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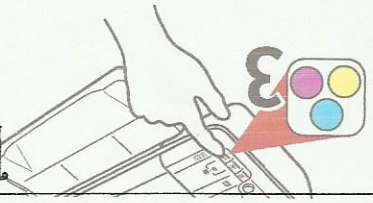

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ALQUSOUR ACADEMY

خاص

للفصل الدراسي الثاني

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ساعات الدوام الرسمي

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الأحد - الأربعاء	11:00 -12:30	10:00 -12:30
الخميس	11:00 -12:30	8:00 -12:30
الجمعة	11:00 - 2:00	8:00 - 2:00
السبت	11:00 -12:30	8:00 -12:30

Lipids and Proteins are Associated in Biological Membranes

☒ What are Lipids?

Lipids are mixture of compounds that are marginally soluble in water but **readily soluble in organic solvents** *such as chloroform or acetone.*

The most striking feature of lipids *is that they consist mostly* of **non-polar groups**, which leads to their **insolubility in water.**

☒ Classification of Lipids:

1) **Open chain compounds** with polar head groups and long non-polar tails, this group includes:

a) Fatty acids
b) Triacylglycerols
c) Sphingolipids
d) Phosphoacylglycerols
e) Glycolipids

2) **Fused-ring compounds**, the **steroid**; an important representative of this group is **cholesterol.**

☒ What is The Chemical Nature of Lipids?

1. Fatty Acids:

A fatty acid (F.A) has a carboxyl group at the polar end and a hydrocarbon chain at the non-polar tail.

- Fatty acids are **amphipathic** compounds because the **carboxyl group is hydrophilic** and the **hydrocarbon tail is hydrophobic**. *The carboxyl group can ionize under the proper condition.*

- Fatty acids that occur in a living system normally contain an **even number** of carbon atoms, and the **hydrocarbon chain** is usually **unbranched**.

Fatty acid can be divided into two groups:

1- Saturated fatty acids:

If there are *only* **single bonds** and no double bonds. The hydrocarbon chain in saturated fatty acids is *fully extended conformation*.

2- Unsaturated fatty acids;

- There are **carbon-carbon double bonds** in the chain.

- The stereochemistry at the double bond is usually ***cis*** rather than ***trans.*** A ***cis*** double bond puts a **kink** in the long –chain hydrocarbon tail, whereas the shape of a ***trans*** fatty acid is like that of a saturated fatty acid in its **fully extended conformation.**

- The double bonds in unsaturated fatty acids are isolated from one another by **several singly bonded** carbons. Fatty acids do not normally have conjugated double bond system.

- We can further divide the unsaturated fatty acids into:

a) Monounsaturated (FA) ===> contains one c=c
b) Polyunsaturated (FA) ===> contains more than one c=c

- The notation used for fatty acids indicates:

1) The number of carbon atoms
2) The number of double bonds
3) The position of the double bonds

Examples ➔

- 18:0 means an 18 carbon saturated fatty acid with no double bonds.
- $18:2-\Delta^{9,12}$ means an 18-carbon fatty acid with two double bonds, one at the ninth carbon atom from the carboxyl end, the other at 12 carbon atom.

- **Unsaturated** fatty acids have **lower melting points** than saturated ones. (Plant oils are liquid at room temperature because they have higher proportions of unsaturated fatty acids than do animal fats, which tend to be solids).

Acid	Number of carbon	Formula	Melting point
Lauric	12	CH3(CH2)10CO2H	44
Myristic	14	CH3(CH2)12CO2H	58
Palmitic	16	CH3(CH2)14CO2H	63
Stearic	18	CH3(CH2)16CO2H	71
Arachidic	20	CH3(CH2)18CO2H	77

- Fatty acids are rarely found free in nature, but they form parts of many commonly occurring lipids.

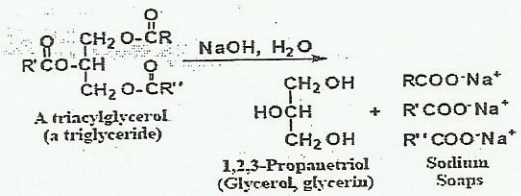
- Conversion of oils to fats is a commercially important process. It involves **hydrogenation**; the *process of adding hydrogen across the double bond of unsaturated fatty acids to produce the saturated counterpart.* **For example**; partially hydrogenated vegetable oils are used in **Oleomargarine**; they tend to include *trans* fatty acids.

