Doctor 022

Biochemistry

Sheet no. 10

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Quick revision :

Eicosanoids are derived from arachidonic acid (omega-6), and it consists of 20 carbons.

Some of them undergo the cyclic pathway:

1-Prostaglandins

2-Prostacyclins

3-Thromboxanes

Others undergo the linear pathway :

Leukotrienes

Arachidonic acid is synthesized from LINOLEIC ACID -18 carbons- (omega-6 fatty acid).

Linoleic acid is the precursor of arachidonic acid (by adding 2 carbons to linoleic acid so it becomes arachidonic acid -20 carbons- (details in metabolism)).

From arachidonic acid we can synthesize all eicosanoids (small molecules involved in inflammatory response , response to injury).

This molecule responds to injury whether we feel it or not (like the injuries in the internal organs or tissue), so it may cause vasodilation, vasoconstriction, recruitment of immune cells and inhibition of platelet aggregation and so on.

How many biochemical reactions take place in one cell per second?

10 billion biochemical reactions occur in one cell per second, and we have 10^14 cells in our bodies, and this huge number of reactions must be regulated.

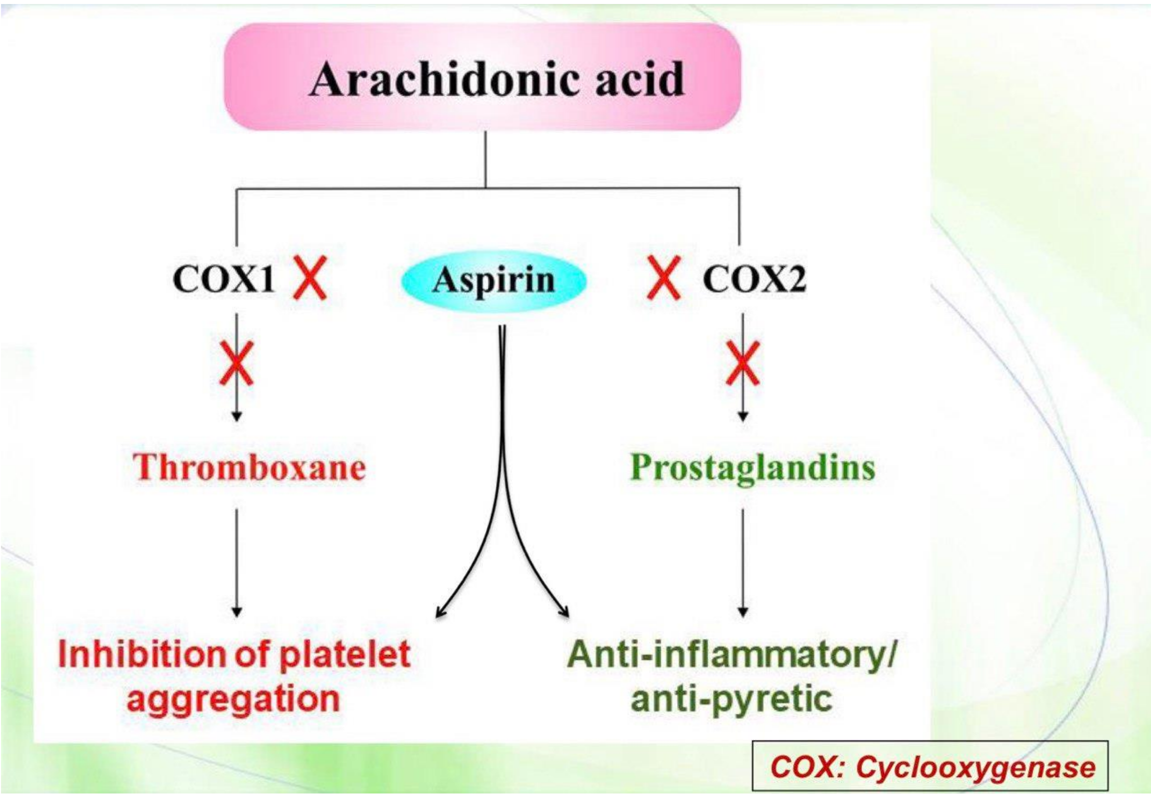
Aspirin:

-anti-inflammatory

-anti-pyretic drug

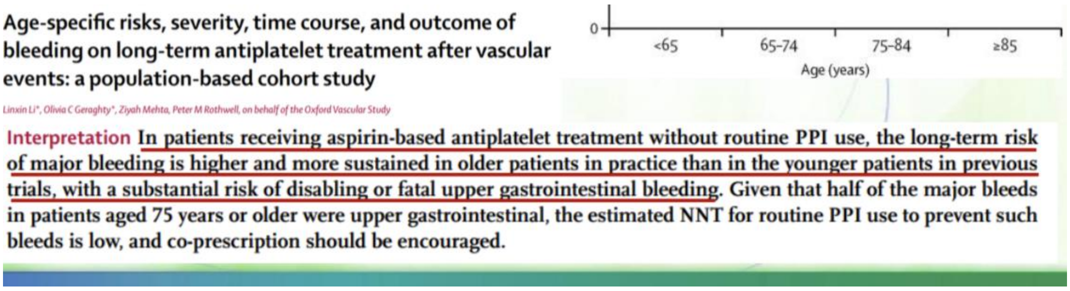
We have 3 forms of cyclooxygenases in our cells, COX-1, COX-2, COX-3

Aspirin targets COX-1 and COX-2, SO it also causes inhibition of platelet aggregation → reducing heart attacks and Atherosclerosis **(accumulation of lipids and cholesterol on the inside of arterial walls), because it inhibits COX-1 and COX-2 that are responsible for synthesis of eicosanoids .**



