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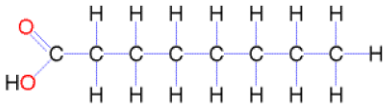
Biochemistry

Lipids

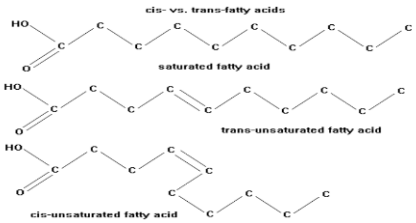
❖ Lipids

- They are a **heterogeneous** class of naturally occurring organic compounds that share some properties based on structural similarities, mainly a dominance of nonpolar groups (Hydrophobic)
  - ➢ They are macromolecules (but not polymers), widely distributed in animals and plants
- They are mostly **amphipathic** in nature
  - ➢ Amphipathic: Molecules have polar (hydrophilic) and non-polar (hydrophobic) groups
- They are mainly **water-insoluble**, but they are **soluble in the non-polar solvents** such as fat or organic solvents (ether, chloroform, benzene, acetone)
- Lipids are classified into:
  - ➢ Simple lipids such as fats, oils, and waxes
  - ➢ Complex lipids such as glycerides, glycerophospholipids, sphingolipids, glycolipids, lipoproteins
  - ➢ Derived lipids such as fatty acids, alcohols, eicosanoids
  - ➢ Cyclic lipids such as steroids
- Lipids functions:
  - ➢ Storage in the adipose tissue forming a major source of energy in the body
    - ✓ They can store unlimited amounts of energy (about 25% of the body needs)
    - ✓ Lipids provide a higher energy value (amount of energy per gram) than carbohydrates & proteins
  - ➢ Structural components in the membranes
  - ➢ Precursor of hormones and lipid-soluble vitamins (D, E, K, A)
  - ➢ Shock absorbance (protect internal organs) and thermal insulators

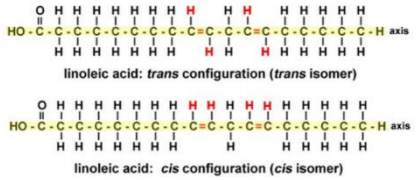
❖ Fatty acids



- Mono-carboxylic acids with long hydrocarbon aliphatic chain
  - ➢ Molecular formula: R-$(CH_2)_n$-COOH
  - ➢ The length normally ranges from 12-24 C (physiological) and the most **abundant** lengths **16-18 C**
- Fatty acids are **Amphipathic** molecules
- Functions of fatty acids:
  - ➢ Building blocks for other lipids (such as triacylglycerol)
  - ➢ Modifications of many proteins (lipoproteins)
  - ➢ Important fuel molecules which can be broken into smaller molecules such as acetyl CoA
  - ➢ Derivatives of important cellular molecules (such as phospholipids & sphingolipids)
- Fatty acids can be classified according to saturation into:
  - ➢ **Saturated:** All the bonds between carbons (C – C) are **single** bonds
  - ➢ **Unsaturated**: Have 1 or more **double** bond between carbons
    - ✓ Mono-unsaturated: Contains only 1 double bond
    - ✓ Poly-unsaturated: Contains 2 or more double bonds



- Unsaturated fatty acids can be either in the Cis or Trans form (isomer):
  - ➢ **Cis:** H atoms on the Carbons forming the double bond have the **same** orientation, **producing a kink** to decrease the steric hindrance between the adjacent H atoms
  - ➢ **Trans:** H atoms on the Carbons forming the double bond have the **opposite** orientation, so there is **no kink**



- Cis isomers are more abundant (predominant) than trans

Short chain F.A. (2-4)	Medium-chain F.A. (6-10)	Long chain F.A. (12-20)
They are liquid in nature	Solids at room temperature	Solids at room temperature
Water-soluble	Water-soluble	Water-insoluble
Volatile at RT	Non-volatile at RT	Non-volatile
Acetic, butyric, caproic	Caprylic & capric F.A.	Palmitic and stearic F.A

