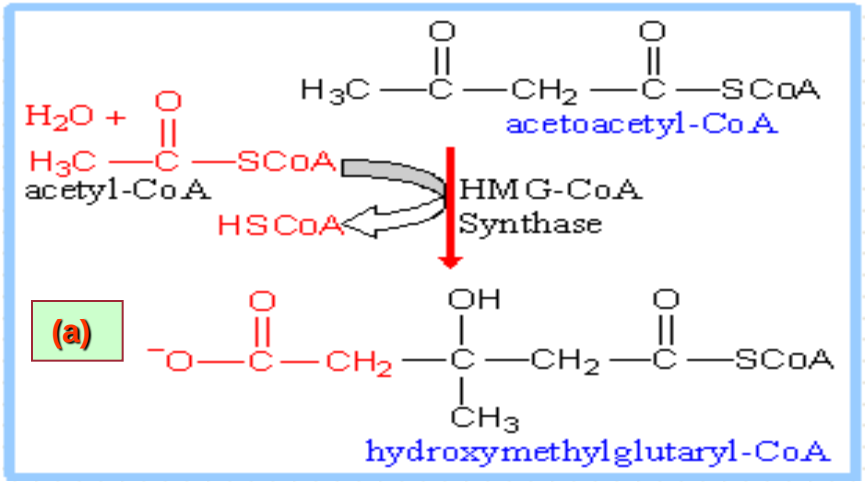
Cholesterol synthesis

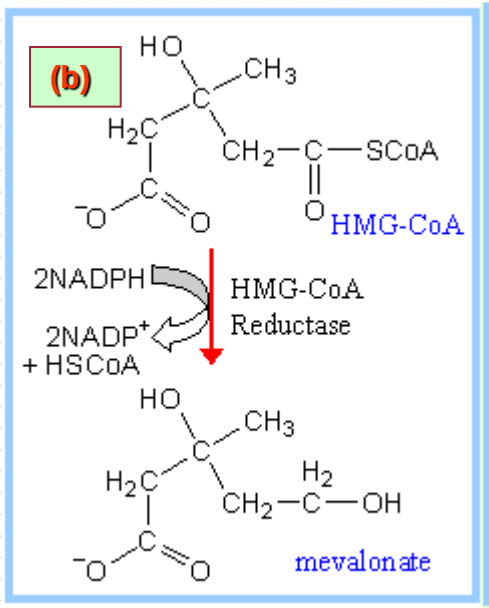
Hydroxy methylglutaryl-coenzyme A (HMG-CoA, the cytosollic type of this enzyme) is the precursor for cholesterol synthesis.

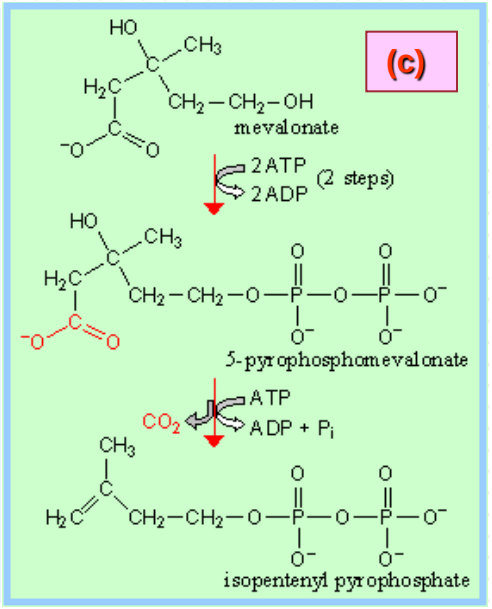
HMG-CoA is formed by condensation of acetyl-CoA and acetoacetyl-CoA, catalyzed by HMG-CoA Synthase (a)..

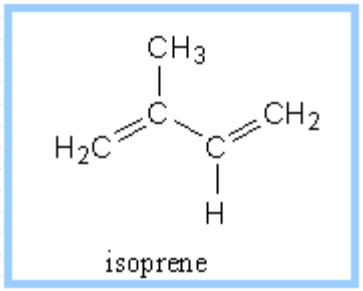
HMG-CoA Reductase catalyzes production of mevalonate from HMG-CoA (b). The carboxyl group of hydroxymethylglutarate that is in ester linkage to the thiol of coenzyme A is reduced first to an aldehyde and then to an alcohol.

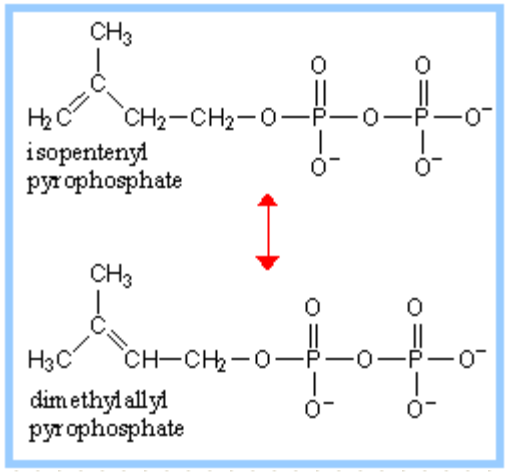
Mevalonate is phosphorylated by 2 sequential phosphate transfers from ATP, yielding the pyrophosphate derivative. Pyrophosphomevolanate Decarboxylase catalyzes ATP-dependent decarboxylation, with dehydration, to yield isopentenyl pyrophosphate (c).

