LIPID METABOLOSIM

المحاضره الأولى

Objectives:

The students are learned to understand the following points

- Brief review about lipids chemistry including fatty acids, Cholesterol,

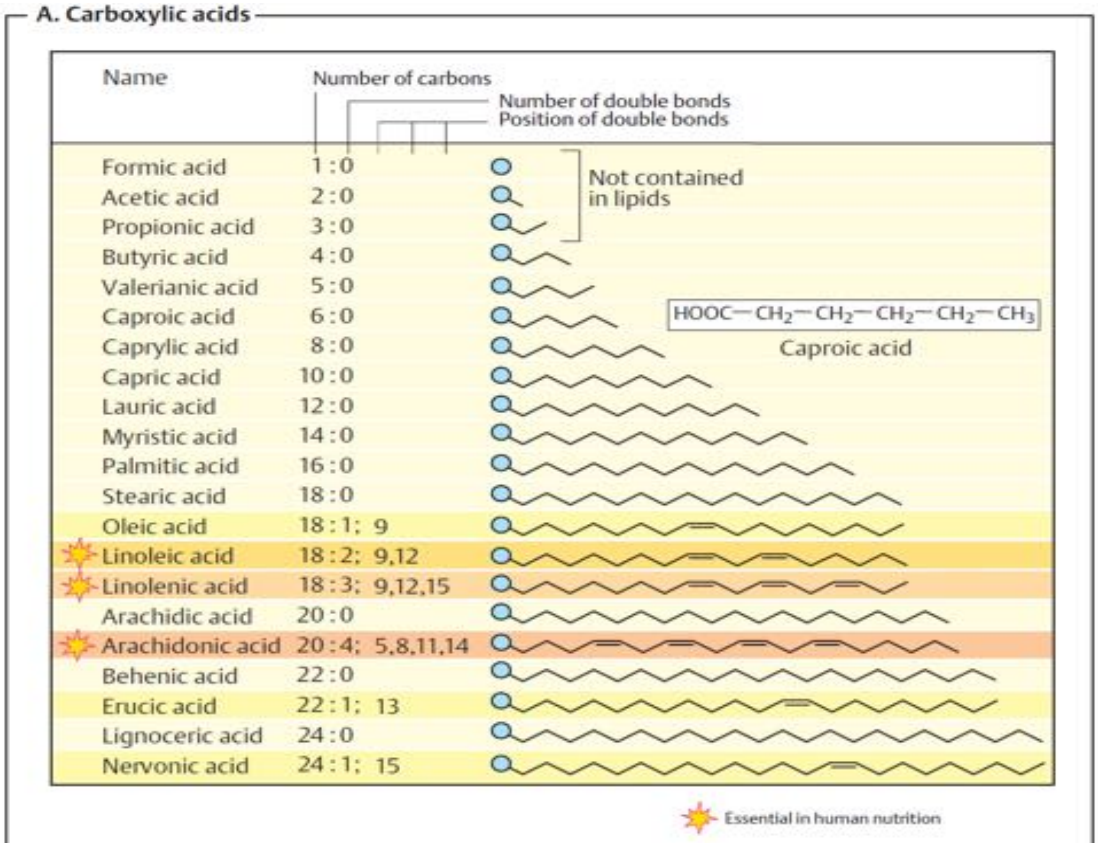
Triglycerides, and Phospholipids

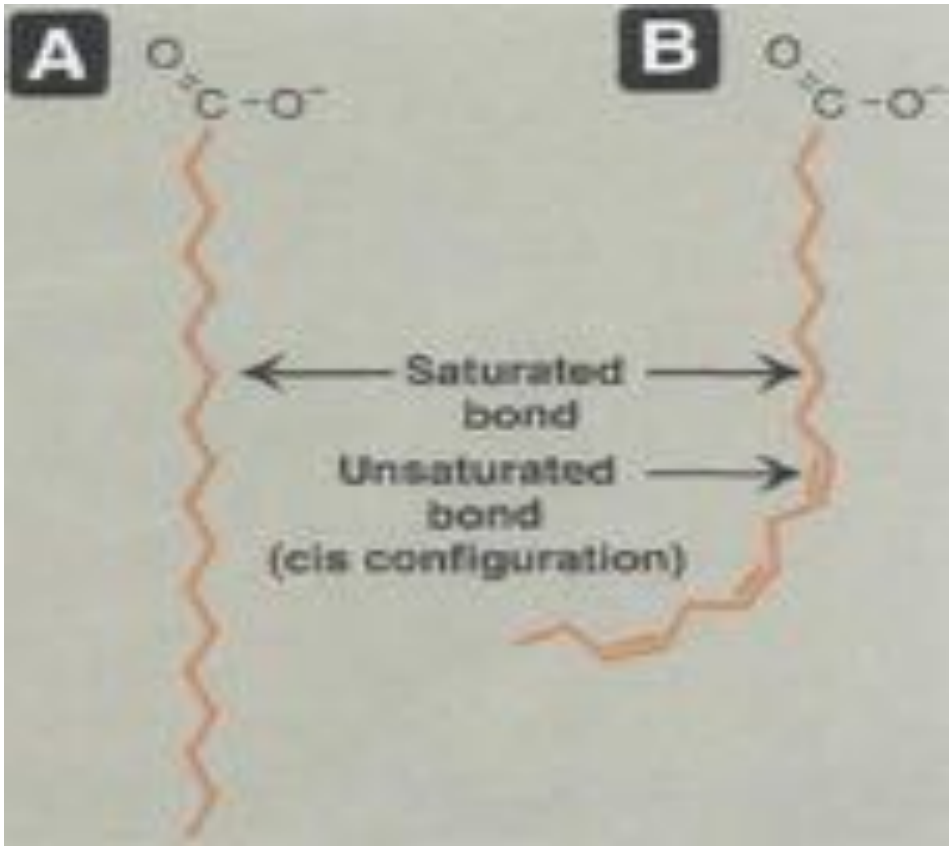
- Their sources, function, and plasma levels

LIPID METABOLOSIM

Brief review about lipid chemistry:

-Fatty Acids structure




A
B
Saturated bond
Unsaturated bond (cis configuration)

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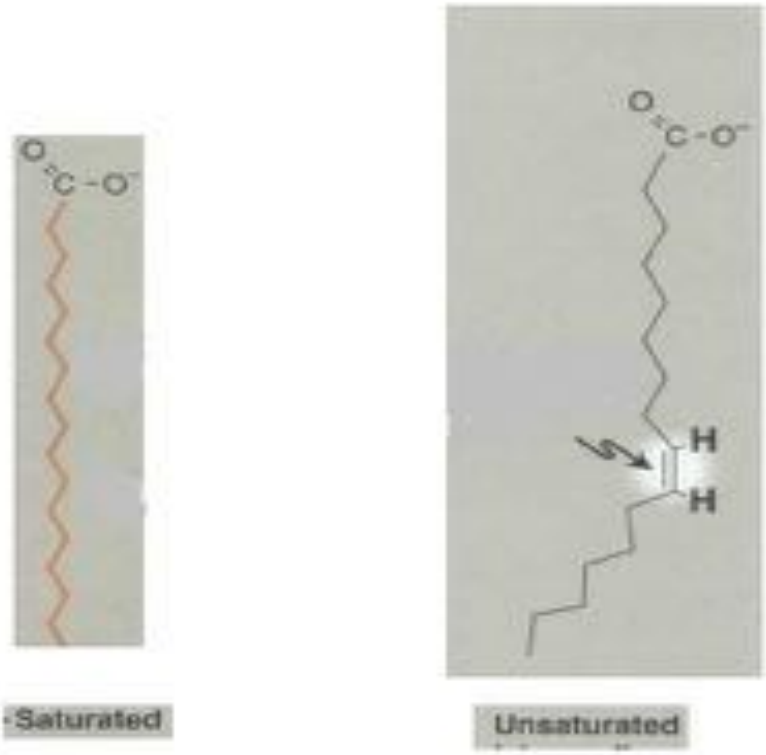
H
H
Saturated
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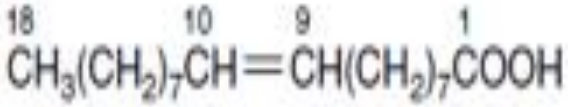
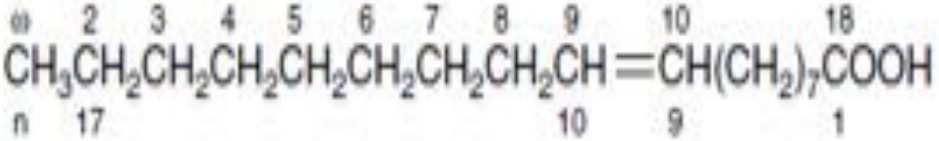
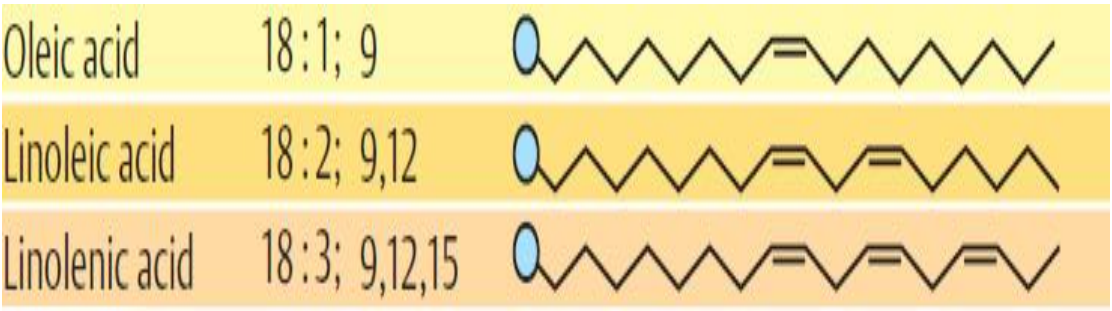
18:1;9 or Δ^9 18:1



or

ω9,C18:1 or n–9, 18:1





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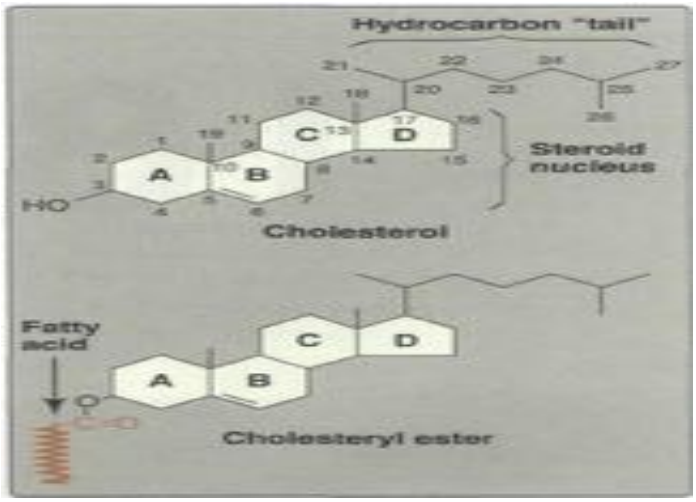
- **<u>Cholesterol</u>**



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Normal serum cholesterol < 200 mg\dl

We have two types of cholesterol :

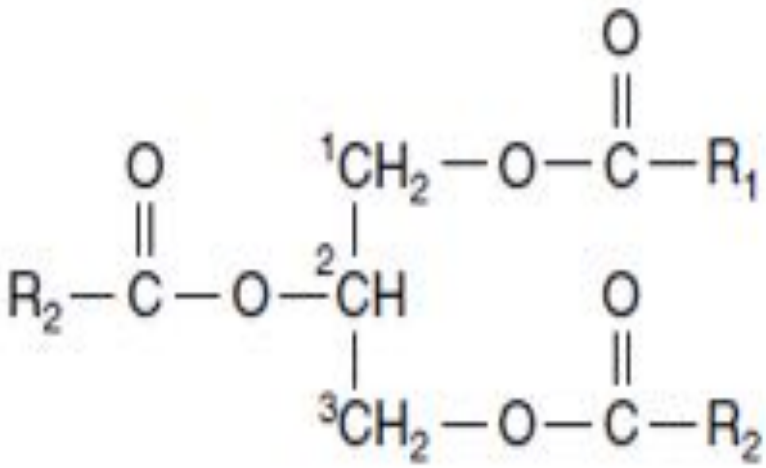
1) Endogenous: greater of the body cholesterol is provided by synthesis of about 700 mg\day (MORE THAN HALF)

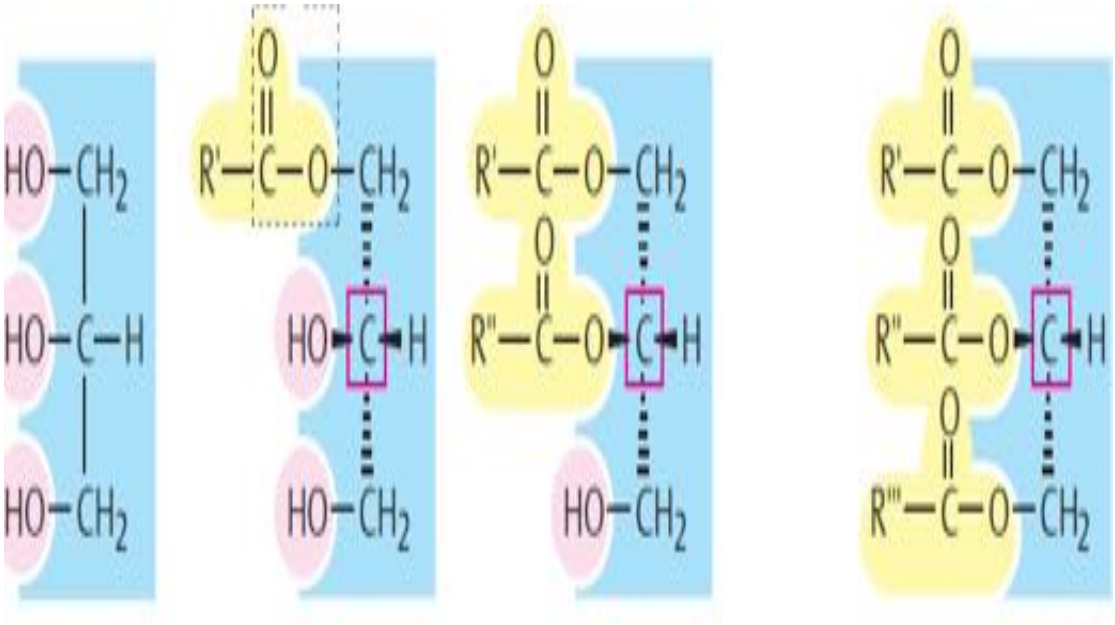
2) Exogenous: daily intake of the cholesterol usually less than 1g\day of which 40-70 % is absorbed.

Uses:

One of the main compound of the cell membrane. Precursor in the steroid hormones ,bile acids ,vitamin D synthesis .(The body can't break the steroid nucleus ,body can eliminate cholesterol either as unchanged or converted to bile acids).

Triglyceride





Normal serum TG concentration is<150 mg\dl .

Uses: energy store

Sources:

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1) Exogenous: main component of the diet ,daily intake is between 100-200 g, by the action of pancreatic Lipase will be hydrolyzed to monoglycerides and 2 fatty acid,these will be absorbed and the TG resynthesised in the mucosal cell and incorporated in structure called "Chylomicron"and release into intestinal lymph and reach systemic circulation through thoracic duct .

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2) Endogenous: the liver is the major site for synthesis from glycerol and fatty acid which incorporated into Lipoproteins and release into the circulation to utilized by peripheral tissue as energy source or stored in adipose tissue.TG that are carried by Lipoprotein and stored by adipose tissue can't be utilized without prior hydrolysis to glycerol and fatty acid.

LP – TG $\xrightarrow{\text{LPL}}$ Glycerol +3F.A.

Adipose tissue–TG $\xrightarrow{\text{Tissue Lipase}}$ Glycerol +3F.A.

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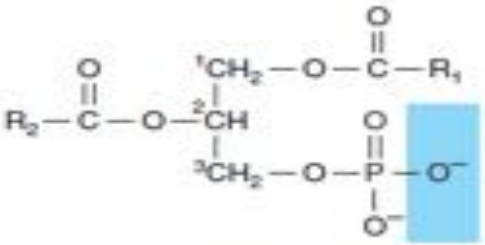
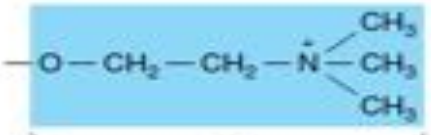
- Phospholipids

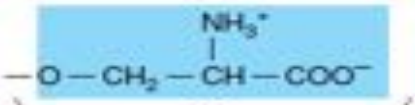


Phosphatidic acid

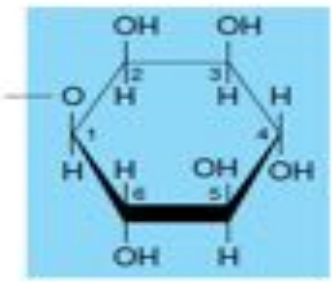


Choline

Ethanolamine



Serine



Myoinositol

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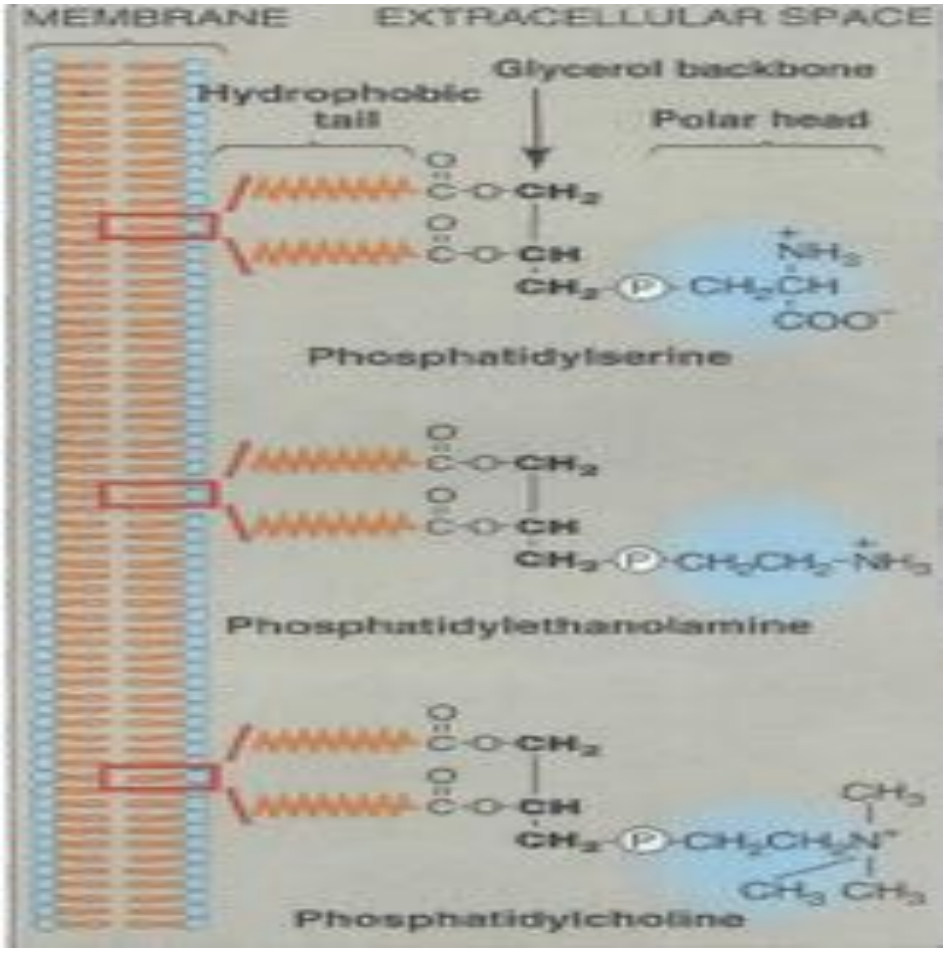

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Serum level: 120-390 mg/dl

mainly synthesized in the liver and small intestine ,it's amphipathic molecule (contain polar and non polar portion) and consequently ideally suited as main component of the cell membrane.

