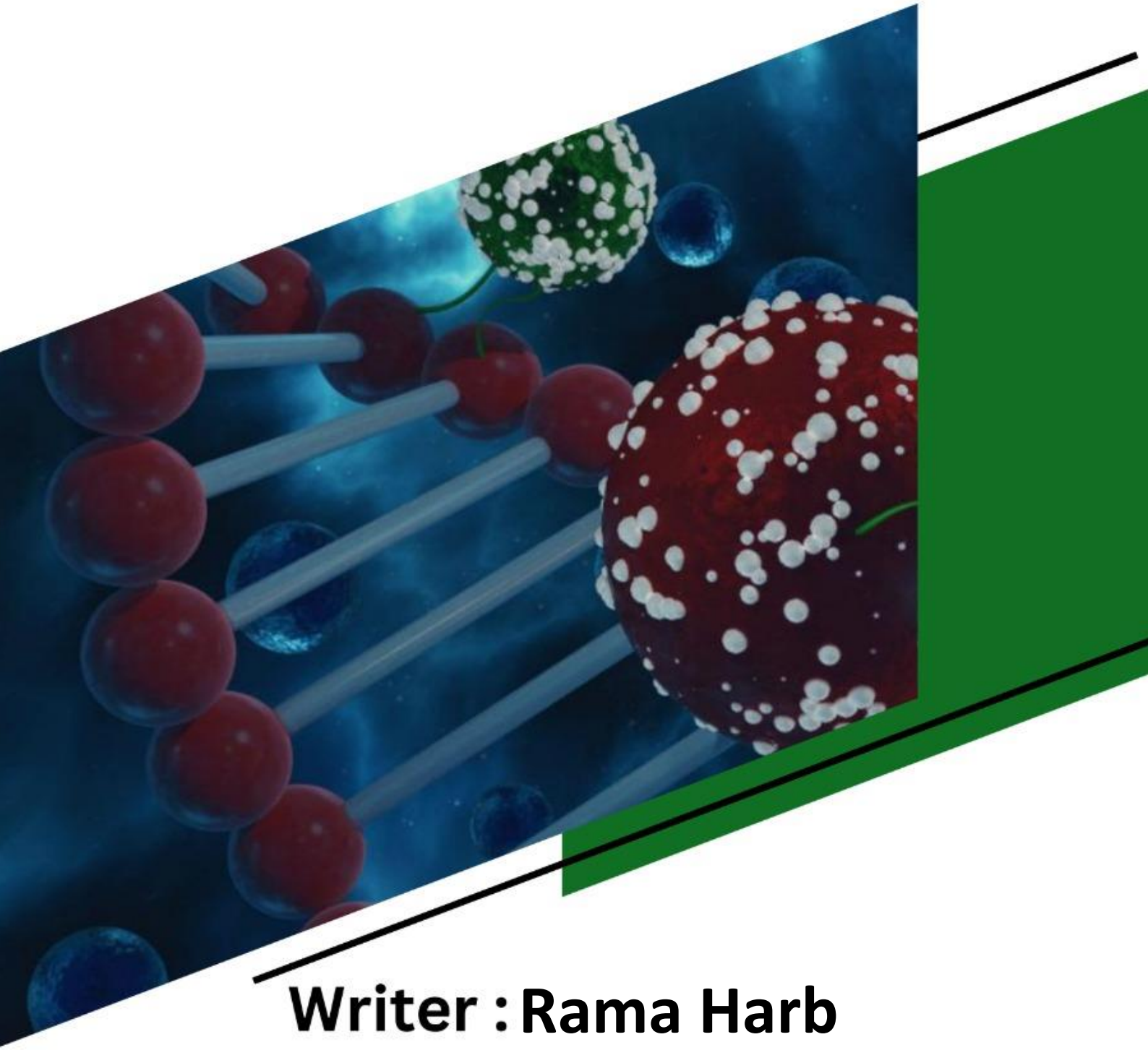
Doctor 021

METABOLISM

Sheet no. 23



Writer : Rama Harb

Corrector : Leen aburumman

Doctor : Prof. Mamoun Ahram

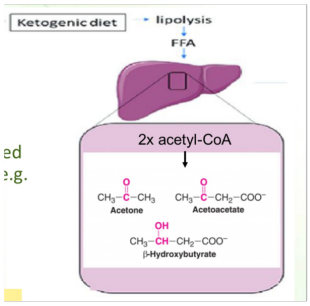
KETONE BODIES

In diabetic patients and when the stored glycogen in our bodies is consumed(starving for three to four hours after meal),then we go to fatty acid metabolism.

Actually in some tissues it becomes ketone bodies formation instead of fatty acid metabolism.

What are ketone bodies?

- At wake-up time: 3-4% of energy
- Prolonged fasting: 30-40%



From 2x acetyl-CoA, the liver produces ketonebodies:

three ketone bodies can be produced in liver

1.Acetoacetate

2.3-Hydroxybutyrate (AKA β-hydroxybutyrate)

3.Acetone (volatile), it can be transported from the liver to the blood and then to the lung, then it is released causing acetone-like odor in fasting and diabetic people.

these ketone bodies are acidic in nature, that's they can cause ketoacidosis: PH of the blood goes down.

Ketone bodies are released from liver to tissue such skeletal muscles and heart and then break up and converted to acetyl co-A which may enter krebs cycle to produce energy.

