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General Biochemistry (BCH 202)

Chapter 4

Lipids

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Topic	No of Weeks	Lectures
• **Lipids:** • Definition, function, fatty acids, classification: -**simple lipids**: structure and function (TAG, waxes) -**compound lipids**: structure and function (phospholipids, sphingolipids) -**derived lipids**: structure and function (cholesterol, bile acids) Lipoproteins, micelle, membrane structure.	1.33	16-19
• Glycerophospholipids (classifications, types& function) Sphingolipids (classifications, types& function) Triglycerides Steroids (structure, properties & functions; cholesterol, terpenes, vitamins& steroid hormones)	1.33	20-23
• Lipoproteins	0.66	24-25
• Introduction to biomembranes and adipocytes Assembly of lipid molecules (membrane and adipose tissue) Fluid mosaic model and types of membrane proteins • Fat storage & mobilization in adipose tissue	1	26-28
• Introduction to lipid metabolism	0.33	29

Lipids

Lipids are esters of fatty acids and alcohol.

The lipids are a heterogeneous group of compounds, including:

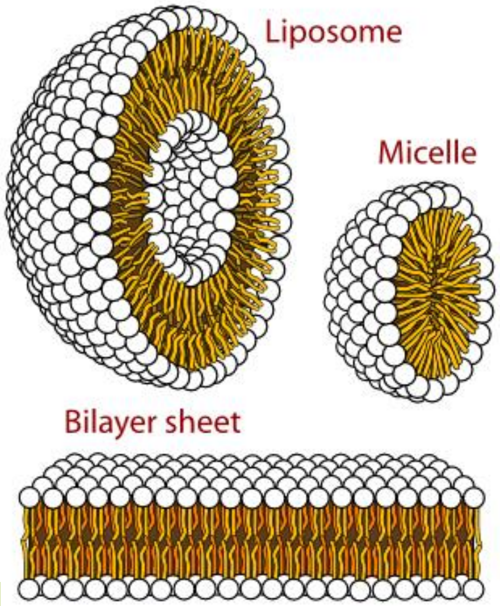
- fats, - oils, -waxes, -steroids, and
- related compounds which are related more by their physical than by their chemical properties.
- Although the term *lipid* is sometimes used as a synonym for fats, fats are a subgroup of lipids called triglycerides.

Lipids have the common property of being:

(1) relatively insoluble in water and

(2) soluble in nonpolar solvents such as ether and chloroform.

Lipids are hydrophobic small molecules; this character allows them to form structures such as vesicles or membranes.



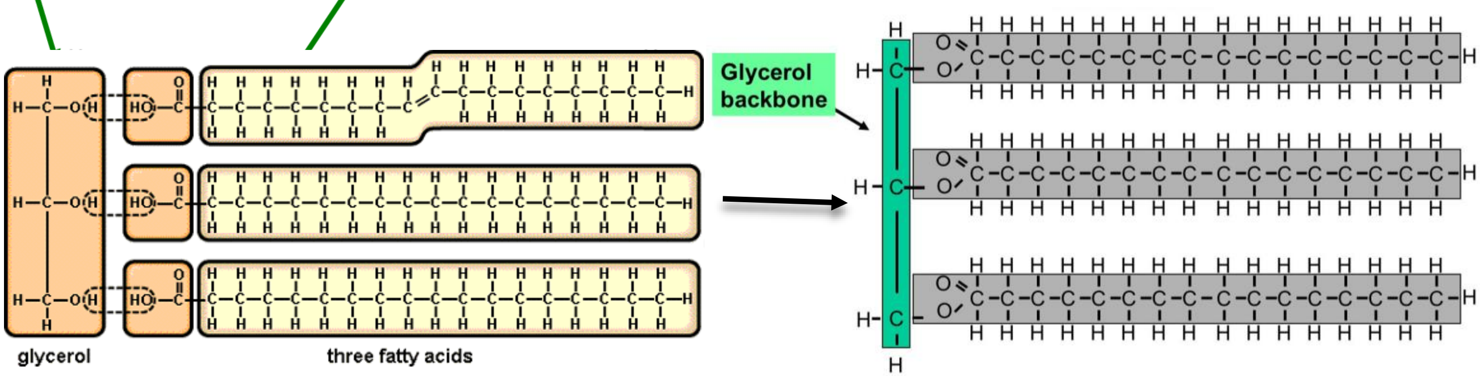
What is the difference between micelle, liposome and bilayer lipid sheet?

Triglycerides

Triglycerides Are Esters of Glycerol and Fatty Acids

Glycerol "backbone" is a water-soluble alcohol

Fatty Acids are chains of carbon atoms with a methyl ($-CH_3$) group at one end and a carboxylic acid ($-COOH$) group at the other



Structures linked by ester bonds (R-COOR') and water is released

Lipids of Physiologic Significance

1. They are important dietary constituents as they are high *source of energy (9.3 cal/g)*
2. It presents in all living organisms, animals, plants, bacteria, etc
3. Animal lipids are *more energetic and more saturated* than plant lipids
4. They are source of the *fat-soluble vitamins*
5. They provide body with the *essential fatty acids* contained in the fat of natural foods.
6. Fat is stored in adipose tissue, where it also serves as a *thermal insulator* in the subcutaneous tissues and around certain organs.
7. Nonpolar lipids act as *electrical insulators*, allowing rapid propagation of depolarization waves along myelinated nerves.
8. Phospholipids and sterols are major structural elements of biological membranes.
9. Other lipids, although present in relatively small quantities, play crucial roles as:
   - enzyme cofactors,
   - electron carriers,
   - Light absorbing
   - pigments,
   - hydrophobic anchors for proteins,
   - “chaperones” to help membrane proteins fold,
   - Emulsifying agents in the digestive tract,
   - hormones, and
   - intracellular messengers.

LIPIDS ARE CLASSIFIED AS SIMPLE OR COMPLEX

1- Simple lipids: Esters of fatty acids with various alcohols.

a. **Fats:** Esters of fatty acids with glycerol (trihydroxylic alcohol). Oils are fats in the liquid state.

b. **Waxes:** Esters of fatty acids with longer chain monohydroxyl alcohol.

2- Complex lipids: Esters of fatty acids containing additional groups besides the alcohol and the fatty acid.

a. **Phospholipids:** Lipids containing a phosphoric acid residue. They frequently have nitrogen containing bases and other substituents, eg, in glycerophospholipids the alcohol is glycerol and in sphingophospholipids the alcohol is sphingosine.

b. **Glycolipids (glycosphingolipids):** Lipids containing a fatty acid, sphingosine, and carbohydrate.

c. **Other complex lipids:** Lipids such as sulfolipids and aminolipids. Lipoproteins may also be placed in this category.

3. **Precursor and derived lipids:** These include fatty acids, glycerol, steroids, other alcohols, fatty aldehydes, and ketone bodies, hydrocarbons, lipid-soluble vitamins, and hormones.

Triacylglycerols, and cholesteryl esters are termed **neutral lipids** because they are uncharged.

Fatty acids are aliphatic carboxylic acids

Fatty acids are long hydrocarbon chain preceded by carboxyl group.

- i.e. They are carboxylic acids with hydrocarbon chains.

i.e. it has small polar, hydrophilic end (the carboxy-end) and long nonpolar, hydrophobic end (the 4-36 hydrocarbon tail).

So, the overall of fatty acids is insoluble in water.

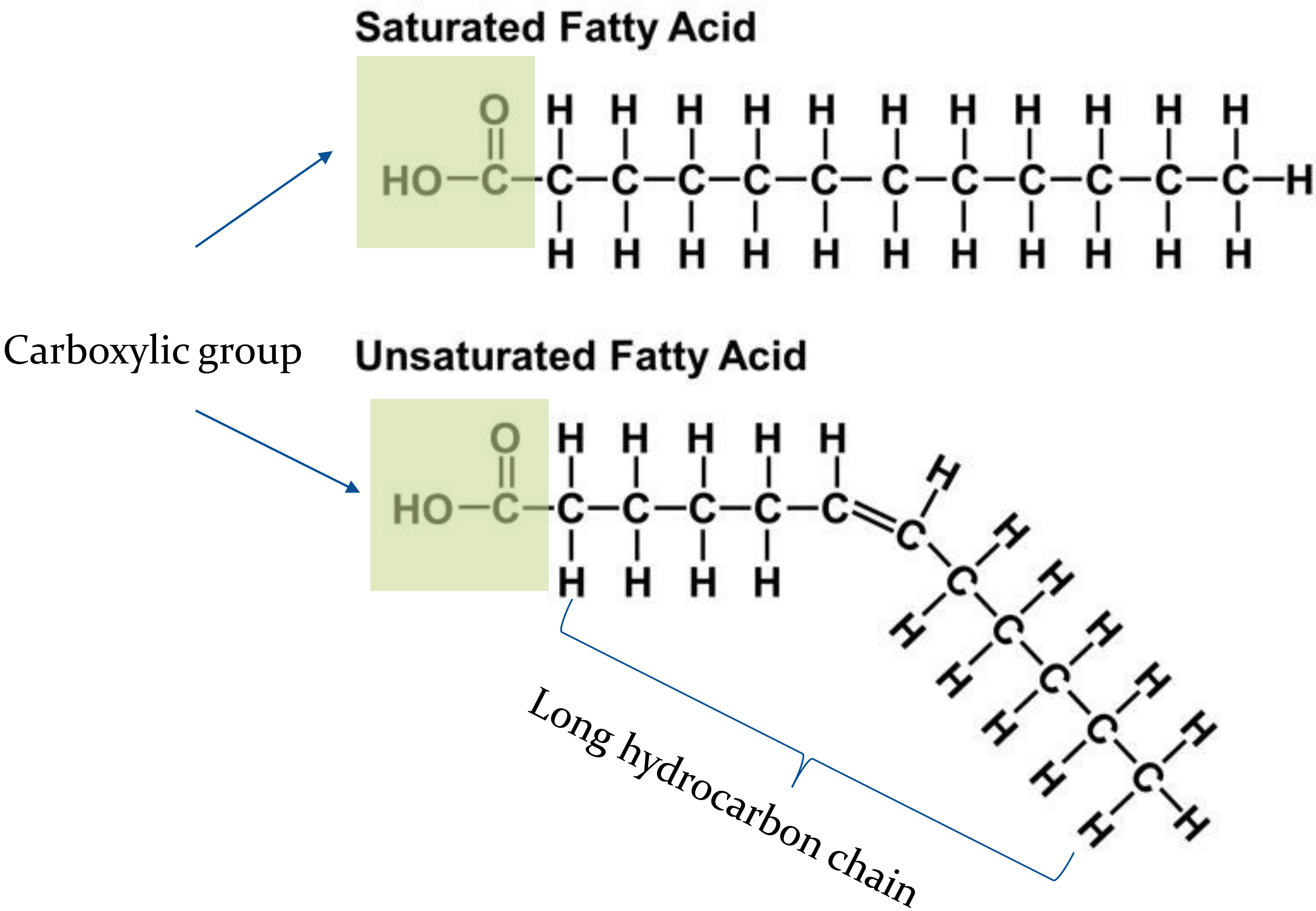
They occur mainly as esters in natural fats and oils.

They are transported in the blood as free fatty acids (unesterified form).

Fatty acids that occur in natural fats are usually *straight-chain* derivatives (unbranched) containing an *even number* of carbon atoms.

A few branched-chain fatty acids have also been isolated from both plant and animal sources.

The chain may be saturated (*containing no double bonds*) or unsaturated (*containing one or more double bonds*).


Saturated Fatty Acid
Unsaturated Fatty Acid
Carboxylic group
Long hydrocarbon chain

Fatty Acids Are Named After Corresponding Hydrocarbons

The most frequently used systematic nomenclature names the fatty acid after the hydrocarbon with the same number and arrangement of carbon atoms, with -oic being substituted for the final -e (Genevan system).

Saturated fatty acids are those containing single covalent bonds between carbon atoms [CH_3-$(CH_2)_n$-COOH]

Their name is composed from the Latin number of the carbons end in -anoic, eg, octanoic acid,

Unsaturated acids are those containing at least one double bond between carbon atoms

Their name end in -enoic, eg, octadecenoic acid (oleic acid).

Carbon atoms are numbered from the carboxyl carbon (carbon No. 1). The carbon atoms adjacent to the carboxyl carbon (Numbers. 2, 3, and 4) are also known as the α, β, and γ carbons, respectively, and the terminal methyl carbon is known as the ω or n-carbon.

Nomenclature of fatty acids

Every fatty acids can be named by three ways:

1- Commercial name

2- Chemical name

3- Simplified code name

1- Commercial name

The name does not reflect the number of carbon atoms or the level of saturation

Example, palmetic, stearic, oleic, arachidonic, linoleic, linolenic, etc.

2- Chemical name

- The systematic name for a fatty acid is derived from the name of its parent hydrocarbon by the substitution of *oic* (+an or en) for the final *e*.

i.e. The Latin number of carbon atoms + suffix

- In saturated fatty acids the suffix is anoic
- In the unsaturated fatty acids the suffix is enoic

Examples

- Palmetic acid contains 16 carbons and is saturated.

  Its name is Hexadec   anoic

- Stearic acid contains 18 carbons and saturated.
- Its name is Octadec anoic

In the unsaturated fatty acids more details are required to indicated the position and number of double bonds

Site of the double bond + Latin number of the carbon atoms + number of double bonds + the suffix enoic

Linoleic acid

It is unsaturated fatty acid.

It contains 18 carbon atoms, 2 double bonds between C9,10 and C12,13

9,12 –octadeca di enoic

Linolenic acid

18 carbon atoms, 3 double bonds between C6,7; C9,10 and C12,13

6,9,12 –octadeca tri enoic

3- The simplified code name

A simplified nomenclature specifies the chain length and number of double bonds, separated by a colon;

Example,

Palmetic is 16-carbon saturated fatty acid. It is abbreviated 16:0,

Oleic is 18-carbon acid, with one double bond, is 18:1.

The positions of any double bonds are specified by superscript numbers following Δ (delta)

Number of carbon atoms: number of double bonds, $^{\Delta \text{ site of the double bonds}}$

Examples:

Palmetic	C16:0
Stearic	C18:0
Linoleic	$C18:2^{\Delta 9,12}$
Linolenic	$C18:3^{\Delta 6,9,12}$

- ω9 indicates a double bond on the ninth carbon counting from the ω- carbon.

In animals, additional double bonds are introduced only between the existing double bond (eg, ω9, ω6, or ω3) and the carboxyl carbon, leading to three series of fatty acids known as the ω9, ω6, and ω3 families, respectively.