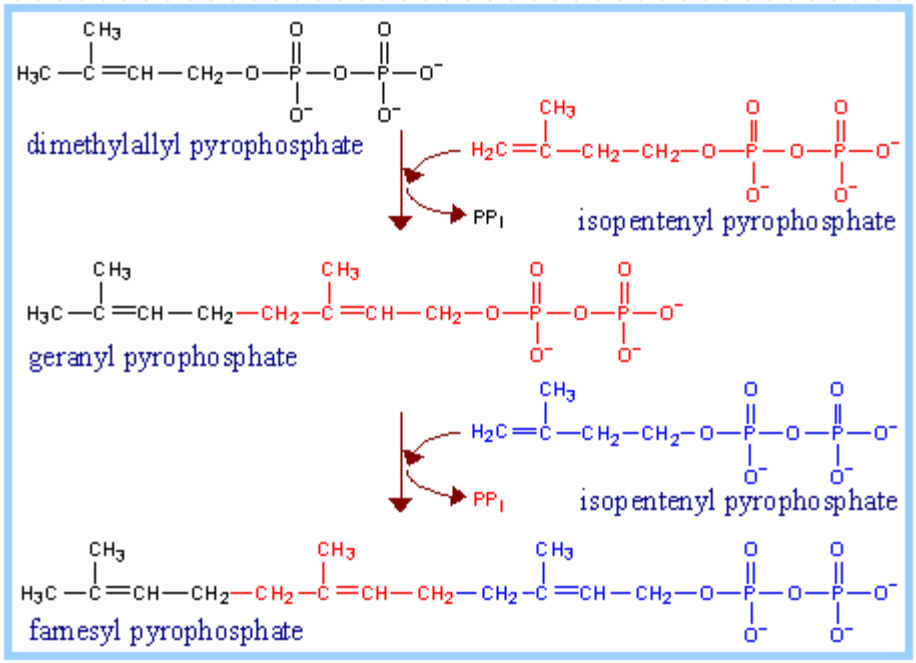












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Pathway for the movement of acetyl-CoA units from within the mitochondrion to the cytoplasm for use in lipid and cholesterol biosynthesis

The acetyl-CoA utilized for cholesterol biosynthesis is derived from an oxidation reaction (e.g., fatty acids or pyruvate) in the mitochondria and is transported to the cytoplasm by the same process as that described for fatty acid synthesis (see the Figure below).

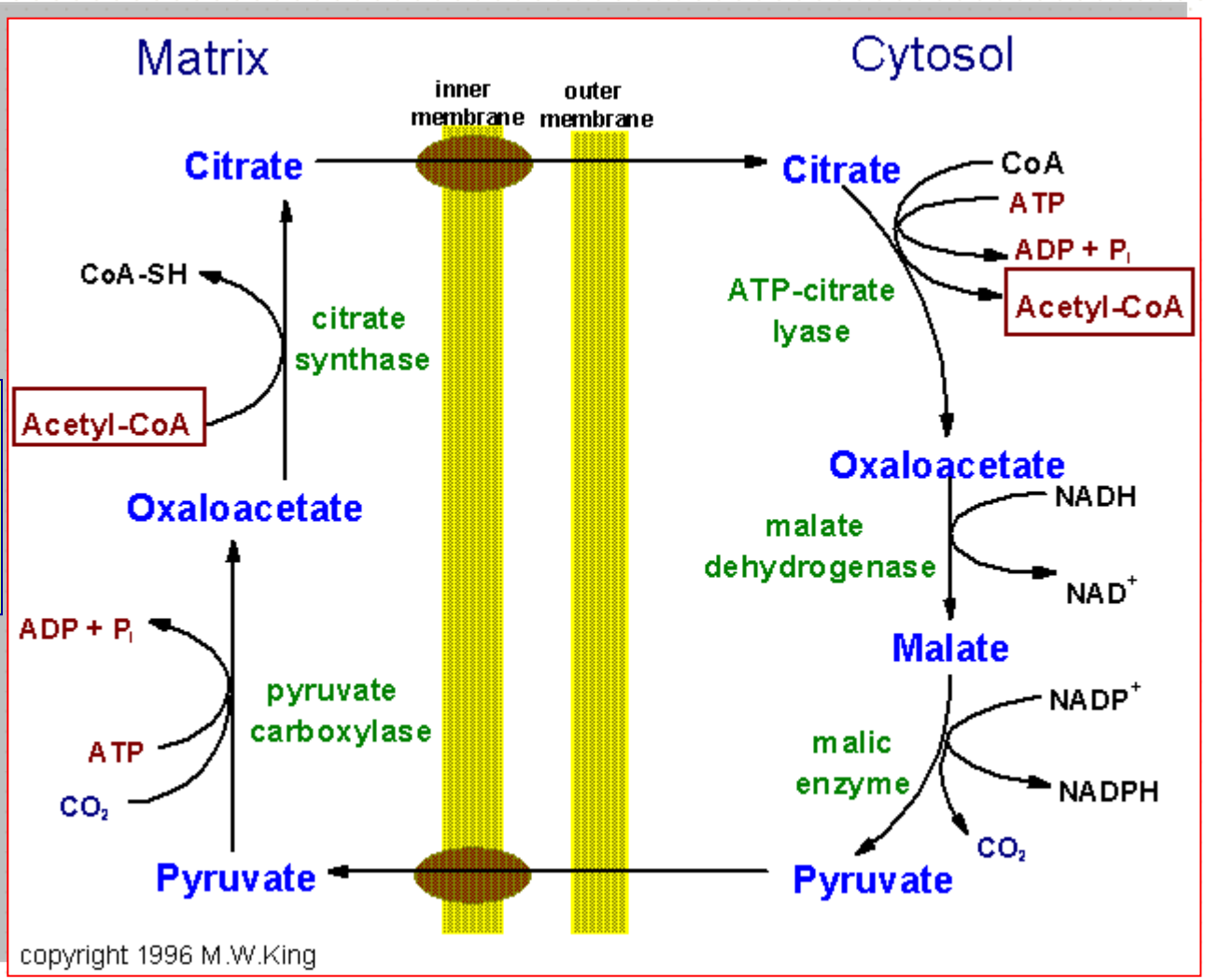
Acetyl-CoA can also be derived from cytoplasmic oxidation of ethanol by acetyl-CoA synthetase.