Acid	Number of carbon	Degree of unsaturation	Melting point
Palmitoleic	16	$16:1–\Delta^{9}$	-0.5
Oleic	18	$18:1–\Delta^{9}$	16
Linoleic	18	$18:2–\Delta^{9,12}$	-5
Linolenic	18	$18:3–\Delta^{9,12,15}$	-11
Arachidonic	20	$20:4–\Delta^{5,8,11,14}$	-50

2. Triacylglycerols (TAG):

- It results from the esterification of F.A & glycerol:
  [3 F.A + glycerol = Triacylglycerol]

- **Glycerol** is a simple compound that contains three hydroxyl groups. When all three of alcohol groups form an **ester linkages** with fatty acids, the resulting compound is a triacylglycerol or (triglyceride; the old name).



- Triacylglycerol could be:
  a) Simple: The three fatty acids are the Same.

  b) Mixed: Different types of fatty acids used.

- Triacylglycerol **do not occur** as components of **membranes, BUT** they accumulate in the **adipose tissue** and serves as concentrated **stores** of metabolic **energy**.

- Triacylglycerols can be **hydrolysed** by:

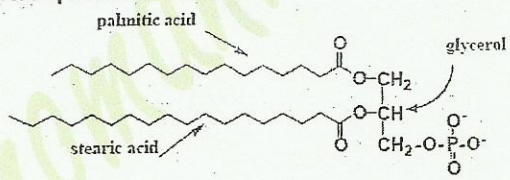
a) **Lipase** enzyme giving 3 ionized fatty acids + glycerol

b) **Base (NaOH, KOH)** giving salt of fatty acid + glycerol, this reaction is called **(saponification)**.

3. **Phosphoacylglycerols (Phospholipids):**

- Have glycerol molecule in which one of the alcohol groups can be esterified by phosphoric acid molecule, while the other two alcohol groups are esterified by carboxylic acids from two fatty acids. The resulting compound called **phosphatidic acid.**

A phosphatidic acid



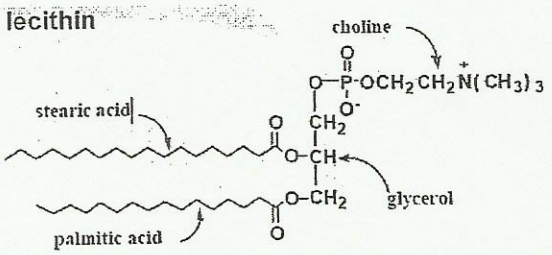
- Fatty acids are usually monoprotic acids with only one carboxyl group able to form an ester bond, but phosphoric acid is triprotic acid and thus can form more than one ester linkage.

One molecule of phosphoric acid can form ester bonds both to glycerol and to some other alcohol, creating a **phosphatidyl ester** (phospholipids). These compounds are classed as phosphoacylglycerols.

- The classification of a phosphatidyl ester depends on the nature of the secondary alcohol esterified to the phosphoric acid. The most important lipids in this class are:

1) phosphatidyl ethanolamine (cephalin)
2) phosphatidyl serine
3) phosphatidyl choline (lecithin)
4) phosphatidyl inositol
5) diphosphatidyl glycerol (cardiolipin)
6) phosphatidyl glycerol

A lecithin



All these compounds have long non-polar hydrophobic tails and polar highly hydrophilic head groups and thus are amphipathic. The polar head is charged at neutral pH. Some times a positive charge may be contributed by an amino alcohol esterified to the phosphoric acid

Phosphoacylglycerols are important components of biological membranes

4. **Waxes:**

Are complex mixtures of esters of long chain carboxylic acids and long chain alcohols, they serve as protective coatings for:

▶ plants (stems, leaves, fruit) ▶ animals (fur, feathers, skin)

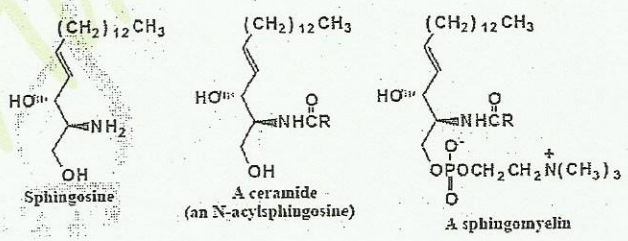
Examples of waxes (Myricyl cerotate, Cetyl palmitate).