18:1;9 *or* Δ^9 18:1

$$\overset{18}{C}H_3(CH_2)_7\overset{10}{C}H=\overset{9}{C}H(CH_2)_7\overset{1}{C}OOH$$

or

ω9,C18:1 *or* n–9, 18:1

$$\underset{n}{\overset{\omega}{C}}H_3\underset{17}{\overset{2}{C}}H_2\overset{3}{C}H_2\overset{4}{C}H_2\overset{5}{C}H_2\overset{6}{C}H_2\overset{7}{C}H_2\overset{8}{C}H_2\underset{10}{\overset{9}{C}}H=\underset{9}{\overset{10}{C}}H(CH_2)_7\underset{1}{\overset{18}{C}}OOH$$

Oleic acid. n – 9 is equivalent **to ω9.**

TABLE 10–1 Some Naturally Occurring Fatty Acids: Structure, Properties, and Nomenclature

Carbon skeleton	Structure*	Systematic name†	Common name (derivation)	Melting point (°C)	Solubility at 30 °C (mg/g solvent)	
					Water	Benzene
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2	0.063	2,600
14:0	$CH_3(CH_2)_{12}COOH$	*n*-Tetradecanoic acid	Myristic acid (Latin *Myristica*, nutmeg genus)	53.9	0.024	874
16:0	$CH_3(CH_2)_{14}COOH$	*n*-Hexadecanoic acid	Palmitic acid (Latin *palma*, "palm tree")	63.1	0.0083	348
18:0	$CH_3(CH_2)_{16}COOH$	*n*-Octadecanoic acid	Stearic acid (Greek *stear*, "hard fat")	69.6	0.0034	124
20:0	$CH_3(CH_2)_{18}COOH$	*n*-Eicosanoic acid	Arachidic acid (Latin *Arachis*, legume genus)	76.5		
24:0	$CH_3(CH_2)_{22}COOH$	*n*-Tetracosanoic acid	Lignoceric acid (Latin *lignum*, "wood" + *cera*, "wax")	86.0		
16:1(Δ^9)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	*cis*-9-Hexadecenoic acid	Palmitoleic acid	1 to –0.5		
18:1(Δ^9)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	*cis*-9-Octadecenoic acid	Oleic acid (Latin *oleum*, "oil")	13.4		
18:2($\Delta^{9,12}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis-,cis*-9,12-Octadecadienoic acid	Linoleic acid (Greek *linon*, "flax")	1–5		
18:3($\Delta^{9,12,15}$)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis-,cis-,cis*-9,12,15-Octadecatrienoic acid	α-Linolenic acid	−11		
20:4($\Delta^{5,8,11,14}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	*cis-,cis-,cis-,cis*-5,8,11,14-Icosatetraenoic acid	Arachidonic acid	−49.5		

*All acids are shown in their nonionized form. At pH 7, all free fatty acids have an ionized carboxylate. Note that numbering of carbon atoms begins at the carboxyl carbon.
†The prefix *n*- indicates the "normal" unbranched structure. For instance, "dodecanoic" simply indicates 12 carbon atoms, which could be arranged in a variety of branched forms; "*n*-dodecanoic" specifies the linear, unbranched form. For unsaturated fatty acids, the configuration of each double bond is indicated; in biological fatty acids the configuration is almost always cis.

Principles of Biochemistry
4ed - Lehninger

Saturated fatty acids.

Common Name	Number of C Atoms	
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms[1]
Propionic	3	An end product of carbohydrate fermentation by rumen organisms[1]
Butyric	4	In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms[1]
Valeric	5	
Caproic	6	
Lauric	12	Spermaceti, cinnamon, palm kernel, coconut oils, laurels, butter
Myristic	14	Nutmeg, palm kernel, coconut oils, myrtles, butter
Palmitic	16	Common in all animal and plant fats
Stearic	18	

Unsaturated Fatty Acids Contain One or More Double Bonds

Fatty acids may be further subdivided as follows:

(1) Monounsaturated (monoethenoid, monoenoic) acids, containing one double bond.

(2) Polyunsaturated (polyethenoid, polyenoic) acids, containing two or more double bonds.

(3) Eicosanoids: These compounds, derived from eicosa- (20-carbon) polyenoic fatty acids, comprise the prostanoids, leukotrienes (LTs), and lipoxins (LXs). Prostanoids include prostaglandins (PGs), prostacyclins (PGIs), and thromboxanes (TXs).

Features of unsaturated fatty acids

- It is NOT closely packed, more fluid, has lower melting point, and are liquid at room temperature.
- **Trans vs Cis Unsaturated Fatty Acids**
  - Trans = pack more regularly than cis, so higher melting point,
    - Formed by partial dehydrogenation of unsaturated fatty acids; higher melting points
  - Cis = packs more loosely than trans, so lower melting point
- Details????

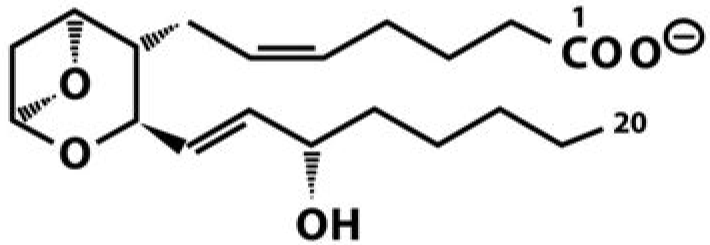
Unsaturated fatty acids of physiologic and nutritional significance

Number of C Atoms and Number and Position of Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
16:1;9	ω7	Palmitoleic	*cis*-9-Hexadecenoic	In nearly all fats.
18:1;9	ω9	Oleic	*cis*-9-Octadecenoic	Possibly the most common fatty acid in natural fats.
18:1;9	ω9	Elaidic	*trans*-9-Octadecenoic	Hydrogenated and ruminant fats.
Dienoic acids (two double bonds)				
18:2;9,12	ω6	Linoleic	all-*cis*-9,12-Octadecadienoic	Corn, peanut, cottonseed, soybean, and many plant oils.
Trienoic acids (three double bonds)				
18:3;6,9,12	ω6	γ-Linolenic	all-*cis*-6,9,12-Octadecatrienoic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	ω3	α-Linolenic	all-*cis*-9,12,15-Octadecatrienoic	Frequently found with linoleic acid but particularly in linseed oil.
Tetraenoic acids (four double bonds)				
20:4;5,8,11,14	ω6	Arachidonic	all-*cis*-5,8,11,14-Eicosatetraenoic	Found in animal fats and in peanut oil; important component of phospholipids in animals.
Pentaenoic acids (five double bonds)				
20:5;5,8,11,14,17	ω3	Timnodonic	all-*cis*-5,8,11,14,17-Eicosapentaenoic	Important component of fish oils, eg, cod liver, mackerel, menhaden, salmon oils.
Hexaenoic acids (six double bonds)				
22:6;4,7,10,13,16,19	ω3	Cervonic	all-*cis*-4,7,10,13,16,19-Docosahexaenoic	Fish oils, phospholipids in brain.

Eicosanoids

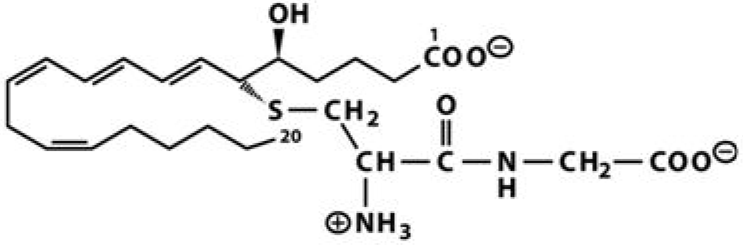
Thromboxane A_2 – involved in blood clot formation

Thromboxane A_2



Leukotriene D_4 – mediator of smooth-muscle contraction and provokes bronchial constriction seen in asthmatics.

Leukotriene D_4



Aspirin alleviates pain, fever, and inflammation by inhibiting cyclooxygenase (COX), an enzyme critical for the synthesis of Prostaglandins. (NSAID family of compounds)

Chemical and physical properties of fatty acids

Q:

- **Describe the dependence of the melting point of a fatty acid upon**

(a) chain length and

(b) unsaturation;

(c) explain these dependencies in molecular terms.

Ans: All other things being equal,

(a) the longer the acyl chain, the higher the melting temperature; and

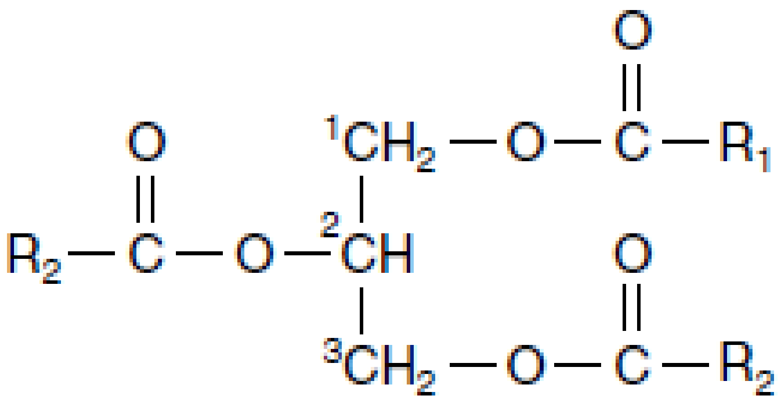
(b) the more unsaturation, the lower the melting temperature.

(c) The melting temperature is a measure of the thermal energy needed to break the intermolecular interactions that stabilize the "solid" form of a lipid, which depends upon how well the individual lipid molecules fit into the nearly crystalline array of lipids. When a shorter acyl chain lies between two longer chains in a nearly crystalline array of lipid molecules, there is a cavity at the end of the short acyl group that allows freer motion to the neighboring acyl chains. A cis double bond introduces a "kink" into the acyl chain, so that it does not pack as easily with its straighter neighbors.

Triacylglycerols (triglycerides) are the main storage forms of fatty acids

- Glycerol is tri hydroxylic alcohol.
- The hydroxyl group of glycerol can bind with one, 2 or 3 fatty acids by ester bond to form mono, di- or tri acyl glycerol.
- They are found in the tissues.

- Triacylglycerols are nonpolar hydrophobic molecules that can be stored in specialized nonaqueous cellular compartments, mainly adipocytes.



Triacylglycerol.

Q:

- **In cells, fatty acids are stored as triacylglycerols for energy reserves.**

(a) What is the molecule to which fatty acids are esterified to form triacylglycerols?

(b) Define the logic behind cells storing fatty acids in esterified form.

(a) Three fatty acids are esterified to glycerol.

(b) Triacylglycerols are uncharged and insoluble in water. They form lipid droplets within adipocytes, which do not contribute to the osmolarity of the cytosol in those cells, and do not require any water of hydration.

Describe three functions of triacylglycerols in mammals and one function in higher plant

Triacylglycerols provide mammals with

- stored fuel,
- insulation, and
- a source of metabolic water.

In some animals, such as camels and desert rats, the oxidation of stored lipids provides water; in hibernating animals, oxidation of stored lipids generates heat to maintain body temperature

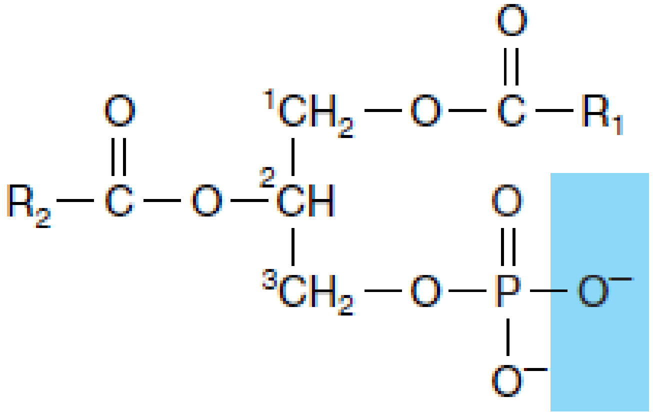
In plants, oxidation of the triacylglycerols stored in seeds provides the energy and precursors for biosynthetic processes during germination, before photosynthetic mechanisms become functional.

Phospholipids are the main lipid constituents of membranes

Phospholipids may be regarded as derivatives of *phosphatidic acid*, in which the phosphate is esterified with the -OH of a suitable alcohol.

Phosphatidic acid is important as an *intermediate* in the synthesis of triacylglycerols as well as phosphoglycerols but is not found in any great quantity in tissues.

Glycerophospholipids are *amphipathic* molecules that can serve as structural components of membranes, which have hydrophilic and hydrophobic regions.

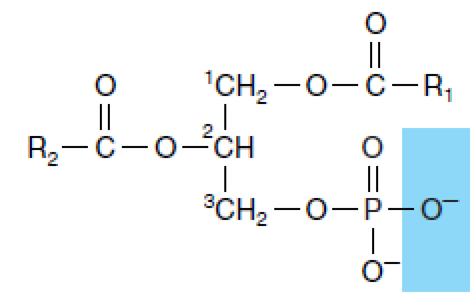


Phosphatidic acid

Phosphatidic acid and its derivatives.

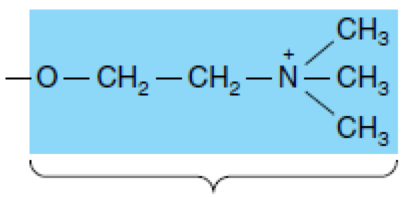
The O^- shown shaded in phosphatidic acid is substituted by the substituents shown to form :

(A) 3-phosphatidylcholine,
(B) 3 phosphatidylethanolamine,
(C) 3-phosphatidylserine
(D) 3-phosphatidylinositol,
(E) cardiolipin (diphosphatidylglycerol).



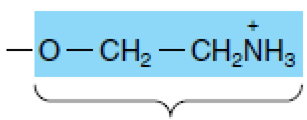
Phosphatidic acid

A



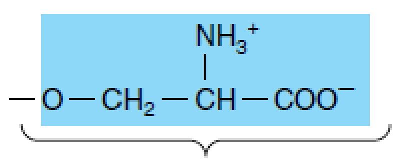
Choline

B



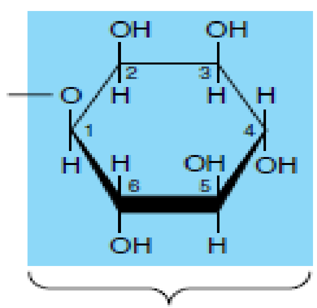
Ethanolamine

C



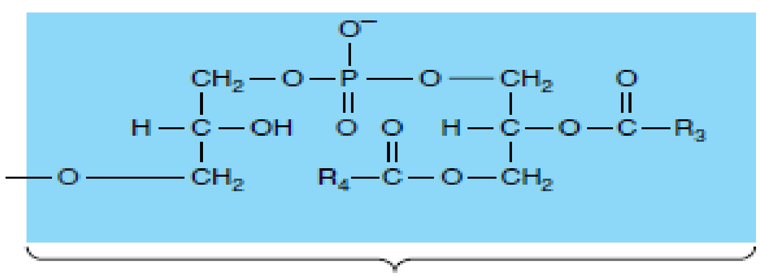
Serine

D



Myoinositol

E



Phosphatidylglycerol

Phosphatidylcholines (Lecithins), Phosphatidylethanolamine (cephalin) and phosphatidylserine Occur in Cell Membranes

Phosphatidylcholines (Lecithins), are the most abundant phospholipids of the cell membrane and represent a large proportion of the *body's store of choline*.

Choline is important in nervous transmission, as acetylcholine, and as a store of labile methyl groups.

Phosphatidyl ethanolamine (cephalin) and **phosphatidylserine** are also found in cell membranes and differ from phosphatidylcholine only in that ethanolamine or serine, respectively, replaces choline.

Phosphatidylinositol Is a Precursor of Second Messengers

Phosphatidylinositol 4,5-bisphosphate is an important constituent of cell membrane phospholipids.

It is **glycerophospholipid** and upon stimulation by a suitable hormone agonist, it is cleaved into diacylglycerol and inositol trisphosphate, both of which act as internal signals or second messengers.

Cardiolipin Is a Major Lipid of Mitochondrial Membranes

Phosphatidic acid is a precursor of phosphatidylglycerol which, in turn, gives rise to cardiolipin. This phospholipid is found only in mitochondria and is essential for mitochondrial function.