Aspirin is bad:

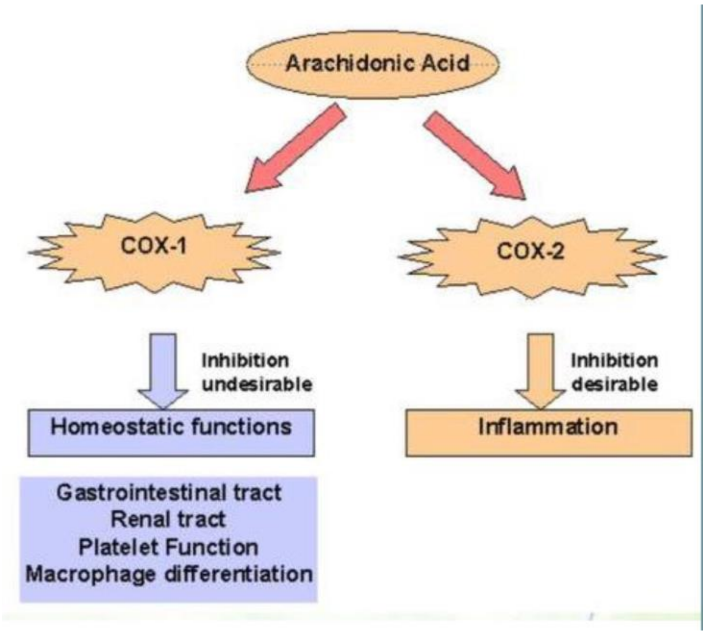
Aspirin also causes excessive bleeding among the elderly .


Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

Linxin Li*, Olivia C Geraghty*, Ziyah Mehta, Peter M Rothwell, on behalf of the Oxford Vascular Study

Interpretation In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding is higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older were upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged.

Aspirin inhibits both COX-1 and COX-2 (it doesn't distinguish the inflammation causing COX2) . So aspirin deprives the body from COX-1's normal function, and inhibits platelet aggregation → which results in no blood clotting which might lead to severe bleeding in case of injury.



A new regeneration drug, Celebrex targets COX-2, but is prescribed with a strong warning of side effects on the label (cardiovascular side effects)

We need drugs that specifically inhibit COX-2 without COX-1 like Celebrex.

Celebrex inhibits COX-2 but not COX-1, so it is an anti-inflammatory and anti-pyretic drug, but it does not inhibit platelet aggregation. On the other hand, its side effects include increasing risk of cardiovascular diseases and heart attacks.

Omega Fatty Acids

Omega-3 fatty acids:

Such as α-linolenic acid (ALA) which is the precursor for the production of Eicosapentaenoic acid (EPA) and Docohexaenoic acid (DHA) in the body (all of which are omega-3 fatty acids.)

Omega-3 fatty acids reduce inflammatory reactions by:

-Reducing the conversion of arachidonic acid into eicosanoids (such as prostaglandins that induce inflammation).

-Promoting the synthesis of anti-inflammatory molecules.

-They also improve memory.

Omega-6 fatty acids:

Such as linoleic acid which is the precursor for the production of Arachidonic acid in the body (which is also an omega-6 fatty acid.)

Omega-6 fatty acids help in:

-Stimulating platelet and leukocyte activation.

-Signaling pain.

-Inducing Bronchoconstriction.

-Regulating Gastric Secretion.

“Don't memorize these specific things; know that arachidonic acid is responsible for inflammation and the response to injury.**”.**

Omega-9 fatty acids:

Such as oleic acid, which reduces cholesterol levels in blood circulation.

It's important to note that both linoleic (omega-6) and linolenic (omega-3) acids are essential fatty acids that the body cannot produce. Therefore, the only way for the body to obtain these fatty acids is through dietary sources such as vegetable oils, nuts, seeds, meats, and eggs.

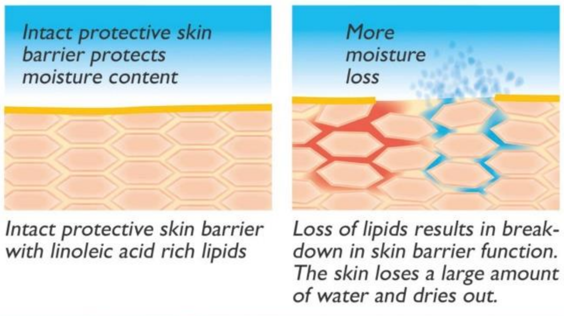
Derivatives of these essential fatty acids play important roles in regulating and preserving bodily functions.

Why is linoleic acid essential?

-It serves as a precursor of Arachidonic Acid.

-It covalently binds another fatty acid attached to cerebrosides (which will later be discussed) in the skin, forming an unusual lipid (acyl glucosylceramide) that makes the skin impermeable to water.

This function of linoleic acid may help explain the red, scaly dermatitis and other skin problems associated with a dietary deficiency of fatty acids.



-It is the precursor of important neuronal fatty acids.

Complex Lipids

Complex lipids are divided into two main groups of lipids:

-Neutral Storage Lipids, which are Triacylglycerols (three fatty acid groups attached to a Glycerol group).

-Polar Membrane Lipids, which can be either Phospholipids or Glycolipids.

-Phospholipids are lipids that have a phosphate group and a fatty acid attached to a common backbone/connecting region (whether this backbone is Glycerol or Sphingosine).