5. **Sphingolipids:**

- Sphingolipids have **no glycerol** but instead they have a long chain amino alcohol called **sphingosine**.
- They found in both plants and animals, and particularly abundant in the nervous system.
- Ceramide the simplest compound of this class, which consists of one fatty acid linked to the amino group of sphingosine by an ***amide bond.***

Ceramide = F.A + sphingosine

- **Sphingomyelines** the primary alcohol group of sphingosine is esterified to phosphoric acid, which in turn, is esterified to another amino alcohol (choline).

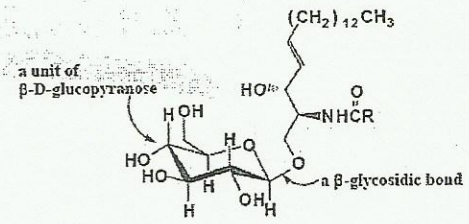


Sphingomyeline = ceramide + p + choline

Sphingomyelins are amphipathic and occur in cell membranes in the nervous system. The 3-D structure of shpingomyelins is very similar to those of phospholipids.

6. **Glycolipds:**

Result when a carbohydrate is bound to an alcohol group of a lipid by a ***glycosidic linkage.*** **Ceramide** are the parent compounds for glycolipid.



The glycosidic linkage takes place between the primary alcohol group of the ceramide and a sugar residue to give what is called **cerebroside**; they are found in nerve and brain cells, primarily in cell membrane.

- Carbohydrates are added to ceramide to make:

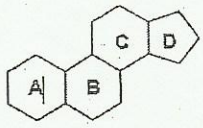
✓ **Cerobrosides:** if monosaccharide used, usually glucose or galactose, e.g. glucocerebroside.

✓ **Gangliosides:** if complex carbohydrate that contains more than 3 sugars (oligosaccarides) used (e.g. sialic acid). They present in large quantities in nerve tissues.

- Glycolipids are present in large quantities in nerve tissues, and are often found as markers on cell membranes and play a large role in tissue and organ specificity.

7. Steroids:

- Steroids include many compounds with different functions, but all share the same general structure: a fused ring system consisting of three six-membered rings (A,B, and C rings) and one five-membered ring (the D ring).
- Sex hormones and cholesterol are examples of steroids.



Cholesterol:-
- The molecule is highly hydrophobic because the only hydrophilic group is the single hydroxyl group.
- Cholesterol is widespread in biological membranes (especially in animals), and their presence can modify the role of membrane–bound proteins.
- Cholesterol has many biological function (not in prokaryotic), including its role as a precursor of other steroids and vitamin D3.
- Excess Cholesterol in the blood has a harmful effect on health and plays a role in development of **atherosclerosis.**

☒ What Is The Nature of Biological Membranes?

Biological membranes include:

- Plasma membrane (every cell has a membrane)
- Membranes that enclosed organelles (only in eukaryotic cells).

Composition of membranes:

- Lipids: phosphoglyceride the principle component.
- Proteins: can make up 20-80% of membranes total weight.
- Carbohydrates

▪ **Phosphoglycerides** are the prime examples of amphipathic molecules, and they are the principle lipid component of membrane.

- The existence of **lipid bilayers** depend on hydrophobic interactions and these bilayers are used as a model for biological membranes. The most important difference between the lipid bilayer and the biological membranes is that the cell membranes contain **proteins** as well **lipids**, while lipid bilayers only lipids.

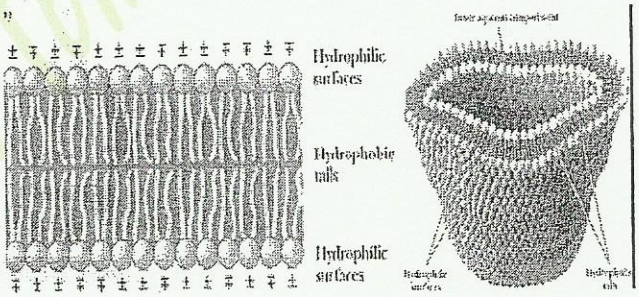
The interaction between lipid bilayers and proteins determine membrane functions.

☒ The Structure of Lipid Bilayers:

What are the types of lipids present in cell membrane?