- The properties of fatty acids (such as melting point and water solubility) depend on:
  - **Chain length** which is the number of carbons forming the chain
    - ✓ Longer chains more non-covalent interactions (Hydrophobic & Van der Waals) between chains and more energy needed to break them, so higher melting point
    - ✓ Longer hydrocarbon part increases the dominance of the non-polar region which decreases water solubility
  - **Saturation** which depends on the number of double bonds
    - ✓ More double bonds, higher level of unsaturation causing more kinks forming a less compacted structure and less energy needed to separate the chains, less melting point

❖ Naming of Fatty acids

A) Systematic naming:

1 = Mono	**5 = Penta**	**9 = Nona**
2 = Di	**6 = Hexa**	**10 = Deca**
3 = Tri	**7 = Hepta**	**20 = Eico**
4 = Tetra	**8 = Octa**	**22 = Doco**

- FA ends with **-oic** acid
  - Number of Carbons (Mono-, Di-,…)
  - Saturation is designated by:
    - ✓ When saturated, it is considered as alkane so ends with **-anoic**
    - ✓ When mono-unsaturated, it is considered as alkene so ends with **-enoic**
    - ✓ When poly-unsaturated, it is considered as alkene so ends with (**di, tri, tetra,…**) and **-enoic**
  - Location & type of double bonds
    - ✓ **Cis/trans-Δ^n** where (n) is the number (position) of the carbon that form a double bond
  - Designation of Carbons : Bonds
    - ✓ 18:0 means 18 C with no double bonds (saturated)
    - ✓ 18: 3 means 18 C with 3 double bonds (poly-unsaturated)

Note:
Counting starts from the carboxyl group (Alpha carbon)

B) Common Names

C) Omega classification

- We use omega (ω) to indicate the location of the double bond
  - If there are many double bonds ω indicates the location only for the last one
  - We start counting from the last carbon (ω carbon)
    - ✓ FA has 2 ends, Carboxylic end (The first carbon and called Alpha carbon), and Hydrocarbon end (the last carbon and called omega carbon)
  - FAs with the same ω classification have **properties, characteristics and function in common**

- **Omega 3 FAs:**
  - Such as ALA which produces EPA producing DHA
  - Used to **reduce inflammatory** reactions by:
    - ✓ Reducing the conversion of Arachidonic acid into eicosanoids
    - ✓ Promoting the synthesis of Anti-inflammatory molecules

Note:
EPA & DHA are **fish oil**

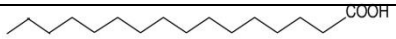
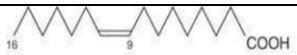
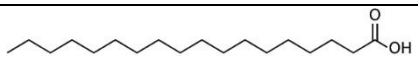
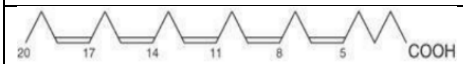
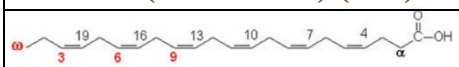
- **Omega 6 FAs:**
  - Such as Linoleic acid which produces Arachidonic Acid
  - Arachidonic acid is a precursor of eicosanoids which are important in the **inflammatory response**
    - ✓ Stimulates platelets & leukocytes activation
    - ✓ Signals pain & induces bronchoconstriction
    - ✓ Regulate gastric secretion

The importance of linoleic acid:

1) precursor of arachidonic acid
2) Forms acyl glucosylceramide which makes the skin impermeable to water
3) Precursor of important neuronal fatty acids

- **Omega 9 FAs:**
  - Such as Oleic acid which **reduces cholesterol** in the blood circulation