PL have specialized function e.g.

*Lecithin is the major component of lung surfactant.

* Also inositol PL in cell membrane act as a precursor of hormone second messenger

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-Free Fatty Acids

normal range 6-16 mg\dl .

Mainly derived from daily TG, but the body is able to synthesis most of the fatty acids except essential fatty acids(poly unsaturated F.A.).F.A. is an alteration energy source of glucose. Polyunsaturated F.As. is substrate for prostaglandin.

المحاضره الثانية

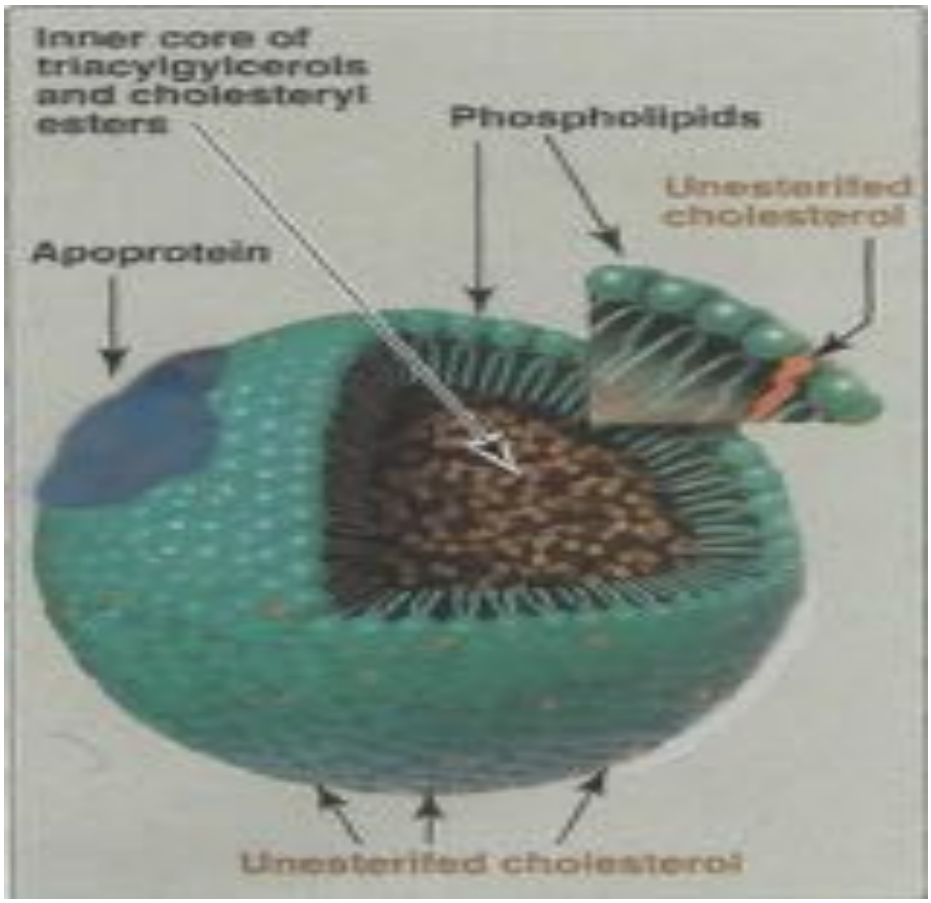
Objectives:

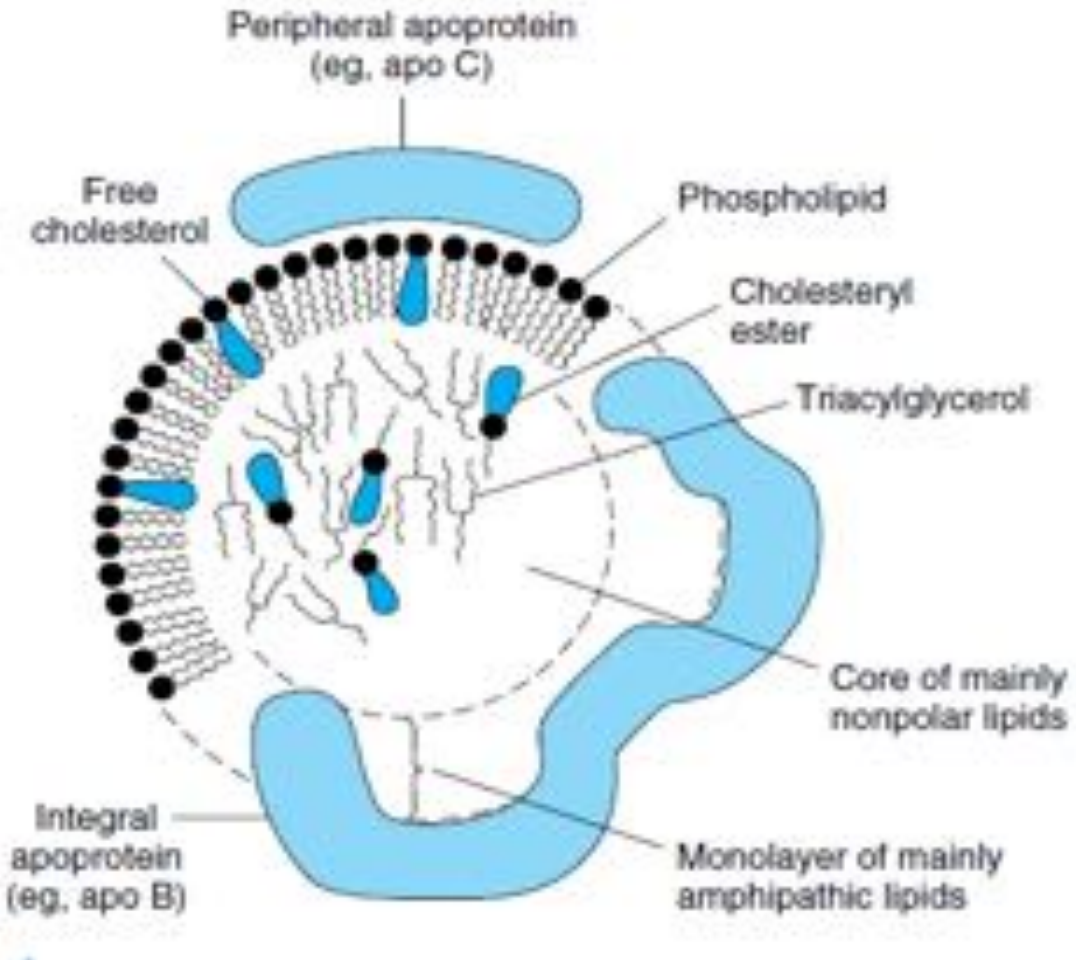
The students are learned to understand the lipoproteins Including: What are the lipoproteins; their structure, classification, composition, and functions

LIPOPROTEINS

The lipids are insoluble in water; therefore they cannot be homogenized with the plasma. This difficulty could be overcome when the neutral lipids are associated with polar phospholipids and proteins in structures known as the lipoproteins. The lipoproteins differ in their lipid and proteins composition, they also differ in the amount of lipids and proteins that present in each type of lipoproteins

The lipids and the proteins in the lipoproteins are held together by non-covalent bonds, and also the phospholipids and the proteins (which are the polar parts of the lipoproteins) are concentrated in the periphery of the molecule.





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Classification of the Lipoproteins:

Numerous types of lipoproteins are present in the plasma; however, we have two principle modes of classification:

- Electrophoresis: Depending on the charge of the lipoproteins.

- Ultra-centrifugation: Depending on the density of the

lipoproteins.

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1. Electrophoresis:

This type of classification depends on the electrical charge of the lipoproteins. As we know, the lipids are usually neutral, so this classification depends on the charge of the proteins and phosphate molecules in the lipoproteins.

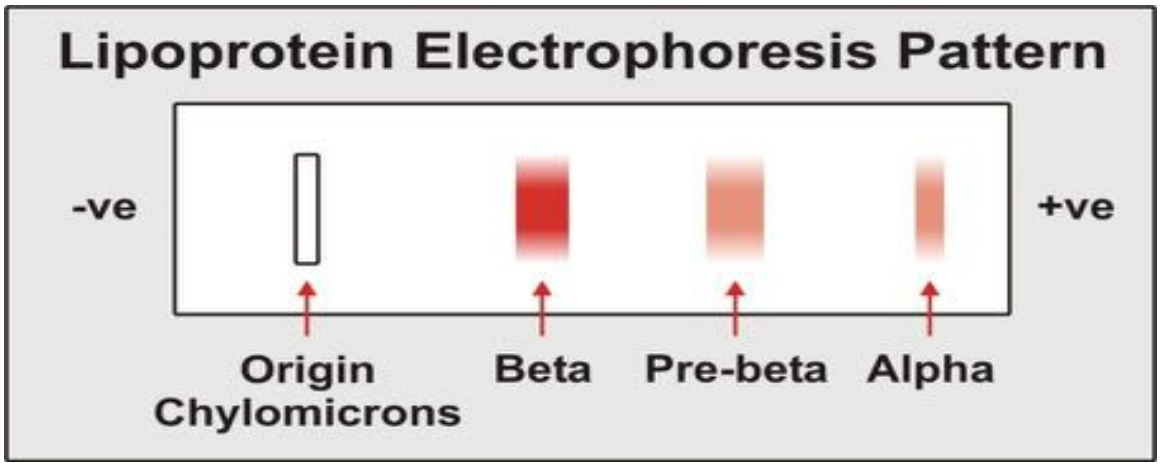
At pH 8.6 , the lipoproteins particles usually carry a negative charge, so they will move toward the positive side; So we get different band of LP according to their charge.

— 1. Chylomicrons.

— 2. Beta Lipoprotein (β LP).

— 3. Pre-beta Lipoprotein (pre-β LP).

— 4. Alpha Lipoprotein (α1 LP).



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2. Ultra-centrifugation:

This type of classification is also known as density fractionation . It depends on the density of the lipoproteins and these lipoproteins can be divided into four types depending on their density through ultra-centrifugation.

Lipids have low density, while proteins have high density; therefore, the more lipids (less proteins) in the lipoprotein means the lower density, while the more proteins (less lipids) means higher density. i.e.The density of lipoproteins is inversely proportional to the lipids contents, while it is directly proportional to the proteins contents in each type of lipoproteins.

Four (or may be five) types of lipoproteins could be seen in the centrifuge tube:

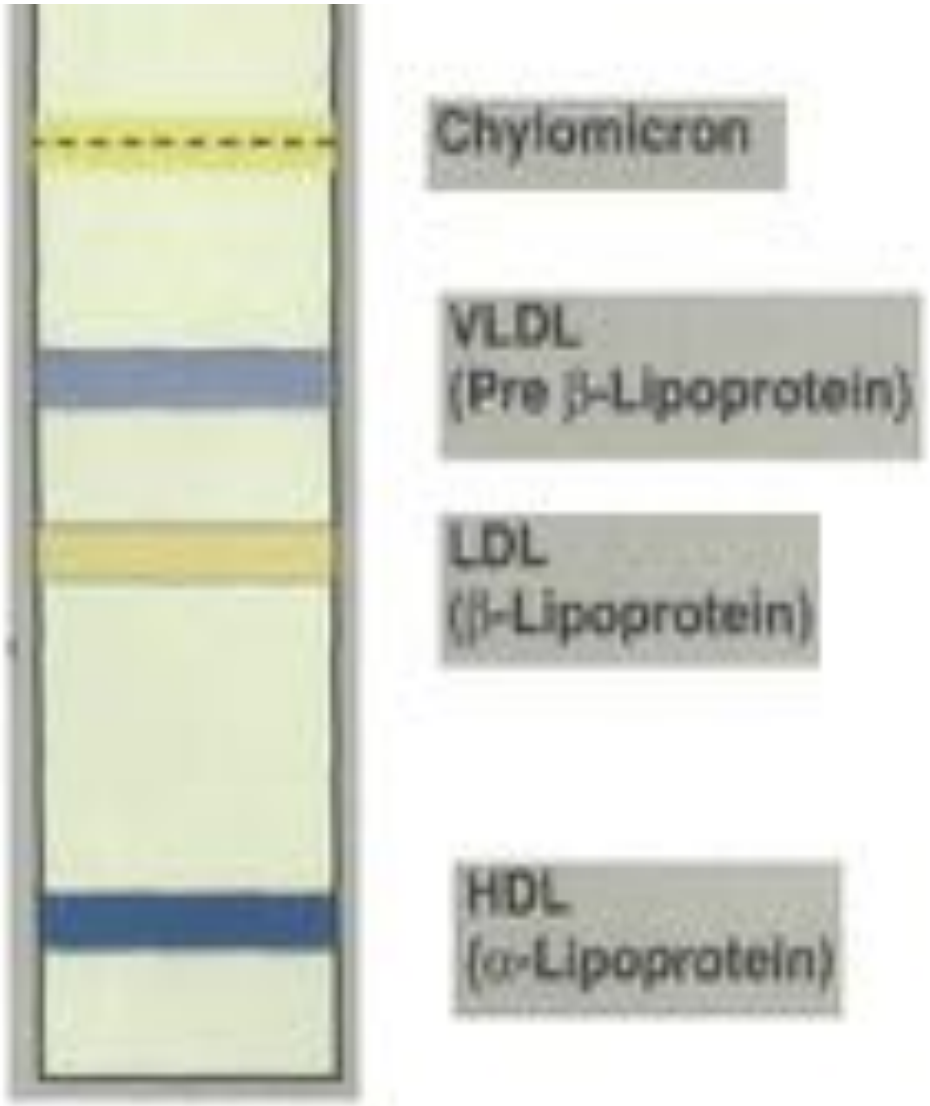
1. Chylomicrons.

2. Very Low Density Lipoprotein (VLDL or pre-β).

3. Low Density Lipoprotein (LDL or β).

4. High density Lipoprotein (HDL or α).

Note: Sometimes, a fifth type could be detected between the VLDL and LDL known as Intermediate Density Lipoprotein (IDL) .



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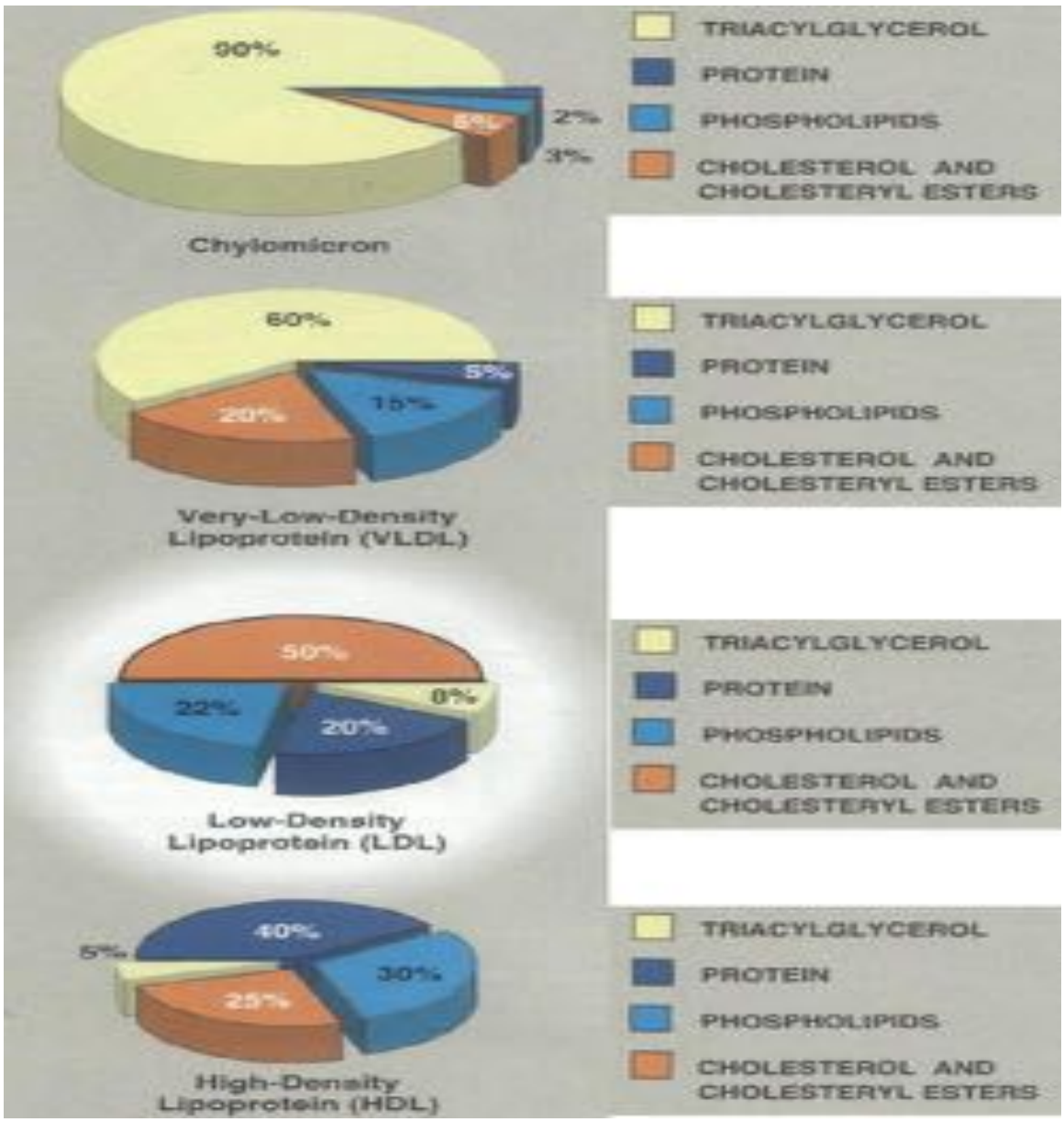
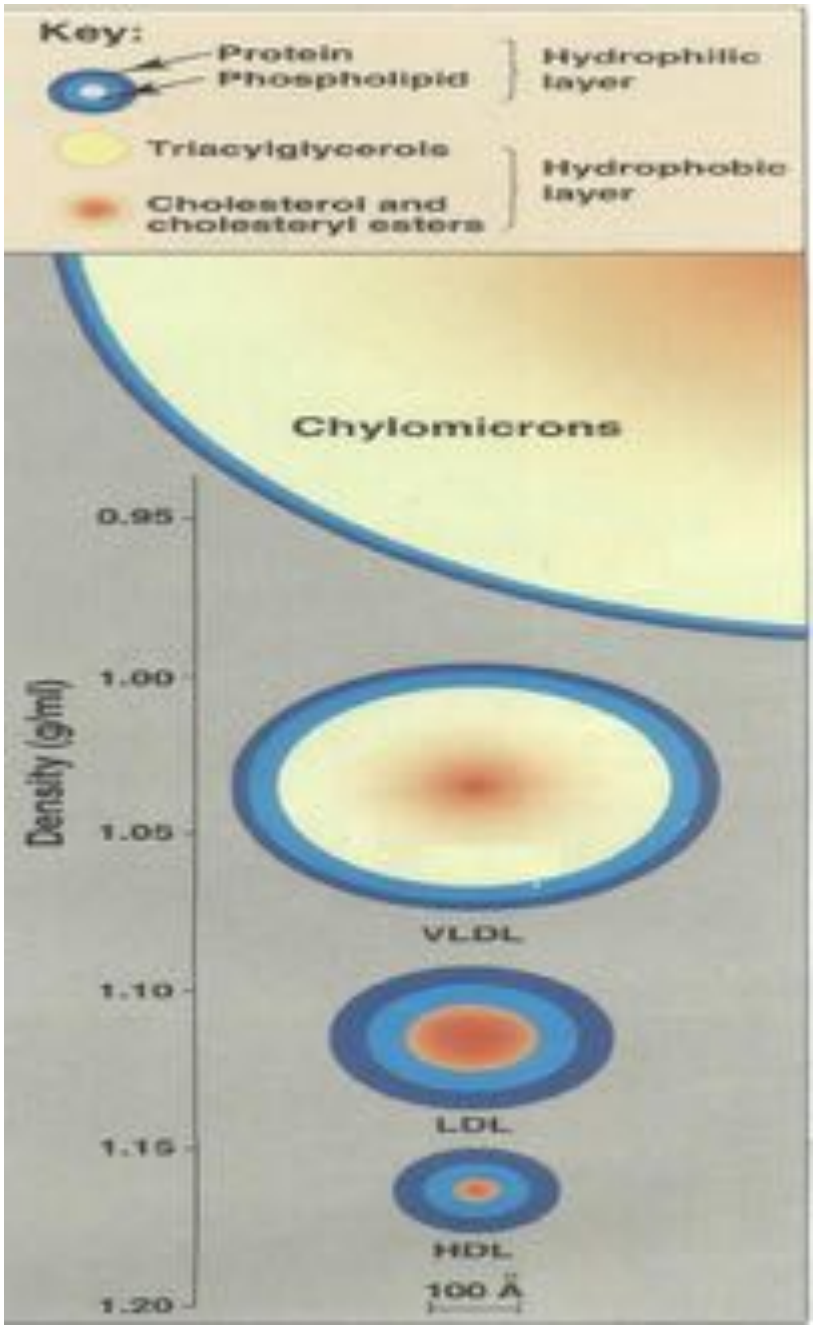
The Composition of the Lipoproteins





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The proteins in the lipoproteins are known as apo-proteins or apo-lipoproteins. There are several types and sub-types of these apo-proteins. Each type of lipoprotein contains different composition of apo-proteins.