- Phosphoglycerides: the principle component
- Glycolipids.
- Sphingolipid: mainly in nervous system cells
- Steroid: in eukaryotes (cholesterol in animal cells, phytosterols in plants)

As we all know, in water the phospholipids spontaneously form an ordered structure, with polar groups in contact with water, and non-polar tails lie in the interior of membrane, this is the **lipid bilayers.**



- The lipid bilayer arrangement is stabilized by non-covalent interactions (van der waals, hydrophobic interactions).

- The bilayer can be thought of as a sandwich with the polar head groups in the role of bread and the non-polar tails as the filling.

The polar heads:

- They are in contact with water, and contain charged groups.
- Both inner and outer surfaces of the bilayer contain mixtures of lipids, but their compositions differ and can be used to distinguish the inner and outer layers from each other. Because the bilayer is curved, the molecules of the inner layer are more tightly packed.
- Bulkier molecules tend to be in the outer layer, and smaller molecules tend to occur in the inner layer.

The non-polar tails:

- Located interior and consists of the saturated and unsaturated chains of fatty acids, and the fused ring system of cholesterol.
- The arrangement of the hydrocarbon interior of the bilayer can be ordered and rigid, or disordered and fluid, depending on its composition. How?

▫ In unsaturated fatty acids there is a kink in the hydrocarbon chain which cause disorder in packing of the chains and make more open structure), and this cause *fluidity* in bilayer.

▫ In saturated fatty acids a linear arrangement of the hydrocarbon chains leads to close packing of the molecules in the bilayer, and thus to *rigidity*.

The presence of cholesterol may also enhance order and rigidity:

1- Its structure is quite rigid.

2- It stabilizes the straight chain arrangement of saturated fatty acids by Van Der Waals interactions.

☒ Comparison between plant and animal cells:

Plant cell	Animal cell
Has higher percentage of unsaturated fatty acids than animal cell	**Less percentage of unsaturated fatty acids**
No cholesterol	**The presence of cholesterol is characteristic.**
More fluid	**Less fluid**

▫ Prokaryotic membranes are the most fluid, because they contain no appreciable amounts of steroids.

▫ The lipid components of a bilayer are always in motion, more in fluid bilayer, the " **flip-flop**" migration of lipid molecules from one layer to another has very little tendency to occur, while **lateral motion** of lipid molecules within one of the two layers frequently take place.

▫ With heat, ordered bilayers become less ordered, and this transition takes place at a characteristic temperature **(transition temperature).** And this transition temperature is higher for more rigid and ordered membranes than it is for relatively fluid and disordered membranes.

☒ **Membrane Proteins:**

Proteins can be associated with the lipid bilayers in either of two ways:

- **Peripheral proteins**: on the surface of the membrane.
- **Integral proteins**: within the lipid bilayers.

- Peripheral proteins are loosely attached to the charged head groups of the lipid bilayres by non-covalent interactions (H-bonds or electrostatic or both), so they can be removed in mild treatment as raising the ionic strength of the medium.

- In integral proteins, removing it from membranes is much more difficult, where harsh conditions are needed (detergents and extensive sonication) and always leads to denature the proteins, and become inactive.

- Proteins can be attached to the membrane in many ways, when the protein completely spans the membrane it is often form of an α-helix or β-sheet. These minimize the contact between polar parts of the peptide with the nonpolar interior of the lipid bilayer. Proteins can be anchored to lipids by forming covalent bond between its cysteines or free amino groups and several lipids, anchors (e.g. Myristoyl and Palmitoyl).

☒ **What are the main functions of membrane proteins?**

- **Transport proteins**: help in moving substances in and out of the cell.
- **Receptor proteins**: transferring of extracellular signals into cells.
- **Enzymes**: are tightly bound to membranes, some are on the outer surface others are on the inner surface.

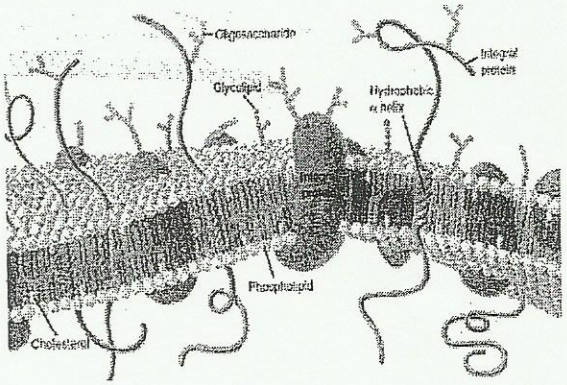
There is asymmetrical distribution of proteins on inner and outer layers, just as the lipids.