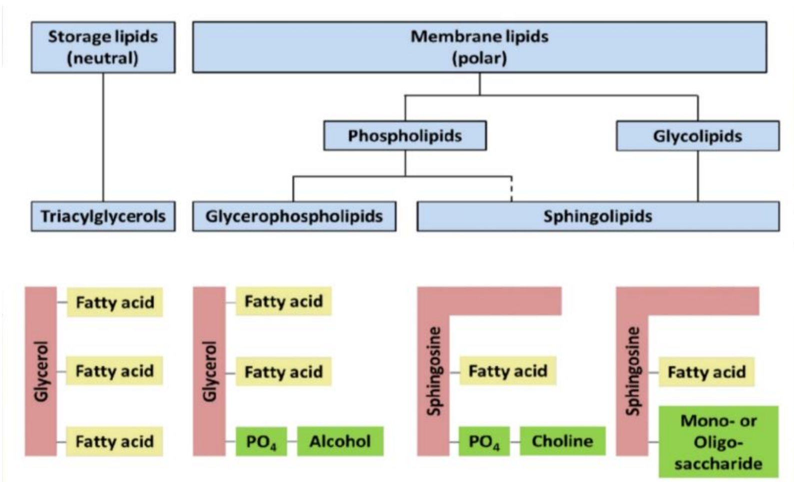
-Glycolipids are lipids that contain a mono/oligosaccharide group and a fatty acid group attached to a common Sphingosine molecule.

***Notes:**

-Any complex lipid that has a Sphingosine backbone is known as a Sphingolipid, whether it's connected to a phosphate group or a mono/oligosaccharide group.

-All Glycolipids are Sphingolipids, but not all Sphingolipids are Glycolipids.

-Phospholipids can either be Glycerophospholipids (having a Glycerol backbone, a phosphate group , and two other fatty acid groups) or Sphingophospholipids.

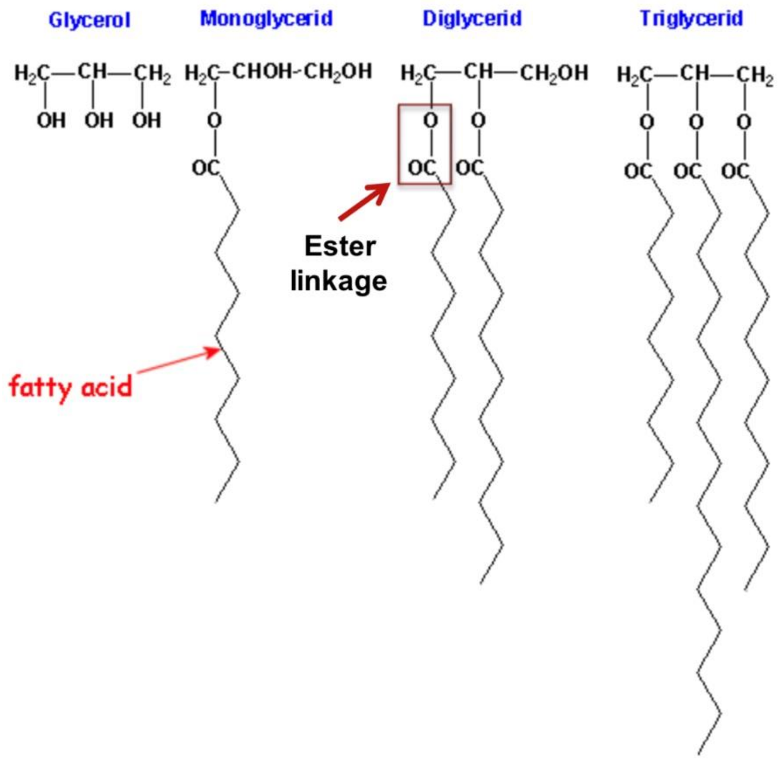


Triglycerides (Triacylglycerols, TAGs):

They are molecules that contain a Glycerol attached to three fatty acids.

One Glycerol molecule has three hydroxyl groups, one on each carbon (glycerol is an alcohol). Each of these hydroxyl groups is reactive, and will react as an alcohol with a carboxyl group present in a fatty acid, creating an ester linkage with the fatty acid group (creating a fatty acyl group).

If only one of the Glycerol molecule's hydroxyl groups reacts with a fatty acid, the product is going to be a Monoacylglycerol (Monoglycerides). If two hydroxyl groups react, the product is a Diacylglycerol (Diglycerides), and if all of the three groups react, the product is a Triacylglycerol (Triglyceride).



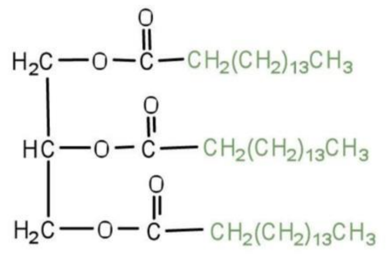
Triacylglycerol is the storage lipid used in the body. They are stored mainly in Adipocytes in adipose tissue, and a small amount is stored in the Liver.

They are used for energy purposes (storage and consumption).

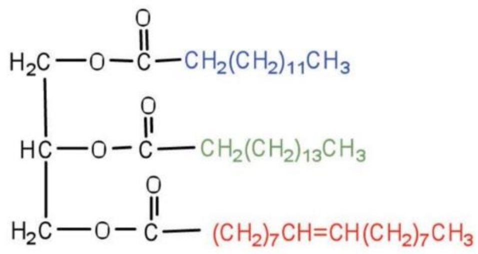
-fatty acyl : when a fatty acid is linked to another group

Types of Glycerides:

The three fatty acid groups in triglycerides could either be identical, resulting in a simple triglyceride such as Tristearin, or different resulting in mixed triglycerides (triacylglycerol).