-**Chylomicrons**: Consist of apo-proteins A, B, C, and E (apo-protein E is found in small amounts in chylomicrons).

-**VLDL**: Consist of apo-proteins B and C.

-I**DL**: Consist of apo-proteins B and E.

-LDL: Consist of apo-protein B and small amounts of apo- protein C.

-HDL: Consist of apo-protein A and small amounts of apo-proteins C, D, and E.

Lipoproteins Functions:

1. Chylomicrons : Their main function is carrying and transport of exogenous (dietary) triglyceride, but to a lesser extent cholesterol, fat soluble vitamins, and other lipids also transported by chylomicrons from the intestine to the systemic circulation.

2. VLDL : Their main function is the transport of endogenous triglyceride from the liver to the peripheral tissues.

3. LDL : Their main function is the transport of cholesterol to the peripheral tissue, but they also have a role in the transport of the phospholipids.

4. HDL :

a. Reservoir of apo-proteins (mainly C and E) which are required in the metabolism of VLDL and chylomicrons.

b. The uptake of the un-esterified cholesterol from the other lipoproteins and from the cell membranes.

c. Esterification of the un-esterified cholesterol by the action of LCAT enzyme (Lecithin-Cholesterol Acyl Transferase).

d. Reveres cholesterol transport (from the peripheral tissue to the liver).

المحاضره الثالثة ـــ

Objectives:

The students are learned to understand the following points

- **The functions of apo-protein**
- **Enzymes involved in lipids transport**
- **Metabolism of Lipoproteins**

The Functions of Apo-proteins

1. Physical Function: promote the solubility of lipoproteins

particles in the plasma.

2. Regulatory Function: Lipoproteins have a role in the control

of the lipid metabolism by :

A) Providing a recognition site for the cell surface receptors.

Ex1: Apo-B (which is the major apoprotein of LDL) plays an important role in the uptake of cholesterol from LDL as most tissues posses cell surface receptors that recognize Apo-B

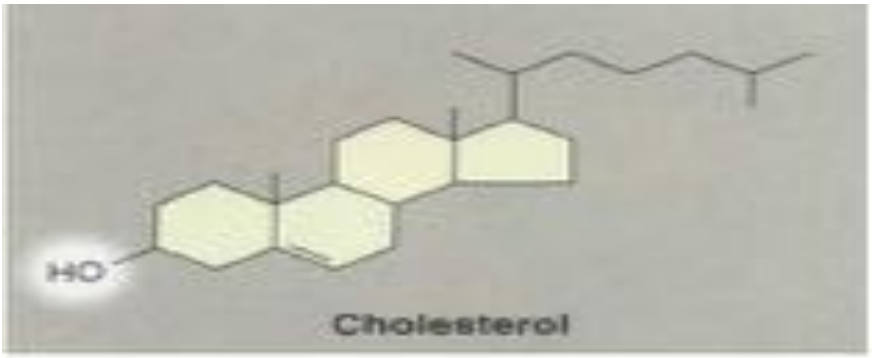
Ex2: Apo-E is probably involved in the hepatic uptake of the chylomicrons remnants .

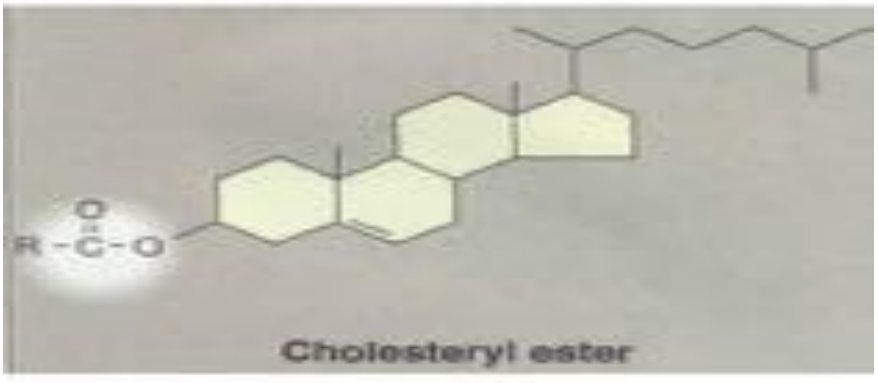
B)) Activation of enzymes involved in lipoproteins metabolism. (Ex1: Apo-AI is an important activator of LCAT) (Ex2: Apo-CII is an activator of LPL).

Enzymes Involved in Lipid Transport

1. LCAT (Lecithin-Cholesterol Acyl Transferase) :

This enzyme is synthesized in the liver and it binds to nascent HDL. It is stimulated by Apo-AI. The reaction which is catalyzed by this enzyme produces cholesterol ester which is more hydrophobic and it is sequestered in the core of HDL .





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2. LPL (Lipoprotein Lipase) :

It is an extracellular enzyme anchored by heparan-sulphate to the capillary endothelium of most tissues, but predominantly in adipose tissue, cardiac, and skeletal muscles.LPL is stimulated by Apo-CII on circulating LP particles and catalyzes the hydrolysis of triglycerides in the in chylomicrons and VLDL into glycerol and three molecules of fatty acids.

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3. Hepatic Lipase :

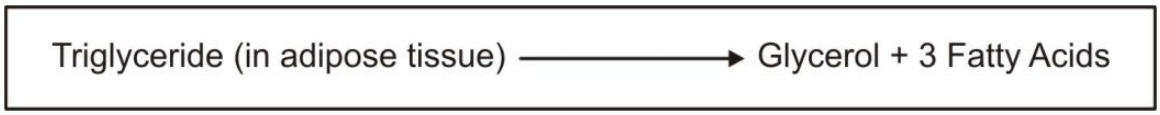
The action of this enzyme is similar to that of the LPL, but it seems to be more effective on the triglycerides that present in smaller particles (such as TG in VLDL remnants).

4. Tissue Lipase

(Hormone Sensitive Lipase or Mobilizing Lipase)

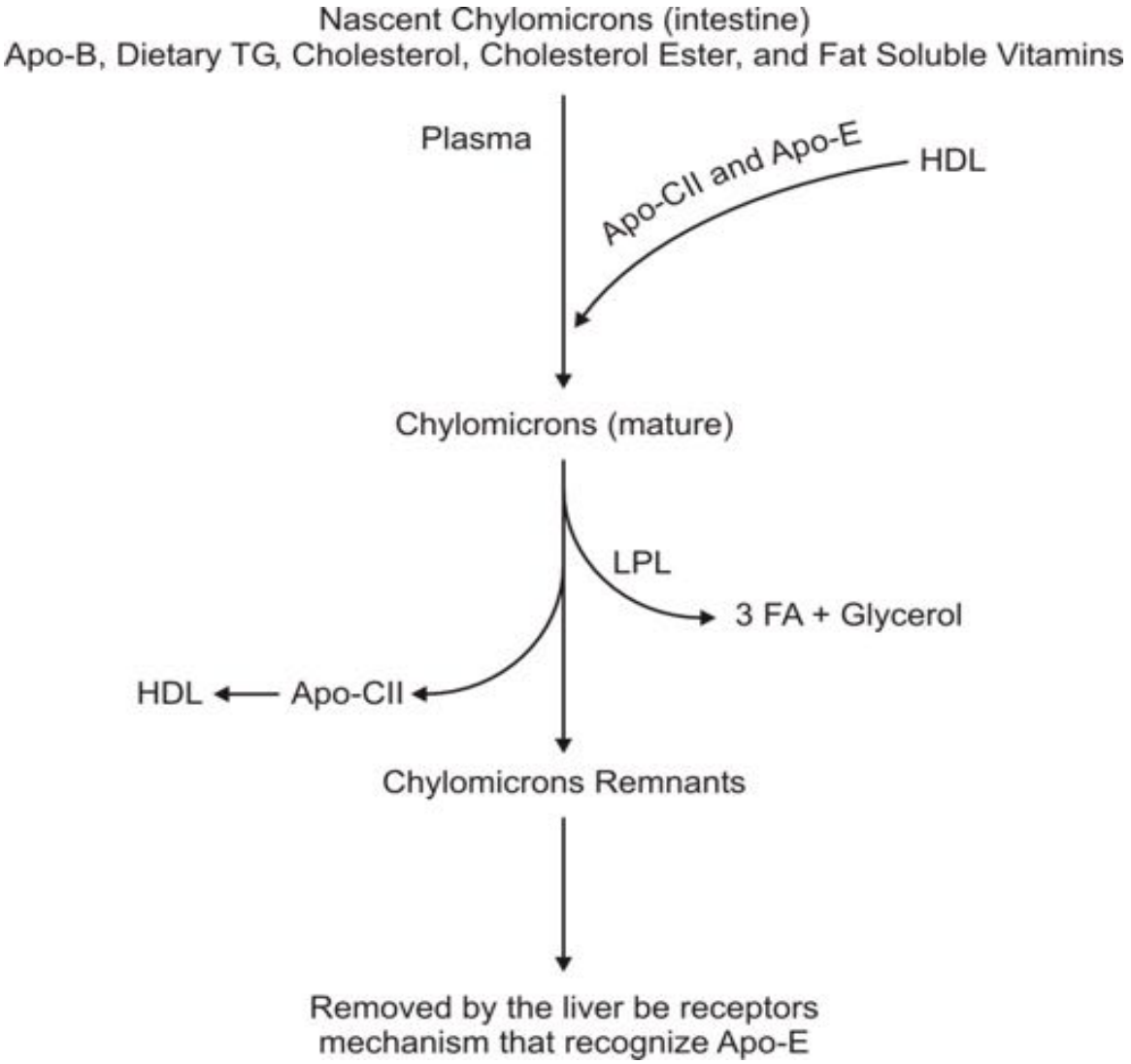
It is present in the adipose tissue. This enzyme is inhibited by insulin , while it is stimulated by many hormones (like epinephrine, nor-epinephrine, ACTH..... etc) . It acts on the triglycerides present in the adipose tissue. It control the rate of release of fatty acids from the adipose tissue to the plasma.

It is activated by phosphorylation mediated by cAMP dependent protein kinase and deactivated by dephosphorylation.

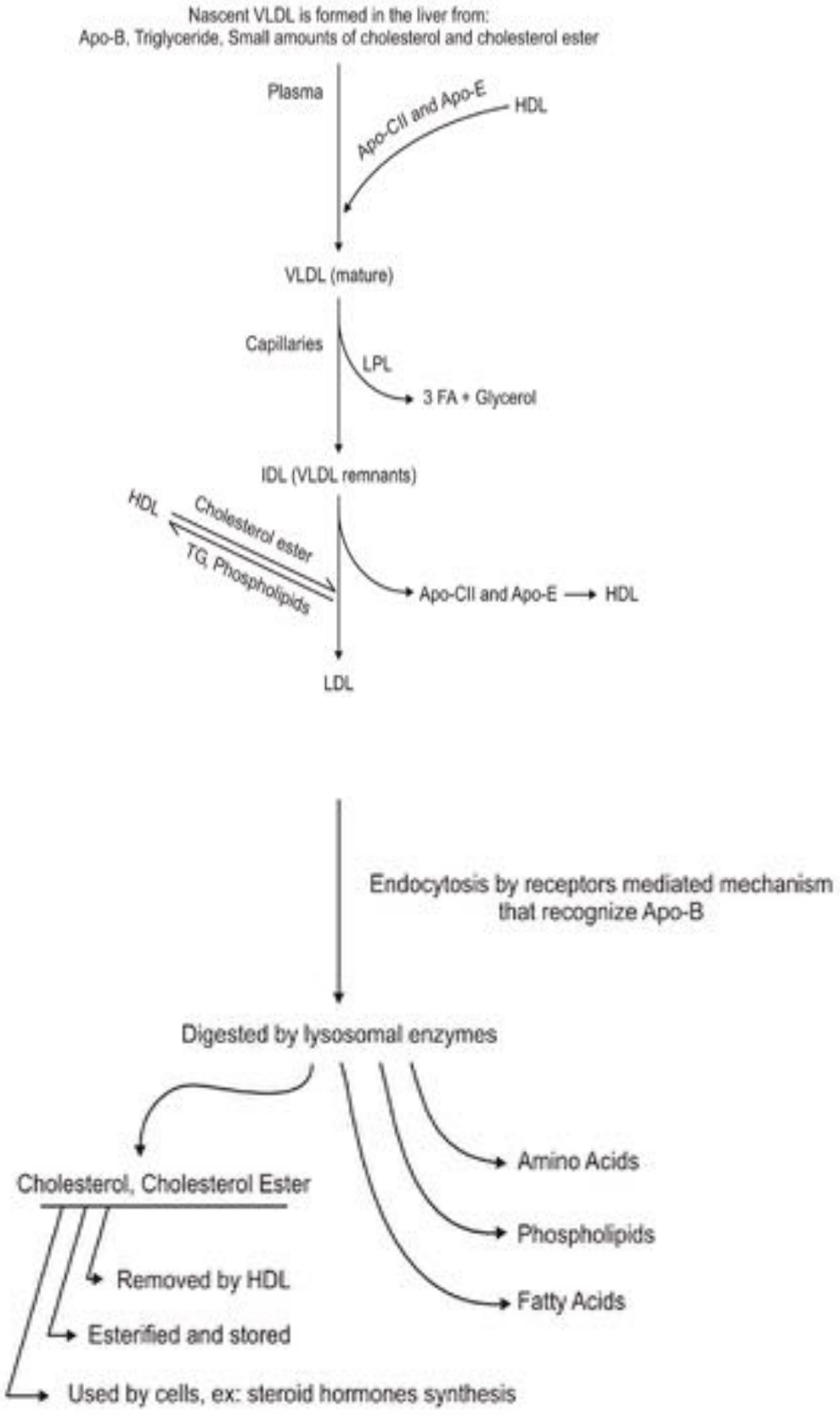


Metabolism of Lipoproteins

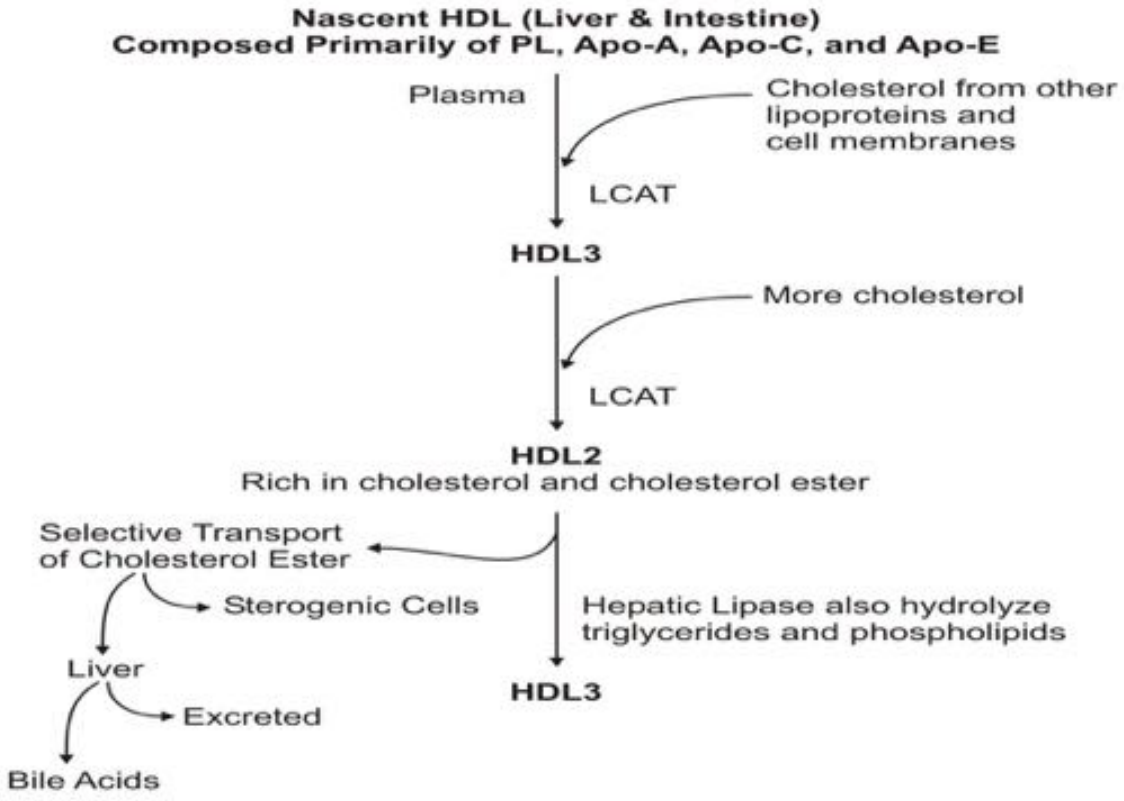
Chylomicrons


Nascent Chylomicrons (intestine)
Apo-B, Dietary TG, Cholesterol, Cholesterol Ester, and Fat Soluble Vitamins
Plasma
Apo-CII and Apo-E
HDL
Chylomicrons (mature)
LPL
3 FA + Glycerol
HDL
Apo-CII
Chylomicrons Remnants
Removed by the liver be receptors
mechanism that recognize Apo-E

VLDL and LDL Metabolism



The Metabolism of HDL



HDL3 will either be removed by the liver or re-converted again into HDL2 by obtaining more cholesterol and so on.