☒ **What Is The Fluid Mosaic Model of Membrane?**

Key features of the fluid mosaic model:

- **Phospholipids bilayers** is the basic structure of biological membranes

- **Proteins** embedded in the bilayer structure, and float in the matrix, producing a mosaic effect.



- Proteins are not fixed in position in the lipid

bilayers, (they can move laterally from place to place within the plane of lipid matrix, but do not"flip-flop" freely from one side to the other).

So **Biological membranes are dynamic structures.**

* **What are some of the functions of membranes?**
1) **Structural:** - role as the boundaries and containers of all cells and organelles within the eukaryotic cells.
2) **Transport:** - of substances into and out of cells and organelles, and this function involve both lipid bilayers as well as membrane proteins. Remember that the membrane is semi permeable.
3) **Catalysis:** - enzymes are attached to membrane and many enzymatic reactions take place on the membrane.
4) **Receptor property:** - in which proteins bind specific biologically important substances that trigger biochemical responses in the cell.

⊠ Membrane Transport:

Transport across the membrane can be:

1) Passive transport
   a) Simple diffusion
   b) Facilitated diffusion
2) Active transport
   a) Primary active transport.
   b) Secondary active transport.

	Passive transport	Active transport
Concentration gradient (CG)	The movement of substances is the same direction of (CG)	The movement of substances is against the direction of (CG)
Use of energy	No	Yes
Types	1) Simple diffusion 2) Facilitated diffusion	1) Primary active transport 2) Secondary active transport

	Simple diffusion	Facilitated diffusion
Definition	A molecule moves directly through the membrane without interacting with another molecule	The process of moving a molecule passively through a membrane using a carrier protein.
Examples	Small, uncharged molecules such as O_2, N_2, CO_2.	Glucose into erythrocytes through glucose permease
The rate of movement	Is controlled solely by the concentration difference across the membrane.	The plots are similar to michaelis-menten enzyme kinetics.

	Primary active transport	Secondary active transport

Definition	The movement of molecule against a gradient is directly linked to the hydrolysis of a high energy molecule, such as ATP	The movement of molecule against a gradient is not directly linked to the hydrolysis of ATP.
Examples	Sodium-potassium ion pump	Galactoside permease in bacteria

☺ **Sodium-potassium ion pump:**

- Under normal circumstances the concentration of K^+ is higher inside a cell than extracellular fluids, but the concentration of Na^+ is lower inside the cell than outside. So energy is needed to move these ions against their gradient, (by hydrolysis of ATP to ADP and Pi (an exergonic reaction).

- The same protein appears to serve as both the enzyme that hydrolysis the ATP and as the transport protein; it consists of several subunits.

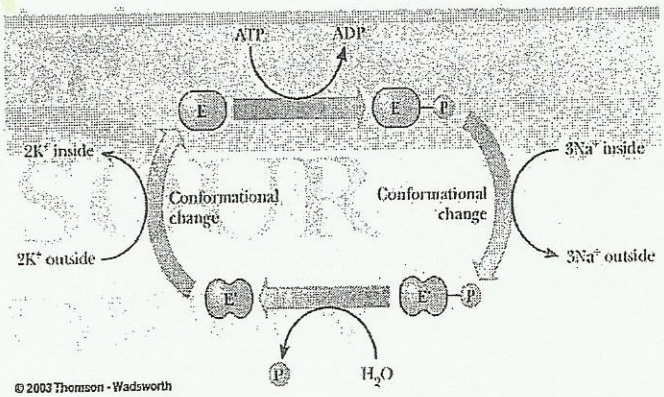
☺ **Steps of transport through Na^+/K^+ pump:**

One subunit of protein hydrolyzed the ATP and transfers the phosphate group to an spartate side chain on another subunit, and at the same time 3 Na^+ ions binding from inside take place.

1. Phosphorylation of one subunit causes a conformational change in the protein, which leads to the opening of a channel and releasing of Na^+ outside.