Tristearin
a simple triglyceride



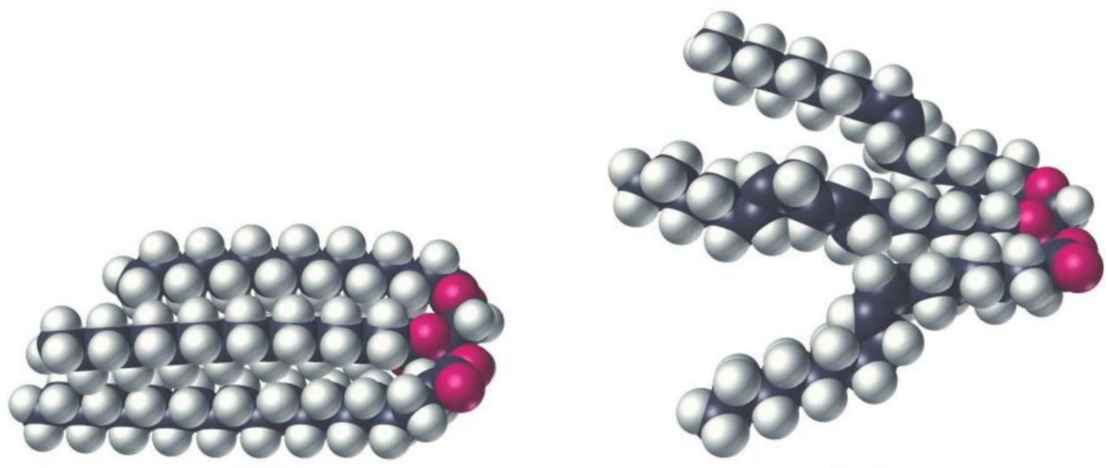
a mixed triglyceride

Solid vs Liquid Fats:

If the three fatty acid groups in most of the triacylglycerol molecules in a mixture were saturated, this would result in a solid fatty mixture with a relatively high melting point. The greater the number of unsaturated fatty acids (more double bonds\kinks) in the fatty mixture, the more liquid it becomes at room temperature, and the less its melting point .

Vegetable oils (liquids) consist almost entirely of unsaturated fatty acids, whereas animal fats (solids) contain a much larger percentage of saturated fatty acids.

This is the primary reason for the different melting points of fats and oils.



A fat An oil

Hydrolysis and Saponification

Triacylglycerols can be separated back to their original components (Glycerol and fatty acids) through either Hydrolysis or Saponification.

- **Hydrolysis:**
  Occurs either by reacting the triglycerides with steam (water vapor), an acid, or with the help of an enzyme catalyst (such as lipases secreted from the pancreas) in the presence of water.
  This reaction produces Glycerol and fatty acid ions.

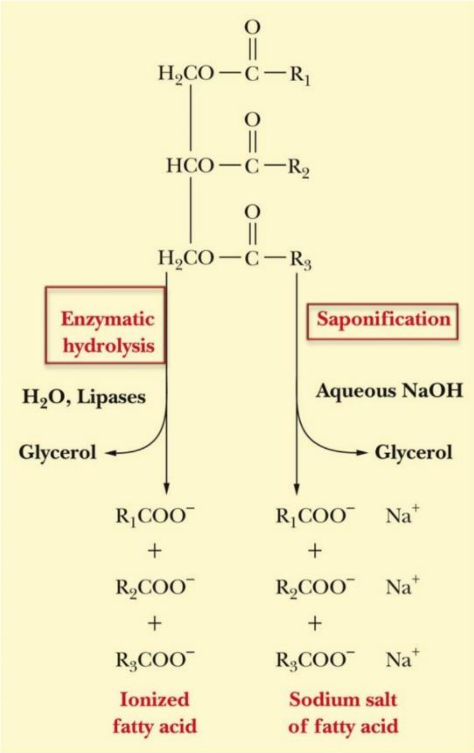
- **Saponification (Alkaline Hydrolysis):**
  Occurs when a triacylglycerol reacts with a strong base such as Sodium Hydroxide, producing Glycerol and fatty acid salts (soaps). These salts cause the emulsification of oily material, which helps in its removal.

How Does Soap Work?

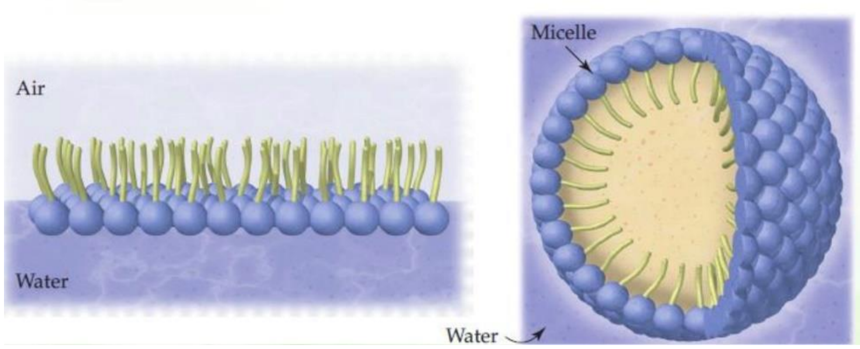
The main reason as to why fatty acid salts function as soaps is because they are amphipathic molecules.

So while they are mixed in water, their hydrophobic hydrocarbon tails cluster together to create a non-polar microenvironment away from water, and their hydrophilic ionic heads (carboxylic groups) interact with water.