Lysophospholipids Are Intermediates in the Metabolism of Phosphoglycerols

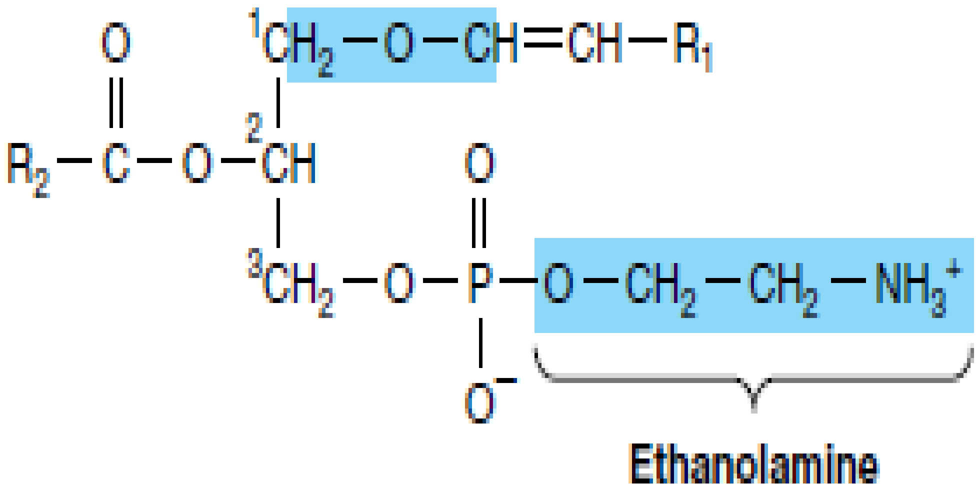
These are phosphoacylglycerols containing only one acyl radical, eg, lysophosphatidylcholine (lysolecithin), important in the metabolism and interconversion of phospholipids.

Plasmalogens Occur in Brain & Muscle

These compounds constitute as much as 10% of the phospholipids of brain and muscle.

Structurally, the plasmalogens resemble phosphatidyl-ethanolamine but possess an *ether link* on the *sn*-1 carbon instead of the ester link found in acylglycerols.

Typically, the alkyl radical is an unsaturated alcohol.



Phospholipids

Phospholipids in animal membranes are derived from either glycerol or sphingosine.

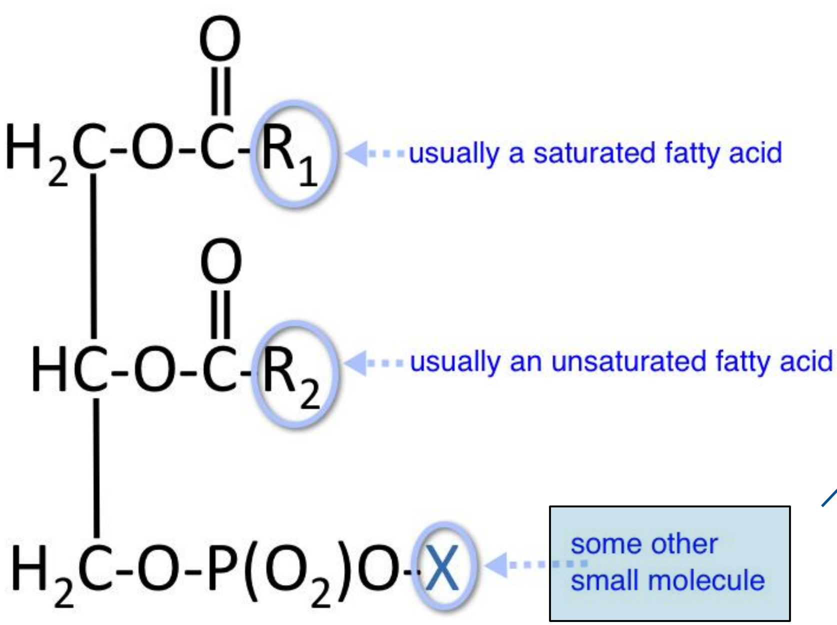
- **GlyceroPhosphoLipids** and called phosphoglyceroids.
- it consists of a glycerol backbone (3-OH, 3-C alcohol), two fatty acid chains and a phosphorylated alcohol.
- **SphingoPhosphoLipids.**
- It consists of sphingosine (complex alcohol) and a fatty acid.

- The fatty acid chain usually contain even number of C atom, between 14-24. the 16 and 18 are most common.
- Fatty acids may be saturated or unsaturated.
- The configuration of double bonds in unsaturated fatty acids is nearly always *cis*.
- The length and the degree of unsaturation of fatty acids chains affect the membrane fluidity.

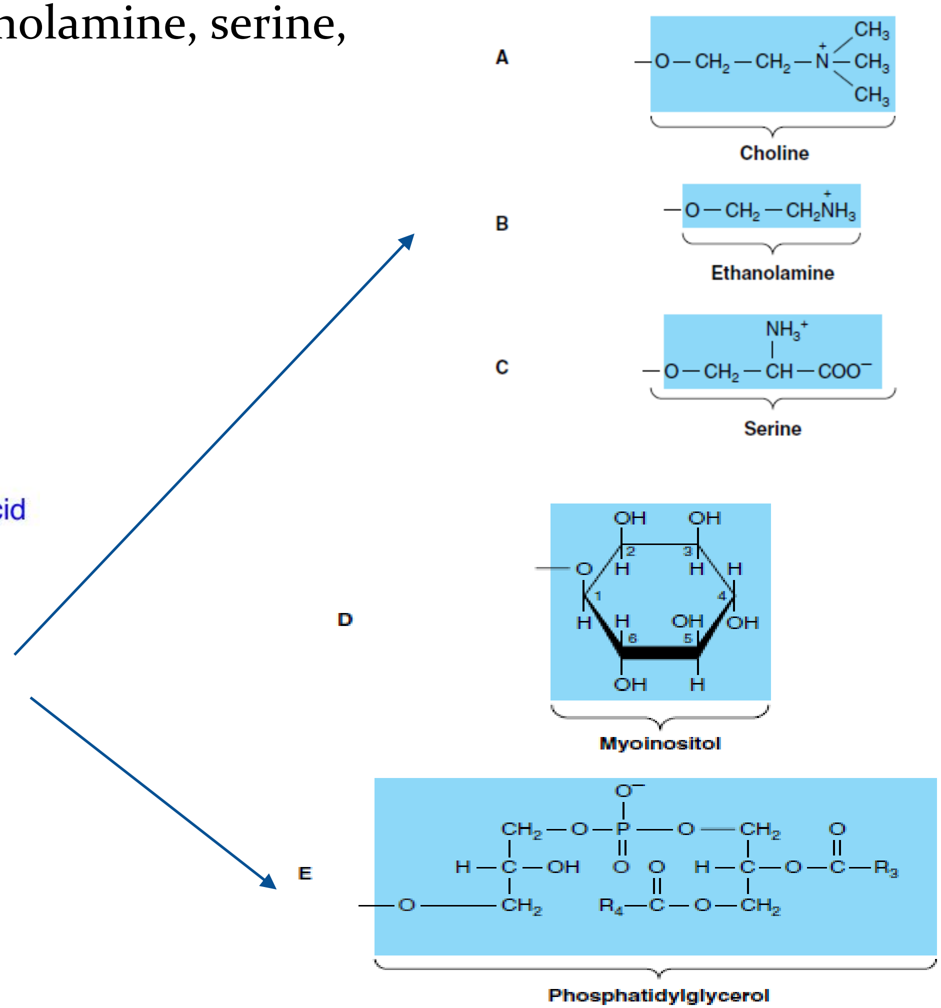
GlyceroPhospholipid structure

Glycerol + R1 saturated fatty acid + R2 unsaturated fatty acid + phosphate

The phosphate is bound to: Choline, ethanolamine, serine, myoinositol or phosphatidylglycerol.

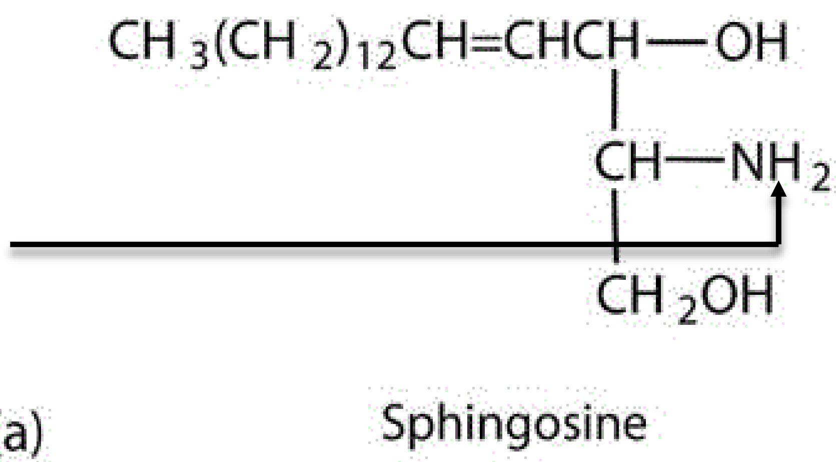


Phosphatidic acid

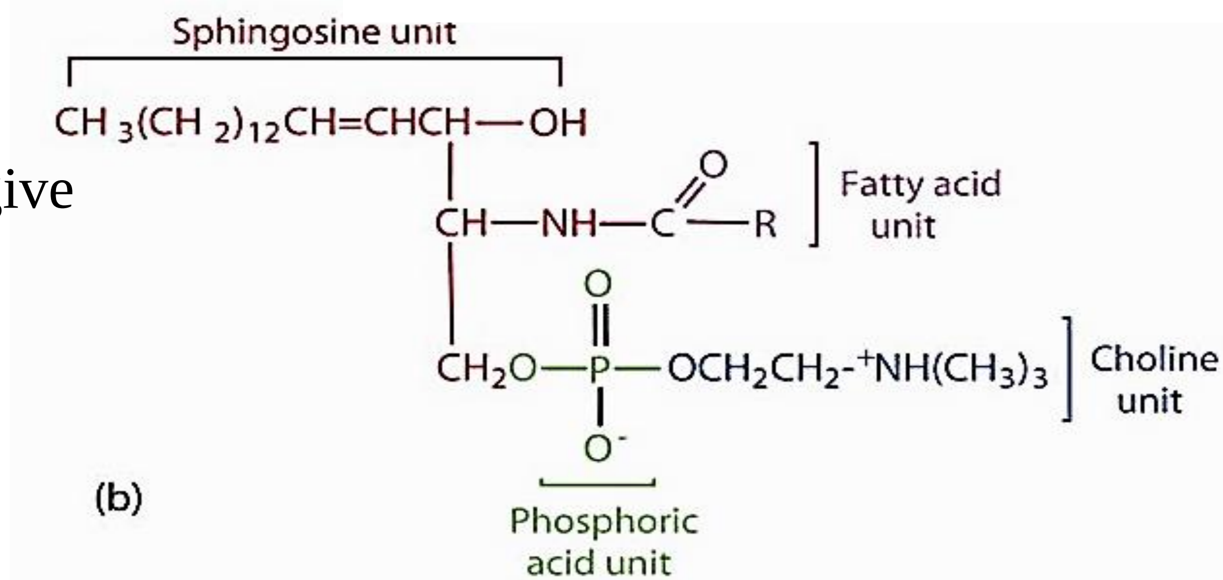


Sphingophospholipids:
Sphingosine and Sphingomyelin Structures

- Sphingosine is *amino* alcohol that contains a long, *unsaturated* hydrocarbon chain ($C_{18}H_{37}NO_2$).
- Sphingosine can bind to ONE fatty acid through AMIDE bond.



- It may also bind to the lateral CH_2OH group to give many derivatives.



Different Derivatives of sphingosine

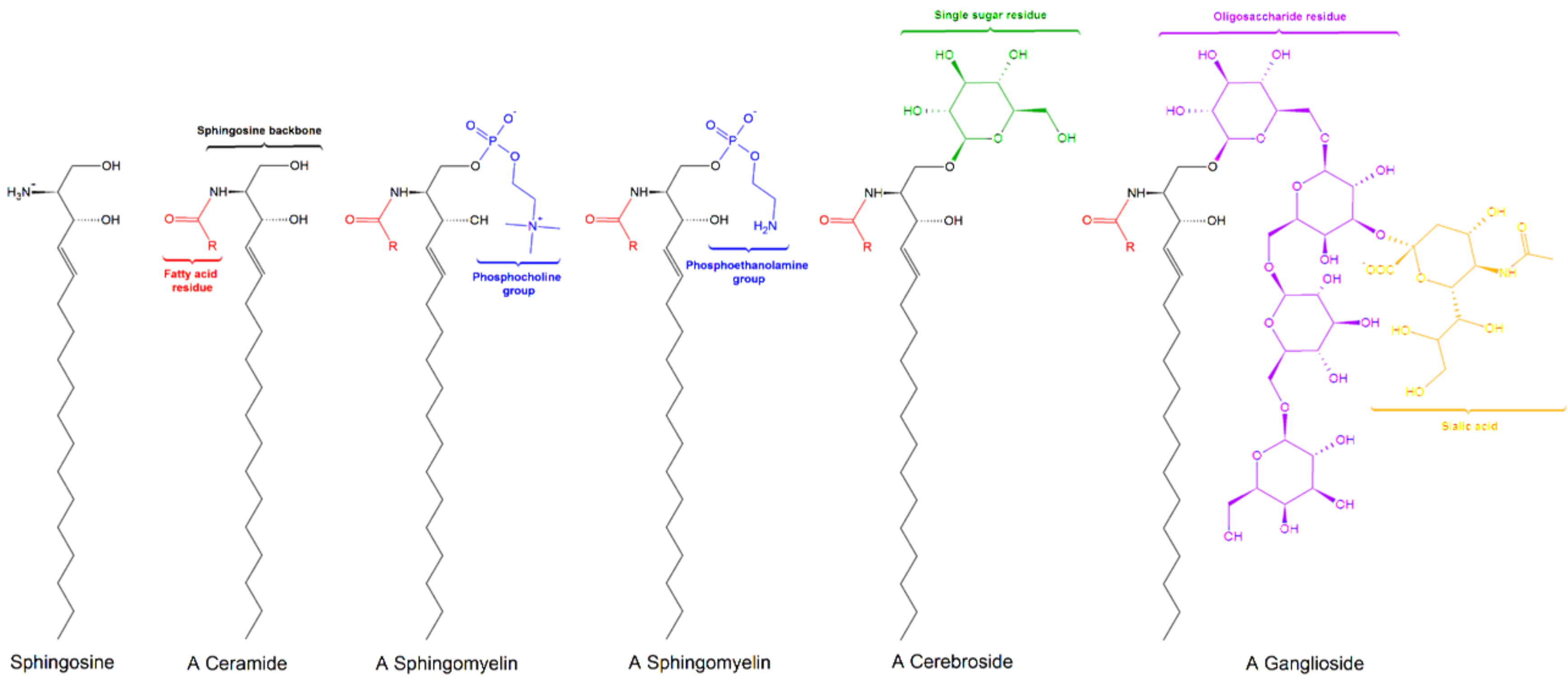
Sphingosine + 1 FF → Ceramide

Ceramide + Phosphocholine → A Sphingomyelin (Phospholipid)

Ceramide + Phosphoethanolamine → A Sphingomyelin (Phospholipid)

Ceramide + Sugar → A Cerebroside (Glycolipid)

Ceramide + many Sugars → A Ganglioside (Glycolipid)



Essential Cell Biology, 4th ed.