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المحاضره الرابعة

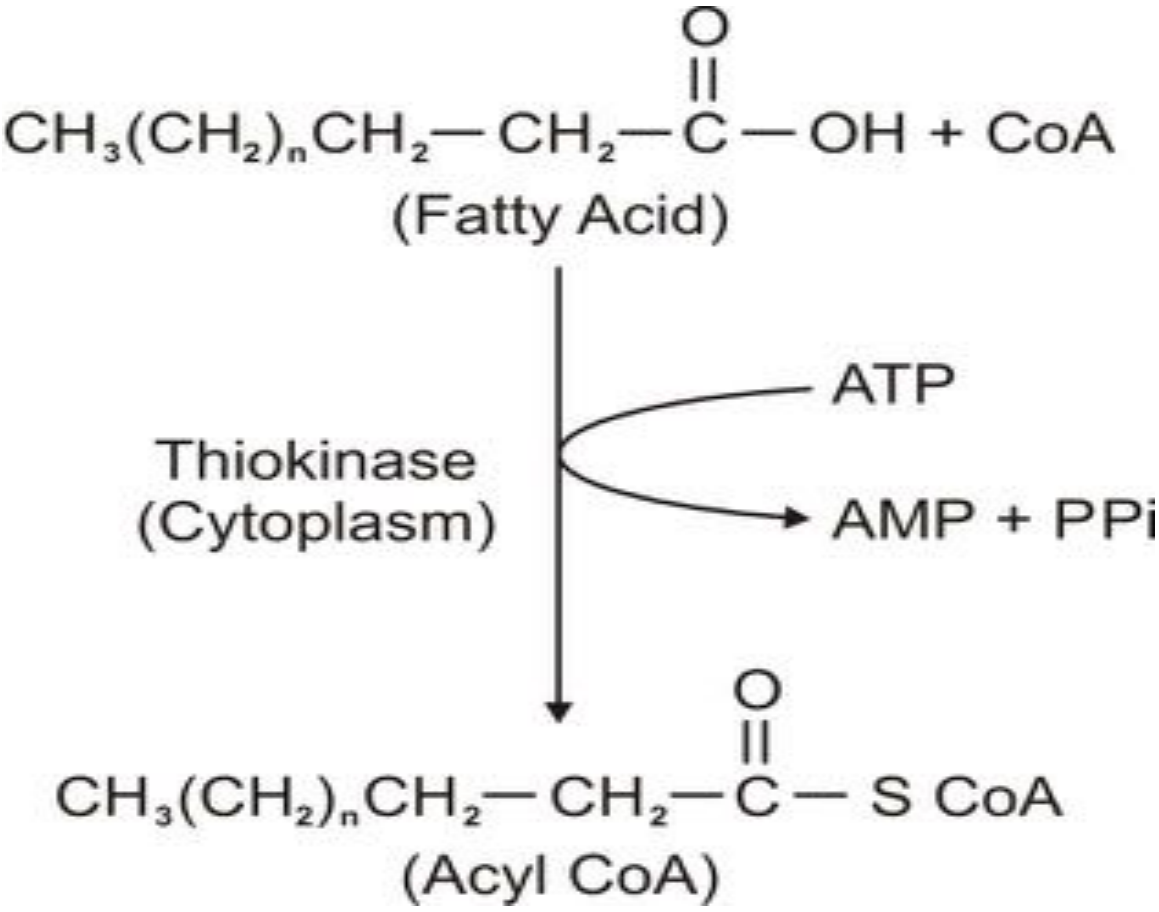
Objectives:

The students are learned to understand the OXIDATION OF THE FATTY ACIDS including the following points:

- **Beta oxidation pathway**
- **Carnitine shuttle**
- **Oxidation of the Fatty Acids with Odd Number of C atoms**
- **Oxidation of the unsaturated Fatty Acids**

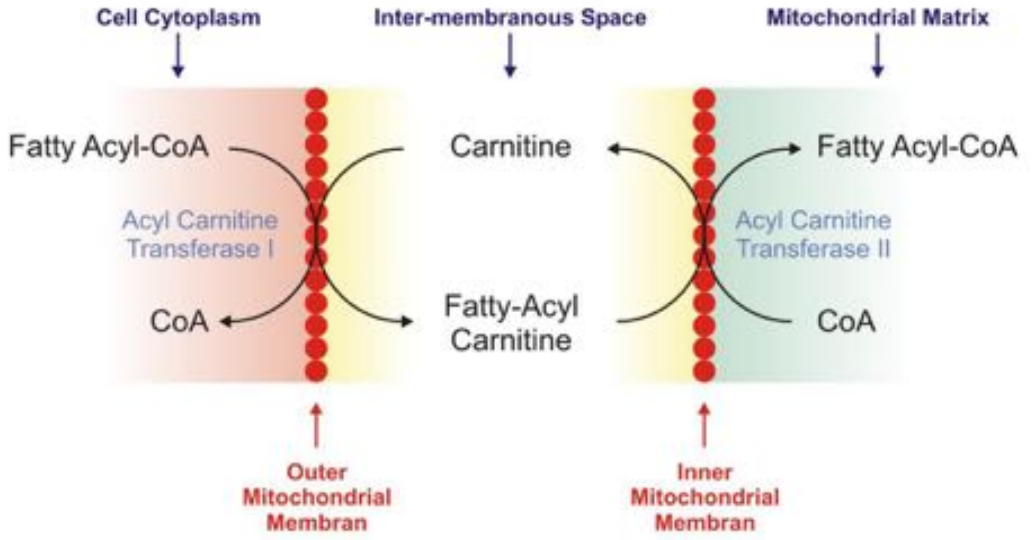
OXIDATION OF THE FATTY ACIDS

The entry of long chain fatty acids to the cell is mediated by fatty acid binding proteins. The fatty acids must be converted into active intermediates by a reaction with ATP before they can undergo any further metabolism.



This is the only step in the fatty acid oxidation that requires ATP and it is irreversible step because the PPi is hydrolyzed by the pyrophosphatase enzyme to yield two inorganic phosphates.

The subsequent steps in the oxidation of the fatty acids occur in the mitochondrial matrix. Since the mitochondrial membrane is impermeable to acyl-CoA, therefore a special mechanism is required for the transport of acyl-CoA from the cytoplasm to the mitochondrial matrix. This mechanism involves a compound called **Carnitine,** and the process is known as **carnitine shuttle.**



Medium chain fatty acids (shorter than 12 carbon atoms) can cross the mitochondrial membrane without the aid of carnitine, and even its entry to the cell does not require fatty acid binding proteins .

Carnitine could be obtained either from the diet (meat and meat products) or by being synthesized inside the body (from amino acids lysine and methionine) through an enzymatic system found in the liver and the kidneys.

The deficiency of carnitine occurs due to many reasons :

-Could be congenital

-Could occur in newborn babies (especially pre-mature) and this is due to immaturity of the enzymatic system which will lead to inadequate synthesis of carnitine.

-Malnutrition and those on strictly vegetarian diet

-Liver disease (because it is a main site for the synthesis).

-Increased requirement to carnitine

*Pregnancy.

*Severe Infection.

*Severe Burns.

*Trauma.

*Hemodialysis.

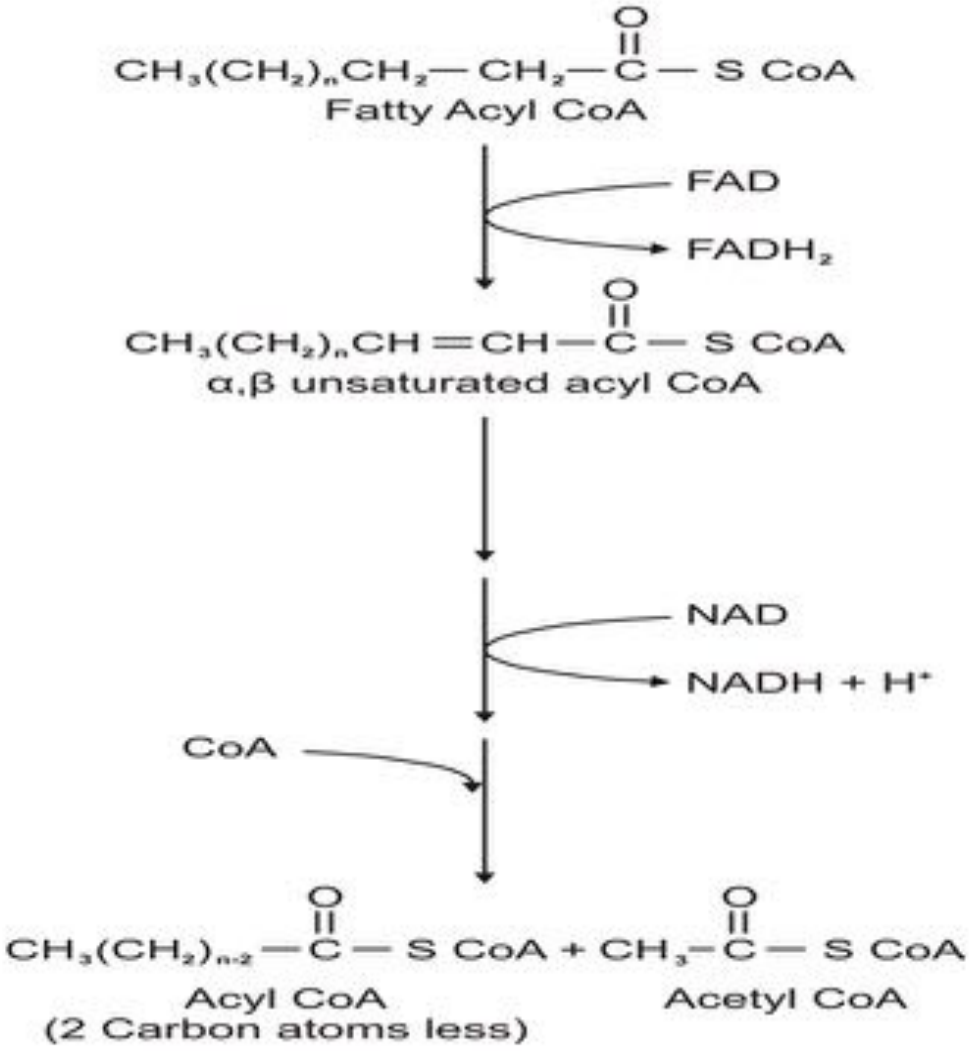
The effect of carnitine deficiency is decrease in the ability of oxidizing long chain fatty acids and this may lead to weight loss, fatty liver, and hypoglycemia.

Why ?
deficiency in Carnitine may lead to hypoglycemia?

Beta oxidation pathway

The oxidation of the fatty acid will take place on the β carbon atom, so in each oxidation for (n carbon atoms) fatty acyl CoA the product is acetyl CoA (two carbon atoms) and (n-2) fatty acyl CoA, and it will also produce one FADH2 and one NADH.

The new fatty acyl CoA will undergo the same reaction again and again until all the carbon atoms are converted into acetyl-CoA.



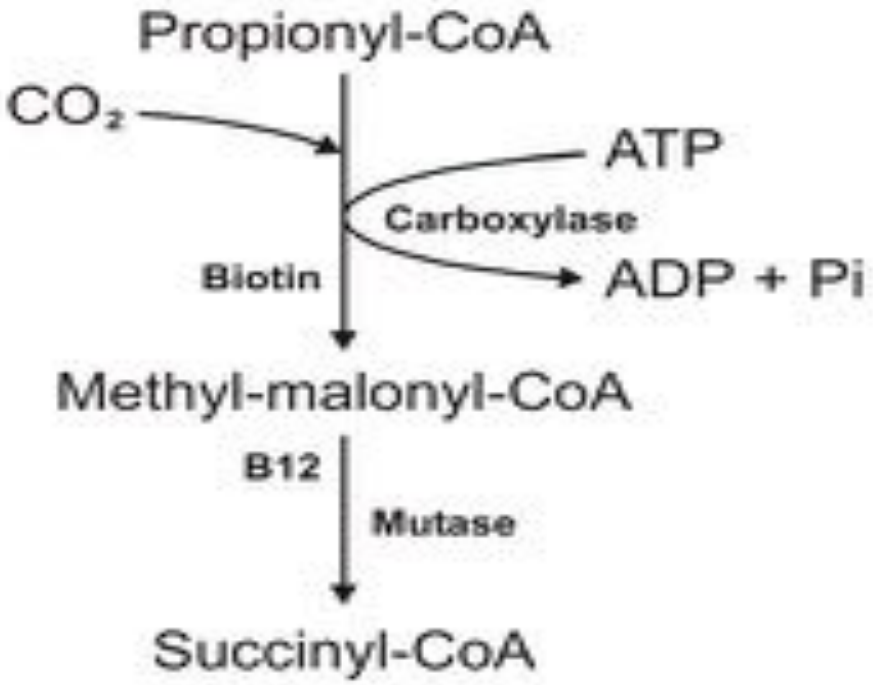
The FADH2 and NADH formed from oxidation of the fatty acid that has even number of carbon atoms equal :

(The number of Carbon atoms / 2) – 1

ex. Palmatic acid(16C)→ 8 acetyl CoA+ 7 FADH2+ 7NADH

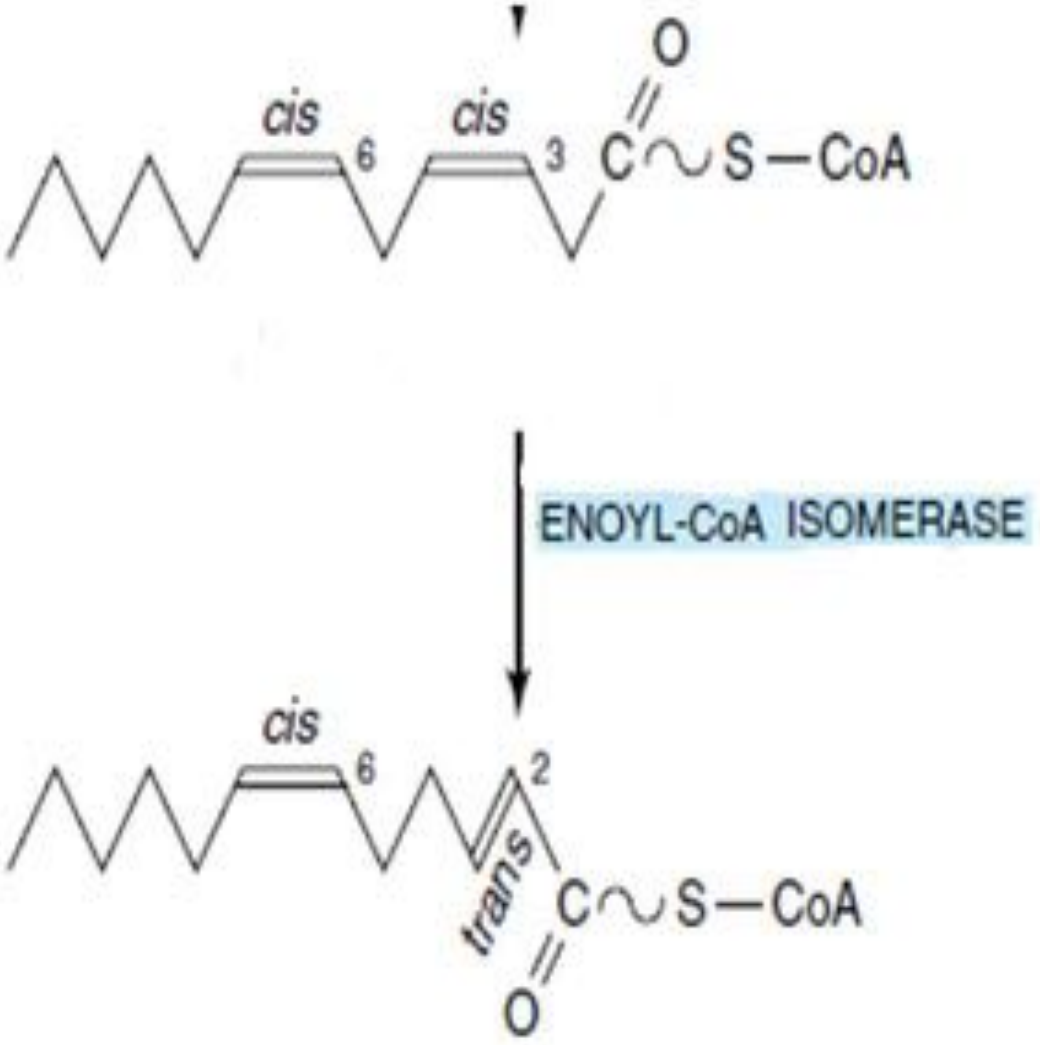
Oxidation of the Fatty Acids with Odd Number of C atoms:

The β oxidation of the fatty acid chains that have odd number of carbon atoms will use the same reaction steps until the final three carbon acids are reached and they are called here propionyl-CoA. The propionyl-CoA will be converted into methyl-malonyl-CoA by a step that requires the use of one ATP. Then the methyl-malonyl-CoA will be converted into the final product which is the succinyl-CoA.



OXIDATION OF UNSATURATED FATTY ACIDS:

Undergo the same sequence of reaction as saturated fatty acid until we reach to the double bond between carbon 3 & 4.Usually the configuration around the double bond is cis.In the saturated fatty acid we make a double bond between C2 & C3 but in the unsaturated fatty acid the last double bond is found between C3 & C4 so we will transfer the double bond to put it between the C2 & C3 by the enzyme **Enoyl CoA isomerase**. This enzyme transfer the double bond and change the configuration from cis to trans.



After the transforming of the double bond to C2-C3 position now the fatty acid will undergo the same reaction of β oxidation but it will not pass in the first step that yield the FADH2.{so the oxidation of unsaturated fatty acid with 16 carbon atom will give only 6 FADH2 and not 7 FADH2). So removal of acetyl CoA in this step will produce only 3ATP not 5ATP.

PROBLEMS

Q.1. saturated fatty acid contain 16 carbon atom {palmatic acid} how many the ATP produced after the oxidation of it ?

Answer: by β oxidation pathway it will give:

7 FADH2 and each FADH2 will give 2 ATP (so 7*2=14 ATP).

7 NADH2 and each NADH2 will give 3ATP (so 7*3=21 ATP).

8 acetyl CoA and each one will enter the citric acid cycle and give 12 ATP (so 8*12=96 ATP).

14+21+96= 131 ATP.

But we need 2ATP IN THIOKINASE REACTION thus the no. Of ATP 131-2= 129 ATP produced from palmatic acid

Q.2. unsaturated fatty acid contain 16 carbon atom how many the ATP produced after the oxidation of it?
Answer: by β oxidation

6 FADH2 (so 6*2= 12 ATP).

7 NADH2 (so 7*3=21 ATP).

8 Acetyl CoA (so 8*12=96 ATP).

12+21+96=129 ATP.

129-2= 127 ATP.

Q.3. saturated fatty acid contain 17 carbon atom how many the ATP produced after the oxidation of it?

7 FADH2 (7x2=14 ATP).

7 NADH2 (7x3= 21 ATP).

7 Acetyl CoA (7x12= 84 ATP).

14+21+84= 119 ATP.

119-2 = 117 ATP.

6 ATP from succinyl-CoA

117+ 5= 122 ATP

Q.4. unsaturated fatty acid contain 17 carbon atom how many ATP produced after its oxidation ?

6 FADH2 (6x2=12 ATP).

7 NADH2 (7x3=21 ATP).

7 Acetyl CoA (7x12=84 ATP).

12+21+84= 117 ATP.

117-2= 115 ATP.

5 ATP from succinyl-CoA

115+ 5= 120 ATP

—

المحاضره الخامسة —

Objectives:

The students are learned to understand the SYNTHESIS OF THE FATTY ACIDS including the following points:

-Transportation of acetyl CoA.

-Formation of malonyl CoA.

-Fatty acid synthase multienzyme complex

- Elongation and Desaturation of the fatty acids chain

- NADPH Sources

—

SYNTHESIS OF FATTY ACIDS

— Should be considered in three phases :

1-Transportation of acetyl CoA.

2-Formation of malonyl CoA.