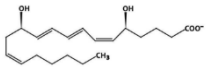
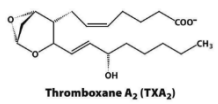
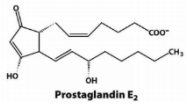
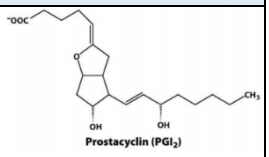
- **Note:**
  - The dietary deficiency of essential fatty acids causes **red scaly dermatitis** and other skin disorders due to the lack of acyl glucosylceramide produced by the linoleic acid

Structure & Formula	Systematic Name / Omega	Common Name	C : Double
 $CH_3(CH2)_{12}COOH$	n-Tetradecanoic Acid	Myristic Acid	14 : 0
 $CH_3(CH_2)_{14}COOH$	n-Hexadecanoic Acid	Palmitic Acid	16 : 0
 $CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	Δ^9 -Hexadecenoic acid ω 7	Palmitoleic Acid	16 : 1
 $CH_3(CH_2)_{16}COOH$	n-Octadecanoic Acid	Stearic Acid	18 : 0
 $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	Δ^9 -Octadecenoic acid ω 9	Oleic Acid	18 : 1
 $CH_3(CH_2)_4(CH=CHCH_2)_2(CH_2)_5COOH$	$\Delta^{9,12}$ -Octadecadienoic acid ω 6	Linoleic Acid	18 : 2
 $CH_3CH_2(CH=CHCH_2)_3(CH_2)_6COOH$	$\Delta^{9,12,15}$ -Octadecatrienoic acid ω 3	Alpha-Linolenic Acid (ALA)	18 : 3
 $CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COOH$	$\Delta^{5,8,11,14}$ -Eicosatetraenoic acid ω 6	Arachidonic Acid	20 : 4
 $CH_3CH_2(CH=CHCH_2)_5(CH_2)_2COOH$	$\Delta^{5,8,11,14,17}$ -Eicosapentaenoic acid ω 3	Eicosapentaenoic Acid (EPA)	20 : 5
 $CH_3CH_2(CH=CHCH_2)_6CH_2COOH$	$\Delta^{4,7,10,13,16,19}$ -Docosahexaenoic Acid ω 3	Docosahexaenoic Acid (DHA)	22 : 6

❖ Derived fatty acids

♦ Arachidonic Acid

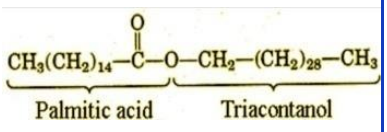
- It is all cis- $\Delta^{5,8,11,14}$ -Eicosatetraenoic acid (20:4)
- Arachidonate can be used to produce different types of **Eicosanoids**, by 2 pathways:
  - ➢ **Linear pathway** by lipoxygenase producing leukotrienes
  - ➢ **Cyclic pathway** by PGH_2 synthase producing Prostaglandin H_2, which can be used to produce:
    - ✓ Thromboxane by Thromboxane synthase
    - ✓ Prostacyclin by Prostacyclin synthase

Leukotrienes	Thromboxanes
o (20:4) o Linear structure o Have **3** conjugated **double** bonds o Causes constriction of smooth muscles especially in the respiratory tract (causing asthma) 	o (20:2) o Cyclic o Induce platelet aggregation o Cause constriction of smooth muscles in the blood vessels 
Prostaglandins	**Prostacyclins**
o (20:3) o Cyclic o Inhibit platelet aggregation o Induce inflammation & fever 	o (20:2) o Cyclic (2 rings) o Inhibit platelet aggregation o Vasodilator 

♦ Aspirin

- A drug reduces fever, inflammations & blood clotting by inhibiting 2 types of COX enzymes
  - ➢ **Inhibits** Cyclooxygenase **(COX) 1 inhibiting** thromboxane production and platelet aggregation
  - ➢ **Inhibits** Cyclooxygenase **(COX) 2 inhibiting** Prostaglandins production and reducing inflammation and fever (Anti-inflammatory & Anti-Pyretic)
    - ✓ The desired effect of aspirin is the inhibition of COX 2
    - ✓ COX 1 inhibition has undesirable effects on the renal & GI tract and macrophage differentiation and also, it can cause bleeding in elderly people
- **Celebrex** inhibits **only COX 2** but is prescribed with a strong warning of cardiovascular side effects