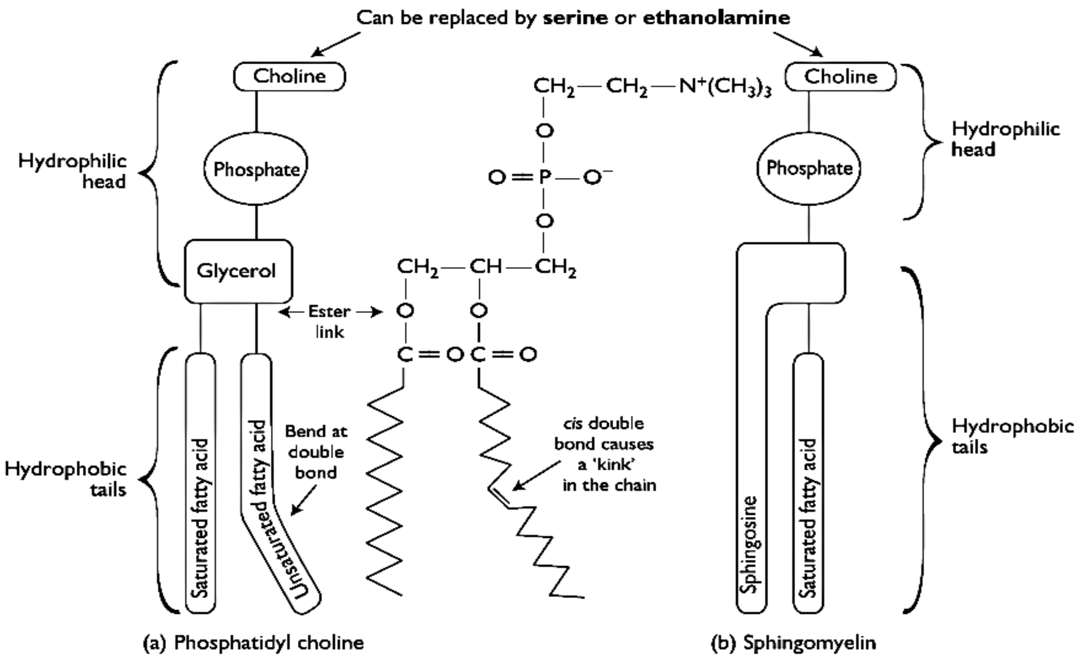
Glycerophospholipid vs sphingomyelin

Both contain:

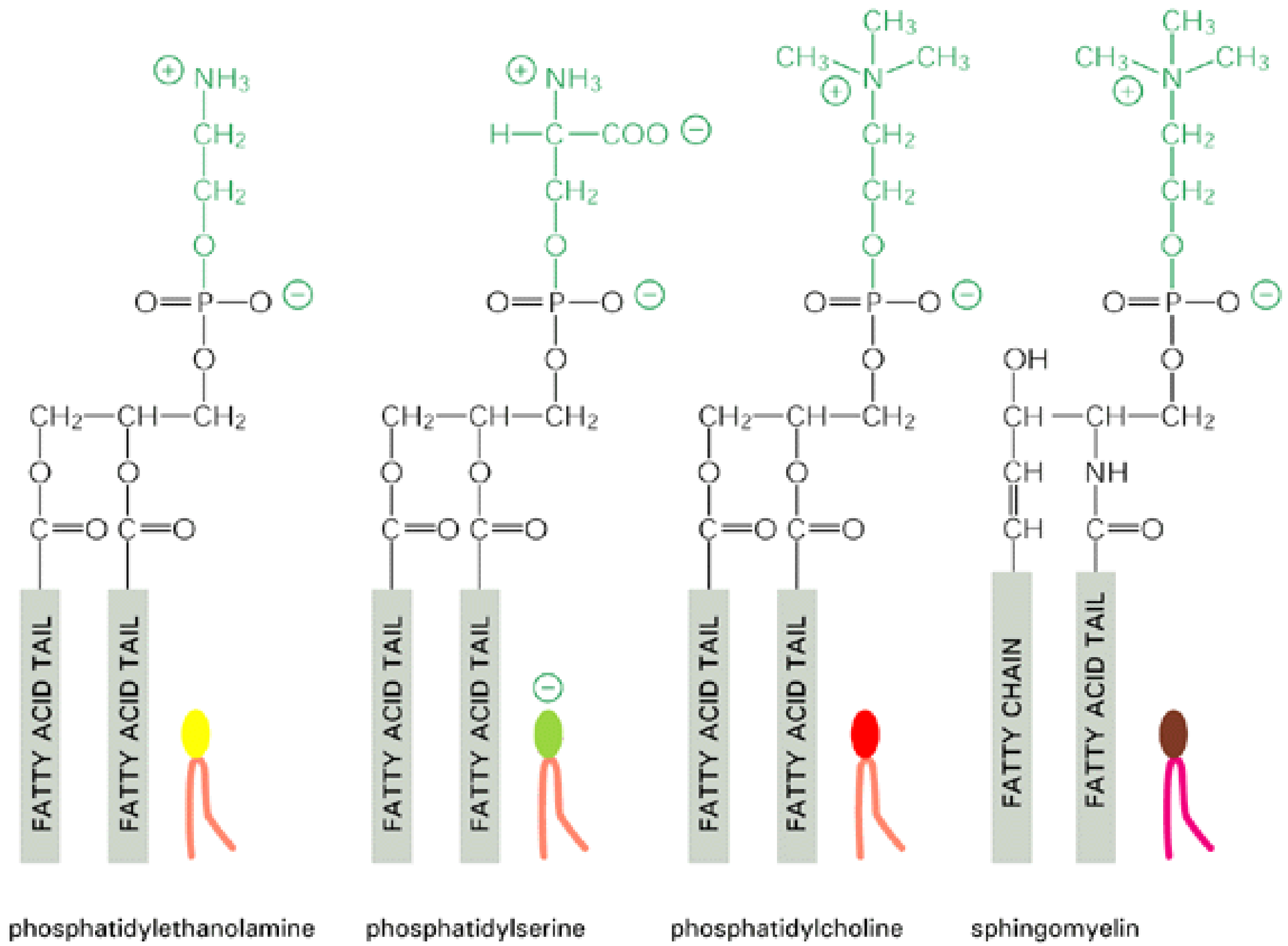
- hydrophilic head composed of alcohol –phosphate and ligand that may be choline, serine or ethanolamine
- 2 Hydrophobic tails (2 FA in case of GPL and 1 FA + side group in SPL)

They differ in:

- Glycerophospholipids have glycerol + 2 fatty acids + Phosphate + ligand
- The bonds between glycerol and each of the two FFs are ester bond
- Sphingomyelin have sphingosine + 1 fatty acid + phosphate + ligand
- The bond between sphingosine and the FF is amide bond



Summary of membrane phospholipids:



Glycolipids

Glycolipids* are *sugar-containing lipids.

Glycolipids exist in both animal and plant tissues.

The animal glycolipids are derived from sphingosine.

Plant glycolipids (mainly galactolipid) are derived from glycerol.

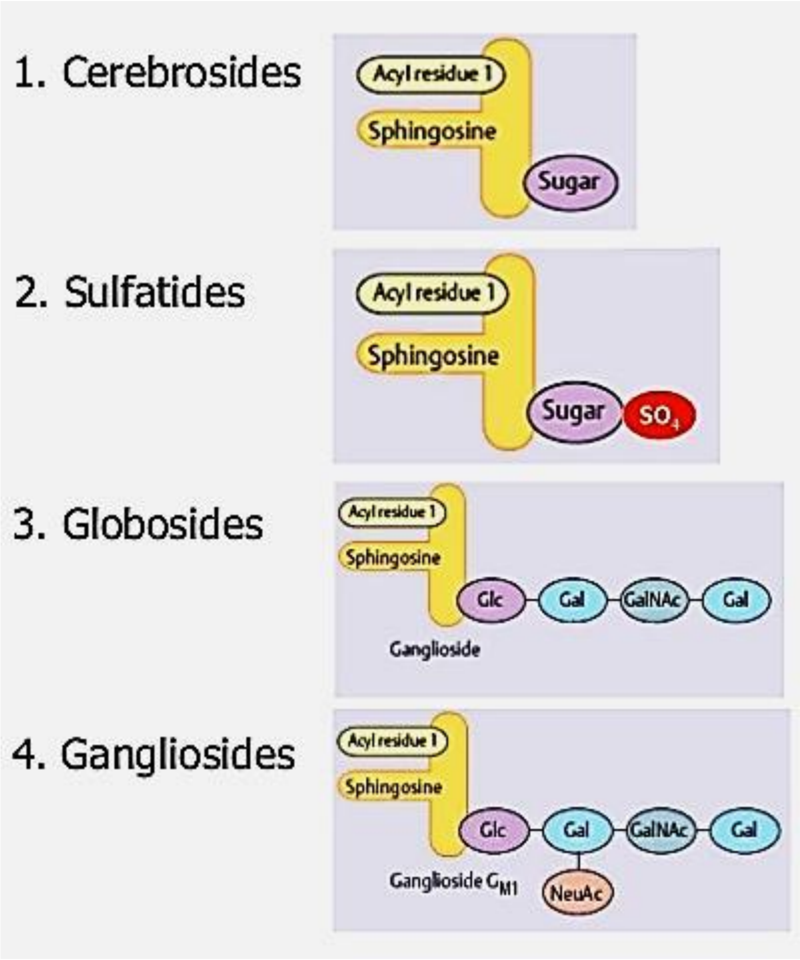
The amino group of the sphingosine backbone is *acylated* by a fatty acid, as in sphingomyelin.

- Glycolipids differ from sphingomyelin in the identity of the unit that is linked to the primary hydroxyl group of the sphingosine backbone.
- In glycolipids, one or more sugars (rather than phosphoryl choline) are attached to this group.
- The simplest glycolipid, called a *cerebroside*, contains a single sugar residue, either glucose or galactose.
- Gangliosides contain a branched chain as many as 7 sugar residues.

Glycolipids: Types and functions

Ex. Cerebrosides, sulfatides, globosides and gangliosides

- The role of membrane glycolipids is to *maintain stability of the membrane* and to *facilitate cellular recognition*.
- The carbohydrates are found on the outer surface of all eukaryotic cell membranes.
- They are used for:
    - cell-cell interaction
    - Identify the blood type
    - Immune response



Glycolipids (Glycosphingolipids) Are Important in Nerve Tissues & in the Cell Membrane

Animal glycolipids:

They contain sphingosine as alcohol.

They are widely distributed in every tissue of the body, particularly in nervous tissue such as brain.

They occur particularly in the *outer leaflet* of the plasma membrane, where they contribute to cell surface carbohydrates.

They contain ceramide and one or more sugars.

Galactosylceramide is a major glycosphingolipid of brain and other nervous tissue, found in relatively low amounts elsewhere.

It contains a number of characteristic C_{24} fatty acids, eg, cerebronic acid.

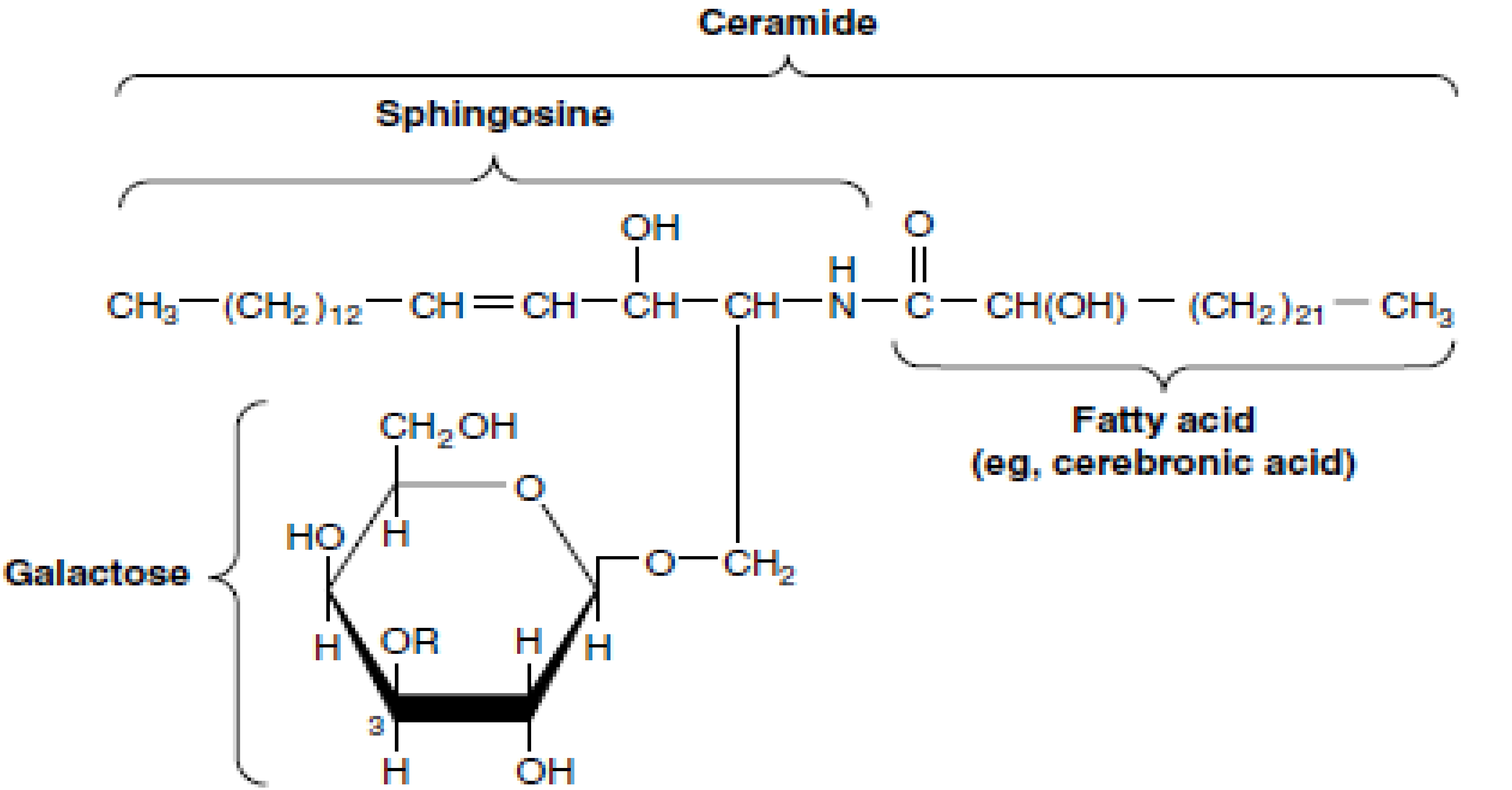
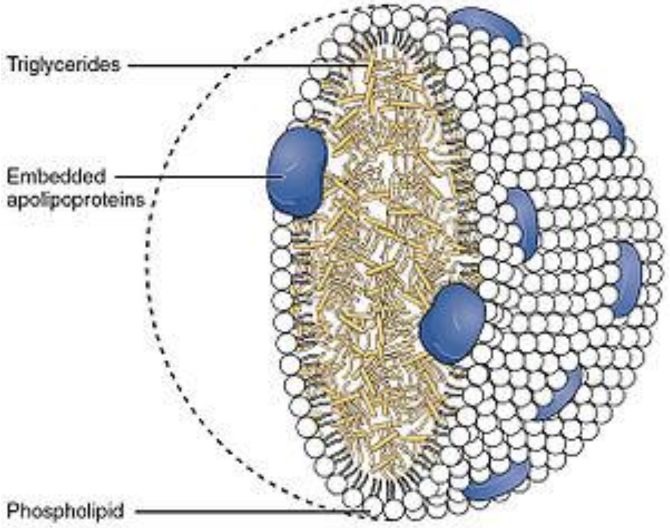


Figure 7. Structure of galactosylceramide (galactocerebroside, R = H), and sulfogalactosylceramide (a sulfatide, R = SO_4^{2-}).