2. Outside the cell, 2 K^+ ions bind to the pump enzyme which is still phosphorylated

3. Hydrolysis of phosphate leads to other conformational change to regenerate the original form of the enzyme and allow the 2 K^+ to enter the cell.



This pumping operation can be reversed when there is no K^+ and high concentration of Na^+ in the extracellular medium. Here ADP will be Phosphorylated and give ATP.

☺ **Galactoside permease in bacteria:**

Lactose concentration inside the bacteria is higher than outside, so moving lactose inside bacteria needs energy.

- The galactose permease dose not uses ATP directly.
- It induces energy by allowing the flow of H^+ through the permease into the cell with their concentration gradient.
- Hydrogen gradient must be established, and this gradient is created by active transport through **proton pumps.**

☒ **Memprane Receptors:**

- Receptors are proteins sit on the exterior of the cells.
- The binding between the receptor protein and the active substance is similar to **enzyme-substrate binding.**
- Receptors are often large oligomeric proteins with molecular weight of 100,000s.

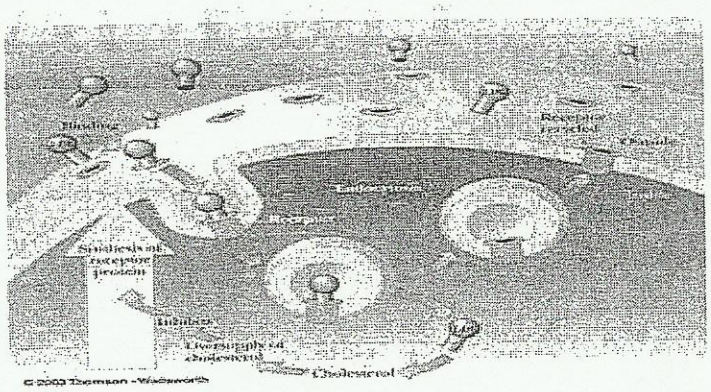
☒ **Low-Density Lipoprotein receptor (LDL- Receptor):**

LDL is the principal carrier of cholesterol in the bloodstream.

LDL is a particle that consists of various lipids, in particular cholesterol and phosphoglycerides as well as protein. **How it work?**

1- The protein portion of LDL binds to LDL receptor of a cell
2- The complex formed is pinched off inside the cell by endocytosis
3- The receptor protein is then recycled back to the surface of the cell. And the lipid portion of LDL (cholesterol) is used by the cell.

Excess level of cholesterol **inside** the cell will inhibits the synthesis of LDL receptors, and this will lead to excess of cholesterol outside the cells in the blood stream leading to atherosclerosis.



☒ **The Lipid Soluble Vitamins:**

The lipid soluble vitamins are (KEDA):

Vitamin K Vitamin E Vitamin D Vitamin A

☺ *Vitamin A:*

- The precursor of vitamin A is ß-carotene (Retinol). ß-carotene will convert to vitamin when there is a need for it.
- Source of vitamin A: abundant in carrots, but also in other vegetables (yellow vegetable).
- A derivative of vitamin A plays a crucial role in vision when it is bound to protein called ***opsin.***

	Cone cells in retina	Rod cells in retina
Types of opsin	Several types of opsin	Contain only one type of opsin
Vision	Responsible for bright light and color vision	Responsible for vision in dim light

1- The alcohol group of **ß-carotene** is enzymatically **oxidized** to an aldehyde and give **retinal** in the **liver.**
2- Then by an isomerizaion reaction, the isomeric form ***trans*-retinal** is converted into the ***cis*-retinal** form.
3- The ***cis*-retinal** aldehyde group forms an imine (called Schiff base) with the side chain amino group of lysine in rod-cell **opsin**
4- The reaction between *cis*-retinal and opsin give **rhodopsin.**

☺ ***Vitamin D:***

The main function of vitamin D is **to regulate the calcium and phosphorus metabolism.** One of the most important of these compounds is D3 (cholecalciferol).

Cholesterol —enzymatic→ 7-dehydrocholesterole —U.V→ cholecalciferol (vit D3)

cholecalciferol (vit D3) —Enzyme (liver) +O2→ 25-hydroxycholecalciferole

25-hydroxycholecalciferole —Enzyme (kidney) +O2→ 1,25dihydroxycholecalciferole

- The presence of vitamin D3 leads to increase synthesis of Ca^{+2} binding proteins, which increase the absorption of dietary calcium in the intestine, and this result in calcium uptake by the bone.