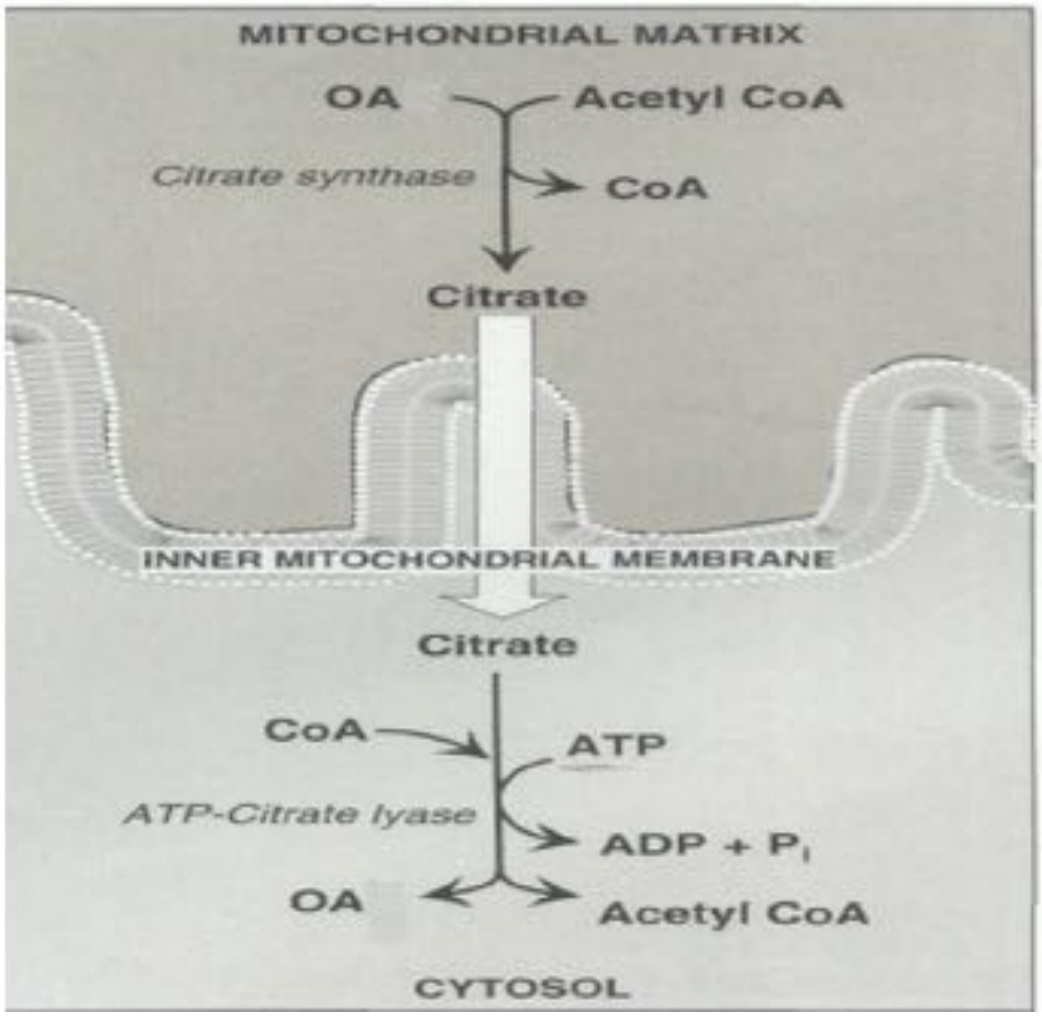
3-Fatty acid synthase multienzyme complex

Transportation of acetyl CoA

In mammal fatty acid synthesis occur primarily in the liver & lactating mammary glands & to lesser extent in adipose tissue.

The primary metabolic substrate for synthesis of fatty acid is Acetyl CoA which is generated from the catabolism of carbohydrate, aminoacids &fatty acids. Acetyl CoA from catabolic reaction is generated mainly in the mitochondria. Whereas the fatty acid synthesis occur in the cytoplasm therefore we need a special transport mechanism for transportation of acetyl CoA from the mitochondria to the cytoplasm because the CoA portion of acetyl CoA can not cross the mitochondrial membrane.

The acetyl CoA will react with oxaloacetate (OA) to form the citrate by the enzyme citrate synthetase. The citrate then will pass the mitochondrial membrane to the cytoplasm where it react with CoA to form acetyl CoA & this step need 1 ATP.



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Formation of malonyl CoA

It is the rate limiting step catalyzed by the allosteric enzyme acetyl CoA Carboxylase which is allosterically stimulated by citrate and inhibited by long chain fatty acyl CoA.

(intake of glucose lead to the formation of fatty acid: explain why ???).

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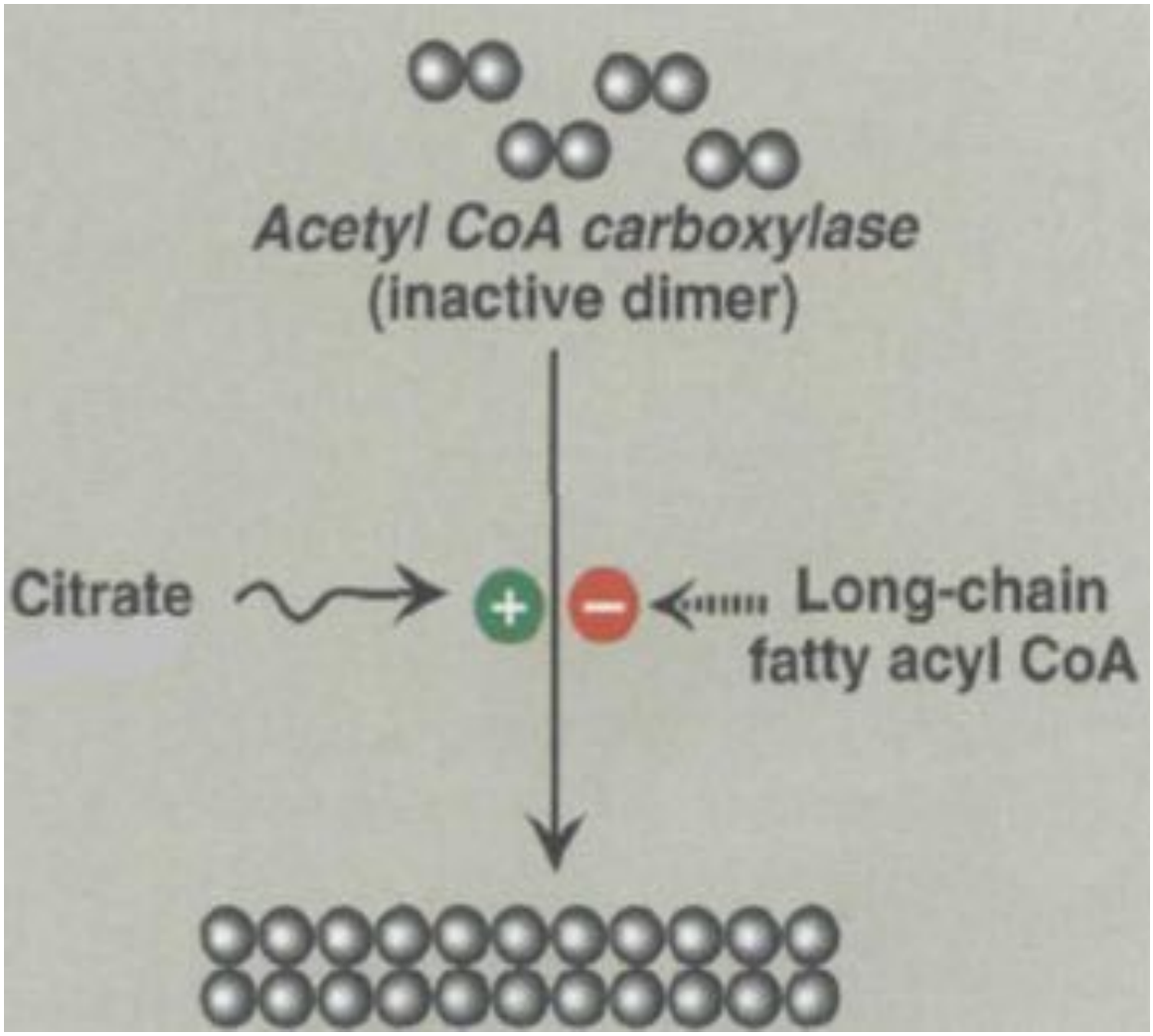
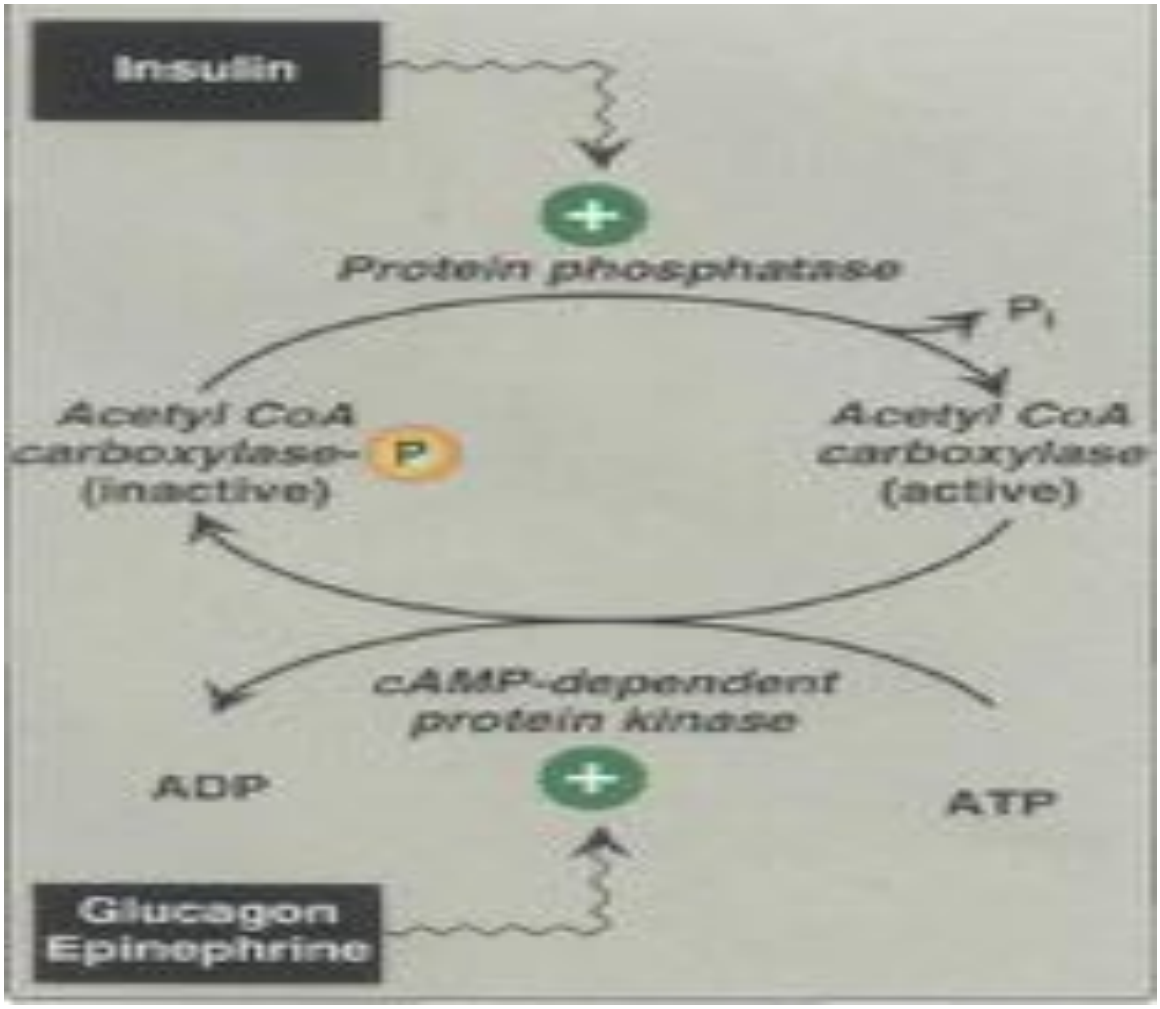
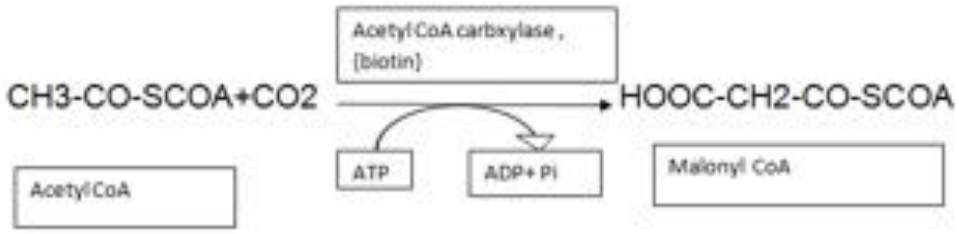


this enzyme also activated by dephosphorylation i.e. adrenalin will reduce the formation of fatty acid , while the insulin will increase the formation of fatty acid .





Fatty acid synthase multienzyme complex

This enzyme consist of two identical polypeptide chain but each chain contain seven enzymes. In contrast to fatty acid oxidation, in F.As synthesis the intermediate is in the form of ACP derivative. This enzymatic system can synthesize fatty acid up to 16 carbon atom.

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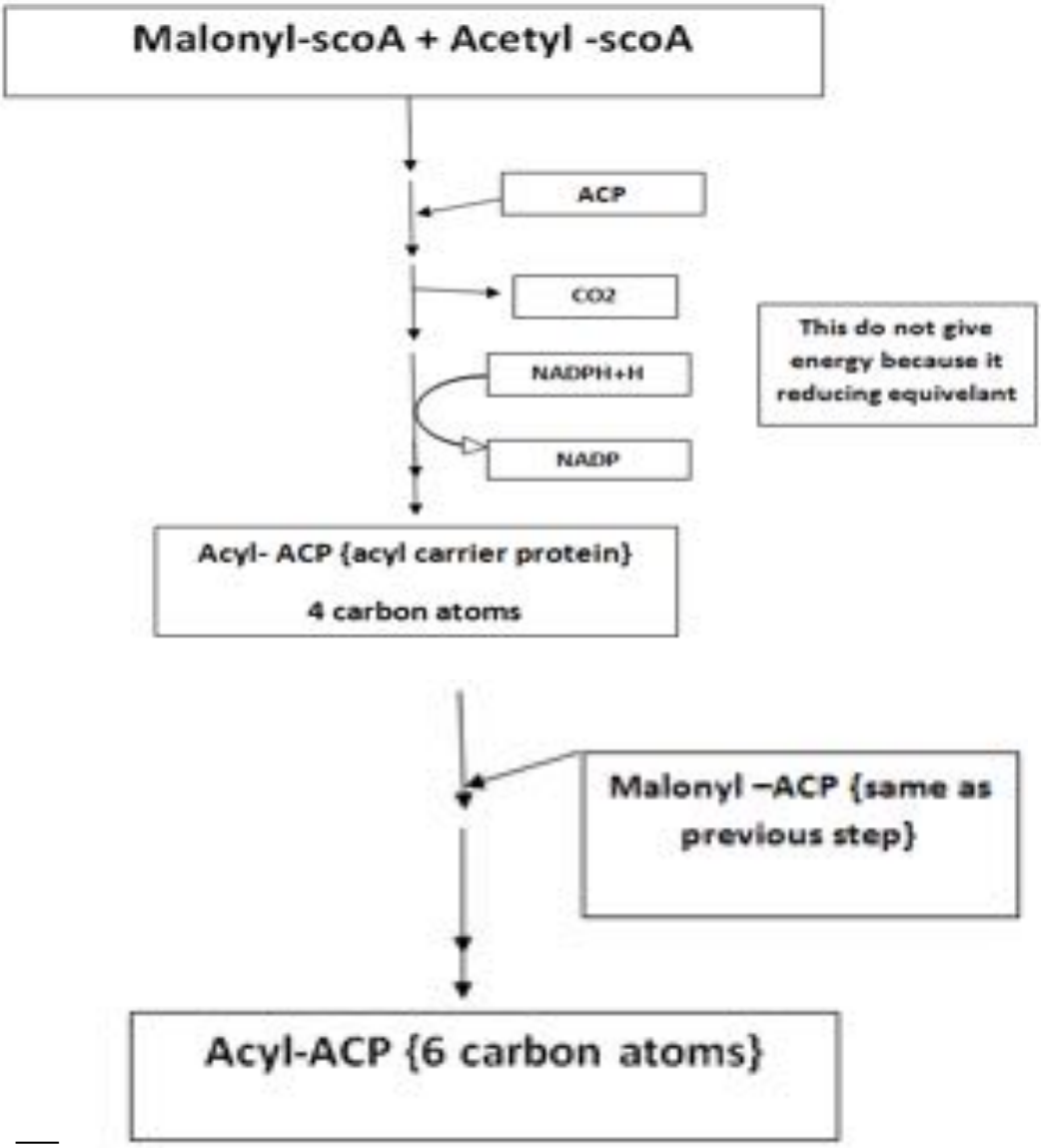
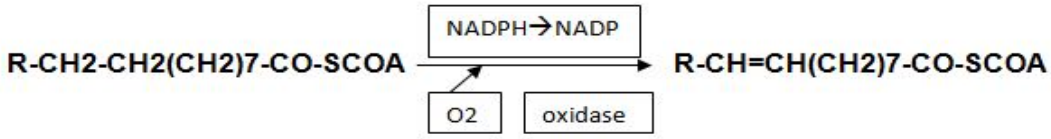


Elongation of the chain

Palmatic acid will be converted it to palmitoyl – SCoA by thiokinase reaction. After that the Chain elongation take place in the endoplasmic reticulum by addition of 2 carbon units as acetyl-CoA to produce stearoyl-SCoA and the intermediate are in the form of CoA derivative.

DESATURATION OF THE CHAIN

Animals can synthesis fatty acid contain only one unsaturated bond between C9 &C10 .Desaturation of the chain : the cell of the liver and the adipose tissue contain the necessary enzyme for conversion of palmitoyl –SCoA and stearoyl – SCoA to the respected unsaturated palmitoleyl –SCoA and oleyl-SCoA (these enzymes called mix function oxidases).



` This reaction occur in the E.R and cytoplasm ,in mammals this enzyme system can only desaturate the fatty acid with double bond between C9-C10 ,therefore, mammals are unable to synthesize polyunsaturated (essential F.A).

NADPH sources

— 1- HMS is the major source

— 2- Malic enzyme(see page 184)

المحاضره السادسة ـــ

Objectives:

The students are learned to understand the Ketone Bodies Metabolism

including the following points:

- **Definition**
- **Ketogenesis**
- **Utilization**
- **Mechanism of Ketosis**

KETONE DODIES METABOLISM

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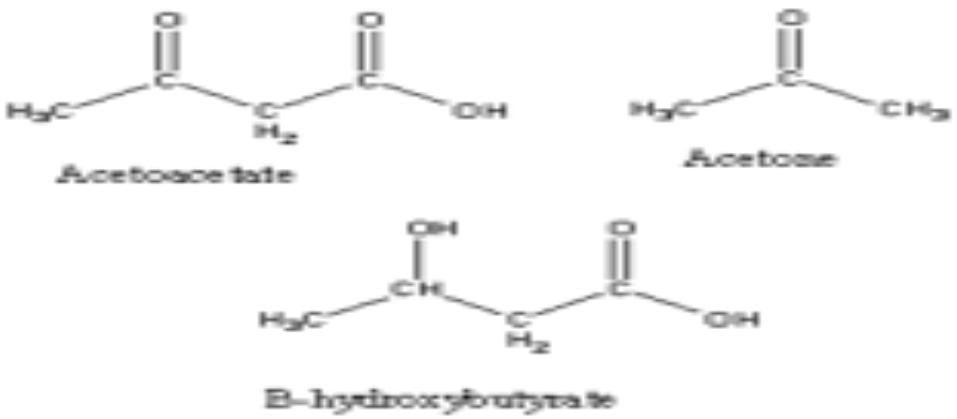

Under certain metabolic conditions associated with high rate of fatty acid oxidation ,the liver produce a considerable quantities of acetoacetate and β-hydroxy butyrate which pass by diffusion from the liver to the blood. Acetoacetate undergo spontaneous decarboxylation to acetone. These three compounds [acetoacetate (acetoacetic acid)+ β hydroxy butyrate+ acetone] are collectively called ketone bodies.