Lipoproteins



Lipoproteins are biochemical assembly whose purpose is to *transport the hydrophobic lipids molecules in water, blood or in Extra Cellular Fluids (ECF).*

- They have a single layer phospholipid and cholesterol outer shell, with the hydrophilic portions oriented outward toward the water and lipophilic portions oriented inwards toward the lipids molecules within the particles.
- *Apolipoproteins* are embedded in the membrane, both stabilizing the complex and giving it functional identity determining its fate.
- Many enzymes, transporters, structural proteins, antigens, adhesins, and toxins are lipoproteins.
  - Examples: the plasma lipoprotein particles are classified under HDL, LDL, IDL, VLDL and ULDL (commonly called chylomicron) lipoproteins, which enable fats to be carried in the blood stream (an example of emulsification), the transmembrane proteins of the mitochondrion and the chloroplast, and bacterial lipoproteins.
- HDL= High Density Lipoproteins; LDL= Low Density Lipoproteins; VLDL= Very Low Density Lipoproteins
- IDL= Intermediate-density lipoprotein; ULDL= Ultra Low Density Lipoproteins

wikipedia

Lipoproteins

Four major groups of lipoproteins that can be separated according to their electrophoretic properties into **chylomicrons α-, β-, and pre-β-lipoproteins** and have been identified as physiologically important compounds and used in clinical diagnosis.

These are:

(1) chylomicrons, derived from intestinal absorption of triacylglycerol and other lipids;

(2) very low density lipoproteins (VLDL, or pre-β-lipoproteins), derived from the liver for the export of triacylglycerol;

(3) low-density lipoproteins (LDL, or β- lipoproteins), representing a final stage in the catabolism of VLDL; and

(4) high-density lipoproteins (HDL, or α-lipoproteins), involved in VLDL and chylomicron metabolism and also in cholesterol transport.

Triacylglycerol is the predominant lipid in chylomicrons and VLDL, whereas cholesterol and phospholipid are the predominant lipids in LDL and HDL, respectively (Table 3).

Table 3. Composition of the lipoproteins in plasma of humans.

Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition: Protein (%)	Composition: Lipid (%)	Main Lipid Components	Apolipoproteins
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL_3		5–10	1.125–1.210	57	43		
Preβ-HDL[3]		< 5	> 1.210				A-I
Albumin/free fatty acids	Adipose tissue		> 1.281	99	1	Free fatty acids	

Abbreviations: HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins.

[1]Secreted with chylomicrons but transfers to HDL.

[2]Associated with HDL_2 and HDL_3 subfractions.

[3]Part of a minor fraction known as very high density lipoproteins (VHDL).

Lipoproteins Consist of a Nonpolar Core & a Single Surface Layer of Amphipathic Lipids

The nonpolar lipid core consists of mainly triacylglycerol and cholesteryl ester

The core is surrounded by a single surface layer of amphipathic phospholipid and cholesterol molecules.

These are oriented so that their polar groups face outward to the aqueous medium,.

The protein moiety of a lipoprotein is known as an ***apolipoprotein*** or **apoprotein,** constituting nearly 70% of some HDL and as little as 1% of chylomicrons.

Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoproteins.

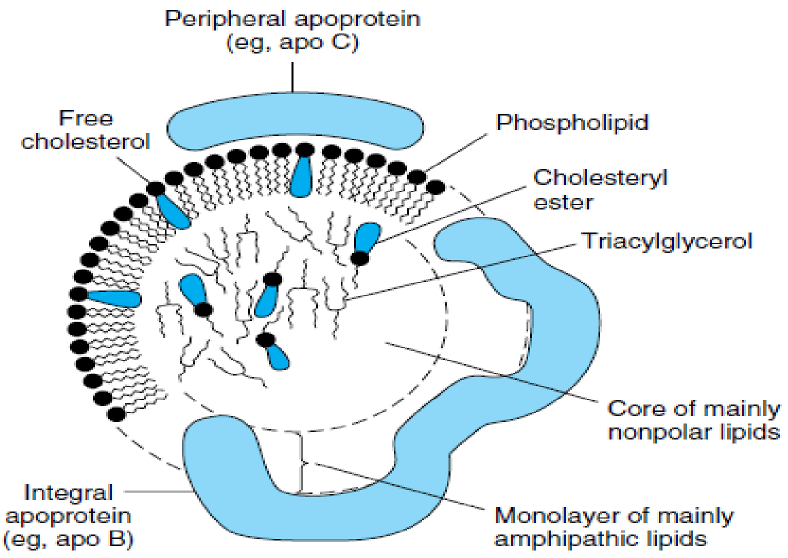


Figure 11. Generalized structure of a plasma lipoprotein. The similarities with the structure of the plasma membrane are to be noted. Small amounts of cholesteryl ester and triacylglycerol are to be found in the surface layer and a little free cholesterol in the core.

The formation and secretion of lipoproteins

- In the Rough Endoplasmic Reticulum (RER), **The protein part of *Apolipoprotein B***, is synthesized.
- In the smooth endoplasmic reticulum (SER)-the main site of synthesis of triacylglycerol- the lipid part is incorporated forming the lipoproteins.
- In Golgi apparatus, the carbohydrate residues are added,
- Hence, the apolipoproteins B are released from the cell by reverse pinocytosis.
  - Chylomicrons pass into the lymphatic system.
  - VLDL are secreted into the space of Disse and then into the hepatic sinusoids through fenestrae in the endothelial lining.

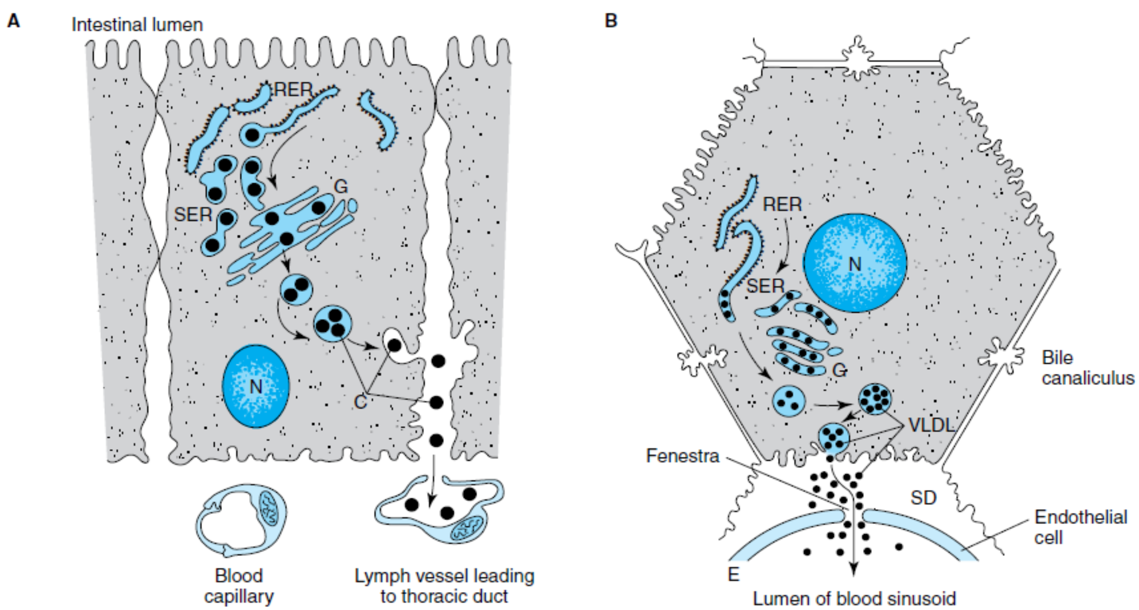


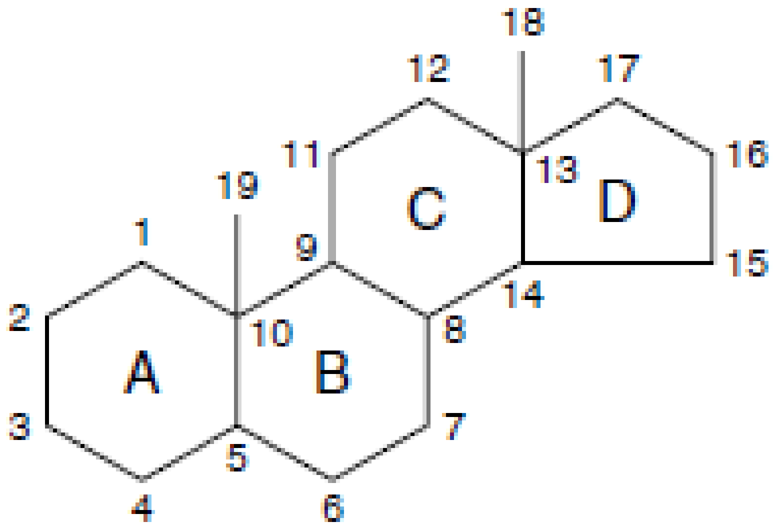
Figure 12. The formation and secretion of (A) chylomicrons by an intestinal cell and (B) very low density lipoproteins by a hepatic cell. (RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum; G, Golgi apparatus; N, nucleus; C, chylomicrons; VLDL, very low density lipoproteins; E, endothelium; SD, space of Disse, containing blood plasma.)

Sterols

- The difference between sterol, steroids and cholesterol
- Sterols
- They have a structure that includes four fused rings.
- They are more common in plasma membranes than in intracellular membranes (mitochondria, lysosomes, etc.).
- They are classified as structural lipids as it presents in the membranes of most eukaryotic cells but not prokaryotes.
- They are precursors of steroid hormones.

Steroids

- **Steroids structure**
- All of the steroids have a similar cyclic nucleus resembling phenanthrene (rings A, B, and C) to which a cyclopentane ring (D) is attached.
- They are oxidized derivatives of sterols; lack alkyl tail; more polar than cholesterol



The steroid nucleus

Steroids play many physiologically important roles (steroid functions)

- **Cholesterol** is probably the best known steroid because of its association with atherosclerosis.
- It is also of significance because it is the precursor of a large number of equally important steroids that include:
  - the bile acids,
  - adrenocortical hormones,
  - sex hormones,
  - D vitamins,
  - cardiac glycosides,
  - sitosterols of the plant kingdom, and
  - some alkaloids.

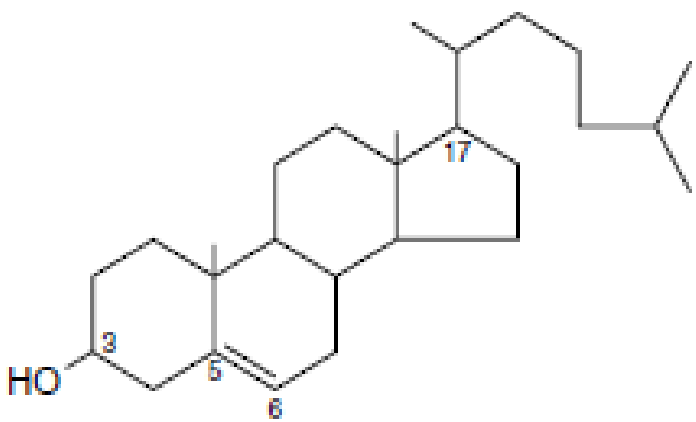
Cholesterol Is a Significant Constituent of Many Tissues

Cholesterol is widely distributed in all cells of the body but particularly in nervous tissue.

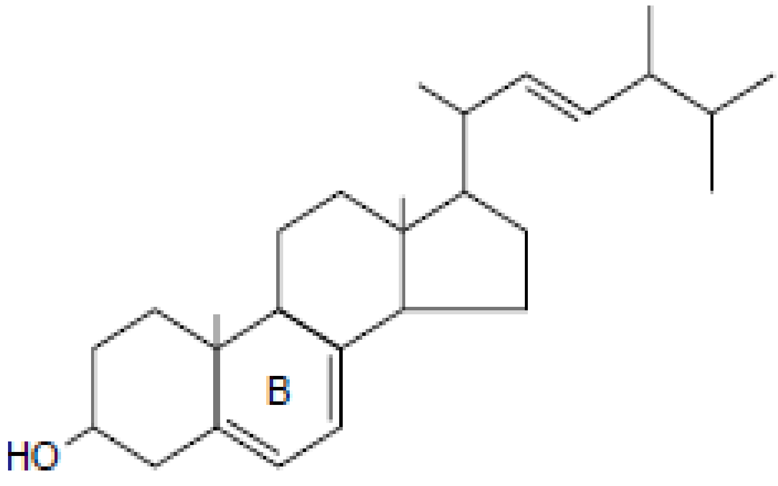
It is amphipathic compound.

It is a major constituent of the *plasma membrane* and of *plasma lipoproteins* of eukaryotes (but not prokaryotes) and less frequently in the intracellular membranes.

It is often found as cholesteryl ester, where the hydroxyl group on position 3 is esterified with a long-chain fatty acid.



Cholesterol, 3-hydroxy-5,6-cholestene



Ergosterol

Q:

- **Which of the following is NOT true of sterols?**

a- Cholesterol is a sterol that is commonly found in mammals.

<u>b- They are commonly found in bacterial membranes.</u>

c- They are more common in plasma membranes than in intracellular membranes (mitochondria, lysosomes, etc.).

d- They are precursors of steroid hormones.

e- They have a structure that includes four fused rings.

- **Which of the following best describes the cholesterol molecule?**
- <u>a- Amphipathic</u>
- b-_ Nonpolar, charged
- c- Nonpolar, uncharged
- d- Polar, charged
- e- Polar, uncharged

Terpenes,

- **Terpenes** are diverse class of organic compounds, produced by a variety of plants, and some insects.
- They are derived biosynthetically from units of *isoprene*,
- They often have a strong odor and may *protect the plants* that produce them by deterring herbivores and by attracting predators and parasites of herbivores.
- Terpenes are the primary *constituents of the essential oils* of many types of plants.
- Essential oils are used widely as fragrances in perfumery, and in medicine.
- Synthetic variations and derivatives of natural terpenes also greatly expand the variety of aromas used in perfumery and flavors used in food additives.
- A range of terpenes have been identified as *high-value chemicals in food, cosmetic, pharmaceutical and biotechnology industries*
- *Vitamin A is a terpene*.