All the reduction reactions of cholesterol biosynthesis use NADPH as a cofactor.

The isoprenoid intermediates of cholesterol biosynthesis can be diverted to other synthesis reactions, such as those for dolichol (used in the synthesis of N-linked glycoproteins, coenzyme Q (of the oxidative phosphorylation) pathway or the side chain of heme *a*.

Additionally, these intermediates are used in the lipid modification of some proteins.

Note that the cytoplasmic malic enzyme catalyzed reaction generates NADPH which can be used for reductive biosynthetic reactions such as those of fatty acid and cholesterol synthesis.



Regulating Cholesterol Synthesis

Normal healthy adults synthesize cholesterol at a rate of approximately 1g/day and consume approximately 0.3g/day. A relatively constant level of cholesterol in the body (150 - 200 mg/dl) is maintained primarily by controlling the level of *de novo* synthesis. The level of cholesterol synthesis is regulated in part by the dietary intake of cholesterol. Cholesterol from both diet and synthesis is utilized in the formation of membranes and in the synthesis of the steroid hormones and bile acids (see below). The greatest proportion of cholesterol is used in bile acid synthesis.

The cellular supply of cholesterol is maintained at a steady level by three distinct mechanisms:

1. **Regulation of HMGR activity and levels**
2. **Regulation of excess intracellular free cholesterol through the activity of acyl-CoA:cholesterol acyltransferase, ACAT**
3. **Regulation of plasma cholesterol levels via LDL receptor-mediated uptake and HDL-mediated reverse transport.**

Regulation of HMGR activity is the primary means for controlling the level of cholesterol biosynthesis. The enzyme is controlled by four distinct mechanisms: feed-back inhibition, control of gene expression, rate of enzyme degradation and phosphorylation-dephosphorylation.

The first three control mechanisms are exerted by cholesterol itself. Cholesterol acts as a feed-back inhibitor of pre-existing HMGR as well as inducing rapid degradation of the enzyme. The latter is the result of cholesterol-induced polyubiquitination of HMGR and its degradation in the proteosome (see proteolytic degradation below).

This ability of cholesterol is a consequence of the sterol sensing domain, SSD of HMGR.

In addition, when cholesterol is in excess the amount of mRNA for HMGR is reduced as a result of decreased expression of the gene.

The mechanism by which cholesterol (and other sterols) affect the transcription of the HMGR gene is described below under regulation of sterol content.

Regulation of HMGR through covalent modification occurs as a result of phosphorylation and dephosphorylation.

The enzyme is most active in its unmodified form. Phosphorylation of the enzyme decreases its activity. HMGR is phosphorylated by AMP-activated protein kinase, AMPK (this is not the same as cAMP-dependent protein kinase, PKA).

AMPK itself is activated via phosphorylation.

The phosphorylation of AMPK is catalyzed by one or more AMPK kinases (AMPKKs).

Regulation of HMGR by covalent modification.

HMGR is most active in the dephosphorylated state.

Phosphorylation is catalyzed by AMP-activated protein kinase, AMPK, (used to be termed HMGR kinase), an enzyme whose activity is also regulated by phosphorylation.