***The organic acids are transported to and re-converted**

to acetyl-CoA in, and utilized by peripheral tissues (e.g.

muscle, heart, brain in case of sever starvation because it depends on glucose metabolism**, …etc., but not RBC and liver)**

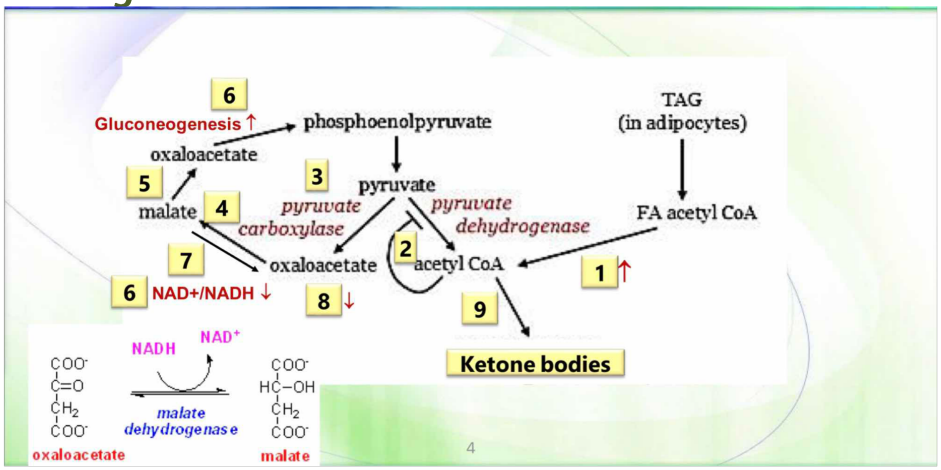
***Advantages:**

1.Soluble (no carrier is needed)

2.Fast, produced and metabolism.

3.Spare glucose

During a fast and diabetes:



Why our bodies produce ketone bodies?

Because we normally use glucose as a source of energy, but if you did not eat for a day, your body will depend on TAG by lipolysis, fatty acids will be released from adipocytes, these FAs will be broken up in acetyl-CoA.

Then, now we have a high level of acetyl CoA, it is even larger than what the tissues can utilize to krebs cycle.

كربس بتبطل ملحقة على هالكمية الكبيرة وبتقول ايبيبيه، ضغوط كتير على كتكوت صغنن، نفسنا مع ال 50 محاضرة المتراكمين يعني.

Which will inhibit pyruvate dehydogenase ,step 2 in the picture, so pyruvate will convert to oxaloacetate.

Then, oxaloacetate is converted to malate,step 7, which will leave mitochondria to cytosol and will be converted to oxaloacetate,step5, then oxaloacetate converts to PEP activating “gluconeogenesis”.

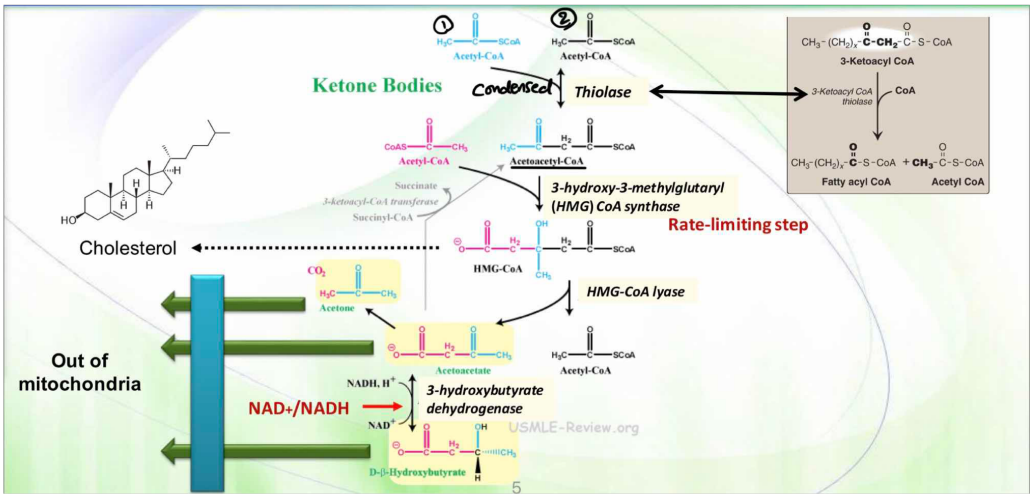
After that, oxaloacetate amount decreases so malate is converted to oxaloacetate because there is an equilibrium between OAA and malate.

لفي بينا يا دنيا مش هيك؟

الفكرة انه بيصير حالة اتزان بين هالمركبين, بخطوة 7 وبيضلهم يتحولوا بين بعض.

As a result of that conversion between OAA and malate NAD+/NADH will decease, and the oxaloacetate already decreased(remember that some of malate leave mitochondria to cytosol) and as a result acetyl CoA will be converted to ketone bodies,step 9.

The reactions:



Formation and degradation of ketone bodies happens mainly in mitochondria, so we said that no formation of ketone bodies in RBCs.

Now, let us study the formation of ketone bodies, step by step with the picture above.

What happens that we have 2 acetyl CoA which will condense by thiolase to form acetoacetyl Co-A, another acetyl CoA enter and react with acetoacetyl CoA by enzyme 3-hydroxy-3-methylglutaryl(HMG)CoA synthse producing HMG CoA, which will produce ketone bodies and release acetyl CoA by HMG CoA lyase.