The resulting spherical clusters are called Micelles. Grease and dirt are trapped inside micelles and the complex can be rinsed away.



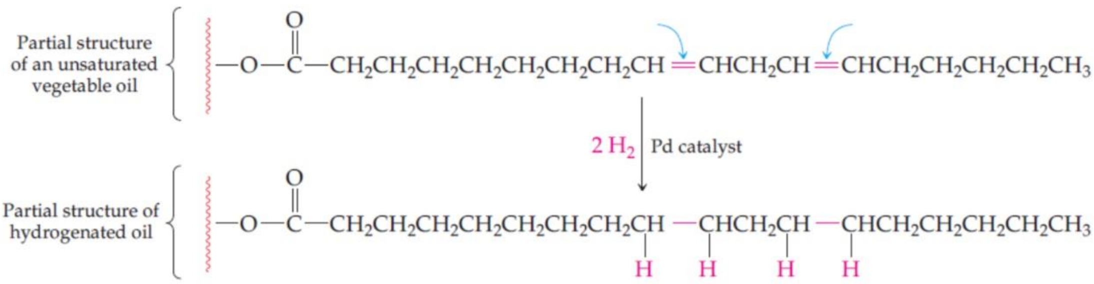
Extra video on soap : https://youtu.be/YnyYsEBJ80I



Hydrogenation

Hydrogenation is the process of converting unsaturated fatty acids into saturated fatty acids by reacting their carbon-carbon double bonds with hydrogen.

The carbon-carbon double bonds in vegetable oils can be hydrogenated to yield saturated fats in the same way that any alkene can react with hydrogen to yield an alkane.

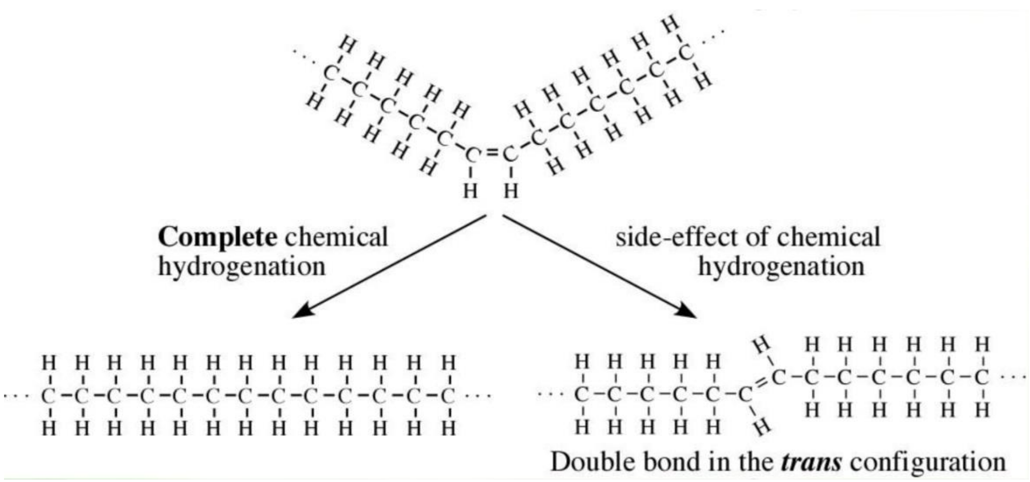


Trans Fat

Although animal fat (which contains saturated fats) is unhealthy, it has far better cooking properties and better taste. Therefore, chemists invented a method of converting unsaturated oil into solid form by partially (not completely) hydrogenating it.

Partial Hydrogenation converts some, but not all double bonds, into single bonds, which leaves the remaining double bonds in trans conformation, generating trans fats.

The primary health risk identified for trans-fat consumption is an increased risk of coronary heart disease (CHD).

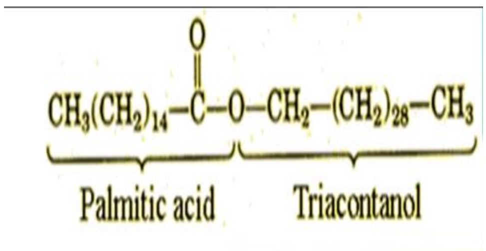


An example of consumable trans fats found in local supermarkets is margarine. Margarine is a solid trans fat made from hydrogenating vegetable oil, producing a good tasting and long lasting food product.

In margarine, only about two-thirds of the double bonds present in the starting vegetable oil are hydrogenated, while the rest become trans double bonds. This is so that margarine remains soft in the refrigerator and melts on warm toast.

Waxes

Wax is a fatty acid molecule linked to a hydrocarbon Alcohol (monohydric alcohol). A link between a repulsive group and an alcohol group via Ester bond (hydrocarbon chains on both sides of the ester bond). Which makes for a very hydrophobic and indigestible molecule in the human stomach.