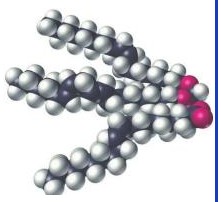
❖ Waxes



- Simple solid lipids containing a monohydric alcohol with a long chain FAs
  - ➢ The monohydric alcohol has only 1 OH group with a high molecular weight with 16-30 Carbons
  - ➢ LCFA has 14-36 Carbons such as palmitic acid
  - ➢ Both groups are linked together by **ester linkage**
- They are **water insoluble**
- Are not easily hydrolyzed but can be **indigested by lipases**
  - ➢ They are very resistant to rancidity (oxidation and hydrolysis)
- They have **no nutritional value**
- They present in the **coatings** that prevent the loss of water from leaves of plants, wetting of feathers and fast deterioration of fruits

❖ Fats and oils

- **Hydrogenation:** Adding H atoms to the double bond forming a single bond and so forming saturated fats or hydrogenated trans oils
  - ➢ Trans fat consumption has risks on health primarily elevated risk of CHD (coronary heart disease)

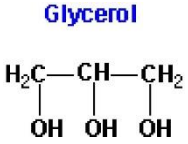


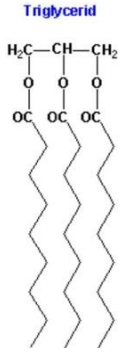
- **Vegetable oils** consist almost entirely of **unsaturated** fatty acids, whereas **animal fats** contain a much larger percentage of **saturated** fatty acids
  - ➢ Margarine has only 2 thirds of the double bonds of the starting vegetable oil hydrogenated (incomplete hydrogenation), so it becomes remains soft in the refrigerator and melts on warm temperatures

❖ Complex lipids

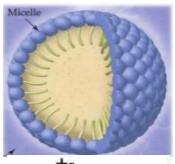
♦ Storage lipids

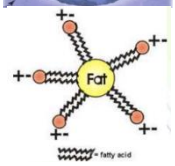
- **Triacylglycerol (TAGs)**
  - ➢ Triglycerides consist of **Glycerol** & **3 Fatty Acids**
  - ➢ Each carbon in the glycerol is attached to a FA by **ester linkage**
  - ➢ The 3 fatty acids can be all similar or different (in length & saturation)
    - ✓ If the 3 FA are similar, it is a simple triglyceride such as tristearin
    - ✓ If the 3 FA are not similar, it is a mixed triglyceride





- We can break TAGs by:
  - ➢ **Hydrolysis** by steam, acids or enzymes (lipases) producing glycerol and 3 FAs in the **ionized** form (RCOO-)
  - ➢ **Saponification** (Alkaline hydrolysis) by adding a base solution (such as NaOH) producing glycerol and 3 FA **salts** (RCOONa) which are highly amphipathic, enabling them of emulsification
    - ✓ Emulsification is the formation of a spherical micelle around non-polar materials
    - ✓ The polar ionized parts face the water surface
    - ✓ The non-polar parts are in the internal microenvironment of the micelle

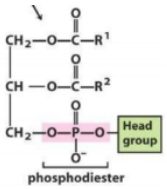




♦ Membrane lipids

- They include glycerophospholipids, sphingolipids and cholesterol (steroid)