Gluta=five carbon molecule

#ketone bodies that are produced from lyase:

1.acetoacetate

2.acetone: it produced by breaking up of acetoacetate

3.D-beta-hydroxybutyrate: it produced by conversion of acetoacetate by

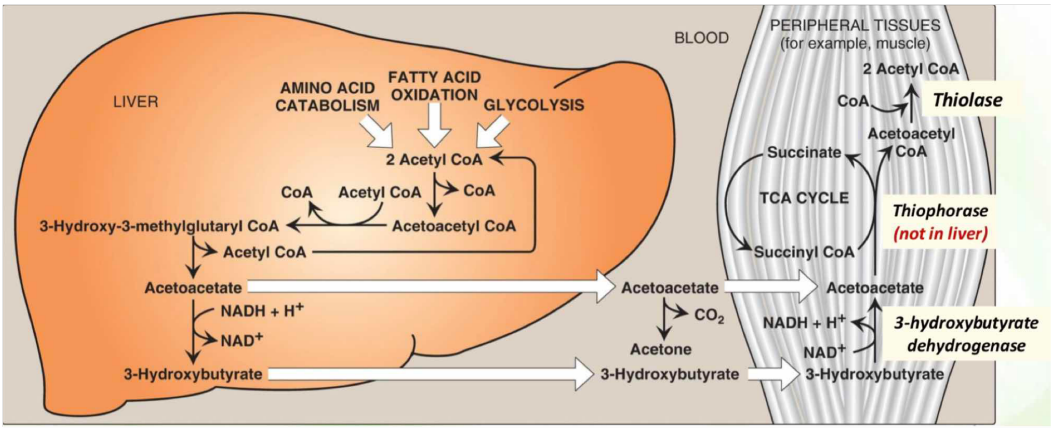
3-hydroxybutyrate dehydrogenase. There ia an equilibrium between these two ketone bodies.

These ketone bodies will leave mitochondria to the blood, acetone goes to lungs and goes out of the body. Acetoacetate and D-beta-hydroxybutyrate go to skeletal muscles, cardiac tissues and they are utilized.

Note: the reaction that happen by 3-hydroxy-3-methylglutaryl(HMG)CoA synthse it is the rate limiting step in the process, it is very important because it is used in the formation of cholesterol, we will talk about that in details.

*note that thiolase is the same enzyme that catalyse the breaking down of 3-ketoacyl into fatty acyl CoA in beta-oxidation.

Use of ketone bodies:



How do the peripheral tissues utilize these ketone bodies? So in liver again there is the formation of these ketone bodies, then they go to the blood and then they are taken up by hydroxybutyrate it is converted into acetoacetate again by the same enzyme dehydrogenase enzyme. Acetoacetate is then provided with a CoA molecule taken from succinyl CoA producing succinate and acetoacetyl CoA, this process is catalyzed by Thiophorase. Now acetoacetyl CoA is converted into 2 Acetyl CoA by the same enzyme thiolase and Acetyl CoA can get into the Kreb's cycle forming GTP, NADH and FADH2.

There are 2 types of cells that can not utilize ketone bodies:

1.RBCs, they don't have mitochondria.

2.And the other is liver, because liver cells don't have thiophorase enzyme, so they stick in the point where they have just acetoacetate and hydroxybutyrate, and this is good because the main function of liver is to make sure that ketone bodies will go to all cells.

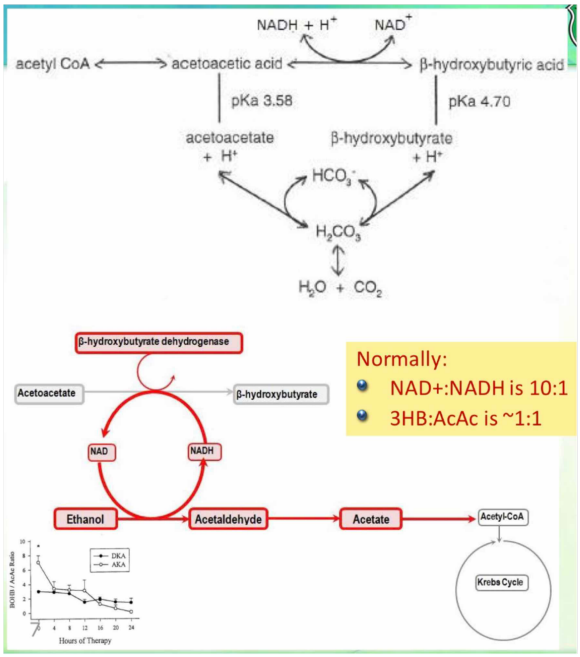
Ketoacidosis

Ketone bodies are really important because diabetic patients will not benefit from glucose, so that they break down fatty acids into acetyl CoA that is converted to ketone bodies.

These ketone bodies will lowe PH, so diabetic people may have ketoacidosis.

Conversion between acetoacetate and D-beta-hydroxybutyrate depends on NAD+/NADH,when we have high level of NADH the reaction will go towards D-beta-hydroxybutyrate, and vice versa.

*look at the picture I think that is important to understand



***Remember pKa!!!**

***Normally, levels of ketone bodies: <3mg/dl**

***People with excessive production: 90 mg/dl and urinary excretion of ketone bodies may be 5,000 mg/24 hour.**

***The end-results:**

1.Dehydration

2.Acidemia (ketoacidosis)

#Diabetic ketoacidosis, prolonged fasting, alcoholism

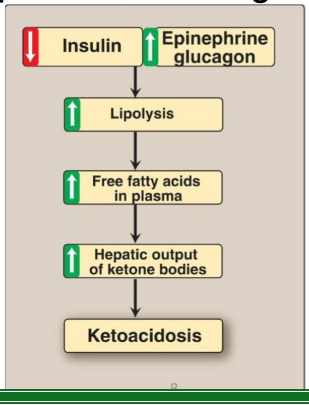
3.Fruity odor of breath

In alcoholic ketoacidosis: 3HB>AcAc
The ratio gets back to 1:1 after a few hours

Alcoholic keto acidosis: normally the NAD+/ NADH ratio is 10:1 and 3HB:AcAc is approximately 1:1, alcoholic people get rid of ethanol by converting it into Acetaldehyde. -which will be converted toacetete,this reaction produces NADH, so the equilibrium will shift towards 3HB causing the increase of the 3HB: AcAc However, after few hours ratio will go back to normal

Hormonal regulation:

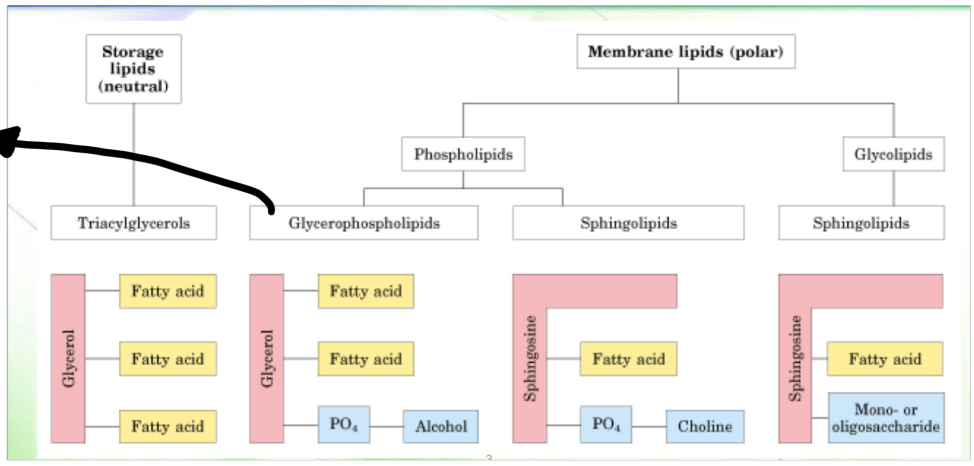
People who have high level of glucagon/EP (hungry people), but they do don't use glucose, they will have high level of lipolysis, FFAs in plasma, then high amount of hepatic output of ketone bodies they will have.



GLYCEROPHOSPHOLIPIDS

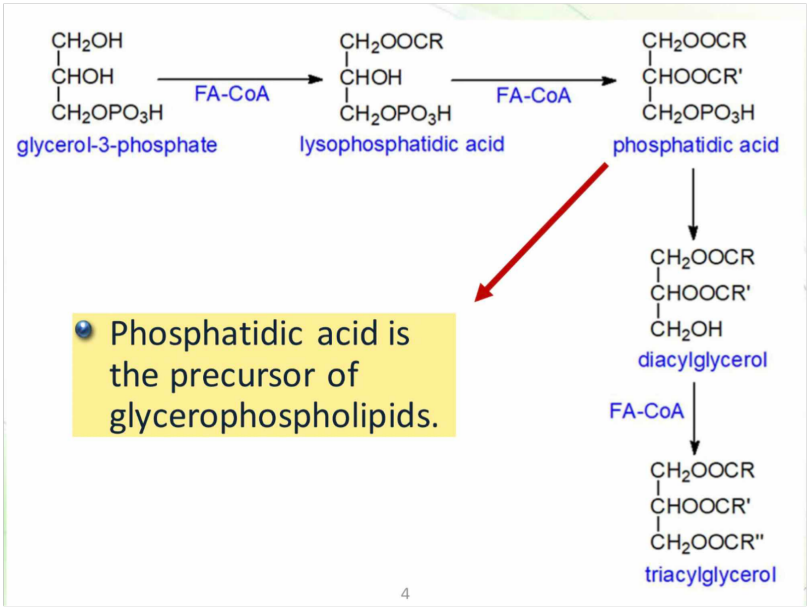
Now, let us continue with lipid metabolism.

The backbone is glycerol that has 2FAs and phosphate group, different groups can be attached with phosphate group.



Phosphatidic acid

We studied that pathway in the previous lecture. Just note that phosphatedic acid is the precursor for glycerophospholipids



Classification of Glycerophospholipids

*Phosphatidic acids

*Phosphatidylcholine (lecithin)

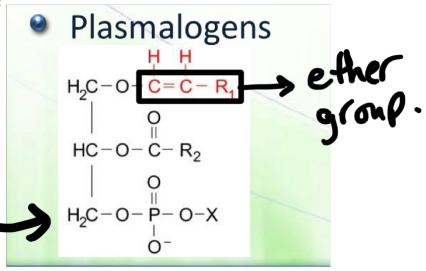
*Phosphatidylethanolamine

*Phosphatidylserine

*Phosphatidylinositol

*Cardiolipin

*Plasmalogens



• Phosphatidic acids: the basic glycerophospholipid, the precursor to all glycerophospholipids.

The head group attached to the phosphate in phosphatidic acid is -H

-different head groups can attach to the phosphate group in phosphatidic acid as the following composing different type of glycerophospholipids:

phosphatidic acid PA(base) + head group → different glycerophospholipids.

*look at the picture to see the head group of different types→

*ethanolamine:two carbon+amino group

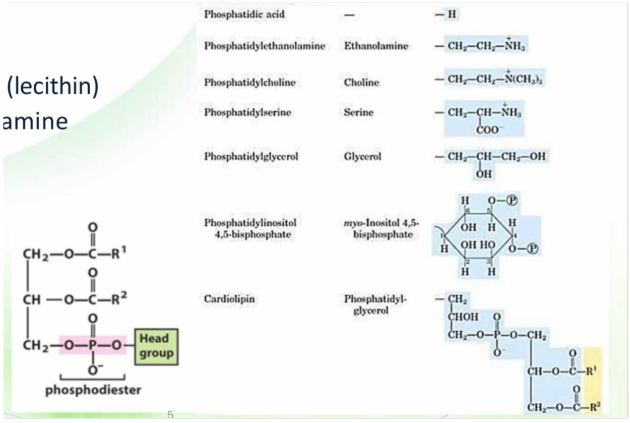
*choline:tertiary amine

*Serine:two carbons+amino group+carboxyl group

*glycerol:3carbons+2OH

*Inositol:complex sugar with 2 phosphate group

Plasmalogens:have ether group



*the doctor mentioned the difference between diphosphate and bisphosphate that diphosphate means that two phosphate group binds to each other while bisphosphate means that two phosphate groups are at different sites.

Synthesis

*Location: smooth ER

+Except for ether lipids

Activation by CDP is necessary.