Fat soluble Vitamins

- Fat soluble vitamins (A, D, E & K) are derived lipids and they have important functions

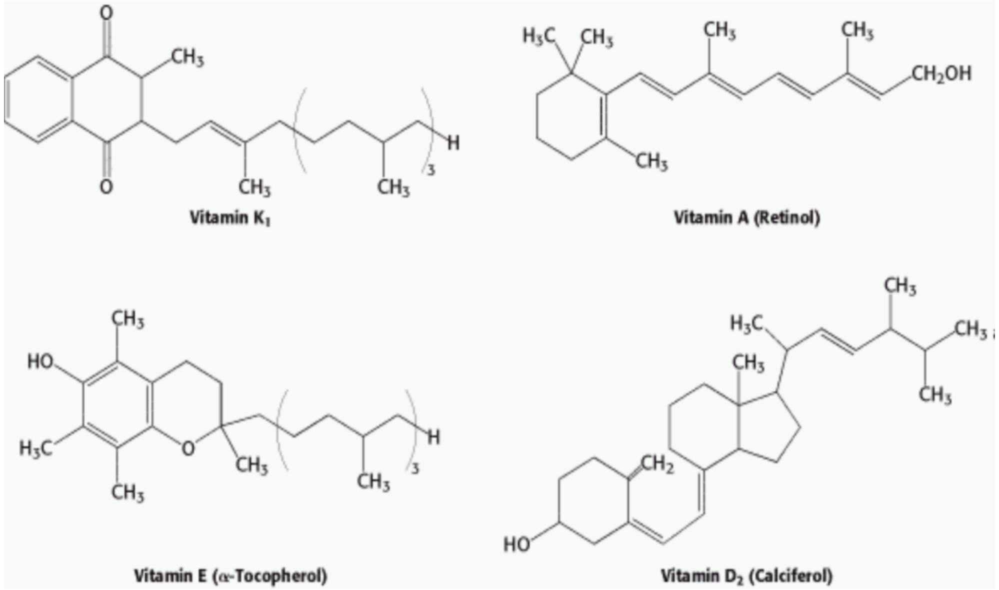


Table 8.10. Fat-soluble vitamins

Vitamin	Function	Deficiency
A	Roles in vision, growth, reproduction	Night blindness, cornea damage, damage to respiratory and gastrointestinal tract
D	Regulation of calcium and phosphate metabolism	Rickets (children): skeletal deformaties, impaired growth Osteomalacia (adults): soft, bending bones
E	Antioxidant	Inhibition of sperm production; lesions in muscles and nerves (rare)
K	Blood coagulation	Subdermal hemorrhaging

Steroid hormones

- Steroid hormones have the nucleus of steroids
- They can be grouped into 2 classes, corticosteroids and sex steroids.
- Among these hormones are:
  - glucocorticoids
  - mineralocorticoids
  - androgens,
  - estrogens,
  - progestogens (sex steroids).
- Vitamin D derivatives are a sixth closely related hormone system with homologous receptors.
- **Steroid hormones** help control metabolism, inflammation, immune functions, salt and water balance, development of sexual characteristics, and the ability to withstand illness and injury.

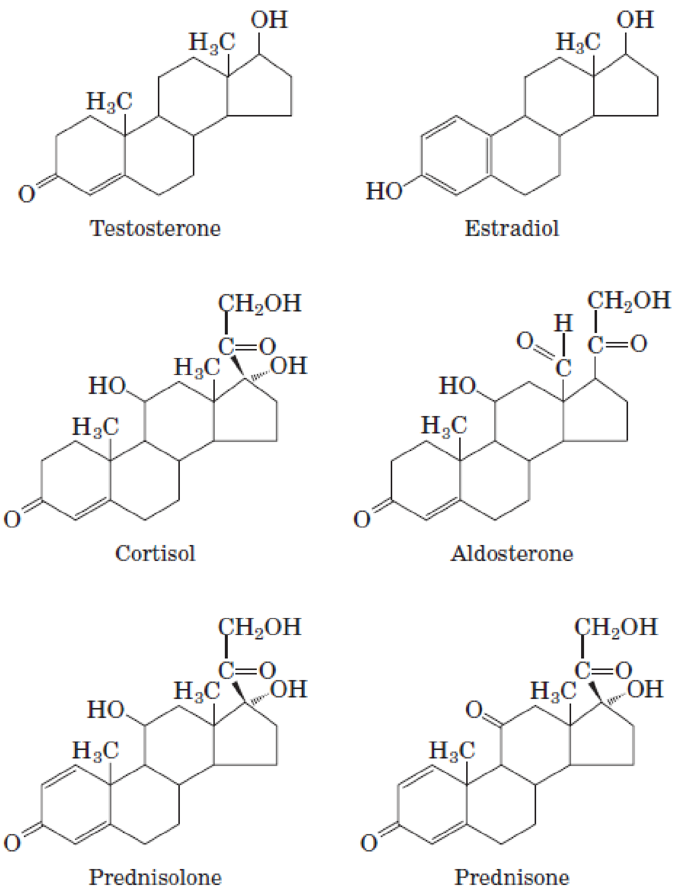


FIGURE 10-19 Steroids derived from cholesterol. Testosterone, the male sex hormone, is produced in the testes. Estradiol, one of the female sex hormones, is produced in the ovaries and placenta. Cortisol and aldosterone are hormones synthesized in the cortex of the adrenal gland; they regulate glucose metabolism and salt excretion, respectively. Prednisolone and prednisone are synthetic steroids used as antiinflammatory agents.

Fat storage & mobilization in adipose tissue

Biomedical importance

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage.

Since lipids are insoluble in water, the problem of how to transport them in the aqueous blood plasma is solved by associating nonpolar lipids (triacylglycerol and cholesteryl esters) with amphipathic lipids (phospholipids and cholesterol) and proteins to make water miscible lipoproteins.

Lipids are transported in the plasma as lipoproteins

Plasma lipids consist of:

- **triacylglycerols (16%),**
- **phospholipids (30%),**
- **cholesterol (14%),**
- **cholesteryl esters (36%) and**
- **unesterified** long-chain fatty acids (free fatty acids) (4%).

The **free fatty acids (FFA), is metabolically** the most active of the plasma lipids.

Because fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases.

Triacylglycerol is transported from the intestines in chylomicrons & from the liver in very low density lipoproteins

Chylomicrons are found in chyle formed only by the lymphatic system **draining the intestine.**

They are responsible for the transport of all dietary lipids into the circulation.

Small quantities of VLDL are also to be found in chyle; however, most of the plasma **VLDL are of hepatic origin.**

They are the vehicles of transport of triacylglycerol from the liver to the extrahepatic tissues.

There are striking similarities in the mechanisms of formation of chylomicrons by intestinal cells and of VLDL by hepatic parenchymal cells (Figure 12)

Chyle is a milky bodily fluid consisting of lymph and emulsified fats, or free fatty acids (FFAs). It is formed in the small intestine during digestion of fatty foods, and taken up by lymph vessels. The lipids in the chyle are colloidally suspended in chylomicrons.

Newly secreted or "nascent" chylomicrons and VLDL contain only a small amount of apolipoproteins C and E, and the full complement is acquired from HDL in the circulation.

In **abetalipoproteinemia or Bassen-Kornzweig syndrome (a rare disease),** lipoproteins containing apo B are not formed and lipid droplets accumulate in the intestine and liver.

A more detailed account of the factors controlling hepatic VLDL secretion is given below.

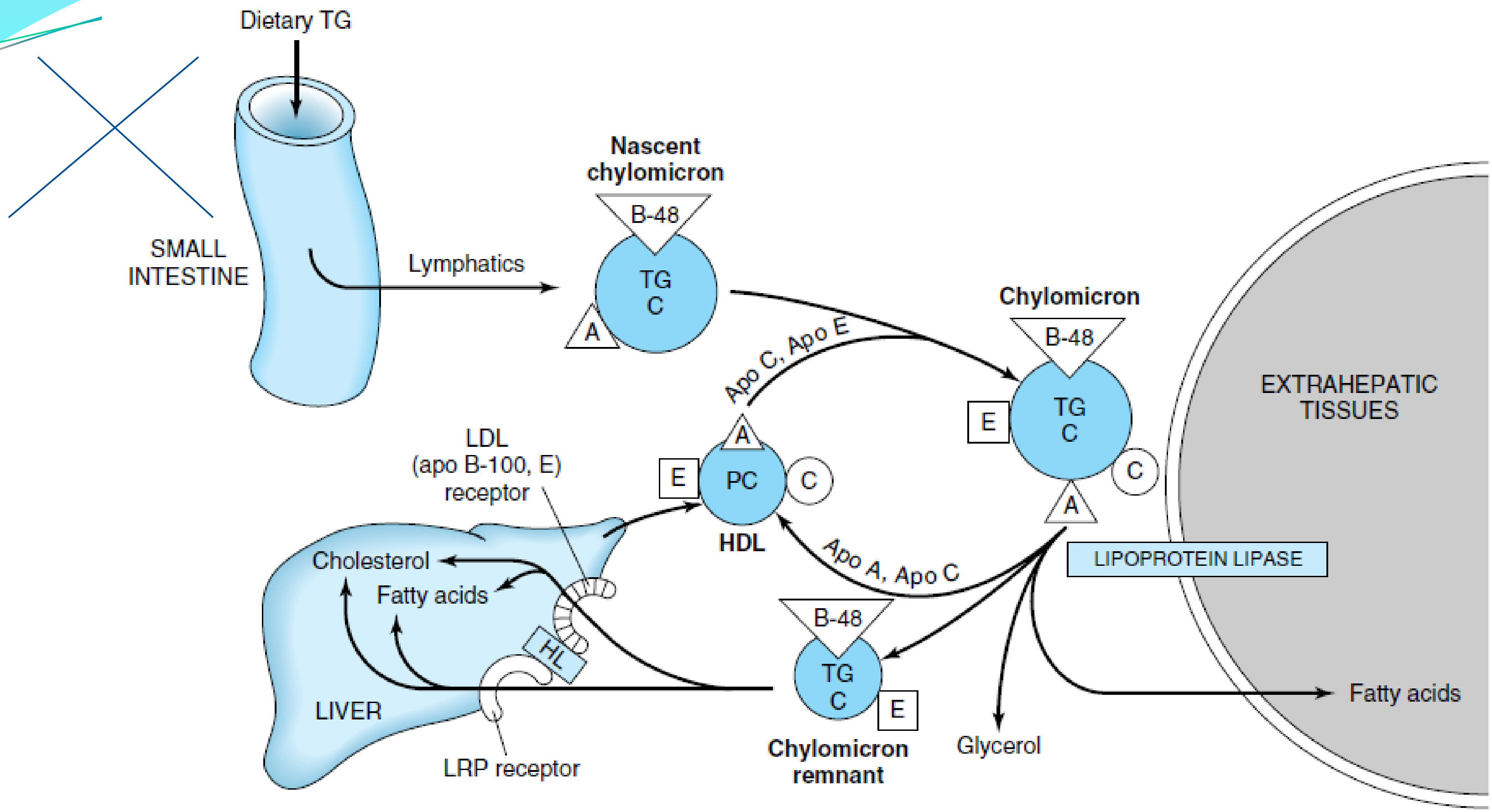


Figure 13. Metabolic fate of chylomicrons. (A, apolipoprotein A; B-48, apolipoprotein B-48; C , apolipoprotein C; E, apolipoprotein E; HDL, high-density lipoprotein; TG, triacylglycerol; C, cholesterol and cholesteryl ester; P, phospholipid; HL, hepatic lipase; LRP, LDL receptor-related protein.) Only the predominant lipids are shown.

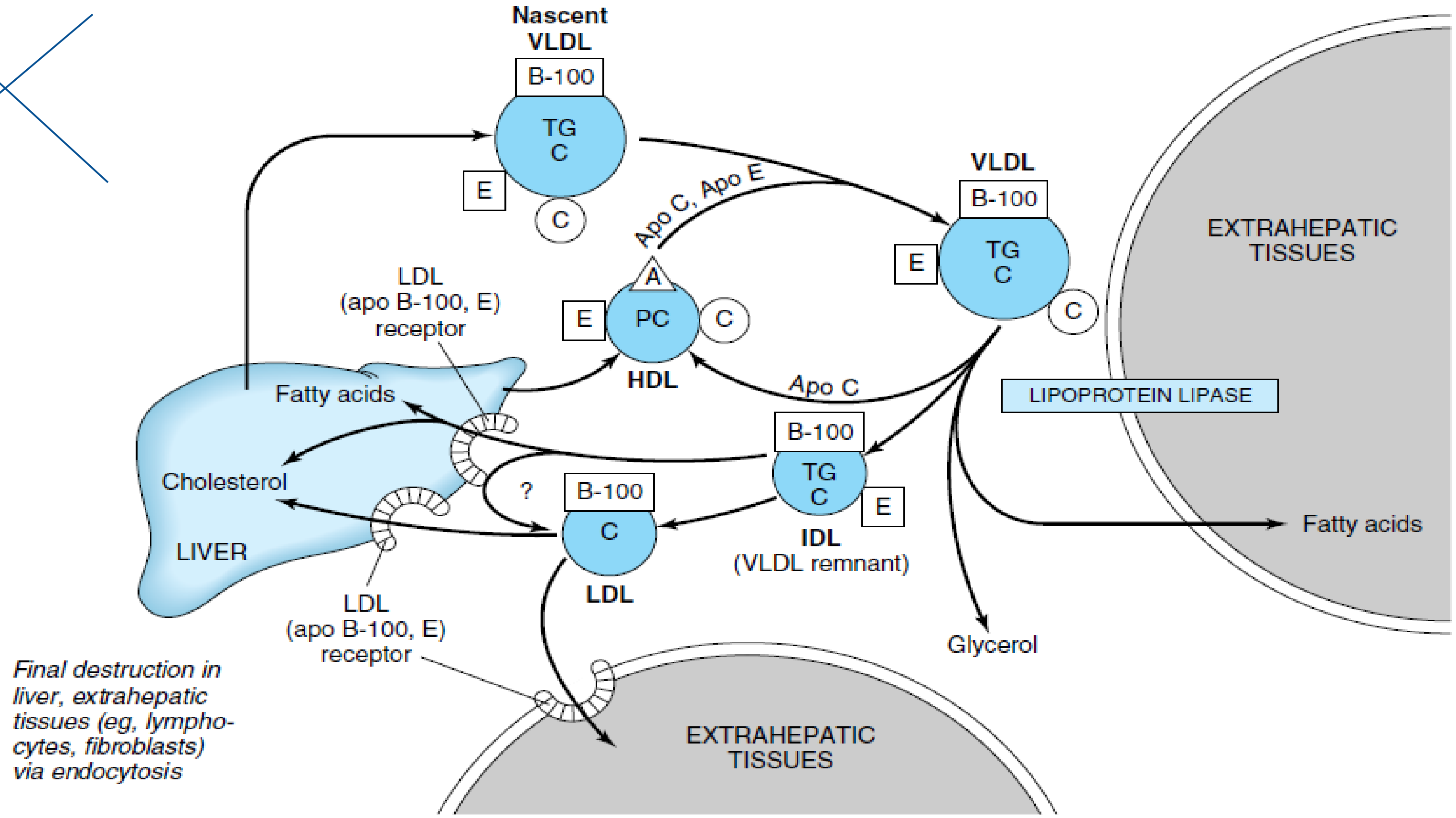


Figure 14. Metabolic fate of very low density lipoproteins (VLDL) and production of low-density lipoproteins (LDL). (A, apolipoprotein A; B-100, apolipoprotein B-100; C , apolipoprotein C; E, apolipoprotein E; HDL, high-density lipoprotein; TG, triacylglycerol; IDL, intermediate-density lipoprotein; C, cholesterol and cholesteryl ester; P, phospholipid.) Only the predominant lipids are shown. It is possible that some IDL is also metabolized via the LRP.