When the liver is flooded with fatty acids mobilize from adipose tissue (ex: in uncontrolled diabetes) the resulting elevated acetyl CoA stimulate pyruvate carboxylase (increase in gluconeogenesis) so oxaloacetate will be directed to gluconeogenesis rather than citric acid cycle, therefore; acetyl CoA cannot be utilized efficiently by citric acid cycle so it directed to ketone bodies formation.

—

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KETOGENISIS

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the formation of the ketone bodies is happen in the liver mitochondria.The starting material is acetoacetyl CoA which come from two sources:

1-During the course of β oxidation pathway (the last four carbon atoms)

2-By condensation of two molecules of acetyl CoA.

In the liver mitochondria the following reaction will occur:

The **acetoacetyl CoA** will react with **acetyl CoA** lead to the formation of HMG CoA {beta – or three- hydroxy methyl glutaryl CoA}.This reaction catalyzed by the enzyme HMG CoA synthase.This is the rate limiting step in the formation of the ketone bodies.

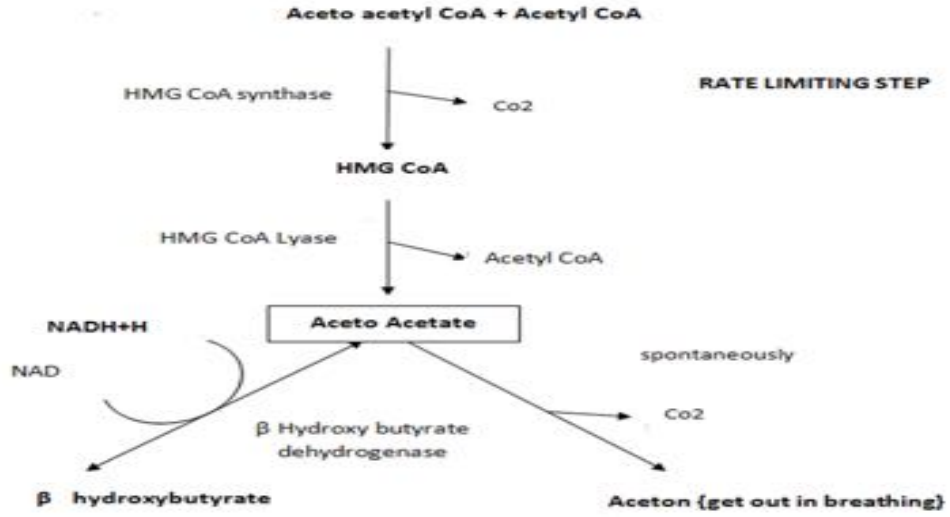
By the action of the second enzyme **HMG CoA Lyase** the HMG CoA will be converted to Acetoacetate (the first ketone body).

Acetoacetate can be reduced to **β hydroxy butyrate** (the second ketone body) by the action of enzyme β hydroxy butyrate dehydrogenase and in reversible reaction. or the acetoacetate can be spontaneously decarboxylated in the blood to Acetone (the third ketone body) which is volatile and nonmetabolized compound and exhaled in the breathing .

β hydroxy butyrate is quantitatively the predominant ketone bodies found in the blood and urine of uncontrolled diabetes (diabetes with ketosis).

Q. Why the β hydroxy butyrate is quantitatively the predominant ketone bodies found in the blood and urine ?

— Because the formation of the ketone bodies is the result of increase the rate of β oxidtion that result in increase the production of NADH (more than the NAD) this NADH catalyze the conversion of acetoacetae to β hydroxy butyrate.



UTILIZATION OF KETON BODIES

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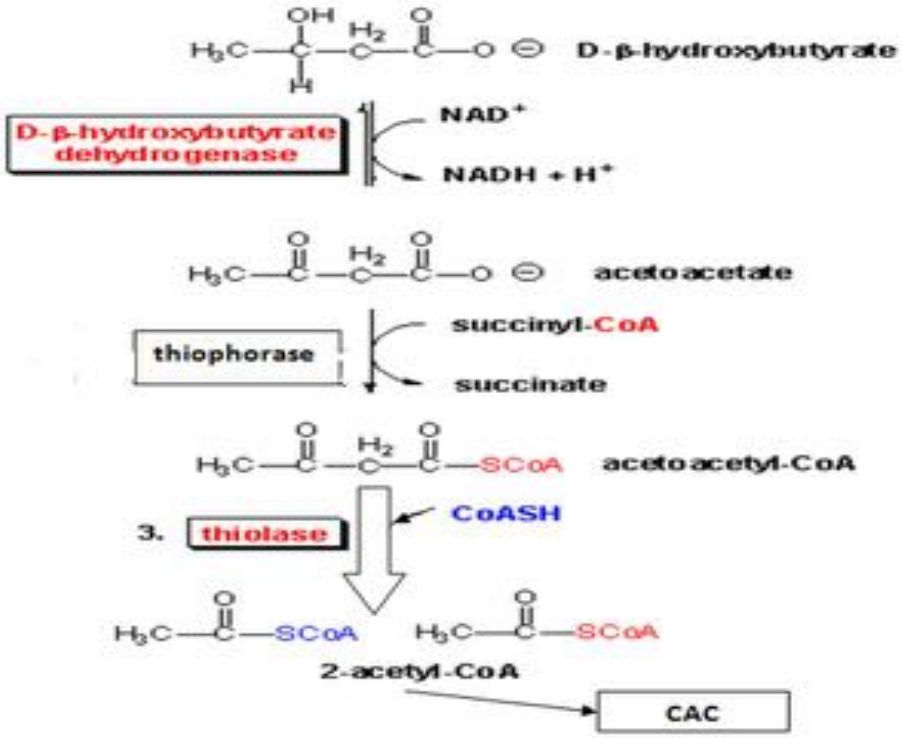

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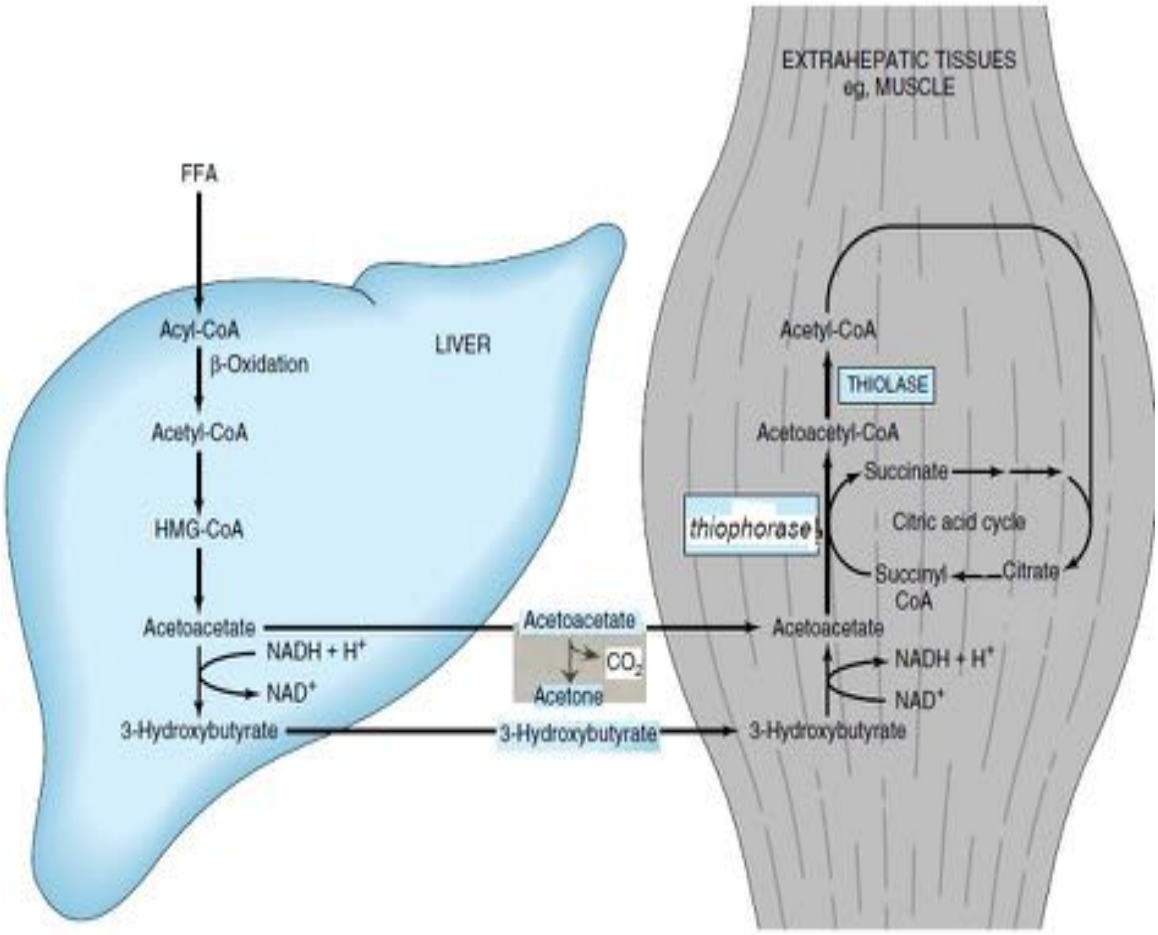


— the liver is equipped with an active enzymatic mechanism for the production of ketone bodies but it cannot be metabolized further these ketone bodies ,however these ketone bodies can be used as energy source by skeletal muscles, heart muscles and to limited extent by brain.(that mean the ketone bodies just like the lactate are waste product to the liver but energy source to other organs).

— β Hydroxy butyrate will converted back to acetoacetate by the same reversible reaction that catalyzed by β hydroxy butyrate dehydrogenase.

— The causes of ketosis mainly :

— 1-Uncontrolled diabetes (type 1).

— 2-Starvation.

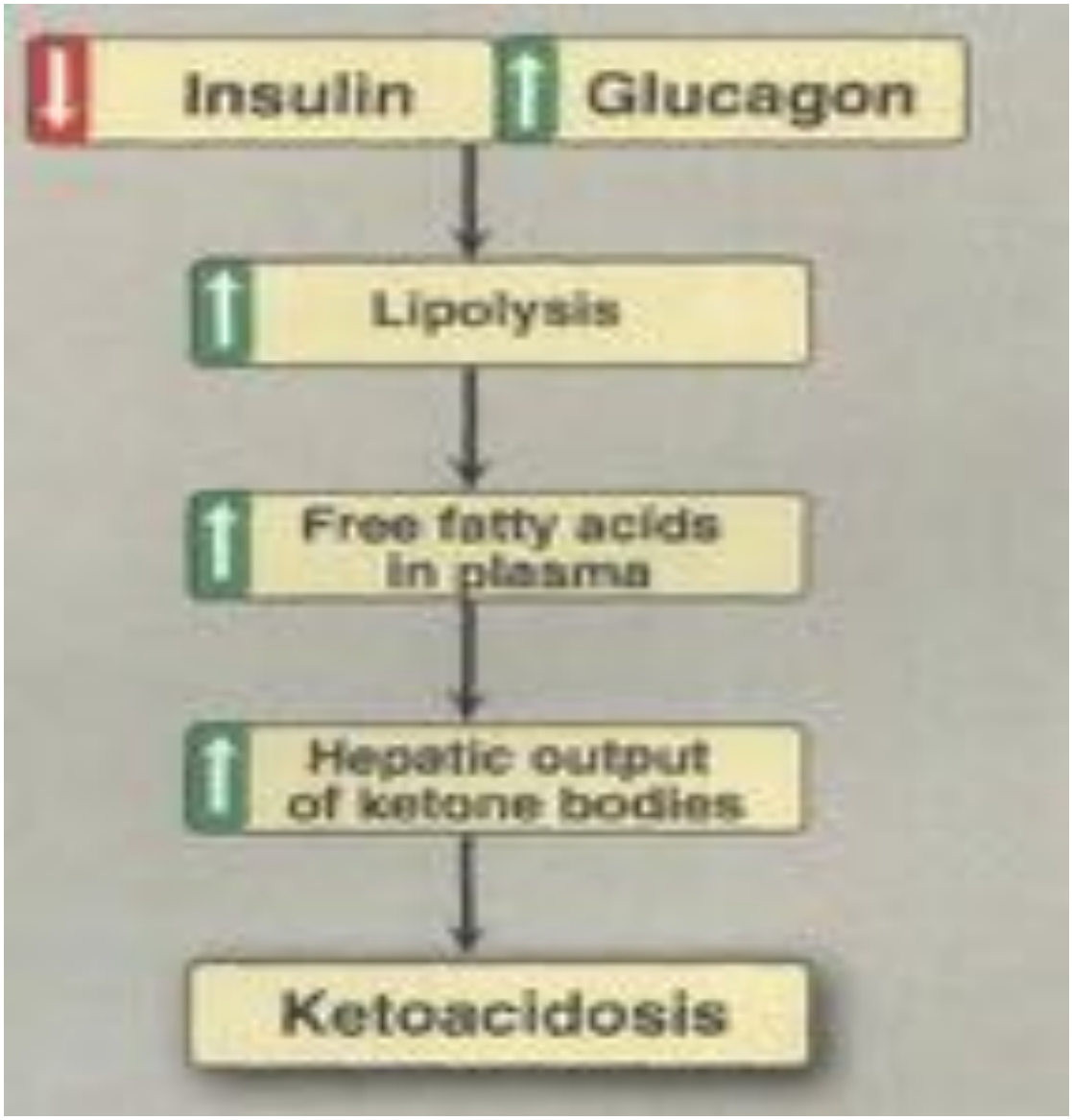
MECHANISM OF KETOSIS

When the rate of ketone bodies production exceed the rate of utilization, there blood level rises this condition called (**ketonemia**)and eventually when exceed the

renal threshold will excreted in urine and this condition called (**ketonuria**) which often seen in cases of uncontrolled type 1 diabetes.

In individual with sever ketosis the blood level of ketone bodies may reach 90 mg/dl (n.v less than 3mg/dl) and the urinary ketone bodies may rises up to 5000 mg/24 hour and the smell of acetone may sense in the breathing of the patient.

Increase in blood ketone bodies lead to acidosis because the acetoacetate and the β hydroxybutyrate are acids (as the carboxyl group of acetacetate has Pka value of 3.8 and β hydroxy butyrate 4.8 therefore they loss there hydrogen when circulating in the blood which lower the PH of the blood) also the excretion of glucose and ketone bodies in urine cause to diuresis leading to dehydration {decrease in plasma volume} so increase in hydrogen ion in the blood associated with decrease the plasma volume leading to sever K**ETOACIDOSIS**.



المحاضره السابعة

Objectives:

The students are learned to understand the Triglycerides metabolism including the following points:

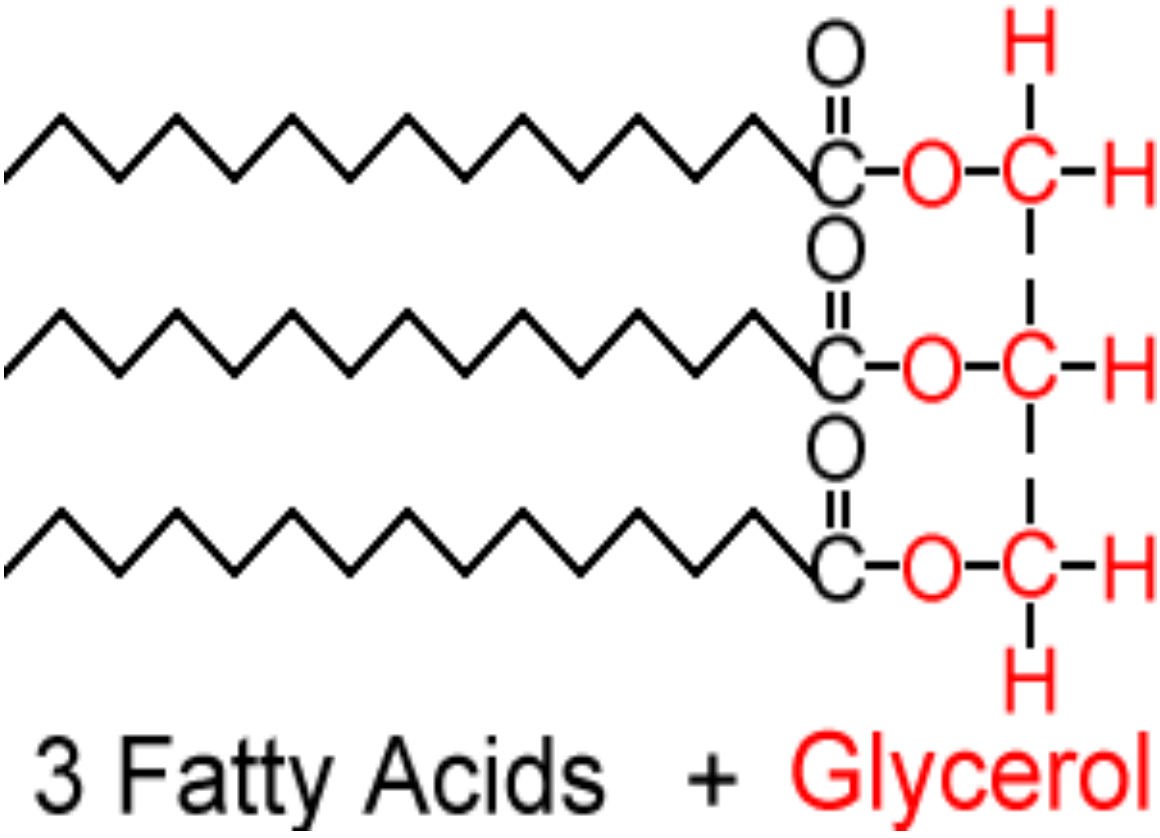
-Synthesis of Triglycerides

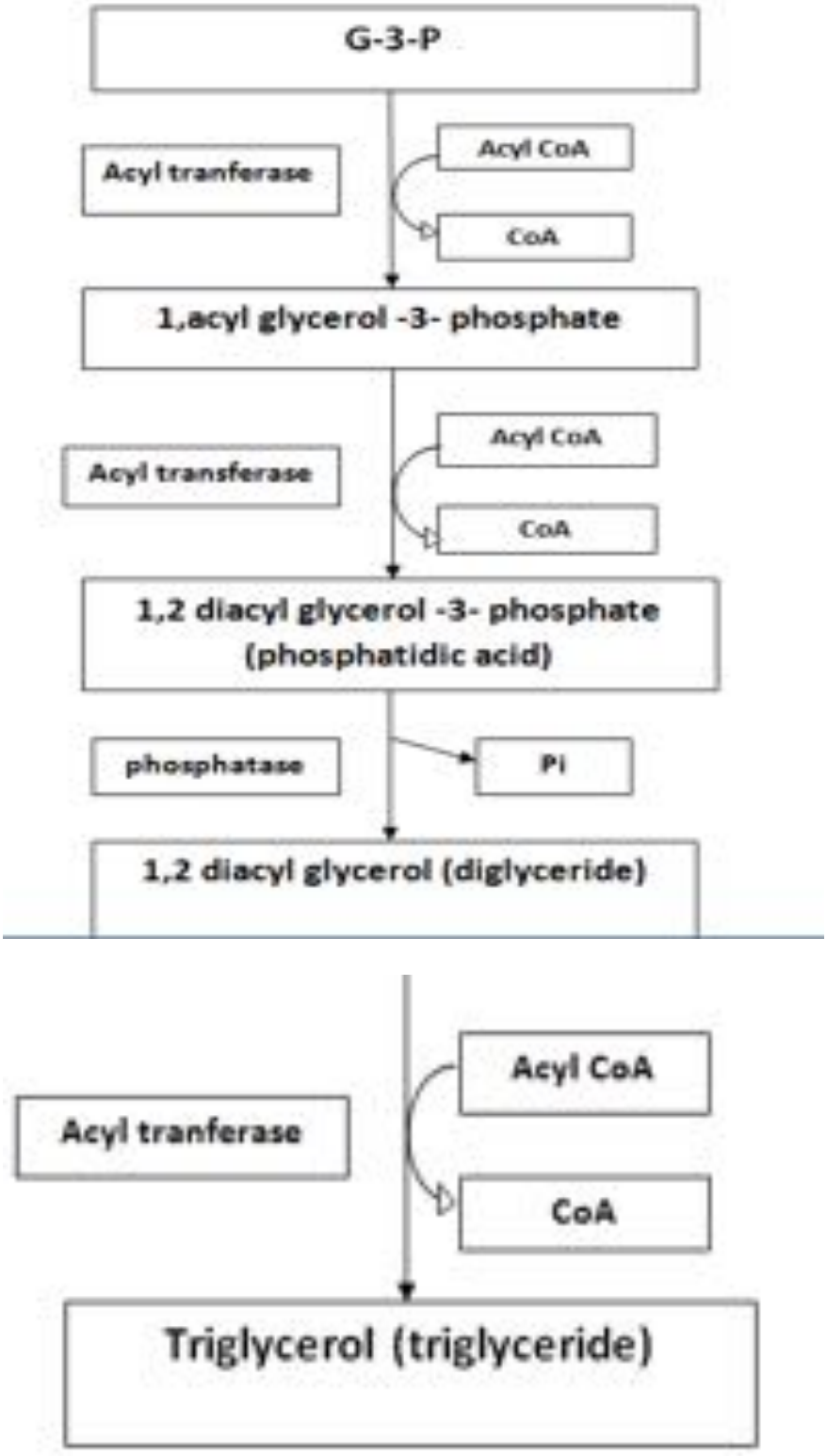
- Source of glycerol -3-Phosphate

- Hormonal Regulation of Triglycerides Degradation in Adipose tissue

TRIGLYCERIDES

SYNTHESIS OF TRIGLYCERIDES





The function of TG in the body is energy store. Saturated and unsaturated fatty acids are store as TG. Mainly the synthesis of TG occur in the liver and excreted as