Either:

1.CDP-DAG

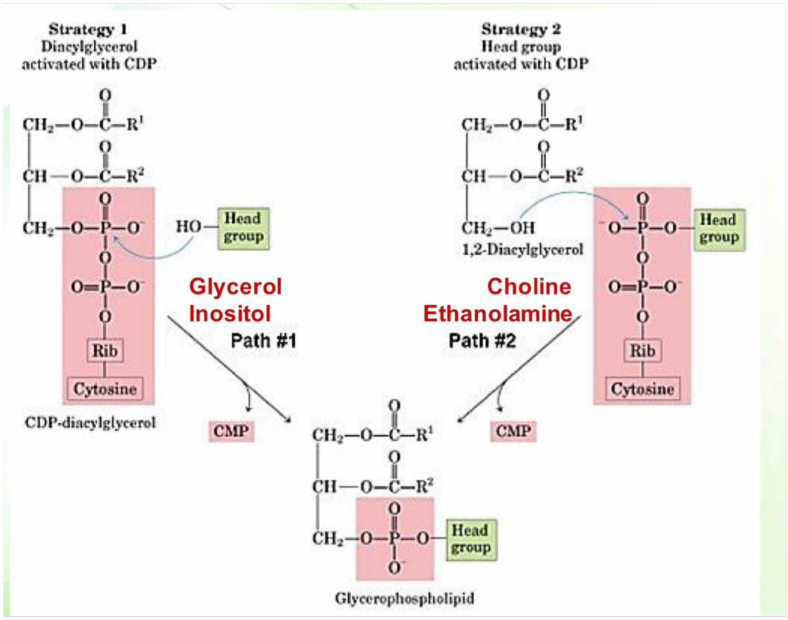
2.CDP-alcohol

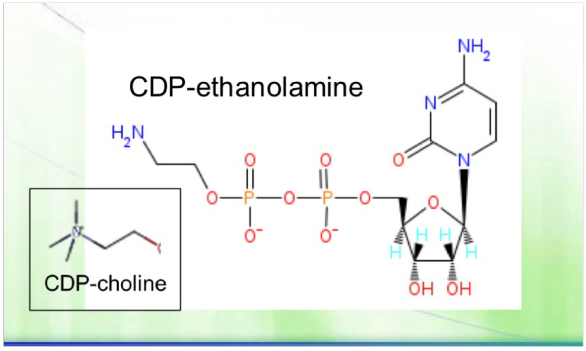
•synthesis of phospholipids requires activation by attaching to CDP.

*we have two choices ethier CDP attached with glycerol then glycerol will be activated or the head group attached to CDP then it will be activated.

To link glycerol with inositol→glycerol must be activated

To link glycerol with ethanolamine or choline→choline or ethanolamine must be activated.





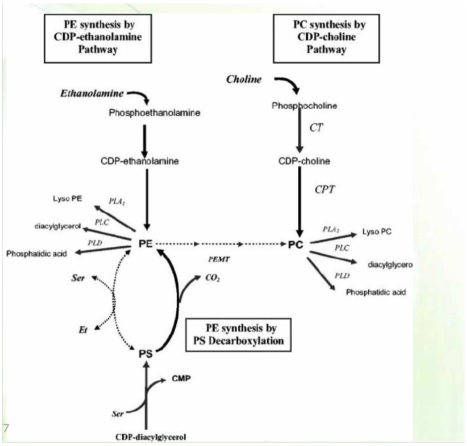
Sources of choline and ethanolamine

Choline and ethanolamine are:

*obtained from diet, synthesized or re-cycled from the turnover of preexisting phospholipids.

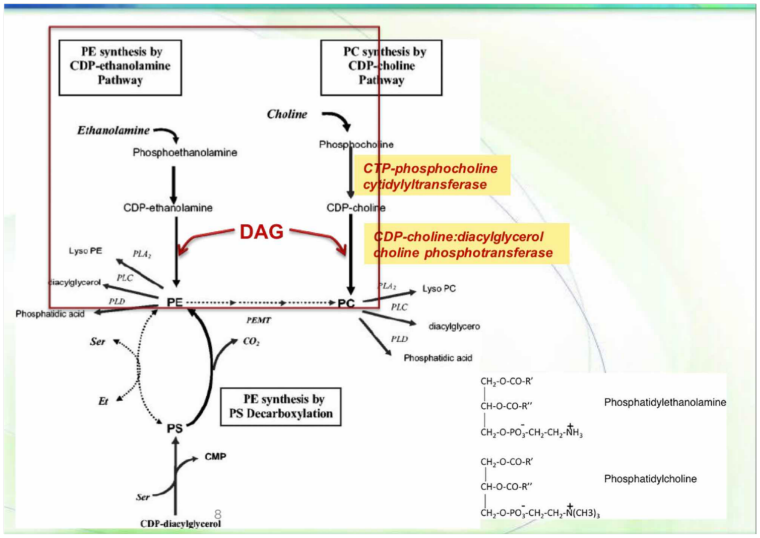
*Diet is still essential since demand>supply

the demand is higher than body mass to make them, so it ia importanat to get them from diet.



Synthesis of ph-choline and ph-ethanolamine

Choline or ethanolamine are phosphorylated by kinases, then activated by transferases to form, CDP-choline or CDPethanolamine. Choline phosphate or ethanolamine phosphate is transferred from the nucleotide (releasing CMP) to DAG.



Ethanolamine becomes phosohoethanolamine,avtivated, then phosphate will be exchanged into CDP to form CDP-ethanolamine. Then we can bind it to DAG so we get phosphatidylethanolamine, we can attach methyl group on amino group by three consecutive reactions, that's how phosphatidylethanolamine is converted to phosphatidylcholine.

Phosphatidylcholine can be formed from phosphtidylethnolamine by adding 3 methyl groups, or by choline. (the same process that produce ph-ethnolamine from ethanolamine).