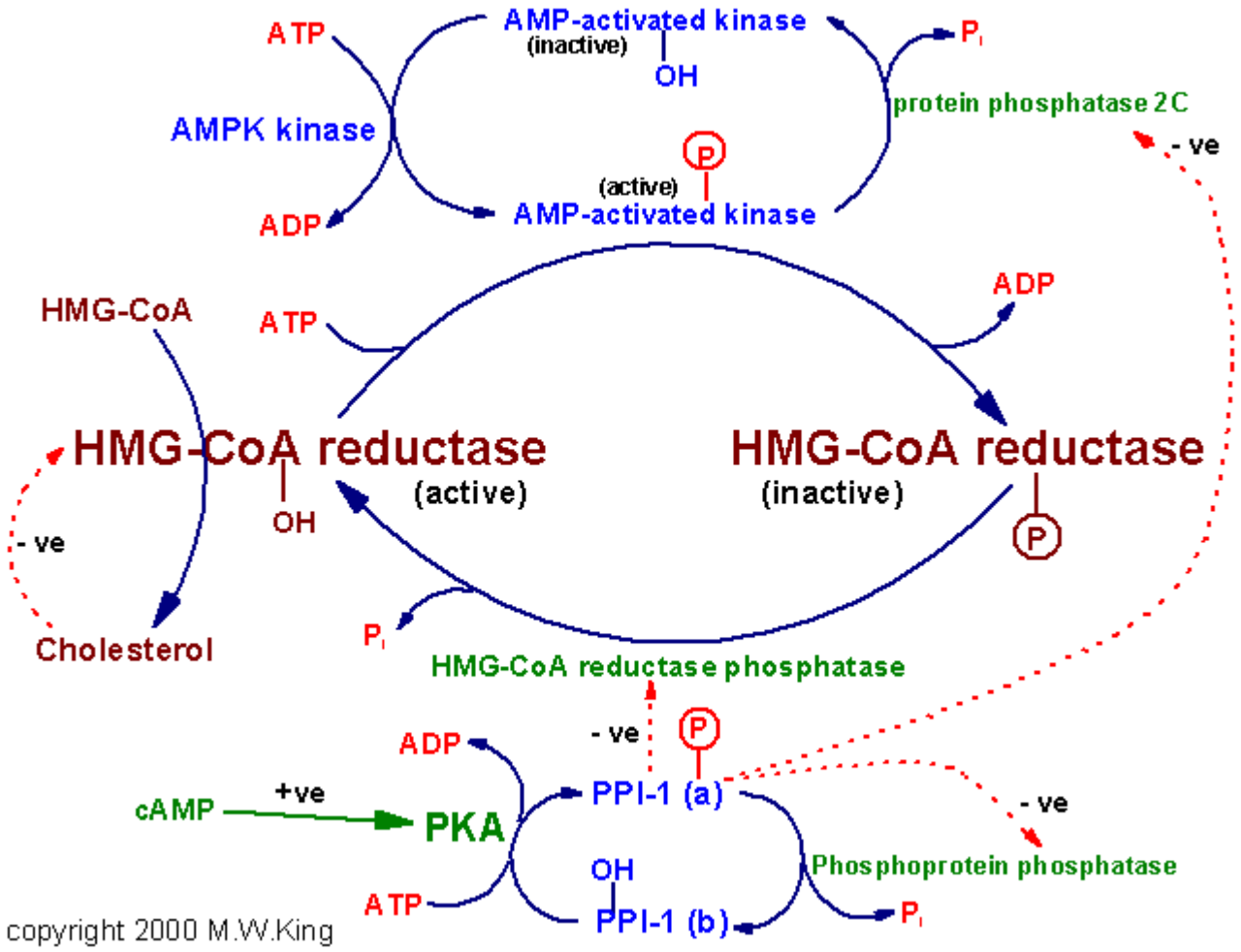
Phosphorylation of AMPK is catalyzed by AMPK kinase (AMPKK).

Hormones such as glucagon and epinephrine negatively affect cholesterol biosynthesis by increasing the activity of the inhibitor of phosphoprotein phosphatase inhibitor-1, PPI-1.

Conversely, insulin stimulates the removal of phosphates and, thereby, activates HMGR activity.

Additional regulation of HMGR occurs through an inhibition of its' activity as well as of its' synthesis by elevation in intracellular cholesterol levels.

This latter phenomenon involves the transcription factor SREBP described below.



The activity of HMGR is additionally controlled by the cAMP signaling pathway. Increases in cAMP lead to activation of cAMP-dependent protein kinase, PKA. In the context of HMGR regulation, PKA phosphorylates phosphoprotein phosphatase inhibitor-1 (PPI-1) leading to an increase in its' activity.

PPI-1 can inhibit the activity of numerous phosphatases including protein phosphatase 2C and HMG-CoA reductase phosphatase which remove phosphates from AMPK and HMGR, respectively.

This maintains AMPK in the phosphorylated and active state, and HMGR in the phosphorylated and inactive state.

As the stimulus leading to increased cAMP production is removed, the level of phosphorylations decreases and that of dephosphorylations increases. The net result is a return to a higher level of HMGR activity.

Since the intracellular level of cAMP is regulated by hormonal stimuli, regulation of cholesterol biosynthesis is hormonally controlled. Insulin leads to a decrease in cAMP, which in turn activates cholesterol synthesis. Alternatively, glucagon and epinephrine, which increase the level of cAMP, inhibit cholesterol synthesis.

The ability of insulin to stimulate, and glucagon to inhibit, HMGR activity is consistent with the effects of these hormones on other metabolic pathways.

The basic function of these two hormones is to control the availability and delivery of energy to all cells of the body.

Long-term control of HMGR activity is exerted primarily through control over the synthesis and degradation of the enzyme.

When levels of cholesterol are high, the level of expression of the HMGR gene is reduced. Conversely, reduced levels of cholesterol activate expression of the gene. Insulin also brings about long-term regulation of cholesterol metabolism by increasing the level of HMGR synthesis.

Proteolytic Regulation of HMG-CoA Reductase

The stability of HMGR is regulated as the rate of flux through the mevalonate synthesis pathway changes.

When the flux is high the rate of HMGR degradation is also high. When the flux is low, degradation of HMGR decreases. This phenomenon can easily be observed in the presence of the statin drugs.

HMGR is localized to the ER and like SREBP (see below) contains a sterol-sensing domain, SSD.

When sterol levels increase in cells there is an concommitant increase in the rate of HMGR degradation.

The degradation of HMGR occurs within the proteosome, a multiprotein complex dedicated to protein degradation.