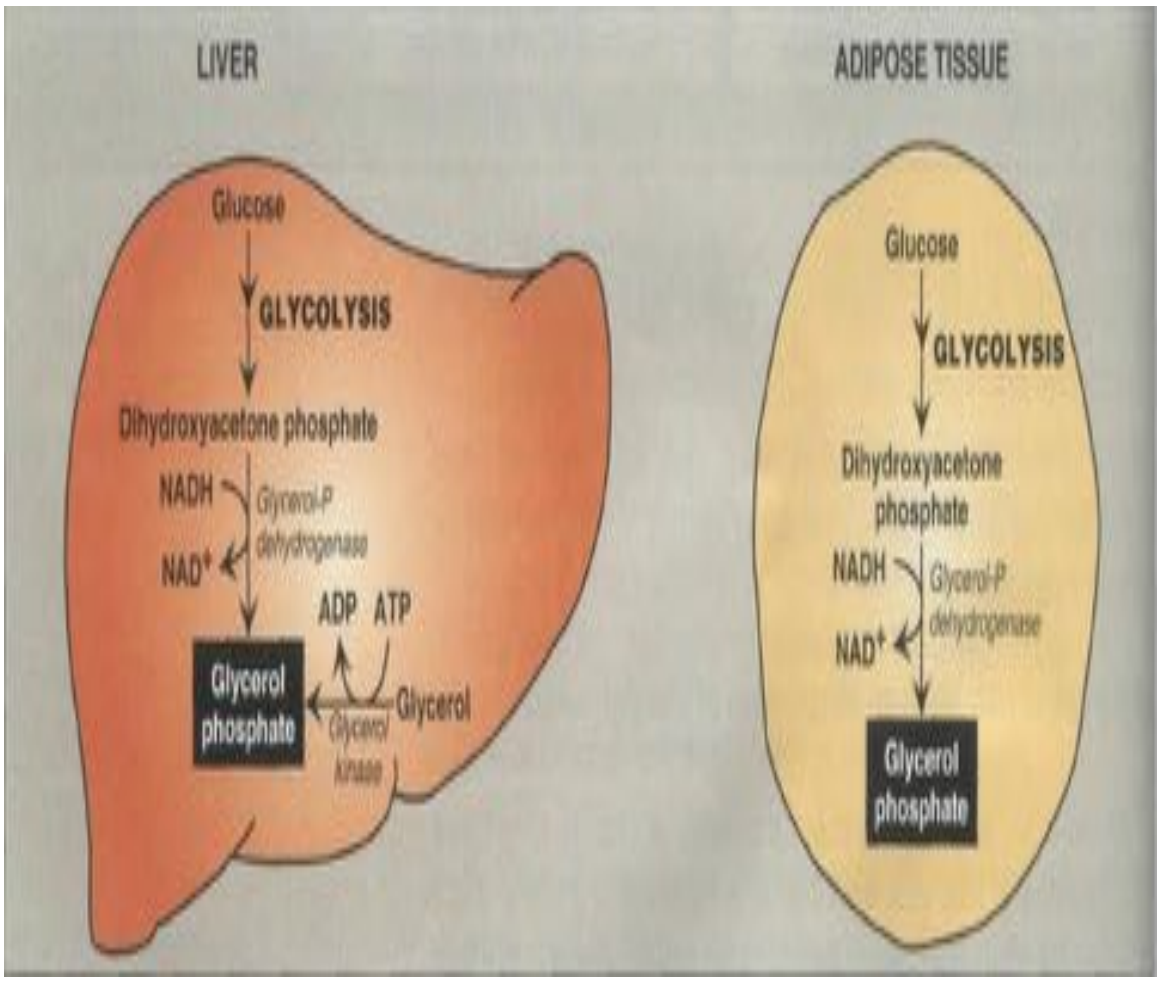
VLDL or in the adipose tissue and store there. Fatty acids in the adipose tissue are derived from the VLDL and the chylomicron by the action of lipoprotein lipase.

Glycerol 3 phosphate is the initial acceptor of fatty acid during TG synthesis. There are two sources for glycerol 3-p in the liver :

1.From **Dihydroxy acetone phosphate** one of the intermediate of glycolysis which reduces by the NADH in the present of the enzyme glycerol p-dehydrogenase.

2.In the liver from the **glycerol** by the action of the enzyme glycerol kinase.

In adipose tissue dihydroxy acetone phosphate is a source of *glycerol 3 phosphate*. The intermediate that give us fatty acid is the **fatty acyl CoA**.



Typically the fatty acid on carbon no.1 is saturated and on carbon no.2 is typically unsaturated and the fatty acid on carbon no.3 could be the either .So the type of the fatty acid on carbon no.3 usually determine the melting point of TG.

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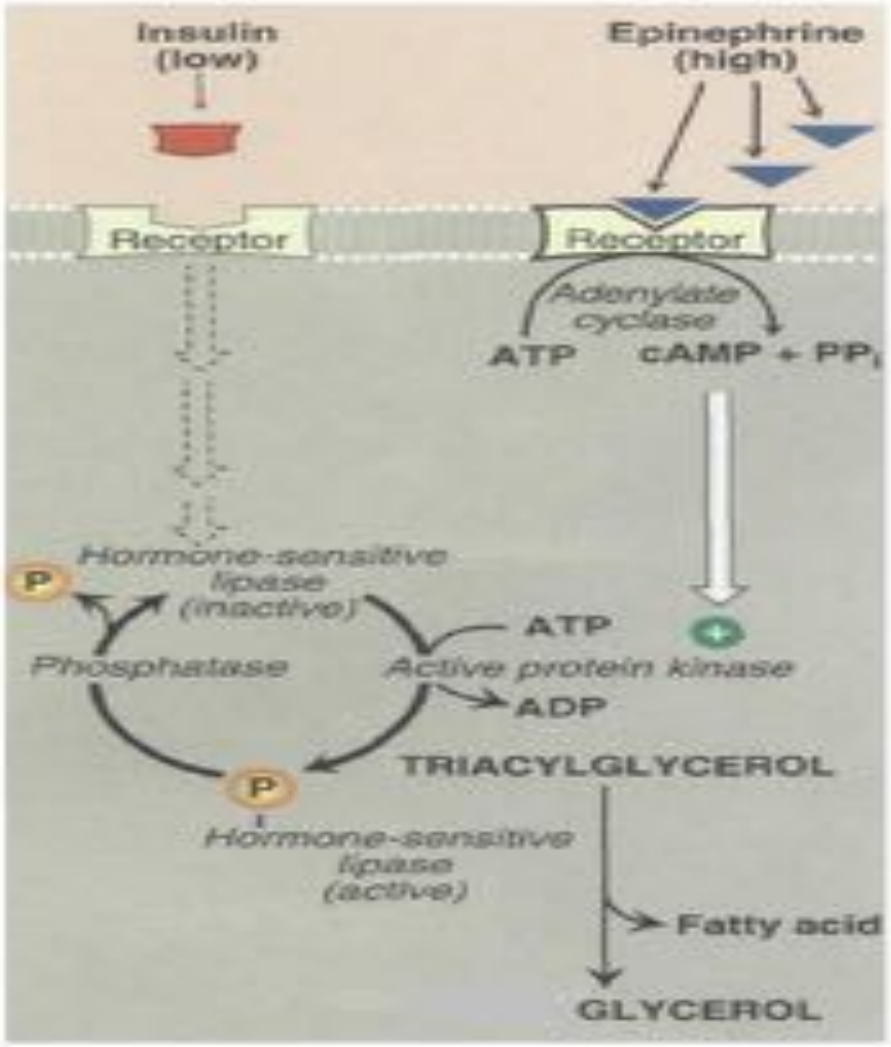
Hormonal regulation of triacylglycerol degradation in the adipocyte.



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المحاضره الثامنة

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Objectives:

The students are learned to understand the Phospholipids metabolism including the :

-The Synthesis of Phospholipids

-The Degradation in Phospholipids

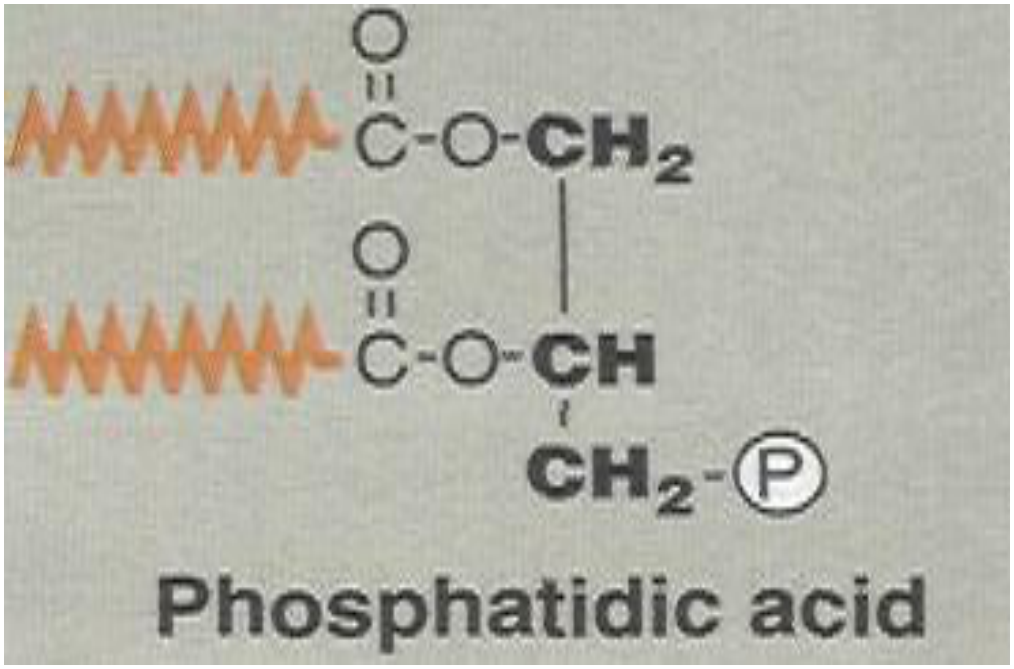
—

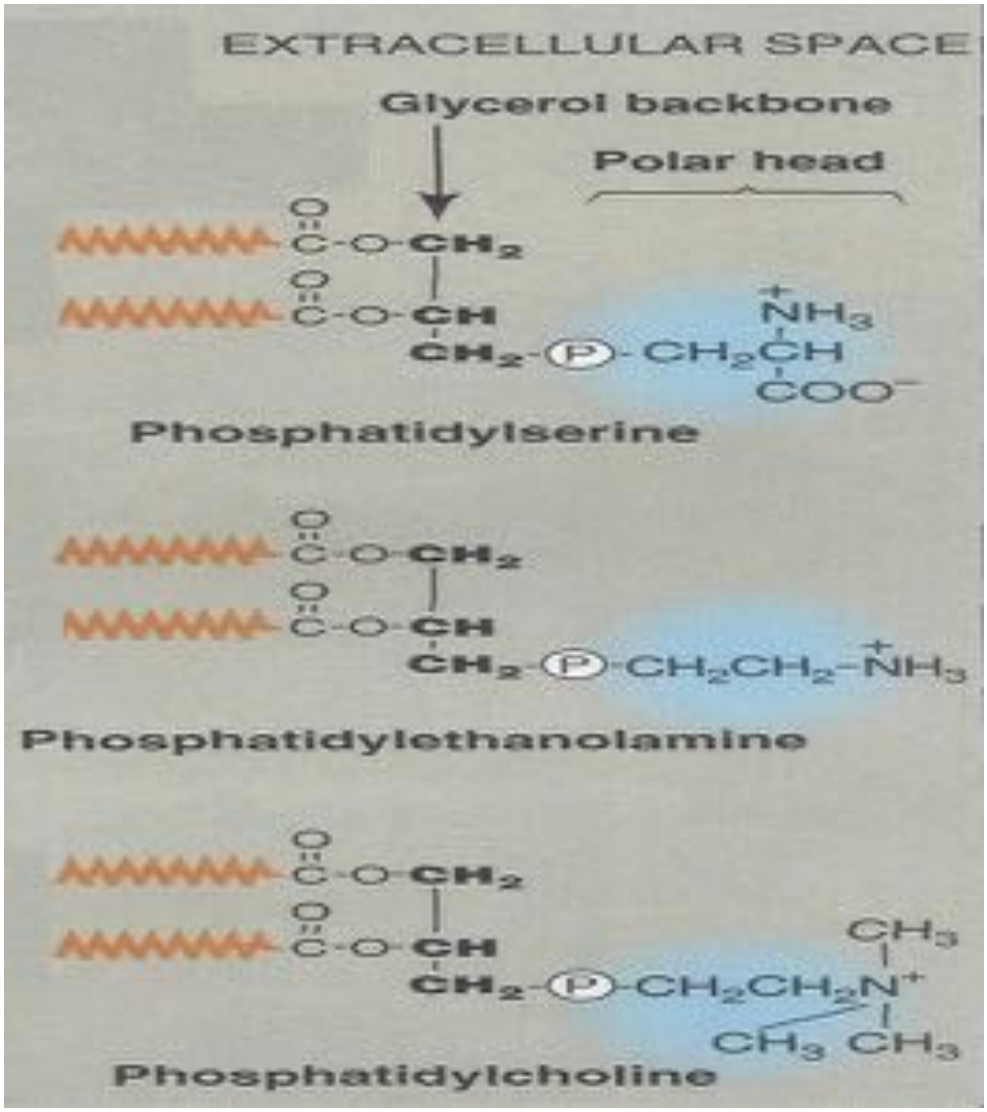
PHOSPHOLIPIDS

SYNTHESIS OF THE PHOSPHOLIPIDS

There are two types of phospholipids either contain the glycerol called { glycerol phospholipids } or do not contain glycerol that called { sphingophospholipids } .

The structure of glycerol phospholipids is similar to that of the TG but on the carbon no.3 contain phosphate or phosphate alcohol.





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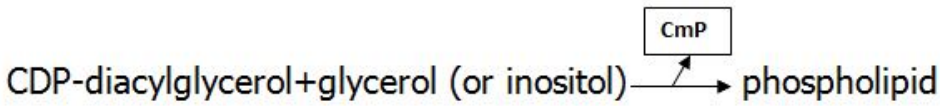
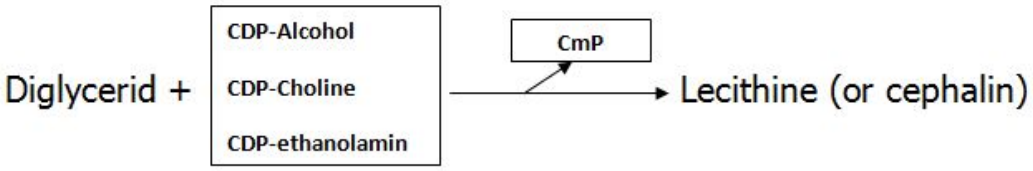
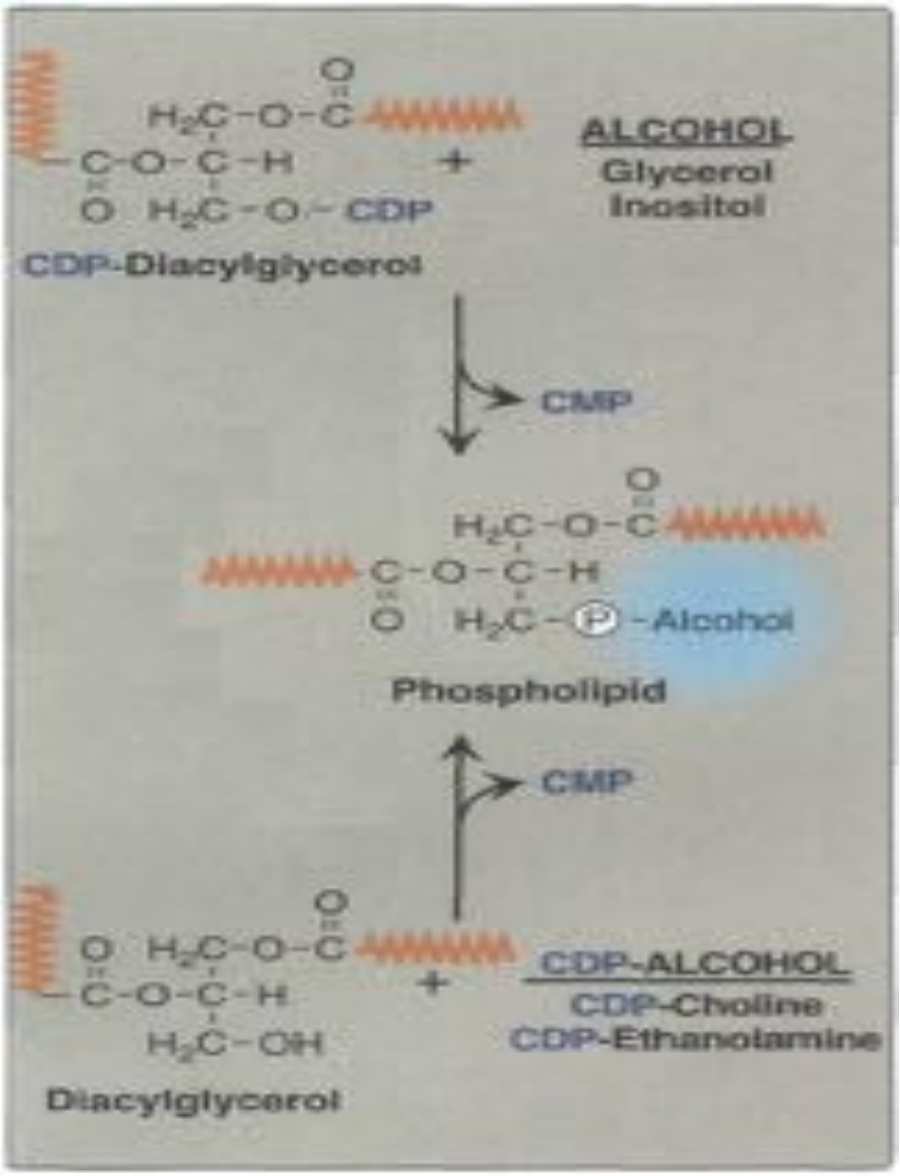
There are two ways for the synthesis of glycerol phospholipids:

1 . Donation of phosphatidic acid from cystidine diphosphate (CDP)diacylglycerol to an alcohol (glycerol or inositol).