Introduction to biomembranes and adipocytes

Assembly of lipid molecules (membrane and adipose tissue)
Fluid mosaic model and types of membrane proteins

Biological membranes and transport

Membranes define the external boundaries of cells and the intracellular components.

They acts as a selectively permeable barrier within living things.

Biological membranes, in the form of cell membranes, often consist of a phospholipid bilayer with embedded, integral and peripheral proteins .

Membranes are flexible, self-sealing, and selectively permeable to polar solutes.

Membrane flexibility permits the shape changes that accompany cell growth and movement (such as amoeboid movement).

With their ability to break and reseal, two membranes can fuse, as in *exocytosis*, or a single membrane-enclosed compartment can undergo fission to yield two sealed compartments, as in *endocytosis* or cell division, without creating gross leaks through cellular surfaces.

Because membranes are selectively permeable, they retain certain compounds and ions within cells and within specific cellular compartments, while excluding others.

Membranes are not merely passive barriers.

Membranes include an array of proteins specialized for promoting or catalyzing various cellular processes.

At the cell surface there are:

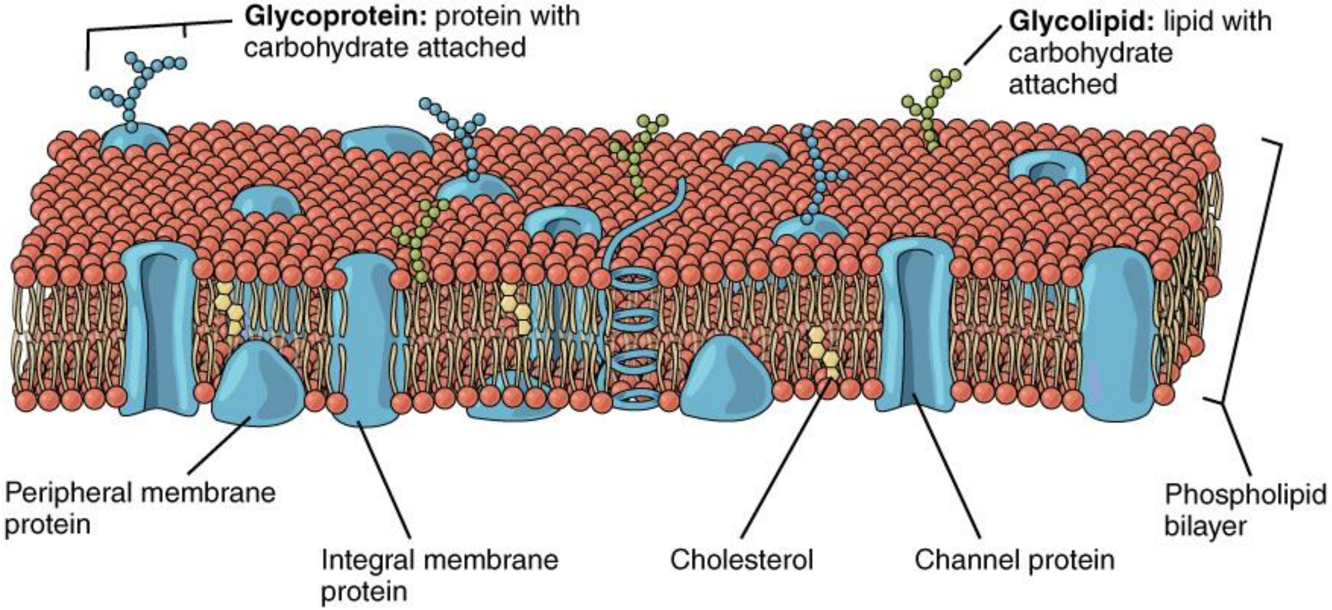
- transporters move specific organic solutes and inorganic ions across the membrane;
- receptors sense extracellular signals and trigger molecular changes in the cell;
- adhesion molecules hold neighboring cells together.

Within the cell, membranes organize cellular processes such as the synthesis of lipids and certain proteins, and the energy transductions in mitochondria and chloroplasts.

The Composition and Architecture of Membranes

One approach to understanding membrane function is to study membrane composition—to determine which components are common to all membranes and which are unique to membranes with specific functions.

So before describing membrane structure and function we consider the molecular components of membranes: proteins and polar lipids, which account for almost all the mass of biological membranes, and carbohydrates, present as part of glycoproteins and glycolipids.



Each type of membrane has characteristic lipids and proteins

The relative proportions of protein and lipid vary with the type of membrane, reflecting the diversity of biological roles.

For example, certain neurons have a myelin sheath, an extended plasma membrane that wraps around the cell many times and acts as a passive electrical insulator.

The myelin sheath consists primarily of lipids, whereas the plasma membranes of bacteria and the membranes of mitochondria and chloroplasts, the sites of many enzyme-catalyzed processes, contain more protein than lipid (in mass per total mass). **WHY?**

Table 4: Major Components of Plasma Membranes in Various Organisms

	Components (% by weight)				
	Protein	*Phospholipid*	*Sterol*	*Sterol type*	*Other lipids*
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	–
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	–
E. coli	75	25	0	–	–

Note: Values do not add up to 100% in every case, because there are components other than protein, phospholipids, and sterol; plants, for example, have high levels of glycolipids.

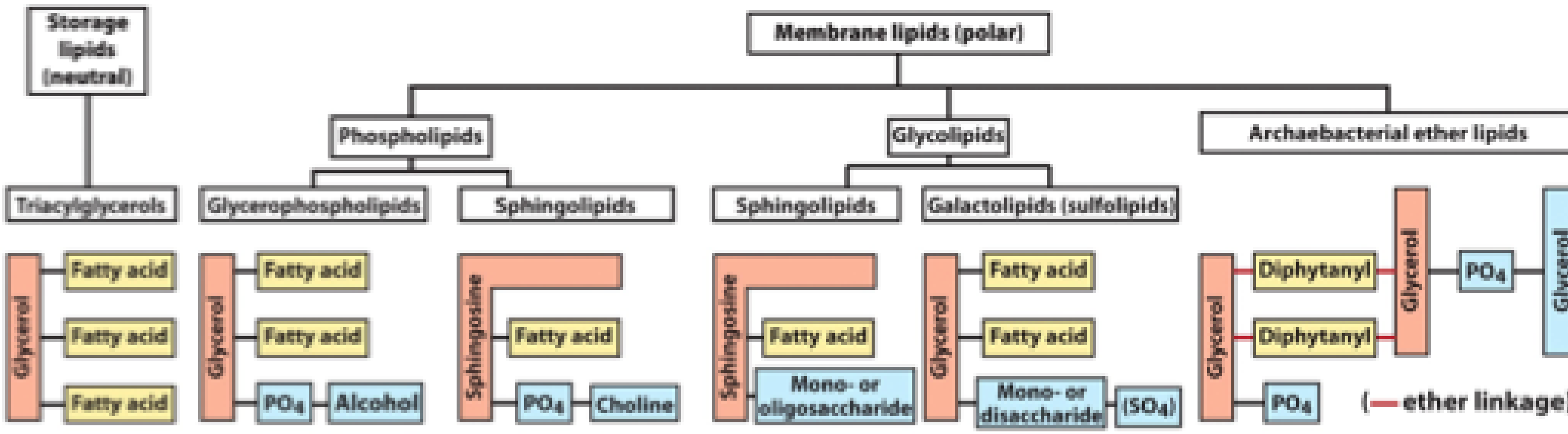


Figure 10-7
Lehninger Principles of Biochemistry, Sixth Edition

All Biological Membranes Share Some Fundamental Properties

Membranes are impermeable to most polar or charged solutes, but permeable to nonpolar compounds;

They are 5 to 8 nm (50 to 80 Å) thick and appear trilaminar when viewed in cross section with the electron microscope.

The combined evidence from electron microscopy and studies of chemical composition, as well as physical studies of permeability and the motion of individual protein and lipid molecules within membranes, led to the development of the **fluid mosaic model for** the structure of biological membranes.

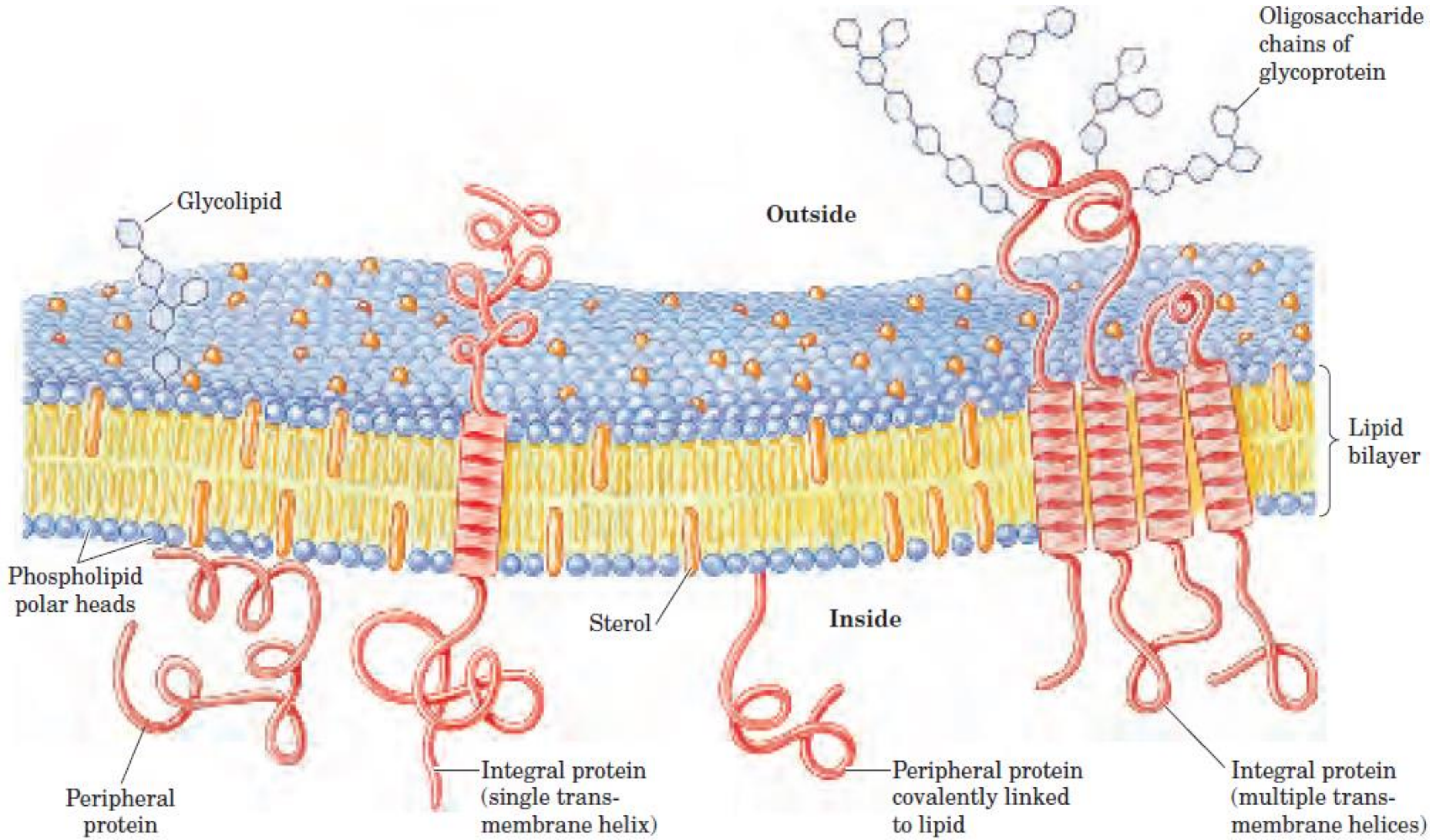


Figure 15 Fluid mosaic model for membrane structure. The fatty acyl chains in the interior of the membrane form a fluid, hydrophobic region. Integral proteins float in this sea of lipid, held by hydrophobic interactions with their nonpolar amino acid side chains . Both proteins and lipids are free to move laterally in the plane of the bilayer, but movement of either from one face of the bilayer to the other is restricted. The carbohydrate moieties attached to some proteins and lipids of the plasma membrane are exposed on the extracellular surface of the membrane.

Introduction to Lipid metabolism

Introduction to lipid metabolism

Triglyceride $\xrightarrow{\text{Pancreatic lipase}}$ **2-monoglyceride + 2 fatty acids**

Adipose tissue is the main store of triacylglycerol in the body

The triacylglycerol stores in adipose tissue are continually undergoing lipolysis (hydrolysis) and re-esterification.

These two processes are entirely different pathways involving different reactants and enzymes. This allows the processes of esterification or lipolysis to be regulated separately by many nutritional, metabolic, and hormonal factors.

The resultant of these two processes determines the magnitude of the free fatty acid pool in adipose tissue, which in turn determines the level of free fatty acids circulating in the plasma.

Since the latter has most profound effects upon the metabolism of other tissues, particularly liver and muscle, the factors operating in adipose tissue that regulate the outflow of free fatty acids exert an influence far beyond the tissue itself.