The primary signal directing proteins to the proteosome is ubiquitination. Ubiquitin is a 7.6kDa protein that is covalently attached to proteins targeted for degradation by ubiquitin ligases.

These enzymes attach multiple copies of ubiquitin allowing for recognition by the proteosome. HMGR has been shown to be ubiquitinated prior to its degradation.

The primary sterol regulating HMGR degradation is cholesterol itself. As the levels of free cholesterol increase in cells, the rate of HMGR degradation increases.

The Utilization of Cholesterol

Cholesterol is transported in the plasma predominantly as cholesteryl esters associated with lipoproteins.

Dietary cholesterol is transported from the small intestine to the liver within chylomicrons.

Cholesterol synthesized by the liver, as well as any dietary cholesterol in the liver that exceeds hepatic needs, is transported in the serum within LDLs.

The liver synthesizes VLDLs and these are converted to LDLs through the action of endothelial cell-associated lipoprotein lipase.

Cholesterol found in plasma membranes can be extracted by HDLs and esterified by the HDL-associated enzyme LCAT.

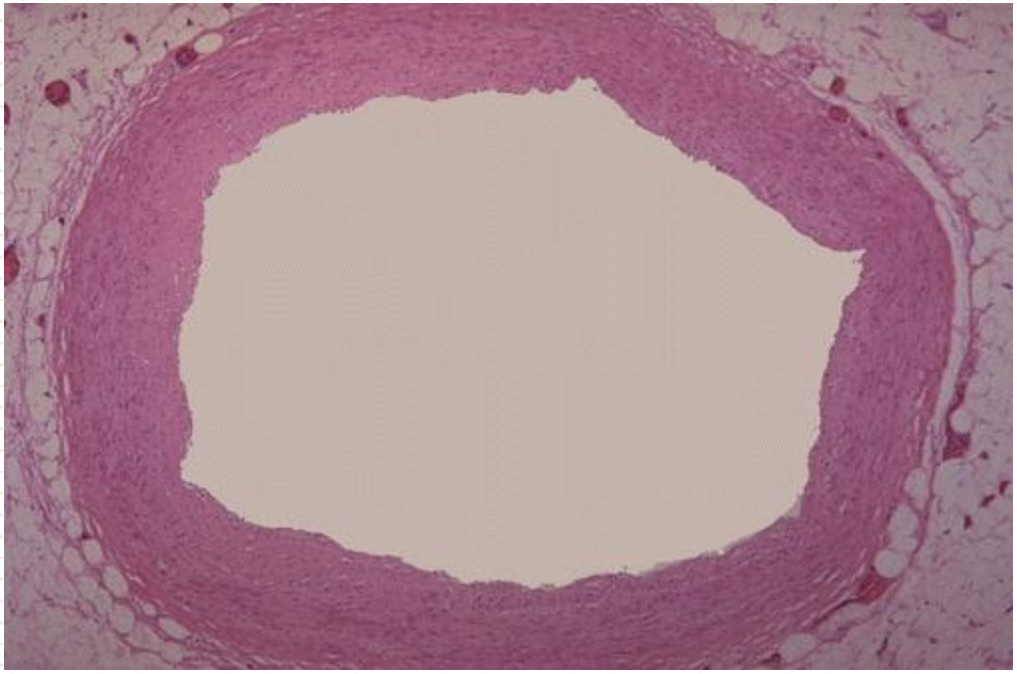
The cholesterol acquired from peripheral tissues by HDLs can then be transferred to VLDLs and LDLs via the action of cholesteryl ester transfer protein (apo-D) which is associated with HDLs.

Reverse cholesterol transport allows peripheral cholesterol to be returned to the liver in LDLs

Ultimately, cholesterol is excreted in the bile as free cholesterol or as bile salts following conversion to bile acids in the liver.