1) Glycerophospholipids

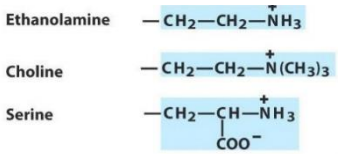


- They are the most prevalent (abundant) class of lipids in the membrane
- They consist of:
  - ➢ Glycerol
  - ➢ 2 FAs linked to the glycerol by ester bonds making up the **hydrophobic tails**
  - ➢ The 3rd carbon bind to a phosphate group which binds to another polar group making up the **hydrophilic head** (polar head)
- Phosphate group and the 2 FAs are bound to the glycerol by **ester bonds**
- It can be divided into many sub-types according to the type of the polar group bound to phosphate:
  - ➢ **Phosphatidic acid:** Phosphate + H
  - ➢ **phosphatidylcholine** (Lecithins): Phosphate + choline
    - ✓ Lecithins are targeted by the snake venom due to the presence of lecithinase converting lecithin into lysolecithin causing RBC hemolysis

Note:

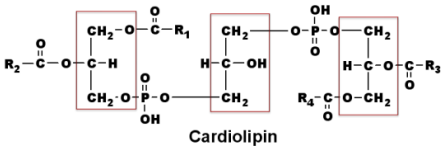
Lecithin is the **most abundant** type

- **Phosphatidylethanolamine**: Phosphate + Ethanolamine
- **Phosphatidylserine:** Phosphate + serine
  - ✓ **Cephalins** are PS and PE which are abundant in the **brain**

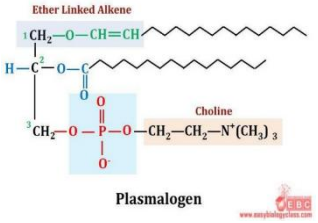


- **Phosphatidylinositol:** Phosphate + inositol
  - ✓ Inositol is a nitrogenous base which consists of a cyclic sugar alcohol
  - ✓ Its source is the brain tissue
  - ✓ PI functions as a membrane component, second messenger in the signal transduction
  - ✓ PIP2 is cleaved by phospholipase C forming DAG and IP3 which liberated calcium

- **Cardiolipin:** It is Diphosphatidyl-glycerol which is found in the inner membrane of **mitochondria**
  - It consists of 3 molecules of glycerol, 4 fatty acids & 2 phosphate


Cardiolipin

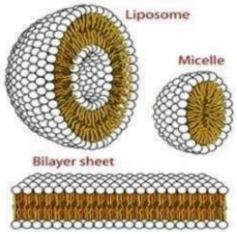
- **Plasmalogens:** Found in the brain, muscle, liver, semen
  - Protect theses tissues against reactive oxygen species
  - Its precursor is **Dihydroxyacetone**
  - It consists of a Glycerol molecule bound to Unsaturated Fatty alcohol on carbon 1 by **ether** bond, Fatty acid on carbon 2 by **ester** bond and a polar head usually containing a phosphate with ethanolamine and choline



Plasmalogen

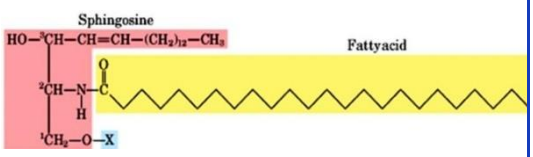
  - It has many classes according to the polar group it has:
    - ✓ Ethanolamine plasmalogen in the myelin sheath of the nervous system
    - ✓ Choline plasmalogen in the cardiac tissue and act as platelet activation factor
    - ✓ Serine plasmalogen

- Almost all glycerophospholipids can perform **emulsification** because they are amphipathic
- Phospholipids are arranged in a **lipid bilayer** in the cell membranes, vesicles and liposomes (used to deliver drugs into the body)
- In the micelle, lipids are arranged in a **single layer** around the non-polar microenvironment



2) Sphingolipids

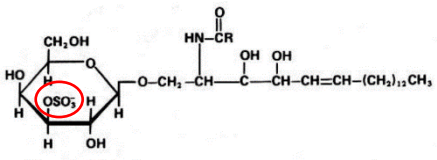
- Found in the cell membrane of all eukaryotes, it is highest in the Central Nervous System
- The core of sphingolipids is sphingosine (long-chain amino alcohol)
  - **Sphingosine: 18-carbon** molecule, the first carbon has OH and the second carbon has amino group and a hydrocarbon chain with a double bond on C4 producing a kink
  - 3rd carbon binds to a molecule (polar)
  - 2nd carbon binds to a FA by **amide bond**