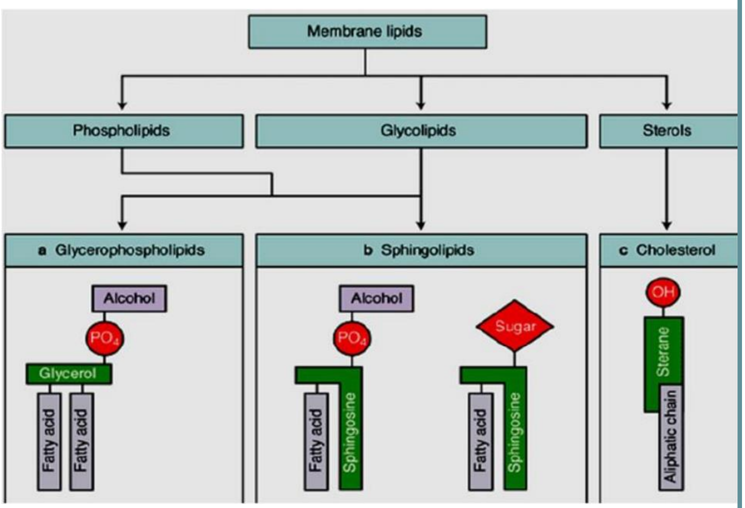
- **solid simple lipids containing a monohydric alcohol (C16 ~ C30, higher molecular weight than glycerol) esterified to long-chain fatty acids (C14 ~ C36). Examples: palmitoyl alcohol**

- Insoluble in water
- Are not easily hydrolyzed (fats) & are indigestible by lipases
- Are very resistant to rancidity
- Are of no nutritional value
- Coatings that prevent loss of water by leaves of plants

(Its not important to know the structure of the Wax molecules or GAGs but you should know their major characteristics.)

Type	Structural Formula	Source	Uses
Beeswax	$CH_3(CH_2)_{14}-C(=O)-O-(CH_2)_{29}CH_3$	Honeycomb	Candles, shoe polish, wax paper
Carnauba wax	$CH_3(CH_2)_{24}-C(=O)-O-(CH_2)_{29}CH_3$	Brazilian palm tree	Waxes for furniture, cars, floors, shoes
Jojoba wax	$CH_3(CH_2)_{18}-C(=O)-O-(CH_2)_{19}CH_3$	Jojoba	Candles, soaps, cosmetics

Membrane Lipids



Membrane lipids are composed of three different types of lipids.

-<u>Glycerophospholipids</u>: As the name implies, are composed of Glycerol backbone with Hydrophilic phosphate group , an alcohol and 2 hydrophobic fatty acid chains tail , this molecule is clearly amphipathic (hydrophobic + hydrophilic regions)

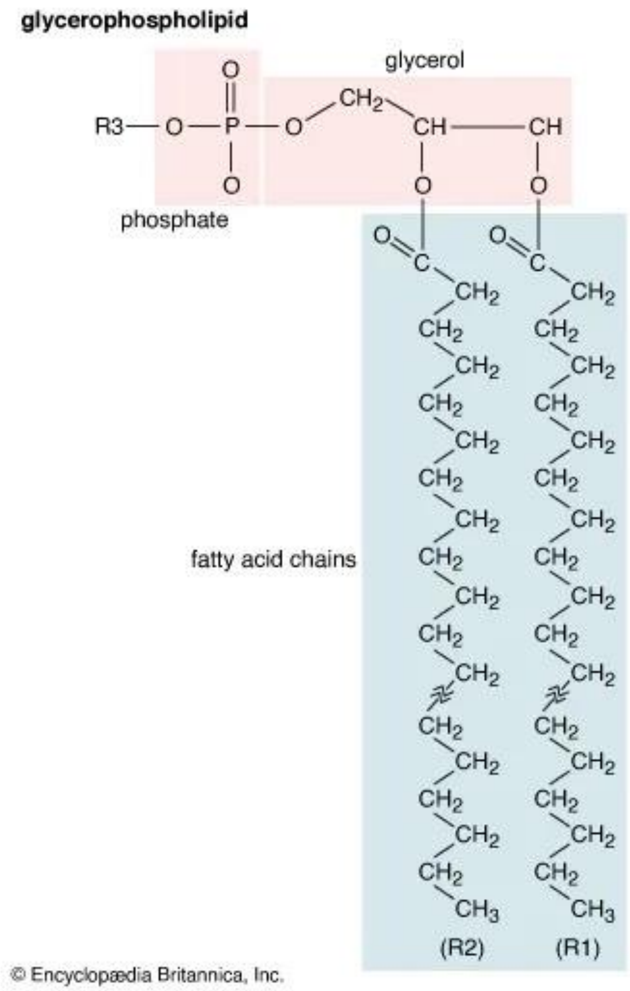
-<u>Sphingolipids:</u> Composed of sphingosine backbone, hydrophilic phosphate head or Sugar (we call it glycolipid if it contains a sugar instead of the phosphate group) and 1 hydrophobic fatty acid tail.

Its important to note that the sphingosine also has a long carbon region that takes one of the fatty acids' place. This is why Sphingolipids have only one Fatty acid molecule.

-Steroids: which are mainly derived from cholesterol , cholesterol exists in plasma membrane

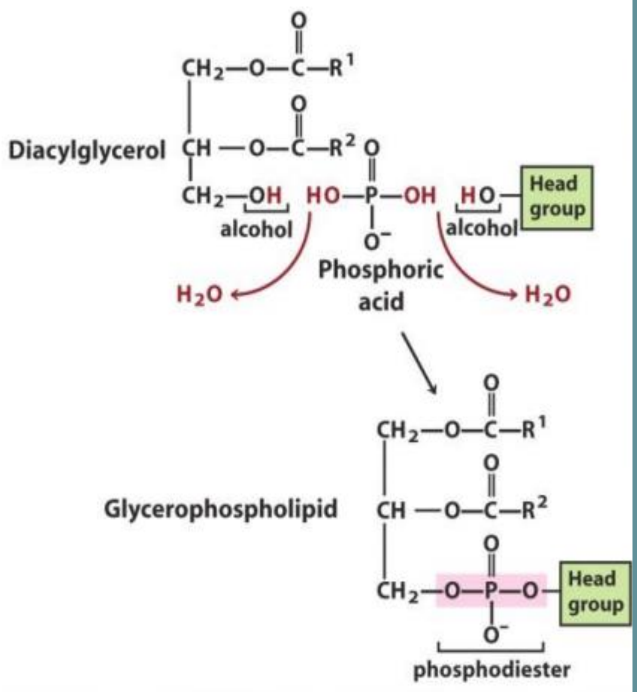
The most prevalent class of lipids in membranes is the glycerophospholipids.