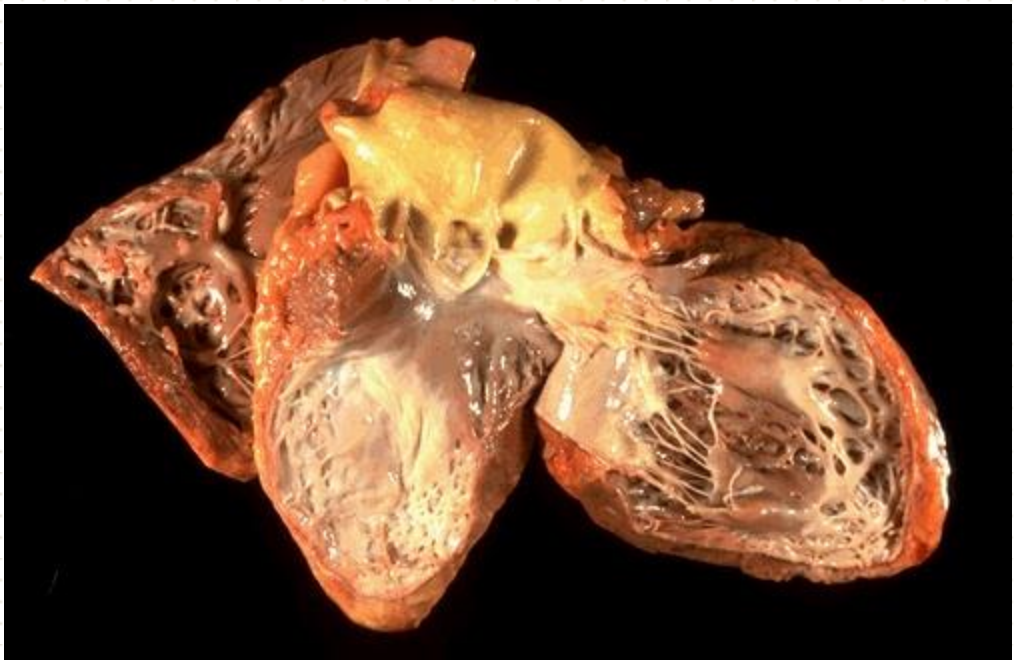
Arthrosclerosis

It is a complex and chronic disease involving the gradual accumulation of lipids, collagen, elastic fibres, and proteoglycans in the arterial walls. Since cholesterol ester and cholesterol are major components of athrosclerotic lesions, the interaction of the cholesterol-carrying lipoproteins in plasma with the cells of the arterial wall seems to be important. An increased level of total plasma cholesterol and an increase in the major cholesterol-carrying lipoprotein, *LDL*, are associated with an increase risk of athrosclerotic cardiovascular disease because the cholesterol of the atherosclerotic plaques is derived from LDL.

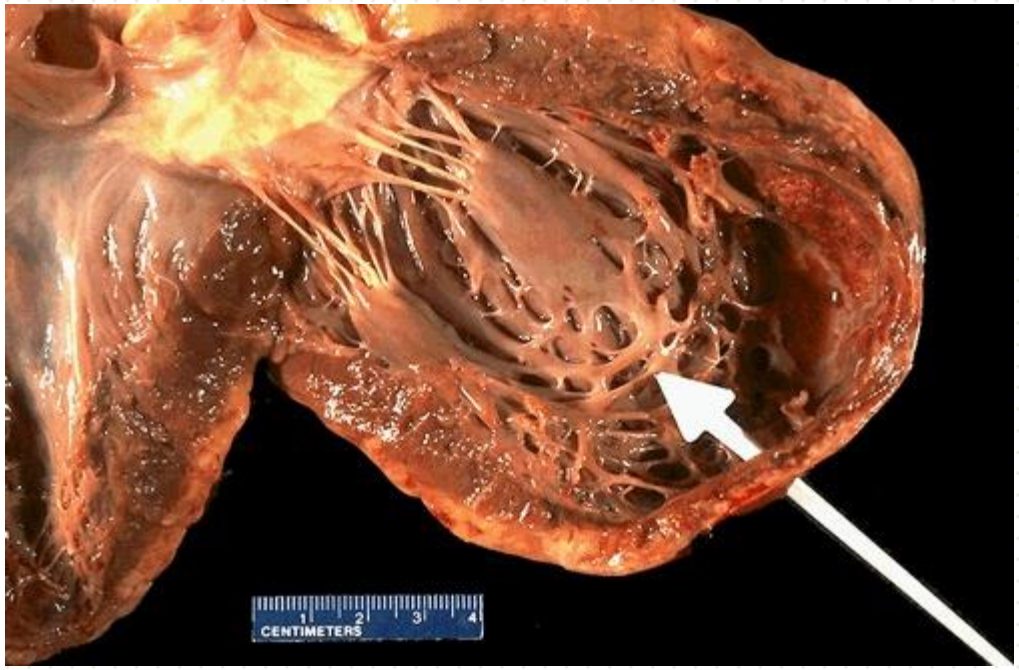


This is a normal coronary artery with a nice, big, unobstructed lumen for supplying plenty of blood to the myocardium.

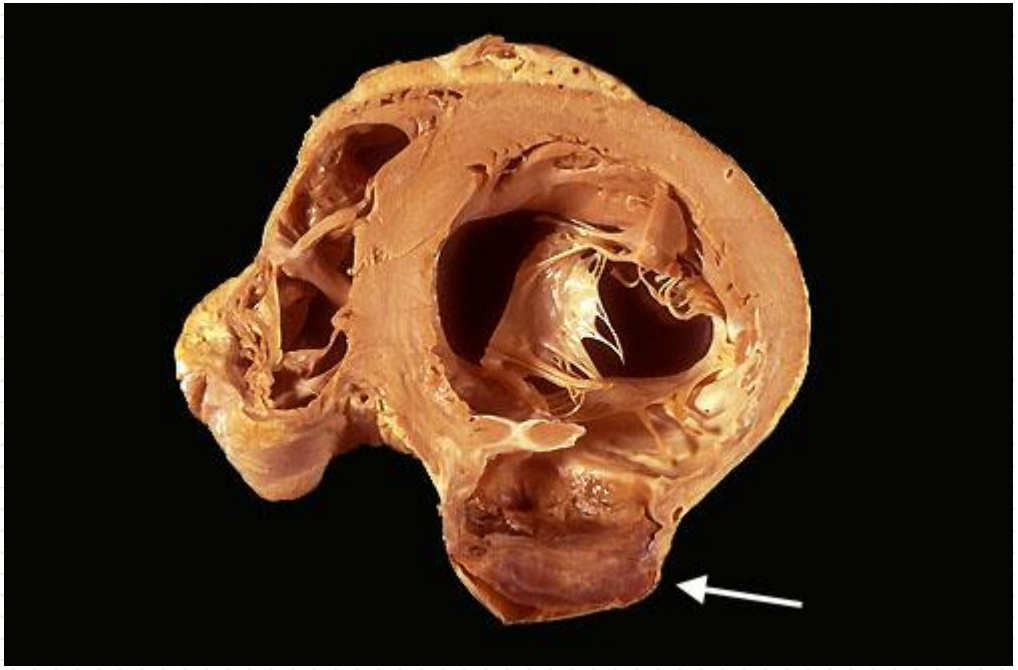
These serial sections of a coronary artery demonstrate grossly the appearance of lumenal narrowing with atherosclerosis.