- A deficiency of vitamin D can lead to **rickets**, a condition in which the growing bone in children become soft resulting in skeletal deformities.

- Adults who are exposed to normal amount of sunlight do not usually require vitamin D supplements.

☺ *Vitamin E:*

- The most active form of vitamin E is **α-tocopherol.**
- A well established chemical property of vitamin E is that it is **antioxidant**, so it reacts with oxidizing agents before they can attack other biomolecules.

- **Free radicals** (compounds have at least one unpaired electron) are highly dangerous substances, and may play a role in development of cancer and in the aging process, and vitamin E helps in removing these free radicals.

☺ *Vitamin K:*

- Vitamin k composed of bicyclic ring system contains two carbonyl groups (the only polar group), and a long unsaturated hydrocarbon chain consists of repeating isoprene units (determine the exact form of vitamin K).

- Vitamin K is very important in **blood clotting** process.

- Vitamin K is needed in the hepatic synthesis of prothrombin and blood clotting factors II, VII, IX, and X.

- Vitamin K is definitely needed to modify prothrombine and other proteins involved in clotting process.

- Dicumarol and warfarin are vitamin K antagonists.

⊠ Prostaglandins and Leukotrienes:

✓ ***Prostaglandins:-***

- Are group of compounds that derived from fatty acid **arachidonic acid** that contain 20 carbon atoms, 4 double bonds. $20:4-\Delta^{5,8,11,14}$.

- The prostaglandins themselves each have five membered rings; they differ from one another in number and position of double bonds and oxygen containing functional groups.

The prostaglandins have many functions:

1. Control of blood pressure
2. Stimulation of smooth muscle contraction
3. Conduction of inflammation (aspirin, cortisone have anti-inflammatory effects because of their inhibition of prostaglandins particularly in blood platelets)
4. Inhibit the aggregation of platelets. Thus may be of therapeutic value by preventing the formation of blood clots.
5. Possible anti-tumor and anti-viral activity.

✓ ***Leukotrienes:***

➢ Is another derivative of arachidonic acid, found in leukocytes, and have 3 conjugated double bonds.

➢ Leukotrine C is a typical member of this group.

The main functions of leukotrienes are:

1. Constriction of smooth muscle specially in the lungs, so it play apart in the pathophysiology of asthma, a drugs that inhibit the synthesis leukotrienes, or block the receptor of leukotrienes are used in the treatment of asthma.

2. May also play a role in induction of inflammation and may be involved in rheumatoid arthritis.

✓ ***Thromboxanes:***

Are a third class of derivatives of arachidonic acid they contain cyclic ethers in their structure.

Thromboxane A_2 (TxA_2), the most widely studied member It is known to:

1. Induce platelets aggregation
2. Smooth muscle contraction.

Questions:

1-Prostaglandins are derived from:

a. Palmitic
b. linoleic
c. Arachidonic
d. none of the above

2- (20: 4 ^{5,8,11,14}) indicates:

a. Linoleic
b. palmitic
c. arachidic
d. arachidonic
e. linolenic

3- Most lipids in the average human diet are:

a. free unsaturated fatty acids
b. free saturated fatty acids.
c. glycerophospholipids
d. triacylglycerols

4- Na^+/K^+ pump is an example of:

a. Primary active transport
b. secondary active transport
c. Diffusion
d. facilitated diffusion

5- The fatty acid with the highest melting point:

a. 16:1
b.16:2
c. 16:0
d. 18:0

6- Phosphatidylcholine is an amphipathic molecule due to the presence of:

a. choline, phosphate, and two fatty acids
b. glycerol and two fatty acids
c. glycerol
d. two fatty acids

7- Which of the followings play a major role in asthmatic patient?

a. Leukotrienes
b. vitamin D
c. Vitmain A
d. Thromboxane A2
e. Prostaglandin

8- Polar molecules (e.g., glucose) can be transported through cell membrane by:

a. pores or channels with very large openings through the center
b. active transport proteins
c. facilitated transport
d. cell receptors and endocytosis

Solutions

Question number	Answer
1	c. Arachidonic
2	d. arachidonic
3	d. triacylglycerols
4	a. Primary active transport
5	d. 18:0
6	a. choline, phosphate, and two fatty acids
7	a. Leukotrienes
8	c. facilitated transport