A fatty acid is added to the 1st CH2OH in the Glycerol molecule , by an ester linkage , another fatty acid is added -next carbon- , and another phosphate group is added as seen in this pic .



Phospholipids (phosphoacylglycerols)

The most basic glycerophospholipids are Phosphatidic Acids (phosphatidate)



To differentiate between the different types of phospholipids we have to look at the Head Region.

Phosphatidylcholine (lecithin): has a Choline molecule added to its head , most abundant membrane lipid.

Cephalins:

-Phosphatidylethanolamine: Has ethanol amine added to its head.

-Phosphatidylserine: Has an amino acid called Serine added to its head.

Abundant in the brain.

Phosphatidic acid	—	$-H$
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-CH(COO^-)-\overset{+}{N}H_3$

Phosphatidylinositol: Inositol is a type of sugar which is important in the cell signaling, and is located in the inner leaflet.

Sends Signals across the cell membrane.

And some complex molecules like Cardiolipins and Plasmalogens.

Lecithins

Snake venom contains lecithinase (breaks phosphatidylcholine), which hydrolyzes polyunsaturated fatty acids converting lecithin into lysolecithin.

Targets RBCs cells and destroys their Membrane, which resorts to their death.

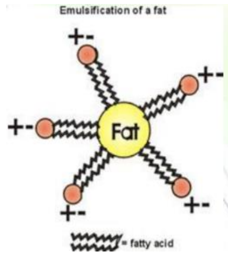
hemolysis of RBCs.

Emulsification

Lecithin acts as an emulsifier because of its amphipathic nature.

To Emulsify means to solubilize fatty molecules in a hydrophilic environment. The Hydrophobic group Surrounds the fatty compound and the Hydrophilic group is exposed to water.

Because of their amphipathic nature, they act as emulsifying agents, which are substances that can surround non-polar molecules and keep them suspended in water.



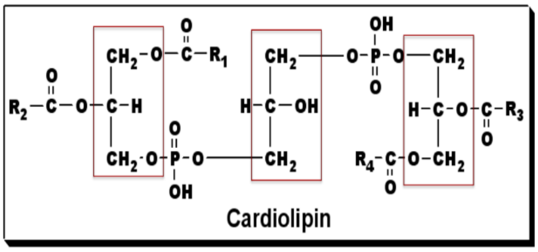
Cardiolipins

Diphosphatidyl-glycerol.

Found in the inner membrane of mitochondria.

Initially isolated from heart muscle (cardio).

Structure: 3 molecules of glycerol, 4 fatty acids & 2 phosphate groups.



Plasmalogens:

They are found in the cell membrane phospholipids fraction of the brain, muscles, liver, and semen.

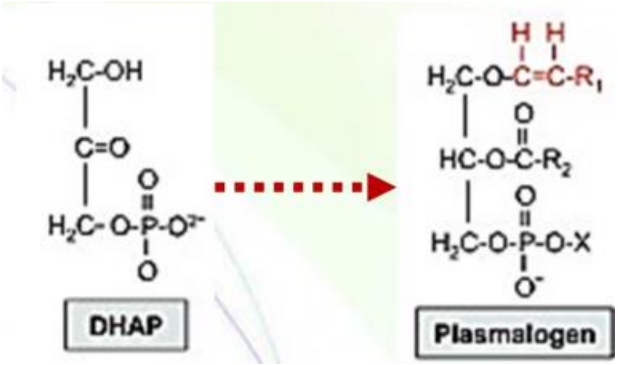
They have a protective role against reactive oxygen species

Structure:

-Precursor: Dihydroxyacetone phosphate (Ketose).

-Unsaturated fatty alcohol at C1 connected by ether bond

- In mammals: at C3; phosphate + ethanol-amine or choline



Notice the ether(ROR) group and alkene (=) , ester group on carbon number 2 , and the phosphate group .

You can differentiate the plasmalogen from these groups .

Major classes of plasmalogens:

- Ethanol-amine plasmalogen (myelin-nervous tissues).

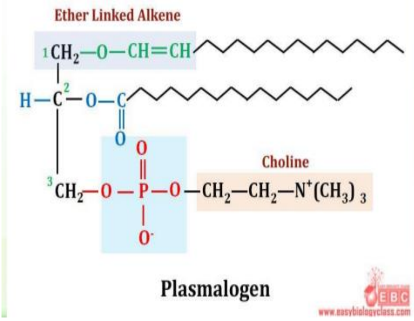
- Choline plasmalogen (cardiac tissue).

Platelet activating factor (EXTRA : doesn't contain an alkene group adjacent to the ether. Generally,ethers only are the defining feature of plasmalogens)

- Serine plasmalogens.

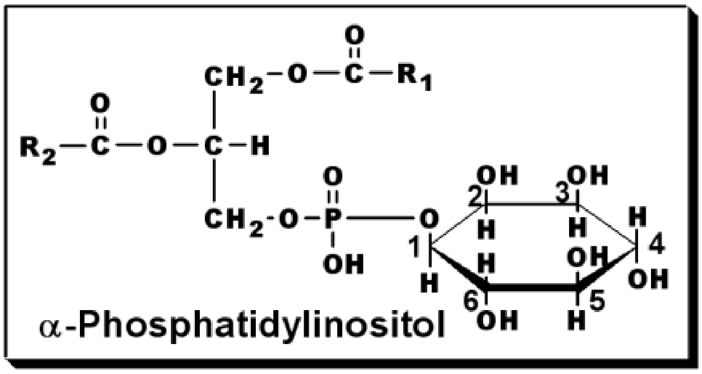
Inositides

Phosphatidyl inositol.