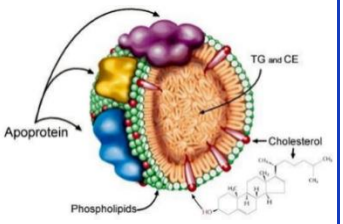
- It has many sub-types:
  - **Ceramide:** consists of sphingosine + FA (on C-2) + H (on C-3)
  - **Sphingomyelin:** The group attached to C1 is a phosphocholine (so it is a phospholipid)
    - ✓ It is a sphingolipid that is a major component of the **coating around nerve** fibers
    - ✓ Defects in this coat causes multiple neurological and sclerosis (mainly in females)
  - **Glycolipids (Glycosphingolipids):** contain carbohydrates attached at C-1
    - ✓ They act as cell surface receptors that can function in cell recognition and chemical messengers

- Glycolipids can be divided into:
  - **Cerebrosides:** Contain only 1 simple monosaccharide (such as glucose or galactose)
  - **Globosides:** Contain 2 or more sugars (more complex)
  - **Gangliosides:** Contain 2 or more sugars (more complex) and must contain **sialic acid**
    - ✓ Gangliosides are bound by cholera toxin in the human intestine facilitating its endocytosis into the cells
    - ✓ The terminal sugar on the glycolipids (especially gangliosides) determines blood type

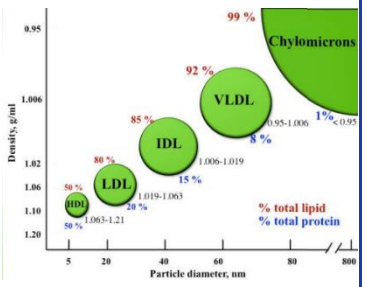
- **Sulfatides:** Synthesized from galactocerebrosides by adding sulfate group to carbon number 3
  - Abundant in the brain myelin



- **Lipoproteins:** Consist of lipids and proteins, used to transport lipids in the plasma of the blood
  - Lipids transported includes Cholesterol, Cholesterol esters, phospholipids and triacyl-glycerides



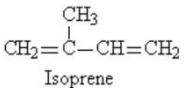
- There are many types of lipoproteins according to the percentage & density of proteins forming them:
  - HDL (High density lipoproteins): The highest protein & least lipid content, the smallest in size
  - Chylomicrons: The least protein & highest lipid content, the largest size

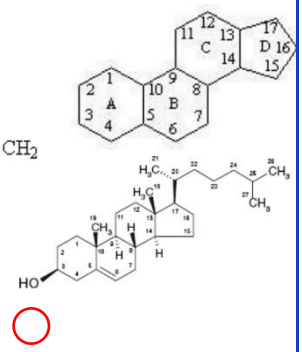


- HDL is used to transport lipids **toward the liver** to be consumed forming bile acids, vitamin D (so they are good)
- LDL is used to transport lipids **toward the tissues** to be stored (so they are bad)

3) Steroids

- Lipids that share the presence of the nucleus (4 fused rings) with a side chain
  - The precursor of steroids is **isoprene** (composed of 5 carbons)





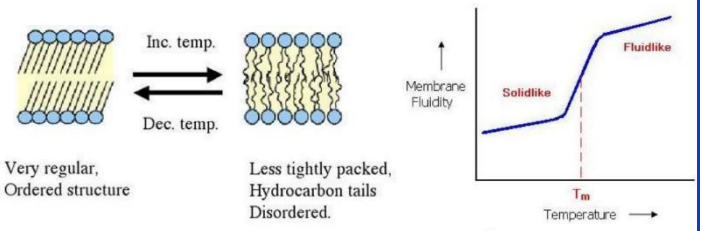
- The most common steroid is **cholesterol** which is **amphipathic**
  - It a **polar OH** group on C3, the rest of the molecule is non-polar
  - Cholesterol is only present in **animal cells**
- Cholesterol is used to produce:
  - Hormones (sex hormones such as androgen, estrogen, progestins)
  - Vitamins (such as vitamin D)
  - Bile acids which contribute in the intestinal absorption of fats (act as emulsifiers)
- Also, cholesterol present in the cell membrane of animal cells