*phosphatidylethanolamine is the precursor for phosphatidylserine by exchanging ethanolamine by serine.

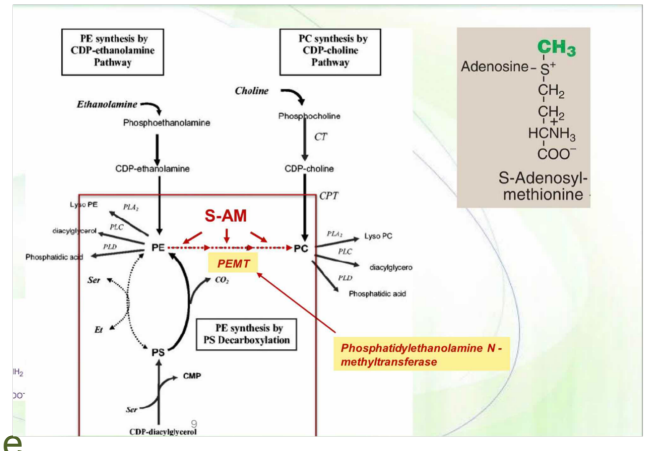
*phoshatidtylserine can be converted back to phosphatidylethanolamine by decarboxylation reaction.

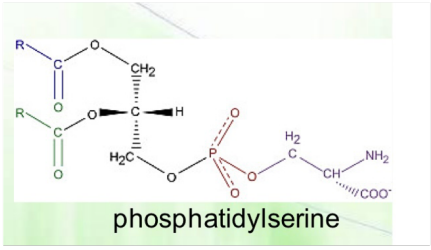
Ph-choline synthesis from ph-serine

*The liver requires a mechanism for producing PC because it uses it for production of bile and other plasma lipoproteins.

*PS is decarboxylated to PE by PS decarboxylase.

*PE is methylated from S-adenosylmethionine.





Synthesis of ph-inositol

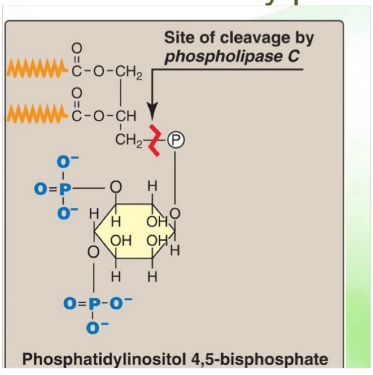
ph-inositol is a reservoir of arachidonate.

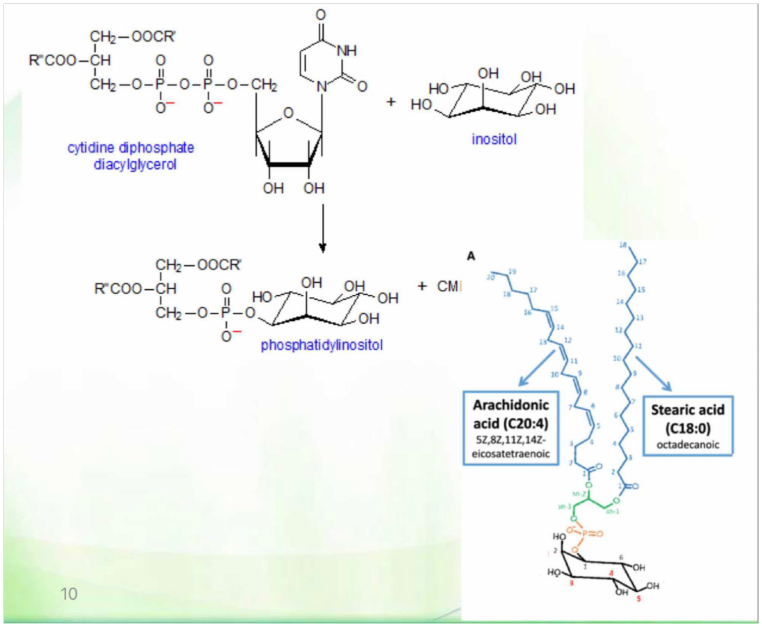
When I have TAG, usually carbon no.1 associated with saturated FA, carbon no.2 with unsaturated FA.

In ph-inositol carbon no.2 associated with arachidonate.

When signaling and releasing of lipid from plasma membrane take place usually arachidonate is released from ph-inositol that is found in plasma membrane.

It produces signaling molecules when cleaved by phospholipase C.

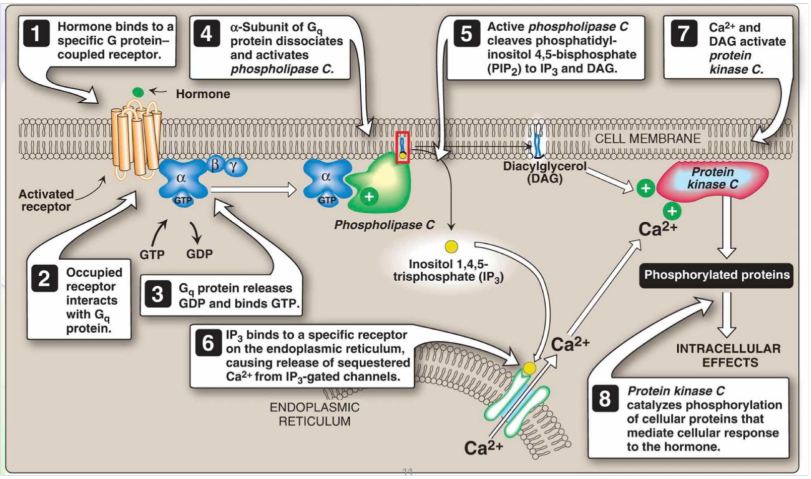




Signaling by PIP2 products

*every step in this picture is important.