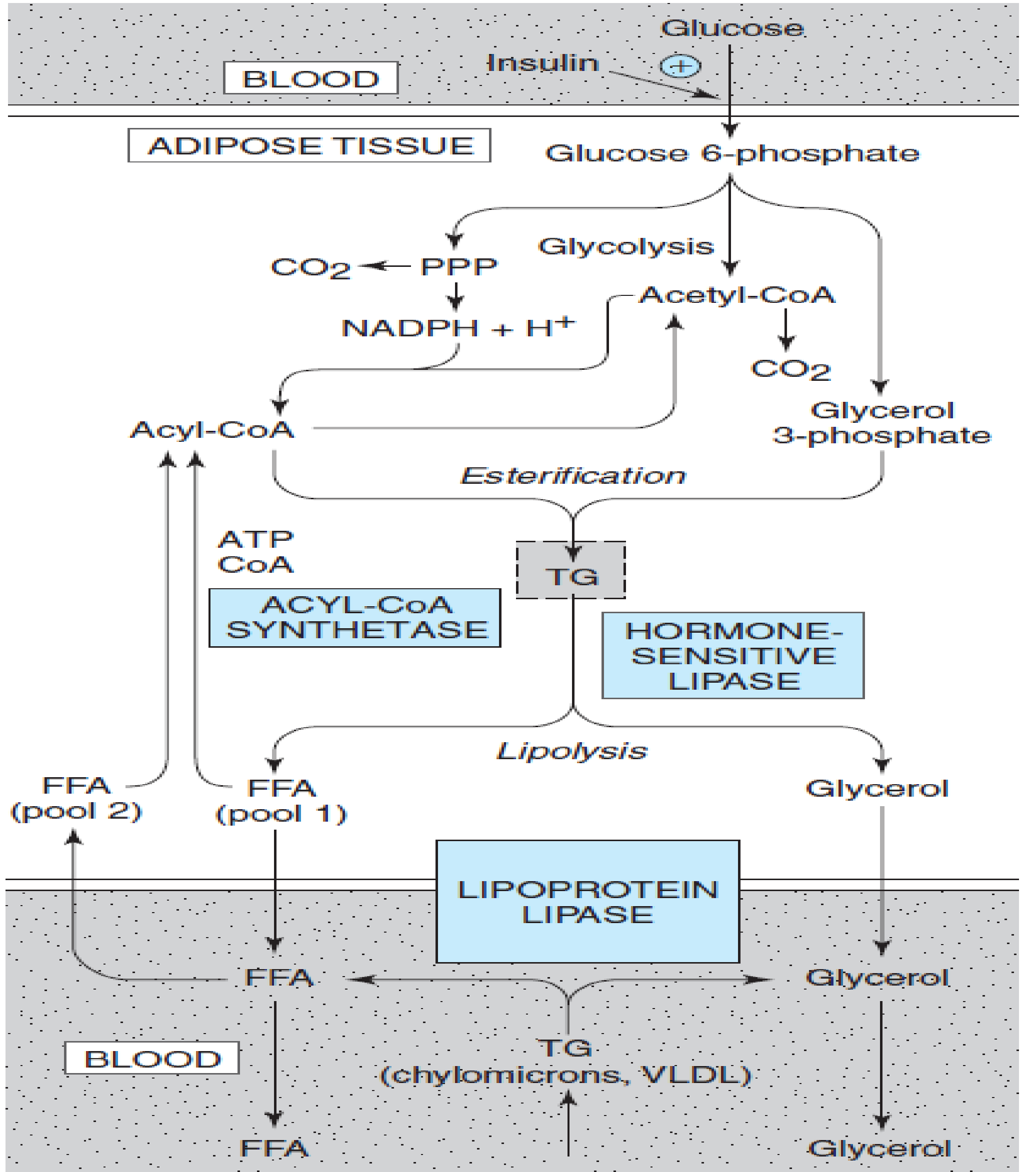
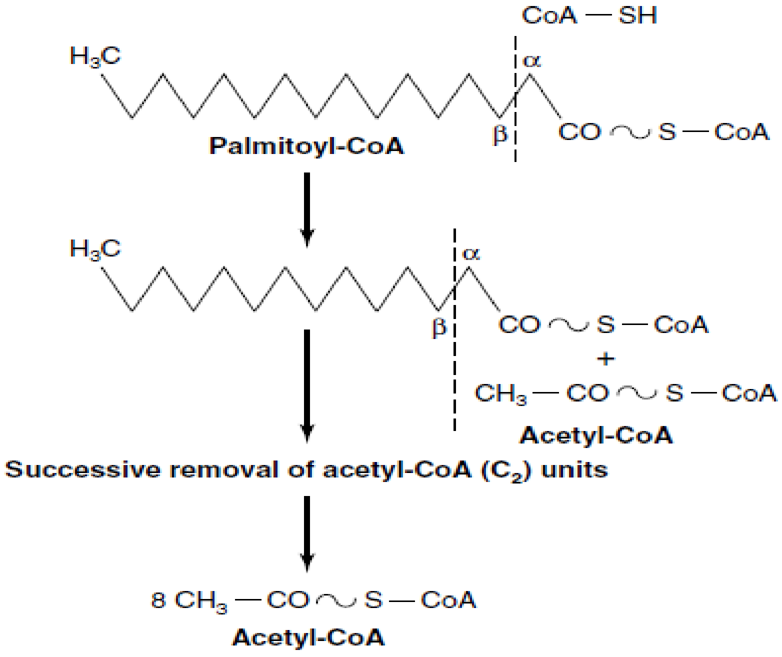
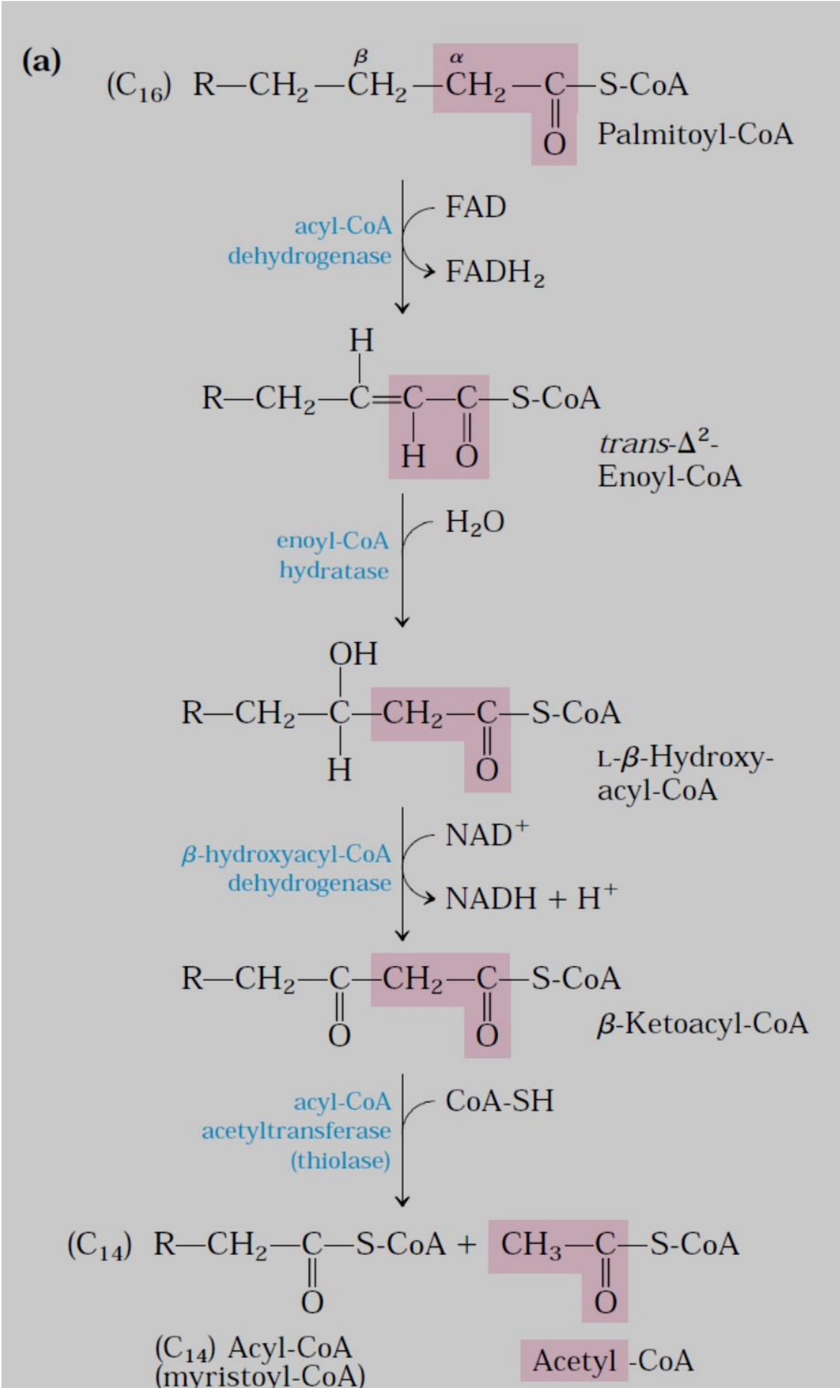


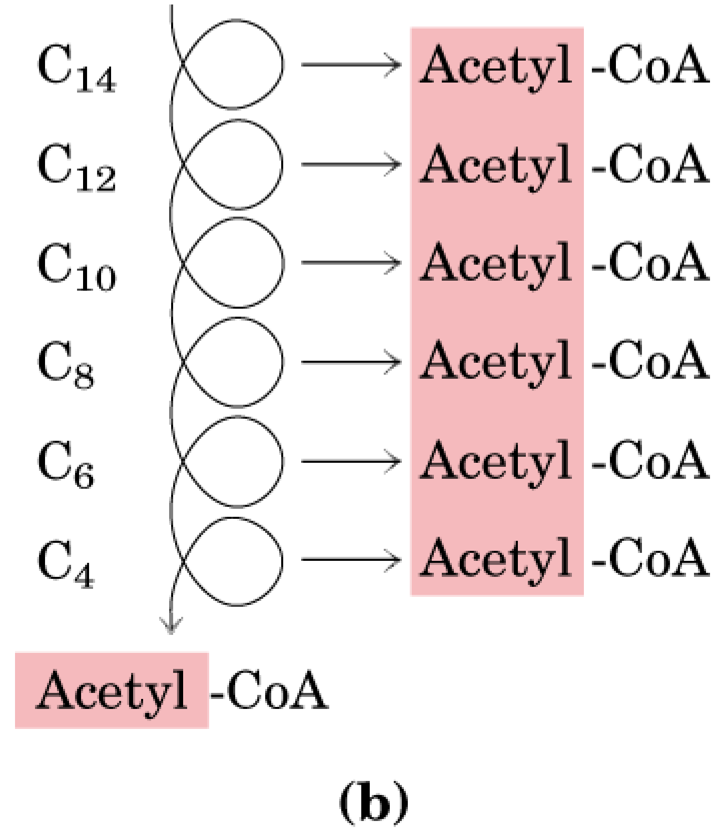
Figure 16. Metabolism of adipose tissue. *Hormone*- sensitive lipase is activated by ACTH, TSH, glucagon, epinephrine, norepinephrine, and vasopressin and inhibited by insulin, prostaglandin E1, and nicotinic acid. Details of the formation of glycerol 3-phosphate from intermediates of glycolysis. (PPP, pentose phosphate pathway; TG, triacylglycerol; FFA, free fatty acids; VLDL, very low density lipoprotein.)

β-Oxidation of fatty acids involves successive cleavage with release of acetyl-CoA

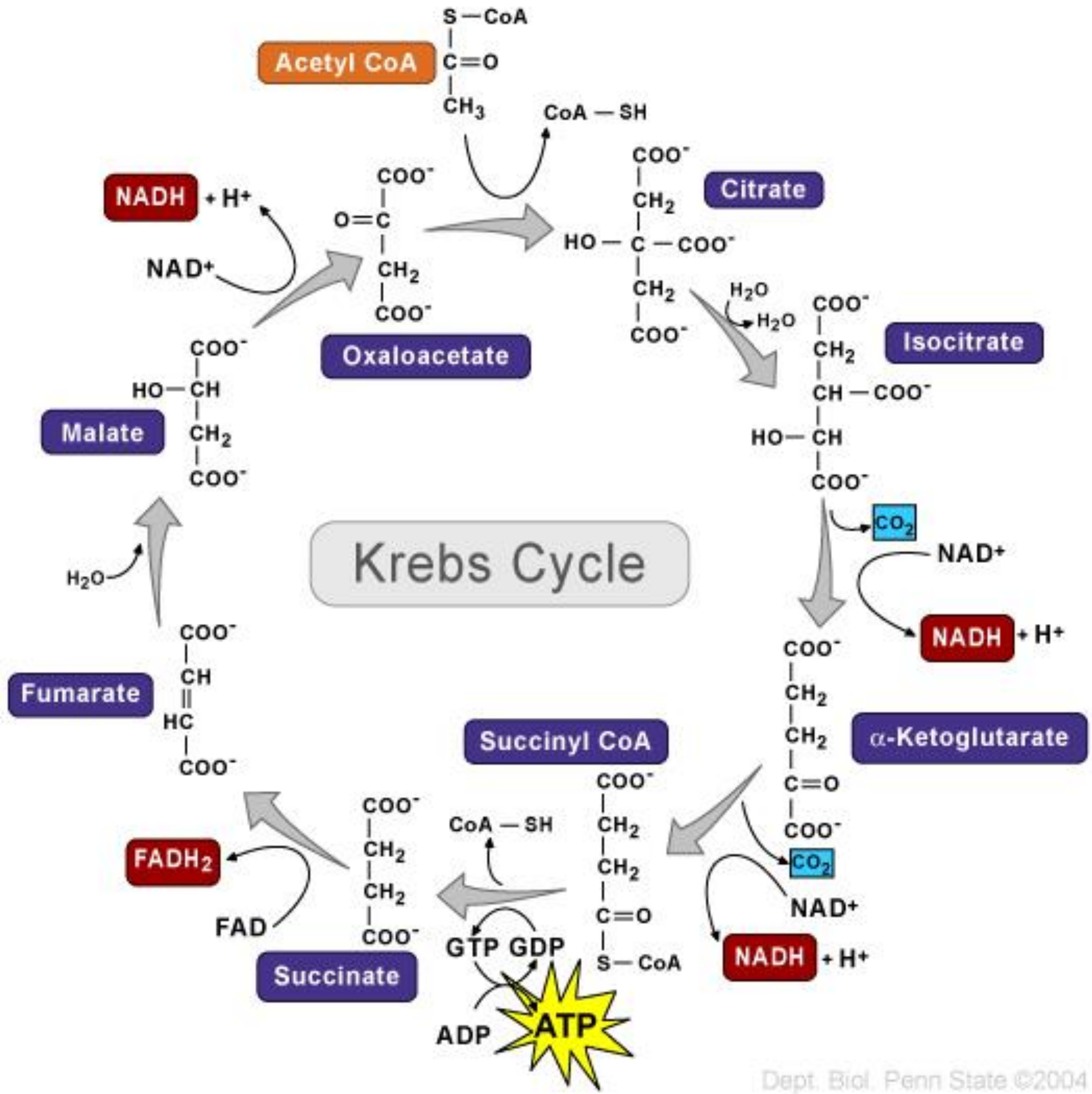
- In β-oxidation, two carbons at a time are cleaved from acyl-CoA molecules, starting at the carboxyl end.
- The chain is broken between the α(2)- and β(3)-carbon atoms—hence the name β-oxidation.
- The two-carbon units formed are acetyl-CoA; thus, palmitoyl- CoA forms eight acetyl-CoA molecules.







Lehninger, 4th ed.


Krebs Cycle
Acetyl CoA
CoA — SH
Citrate
H_2O
H_2O
Isocitrate
CO_2
NAD+
NADH + H+
α-Ketoglutarate
CO_2
NAD+
NADH + H+
Succinyl CoA
CoA — SH
GTP GDP
ADP
ATP
Succinate
FAD
$FADH_2$
Fumarate
H_2O
Malate
NAD+
NADH + H+
Oxaloacetate
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The Cyclic Reaction Sequence Generates $FADH_2$ & NADH

- Several enzymes, known collectively as "fatty acid oxidase," are found in the mitochondrial matrix or inner membrane adjacent to the respiratory chain.
- These catalyze the oxidation of acyl-CoA to acetyl-CoA, the system being coupled with the phosphorylation of ADP to ATP.
- The first step is the removal of two hydrogen atoms from the 2(α)- and 3(β)-carbon atoms, catalyzed by acyl-CoA dehydrogenase and requiring **FAD.**
- This results in the formation of Δ^2-*trans-enoyl-CoA and* **$FADH_2$.**
- The reoxidation of **$FADH_2$** by the respiratory chain requires the mediation of another flavoprotein, termed electron-transferring flavoprotein.

Water is added to saturate the double bond and form 3-hydroxyacyl-CoA, catalyzed by **2-enoyl-CoA hydratase.**

The 3-hydroxy derivative undergoes further dehydrogenation on the 3-carbon catalyzed by **L(+)-3- hydroxyacyl-CoA dehydrogenase to form the corresponding** 3-ketoacyl-CoA compound. In this case, **NAD^+** is the coenzyme involved and it gave **NADH**.

Finally, 3-ketoacyl- CoA is split at the 2,3- position by **thiolase (3-ketoacyl-CoA-thiolase)**, forming acetyl-CoA and a new acyl- CoA two carbons shorter than the original acyl-CoA molecule.

The acyl-CoA formed in the cleavage reaction reenters the oxidative pathway at reaction 2.

NADH → NAD^+ + **3ATP**

$FADH_2$ →FAD **+ 2ATP**

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