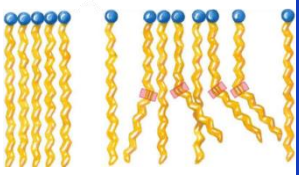
- **Cholesterol ester** are modified cholesterol with a FA added to the OH group of C3
  - They are important in transporting cholesterol inside lipoproteins (mainly HDL) transporting the largest amount of cholesterol and lipids

- **Atherosclerosis:** It is a disease caused by the accumulation of lipids (such as **LDLs**) on the walls of the blood vessels (such as the coronary artery)
  - It causes impaired blood flow and decreased elasticity and flexibility of the walls of blood vessels

❖ Cell membrane

- **Fluid mosaic model:** a model describes the membrane
  - ➢ Membranes are composed of 45% lipids, 45% proteins & 10% carbohydrates exciting side by side
  - ➢ Membranes are a bilayer of lipids with proteins inserted or attached to the membrane
- Lipid components in the cell membrane includes phospholipids, sphingolipids & cholesterol
  - ➢ The outer leaflet is rich of Phosphatidylcholine, sphingomyelin & glycoproteins
    - ✓ Important for **cell recognition**
  - ➢ The inner leaflet is rich of Phosphatidylethanolamine, phosphatidylserine & Phosphatidylinositol
    - ✓ Important for **signaling**
  - ➢ Cholesterol is distributed in both leaflets
- Temperature affects the fluidity of the membrane:
  - ➢ As temperature increases, lipids move faster and more irregularly and so become more fluidic and vice versa

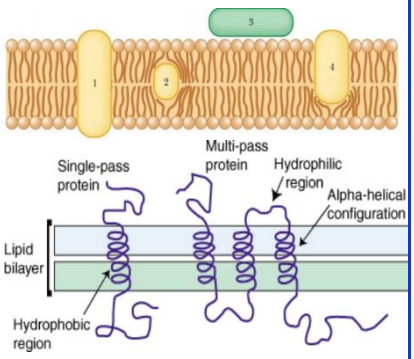




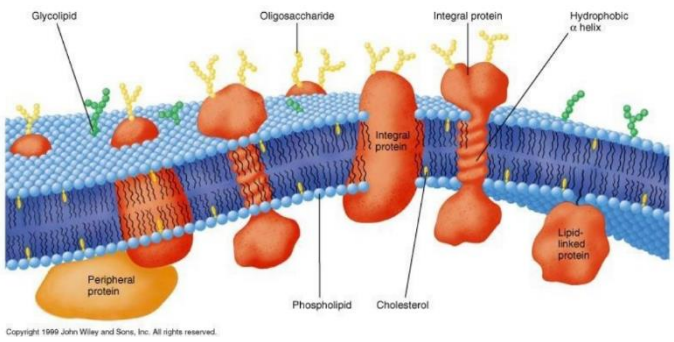
- Saturation affects the fluidity of the membrane
  - ➢ More saturated FAs, more compacted, more solid
- Cholesterol affects the fluidity of the membrane (stabilizes the fluidity)
  - ➢ Cholesterol is a rigid structure so it:
    - ✓ Prevents the over-fluidity and motility of the lipids at High temperature
    - ✓ Prevents the over-solidifying and tightly packing of the lipids at Low temperature

❖ Membrane proteins

- There are many types of membrane proteins:
  - ➢ Integral membrane proteins
    - ✓ The are **anchored** into the membrane via hydrophobic regions
    - ✓ Their transmembrane domains consist of α-helix (in humans) and
    - ✓ β-sheets (in bacteria)
    - ✓ They can have a single or multiple α-helix domains
    - ✓ They can be channels and carriers