Note that:protein kinase c needs ca++ to be activated



GPI for membrane attachment

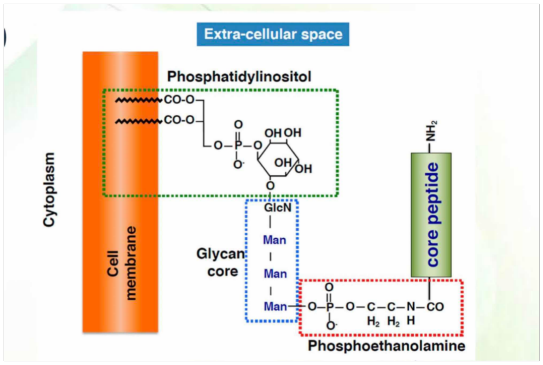
*glycosyl phosphatidylinositol (GPI)is used to attach proteins into the plasma membrane.

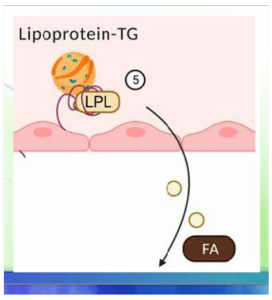
It is important because it is usually in extracellular surface of the plasma membrane and attaches further sugars on molecules.

These sugar are important for the recognition between cells, cell-cell interaction and so on.

*Advantage: lateral mobility of proteins

*Example: lipoprotein lipase, that found on the surface of endothelial cells via GPI.





Phosphatidylglycerol and cardiolipin

*Phosphatidylglycerol is synthesized from CDP-DAG and glycerol 3-phosphate.

*Cardiolipin is synthesized by the transfer of DAG from CDP-DAG to a pre-existing molecule of phosphatidylglycerol.

phosphatidylglycerol has the basic structure of phosphatidic acid (2 Fatty acids attached to a glycerol backbone) + phosphate group PO4 attached to a glycerol head.

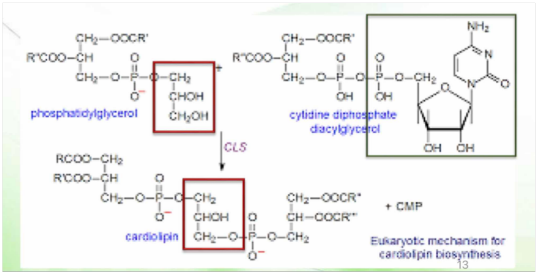
•Phosphatidylglycerol is synthesized from CDP-DAG and glycerol 3-phosphate:

phosphatidic acid is activated by adding CTP forming CDP-DAG,

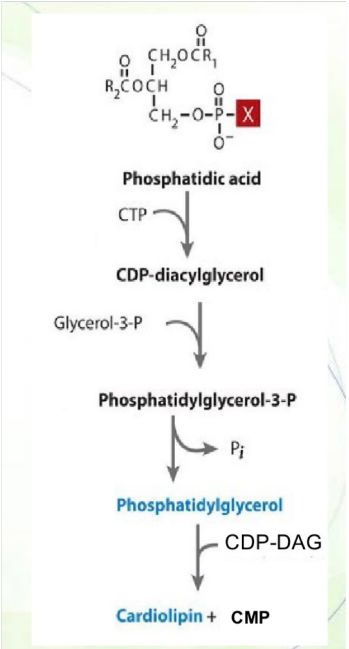
glycerol 3-P reacts with CDP-DAG forming phosphatidyl glycerol 3-P,

the phosphate is removed to form phosphatidyl glycerol

•Phosphatidylglycerol can react with CDP-DAG through the glycerol head synthesizing Cardiolipin, in which the DAG from CDP-DAG is added the glycerol head & CMP is released.

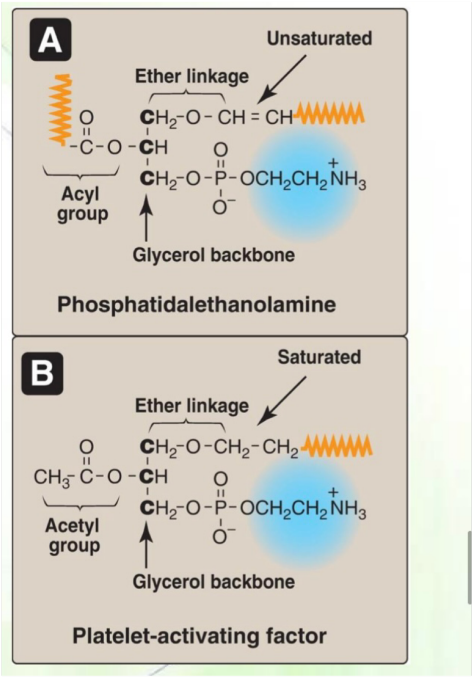


*Cardiolipin is also known as Diphosphatidylglycerol (2 phosphatidates + glycerol), it is found in the mitochondria.



Ether glycerophospholipids

The FA at carbon 1 is replaced by an unsaturated alkyl group attached by an ether



*Plasmalogens: PhosphatidAlethanolamine (abundant in nerve tissue, is similar in structure to phosphatidylethanolamine.

+Phosphatidalcholine (abundant in heart muscle) is the other quantitatively significant ether lipid in mammals

*Platelet-activating factor: has a saturated alkyl group in an ether link to carbon 1 and an acetyl residue at carbon 2 of the glycerol backbone.

+Prothrombotic and inflammatory factor.

Surfactants

Found in lung tissue.

*Surfactants are a complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer lining the alveoli and are secreted by type II pneumocytes in the lungs.

*Dipalmitoylphosphatidylcholine (DPPC) is the major lipid in surfactants.