Nitrogenous base: cyclic sugar alcohol (inositol).

Structure: glycerol, saturated FA (usually on the first carbon), unsaturated FA (usually on the second carbon), usually arachidonic acid, ester groups , phosphoric acid, & inositol.



Source: Brain tissue.

Functions:

- **Major component of cell membrane.**
- **Second messenger during signal transduction.**
- **Upon hydrolysis by phospholipase C, phosphatidyl-inositol-4,5-diphosphate produces diacyl-glycerol (DAG) & inositol-triphosphate (IP3); which liberates calcium.**

-The different structures of phospholipids

-Lipids can form either a bilayer structure called Liposome or a monolayer structure called Micelle.
-The difference between these structures is that Liposomes have a hydrophilic core while micelle has a hydrophobic core.

-liposomes : phosphate groups are exposed to the outside and inside , and in the middle we have fatty acids (2 LAYERS)

Micelle : ONE layer , phosphate groups to the outside, while the fatty acids are extended to the inside

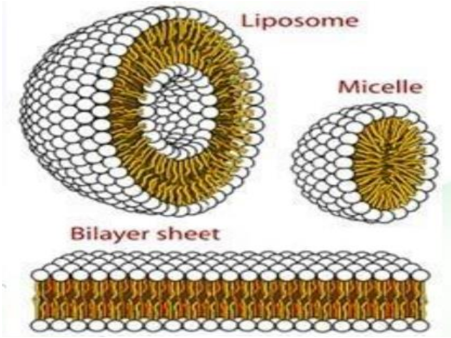
-**Important Note (الدكتور شد عليها بالحكي):**

-**The interior of micelle is ?**

Ans: hydrophobic

-**The interior of liposome is ?**

Ans: hydrophilic



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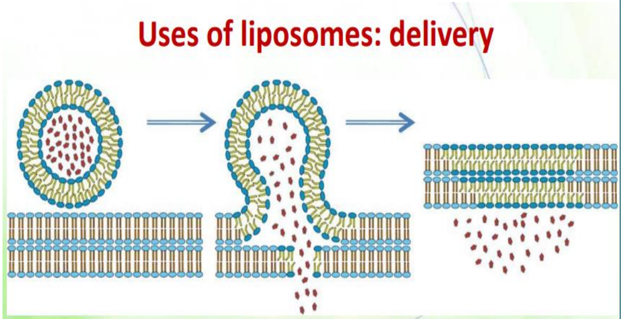
-**Liposomes can fuse with the plasma membrane and become a part of it , releasing the drug it contains.**

-**Liposomes can be used to deliver drugs to specific cells. (cell targeting)**



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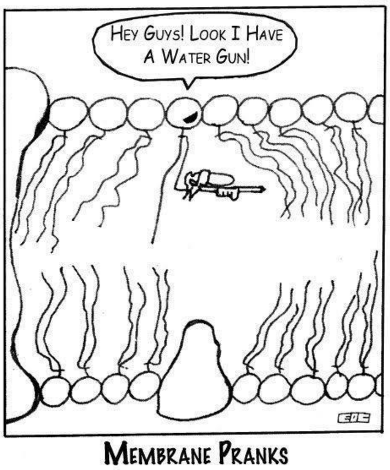

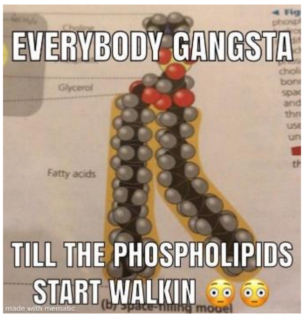

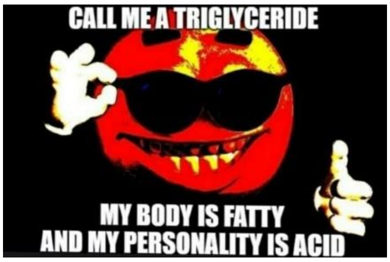

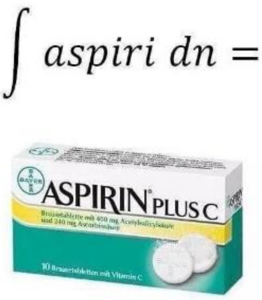

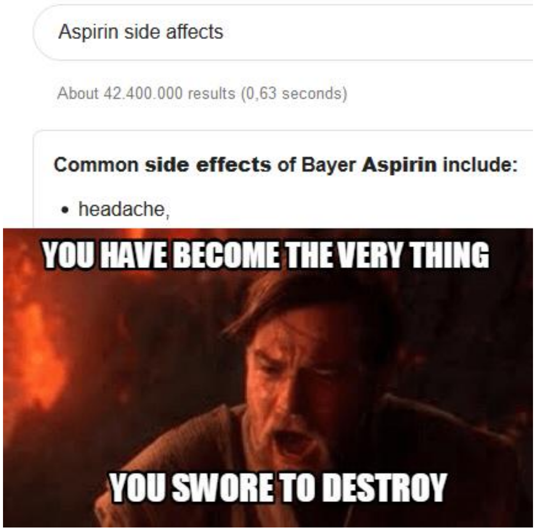

A COLLECTION OF RELEVANT MEMES