  - ➢ Peripheral membrane proteins
    - ✓ They are associated with membranes but do not penetrate the hydrophobic core of the membrane
    - ✓ They are associated to the membrane or integral proteins by **non-covalent interactions**
    - ✓ They are not strongly bound to the membrane and can be removed without disrupting the membrane structure such as treatment with mild detergents
  - ➢ Lipid-anchored membrane proteins
    - ✓ They are peripheral proteins attached to the membrane **covalently** via a lipid group

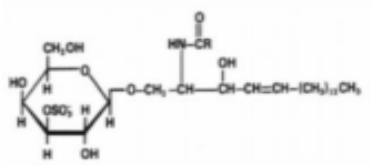


- Functions of the membrane:
  - ➢ Transport (selective permeable barrier)
  - ➢ Signaling
  - ➢ Catalysis

1. **The myelin sheath is composed of:**
   A. Glycolipids
   B. Phospholipids
   C. GAGs

2. **EPA & DHA are omega 6 Fatty acids:**
   A. True
   B. False

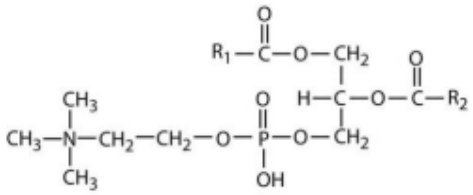
3. **Which of the following is true:**
   A. Sulfatide
   B. Phosphatide
   C. Found in muscle cells Glycerides



4. **Which of the following has the least solubility in water:**
   A. Palmitate
   B. Oleate
   C. Linoleate
   D. Myristate
   E. Arachidonate

5. **Which of the following can't be hydrogenated:**
   A. Arachidonic acid
   B. Palmitic acid
   C. Oleic acid
   D. Linocleic acid

6. **This structure is:**
   A. Bile acids
   B. Prostaglandins
   C. Monoacylglecerol
   D. Sphingolipid
   E. Phosphatidylcholine



7. **Which of the following is common in all sphingolipids:**
   A. Glycerol
   B. Phosphate
   C. N-acetylgalactosamine
   D. Ceramide

8. **The following membrane lipid is a major component of the inner mitochondrial membrane:**
   A. Lecithin
   B. Cardiolipins
   C. Cephalins
   D. Phosphatidyl-inositol

9. Gangliosides contain all the following EXCEPT:

A. Fatty acid
B. Phosphate
C. Ceramide
D. Hexose
E. N-acetyl neuraminic acid (sialic acid)

10. Arrange the following fatty acids according to their melting point starting from the largest to the smallest (oleic acid, linoleic acid, palmitic acid and palmitoleic acid)

A. Oleic acid, palmitic acid, linoleic acid and palmitoleic acid
B. Palmitic acid, palmitoleic acid, oleic acid and linoleic acid
C. linoleic acid, palmitoleic acid, palmitic acid and oleic acid
D. linoleic acid, palmitoleic acid, oleic acid and palmitic acid
E. oleic acid, linoleic acid, palmitoleic acid, and palmitic acid

11. An omega-3, 24-carbon Fatty acid has:

A. A double bond between carbon 22 & 23
B. 3 double bonds
C. A double bond between carbons 21 & 22
D. A double bond between Carbons 3 & 4

12. Omega-9 Fatty acid can do the following:

A. Treat asthma
B. Reduce inflammation
C. Relieve gastric pain caused by aspirin
D. Reduce cholesterol
E. Block formation of eicosanoids

13. Creating a cholesterol ester from cholesterol results in:

A. Facilitating the transport of cholesterol via lipoproteins
B. Cholesterol being more hydrophobic
C. Increasing the density of lipoproteins

14. Which of the following is a sphingolipid:

A. Phosphatidylinositol
B. Cardiolipin
C. Cephalins
D. Myelin