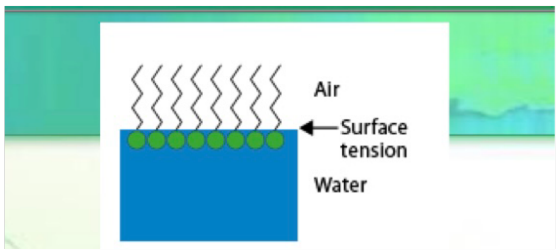
*Surfactants serve to decrease the surface tension of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis).

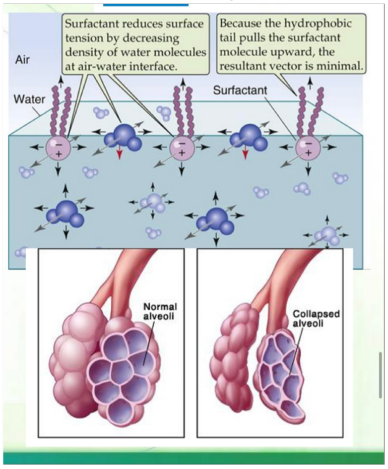
When the air-which is hydrophobic-enter to our lungs, the cell surface is hydrophilic and have phosphate group, as a result our lungs will shrink, to avoid that surfactants are produced, they coat the lung preventing the surface tension.

They are importanat in protecting the lungs from infections.

*Respiratory distress syndrome (RDS) in preterm infants is associated with insufficient surfactant production and/or secretion.

*Prenatal administration of glucocorticoids shortly before delivery to induce expression of specific genes.





Degradation of Phospholipids

• Phospholipase A1 is responsible for releasing the FA attached to carbon no.1 present in many mammalian tissues.

• Phospholipase A2 released as a proenzyme (zymogen), activated by trypsin.

Is responsible for releasing the 2nd FA attached to carbon no.2and responsible for releasing the arachidonic acid from the phosphatidyl inositol PI.

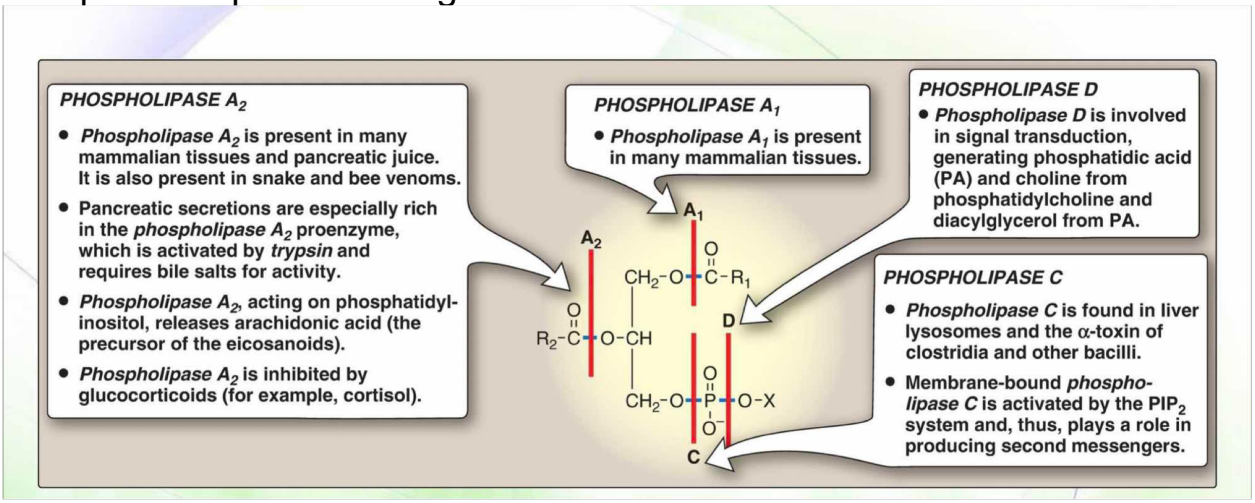
present in snakes and bee venoms: damages glycerophospholipids which causes cell damage like RBCs damage resulting in excessive bleeding which explains why snakes are fatal.

• Phospholipase C acts before the phosphate group, as mentioned previously PLC removes the phosphorylated inositol releasing IP3

• Phospholipase D acts after the phosphate group, would release the inositol molecule only from PI.

Note: the doctor said: read the description that wrote in the picture, and you should know that every enzyme work in specific site.

The previous points I brought them from 020 sheet.



مُت آخرسًا إن عزَّ أن تحيا بـ"لا"

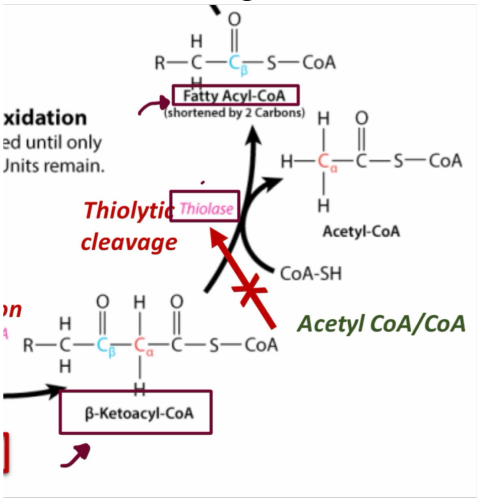
أدنى الدناءةِ أن تعيش مُطبلًا

V3

Page 11, surfactants.
Cell surface is hydrophilic
not hydrophobic.

Page4.
The note about thiolase.
Acually the enzyme breaking down
B-ketoacyl CoA NOT 3-ketoacyl.

ضفتلكم الصورة يلي بتمثل الخطوة من
المحاضرة السابقة لتعرفوا وين عم بحكي.



Page5.
Ethanol converted to acetaldehyde NOT
acetyl CoA.
التحويل موّضح بالصورة وال acetyl CoA هي الend
وبتدخل كربس بعدين. product