Grossly, a remote myocardial infarction is evidenced by white collagenous scar.



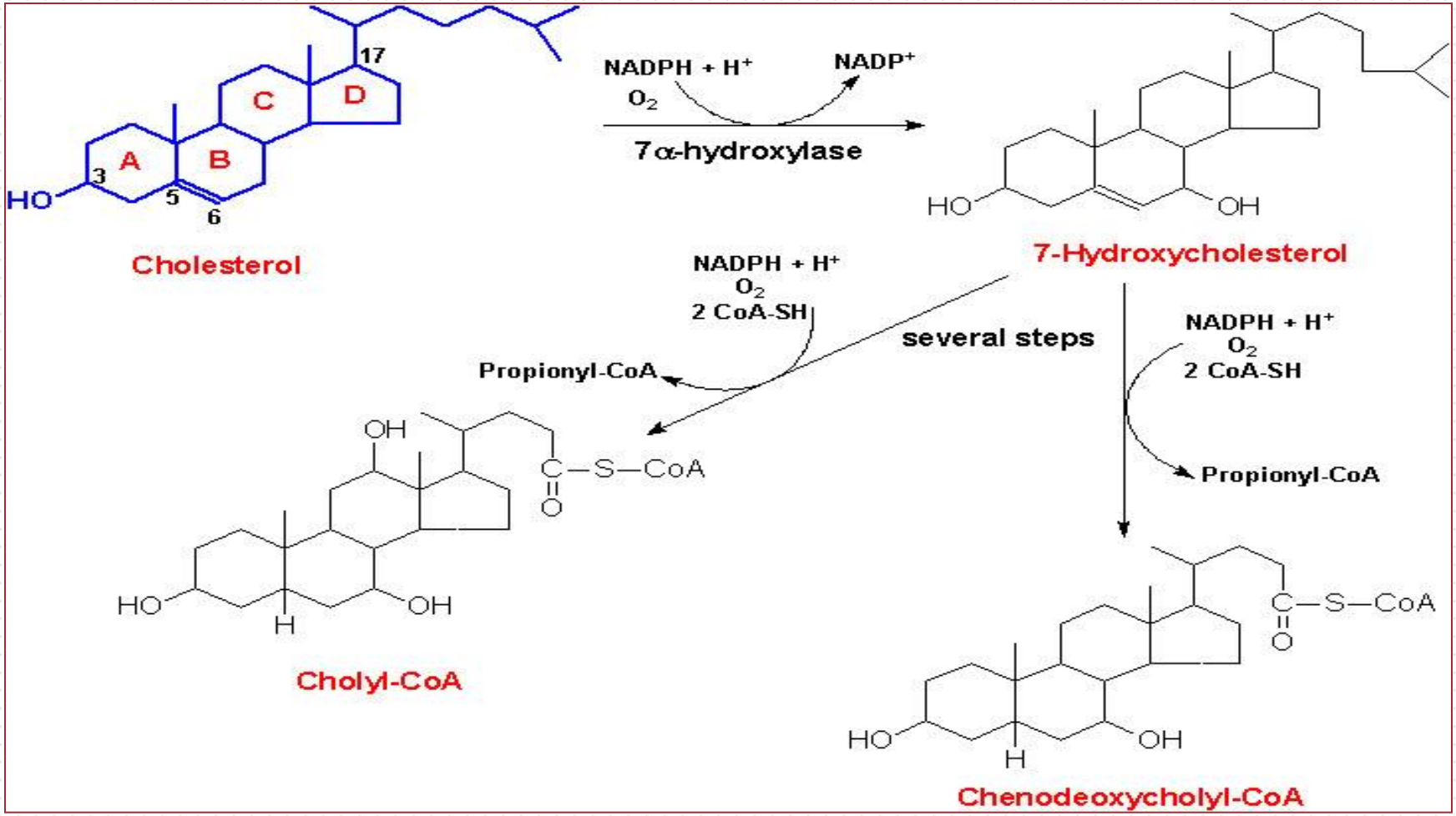
When the infarction is 3 to 5 days old, the necrosis and inflammation are most extensive, and the myocardium is the softest, so that transmural infarctions may be complicated by rupture. A papillary muscle may rupture as well to produce sudden valvular insufficiency. Rupture through the septum results in a left-to-right shunt and right heart failure.



The wall of the aneurysm is thin, as seen here in cross section, but it is formed of dense collagenous tissue, so it does not rupture. However, the aneurysm is formed of non-functional tissue that does not contract, so the ejection fraction and stroke volume of the heart are reduced. In addition, mural thrombus can form in the aneurysm, and is seen here as the dark red layers extending inward from the thin aneurysmal wall. Portions of the mural thrombus could break off and embolize to the systemic circulation.

Bile Acids Synthesis and Utilization

The end products of cholesterol utilization are the bile acids, synthesized in the liver. Synthesis of bile acids is one of the predominant mechanisms for the excretion of excess cholesterol. **However,** the excretion of cholesterol in the form of bile acids is insufficient to compensate for an excess dietary intake of cholesterol..



Synthesis of the 2 primary bile acids, cholic acid and chenodeoxycholic acid. The reaction catalyzed by the 7α-hydroxylase is the rate limiting step in bile acid synthesis. Conversion of 7a-hydroxycholesterol to the bile acids requires several steps not shown in detail in this image. Only the relevant co-factors needed for the synthesis steps are shown.

The most abundant bile acids in human bile are chenodeoxycholic acid (45%) and cholic acid (31%).

These are referred to as the primary bile acids.

Within the intestines the primary bile acids are acted upon by bacteria and converted to the secondary bile acids, identified as deoxycholate (from cholate) and lithocholate (from chenodeoxycholate).

Both primary and secondary bile acids are reabsorbed by the intestines and delivered back to the liver via the portal circulation.

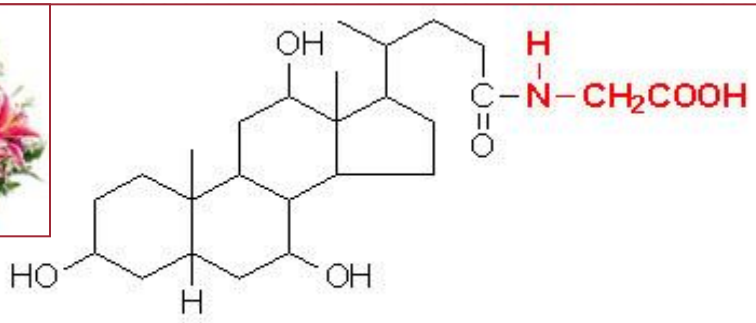
Within the liver the carboxyl group of primary and secondary bile acids is conjugated via an amide bond to either glycine or taurine before their being re-secreted into the bile canaliculi.

These conjugation reactions yield glycoconjugates and tauroconjugates, respectively.

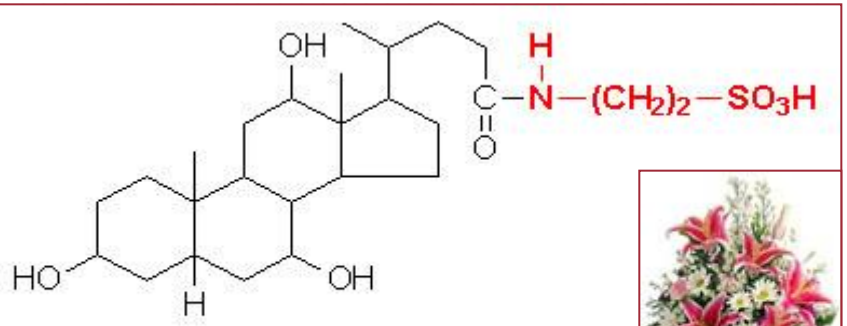
The bile canaliculi join with the bile ductules, which then form the bile ducts. Bile acids are carried from the liver through these ducts to the gallbladder, where they are stored for future use.

The ultimate fate of bile acids is secretion into the intestine, where they aid in the emulsification of dietary lipids. In the gut the glycine and taurine residues are removed and the bile acids are either excreted (only a small percentage) or reabsorbed by the gut and returned to the liver.

This process of secretion from the liver to the gallbladder, to the intestines and finally re-absorbtion is termed the enterohepatic circulation.



Glycocholic acid



Taurocholic acid

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Clinical Significance of Bile Acid Synthesis

Bile acids perform four physiologically significant functions:

1. Their synthesis and subsequent excretion in the feces represent the only significant mechanism for the elimination of excess cholesterol.

2. Bile acids and phospholipids solubilize cholesterol in the bile, thereby preventing the precipitation of cholesterol in the gallbladder.

3. They facilitate the digestion of dietary triacylglycerols by acting as emulsifying agents that render fats accessible to pancreatic lipases.

4. They facilitate the intestinal absorption of fat-soluble vitamins.

Lipid storage diseases

Complex lipids are constantly being synthesized and decomposed in the body. In several genetic diseases classified as lipid storage diseases, some of the enzymes needed to decompose the complex lipids are defective or even missing. As a consequence, the complex lipids accumulate and causes an enlarged liver and spleen, mental retardation, blindness, and, in certain cases, early death (See below).

At present, no treatment is available for these disease. The best way to prevent them is by genetic counseling. Some of these diseases can be diagnosed during fetal development. For example, Tay-Sachs disease, which affects about 1.0 in every 30Jewish American (versus 1.0 in 300 in the non-Jewish American) can be diagnosed from amniotic fluid obtained by amniocentesis.

1-CH3(CH2)12CH=CHCHOHCHNHC=ORCH2O (Glucose) (Glucocerebroside)

2- (Beta-galactose) (Galacocerbroside)

3-(Tri-alpha-galacose) (CeramideTrihexoside)

In Glucocerebroside the enzyme **beta-Glycosidase is deficient (Gaucher,s disease), Galacocerbroside the enzyme beta-glactosidase is deficient (Krabbe,s disease), and in CeramideTrihexoside (Fabry,s disease) the enzyme alpha-glactosidase** is deficient.

In Gaucher,s disease, the glucocerebrosides in cell called Gaucher,s cells which infiltrate the bone marrow.