2 . Donation of phosphate alcohol from cystidine diphosphate alcohol to diglycerides.

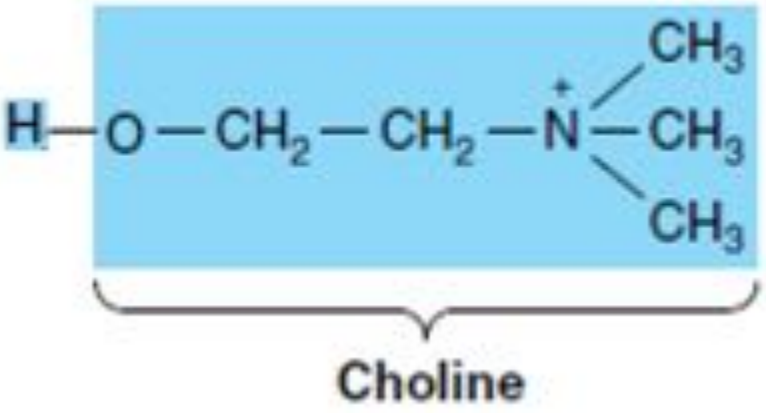




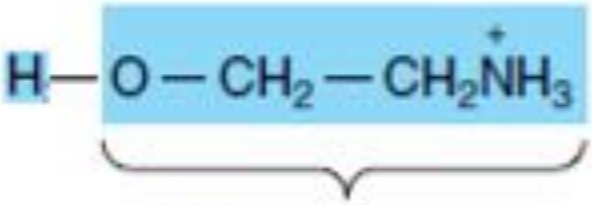
Although human can synthesize choline but the amount that is synthesized is insufficient thus the reutilization of choline is important and choline is consider of the essential nutrient (in male 550mg daily and in female 420 mg daily).

The liver is equipped with additional mechanism for the production of phosphocholine (lecithin) even when choline level is low because the liver excrete choline in significant amount in bile and as a component of lipoprotein.

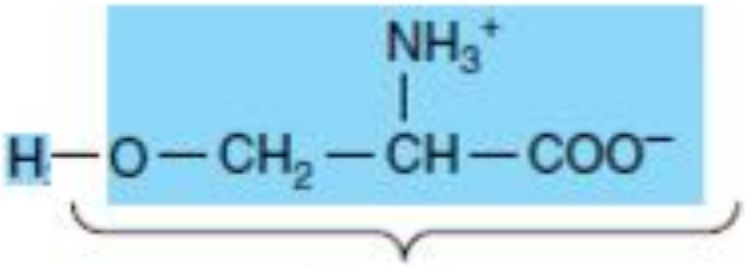
The decarboxylation of serine give ethanolamine .When we add three methyl group to the ethanolamine we will be converted to choline.



Choline



Ethanolamine



Serine

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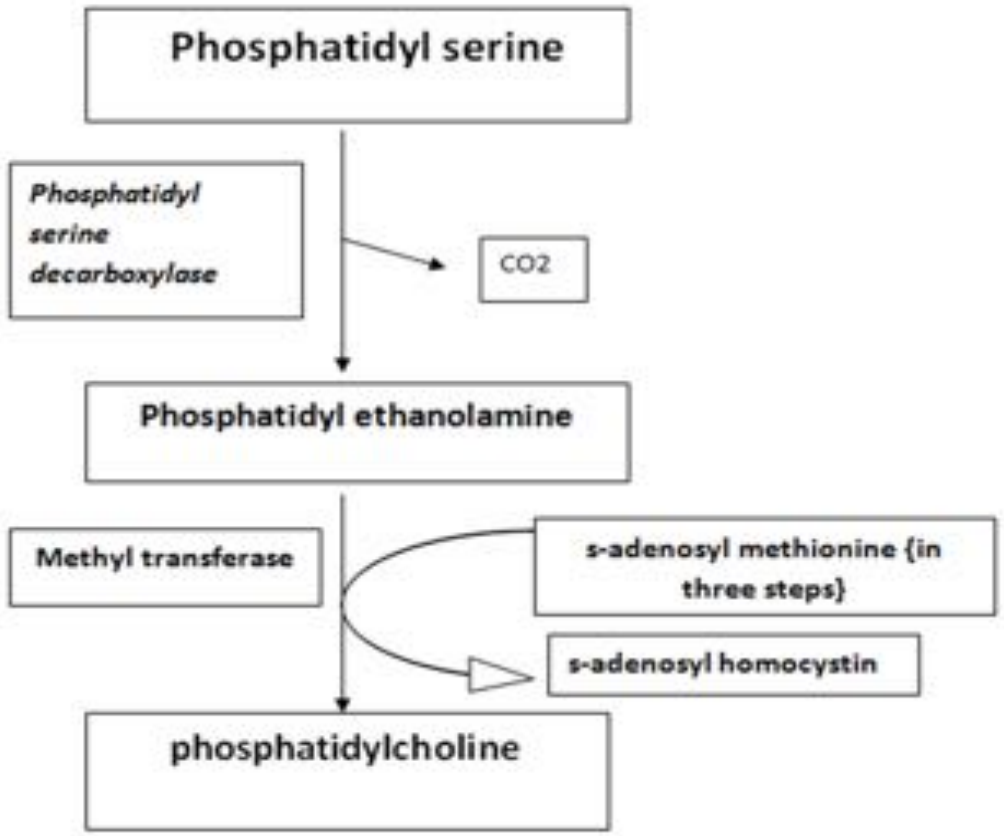
The mechanism by which the liver synthesized choline:

The decarboxylation of phosphatidyl serine yield phosphatidyl ethanolamine .the addition of 3 methyl group to phosphatidyl ethanolamine will produce phosphatidyl choline. { the donor of the methyl group is S- Adenosyl methionine } .



DEGREDATION OF PHOSPHOLIPIDS

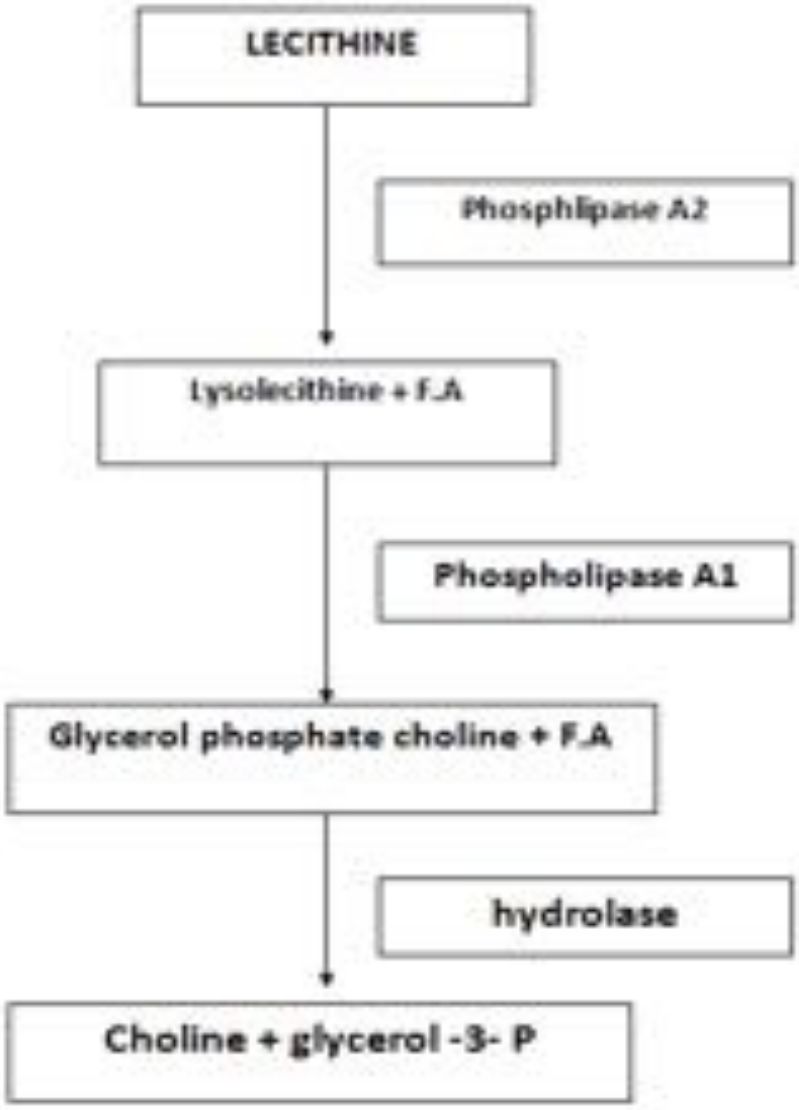
e.g. Lecithin .

The lecithin composed of glycerol that have fatty acid in the carbon no.1 and fatty acid on carbon no.2 and phosphocholine on carbon no.3 .

By the action of the enzyme phospholipase A2, the fatty acid will be removed from the carbon no.2 and this lead to the formation of lysolecithin and fatty acid .

By the action of the enzyme phospholipase A1, the fatty acid will be removed from the carbon no.1 and this lead to the formation of glycerol phosphocholine and fatty acid.

By the action of the enzyme hydrolase, the choline will be removed and this lead to the formation of glycerol 3 phosphate and choline.


LECITHINE
Phosphlipase A2
Lysolecithine + F.A
Phospholipase A1
Glycerol phosphate choline + F.A
hydrolase
Choline + glycerol -3- P

المحاضره التاسعة

Objectives:

The students are learned to understand the Sphingolipids metabolism including the following points:

- The Synthesis of the Sphingosine

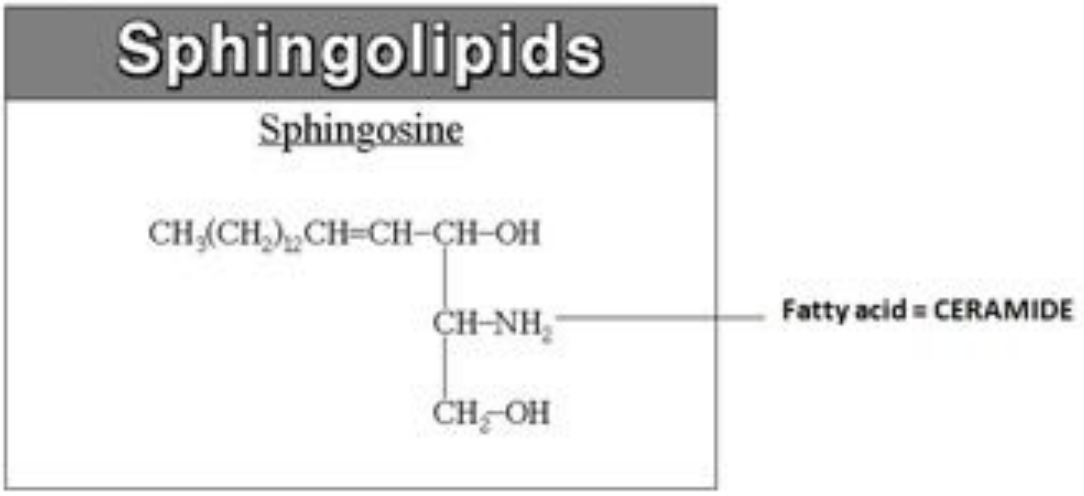
- The Type of Sphingolipids

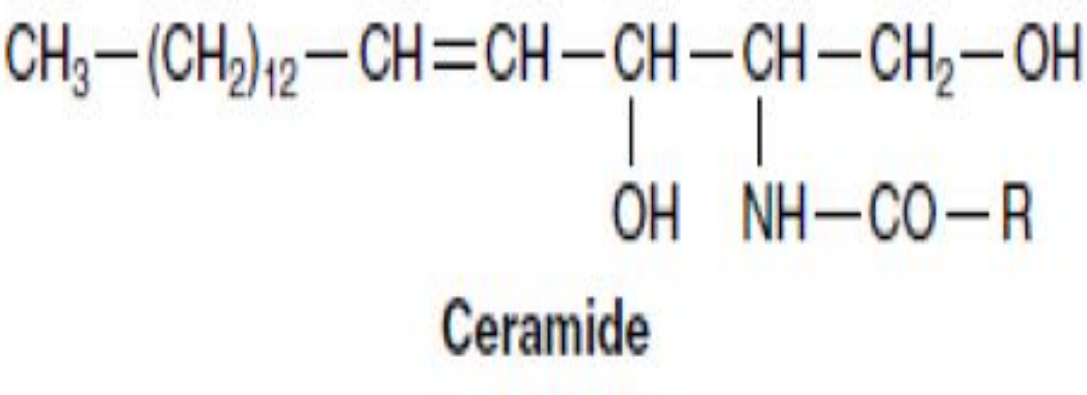
- The Synthesis of the Sphingolipids

-The Gangliosides metabolism

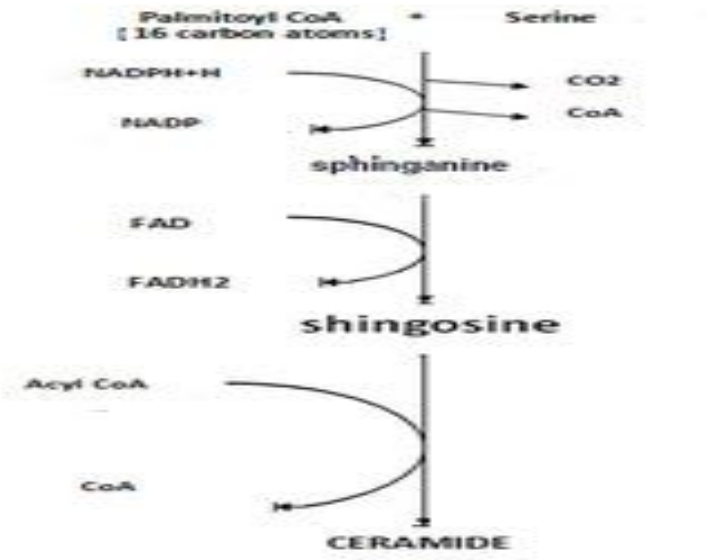
SPHINGOLIPIDS

All sphingolipids are synthesized from CERAMIDES (which is an acyl sphingosine), the sphingosine is long unsaturated amino alcohol.





— Sphingosine Synthesis



THE TYPES OF SPHINGOLIPIDS

1 . Sphingophosphlipids {sphingomyelins}

— Shingomyelins = Ceramide + choline phosphate.

2 . glycosphingolipids:

A)) Neutral glycosphingolipids:

— **a . Cerebrosides:**

— Glucocerebrosides (ceramide+glucose).

— Galactocerebrosides (ceramide+galactose).

— **b. Globoside :**

— Glucocerebroside+additional monosaccharide.

— EX. lactosyl ceramide (cer.+glucose+galactose).

B)) Acidic glycosphingolipids:

— **1 . Gangliosides** :

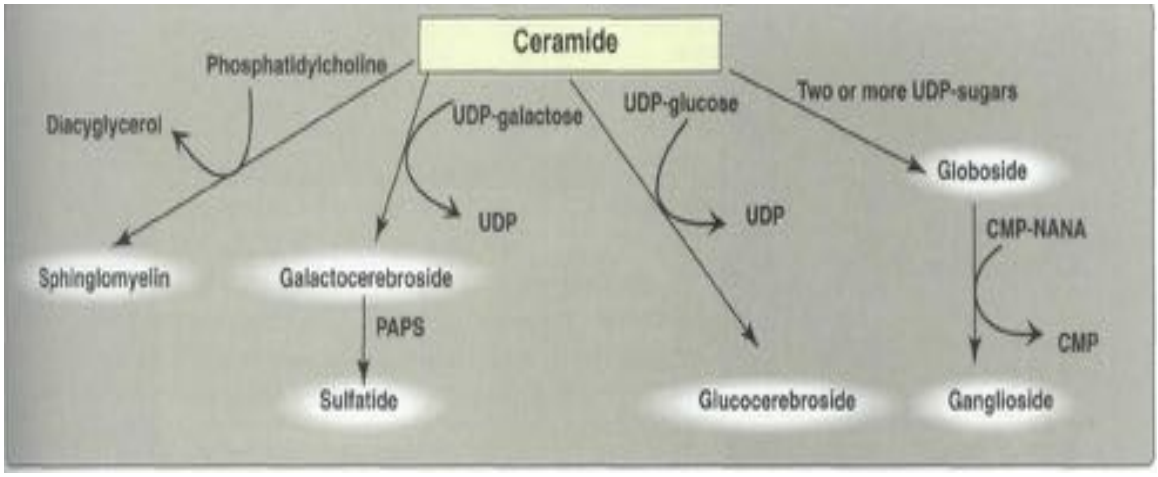
— {cer.+oligosaccharide+one or more NANA.

— NANA: N.acetyl neuraminic acid.

2. Sulfatides :

— {cerebroside that contain sulfated galactosyl residues}.

Synthesis of sphingolipids



— **UDP-GAL = uridine diphosphate galactose.**

— **UDP-GLU = uridine diphosphate glucose.**

— **PAPS = phosphoadenosine phospho sulfate**

GANGLIOSIDES

1. GM1:

Ceremide-glu-gal-galNAC-gal

|

NANA

2. GM2:

Ceremide-glu-gal-galNAC

|

NANA

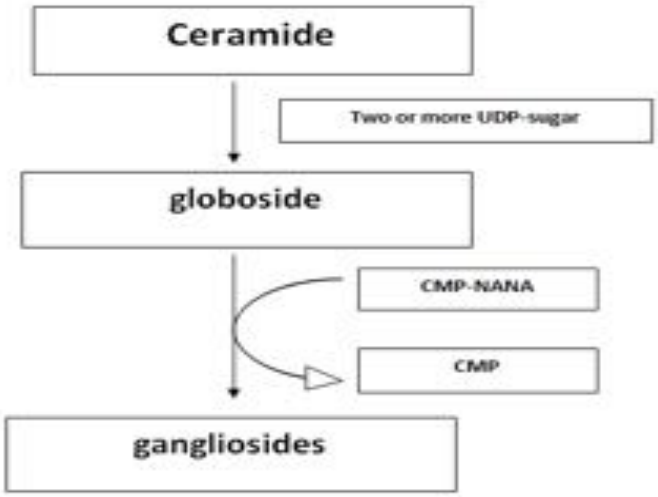
— **G: Gangliosides.**

— **M:(or D,T,Q) :mono-dual-three-quatral**

— number of sialic acid unite (NANA)

— **number : sequence of CHO attach to ceramide.**

Gangliosides synthesized from ceramide step by step by the addition of individual sugar & sialic acid by their nucleotide derivatives. Enzyme transferring these compound called {glycosyl transferases} found in the Golgi apparatus



*CMP-NANA = cystidine monophosphate – N ,acetyl neuraminic acid.

Gangliosides undergo continuous degradation & synthesis. As biosynthesis the degradation is operate by sequential hydrolysis of sugar residues & sialic acid by specific lysosomal glycosidases & neuraminidases.

The absence of specific enzyme result in accumulation of the involved Ganglioside or one of its metabolic intermediates lead to inborn error of metabolism called {sphingolipidosis}.

The syndrome	Enzymes	accumulation
Tays-sachs disease	β-hexosaminidase	GM2
Gaucher disease	β-glucosidase	glucocerebroside
Niemann-pick disease	sphingomylinase	shingomyelin

المحاضره العاشرة

Objectives:

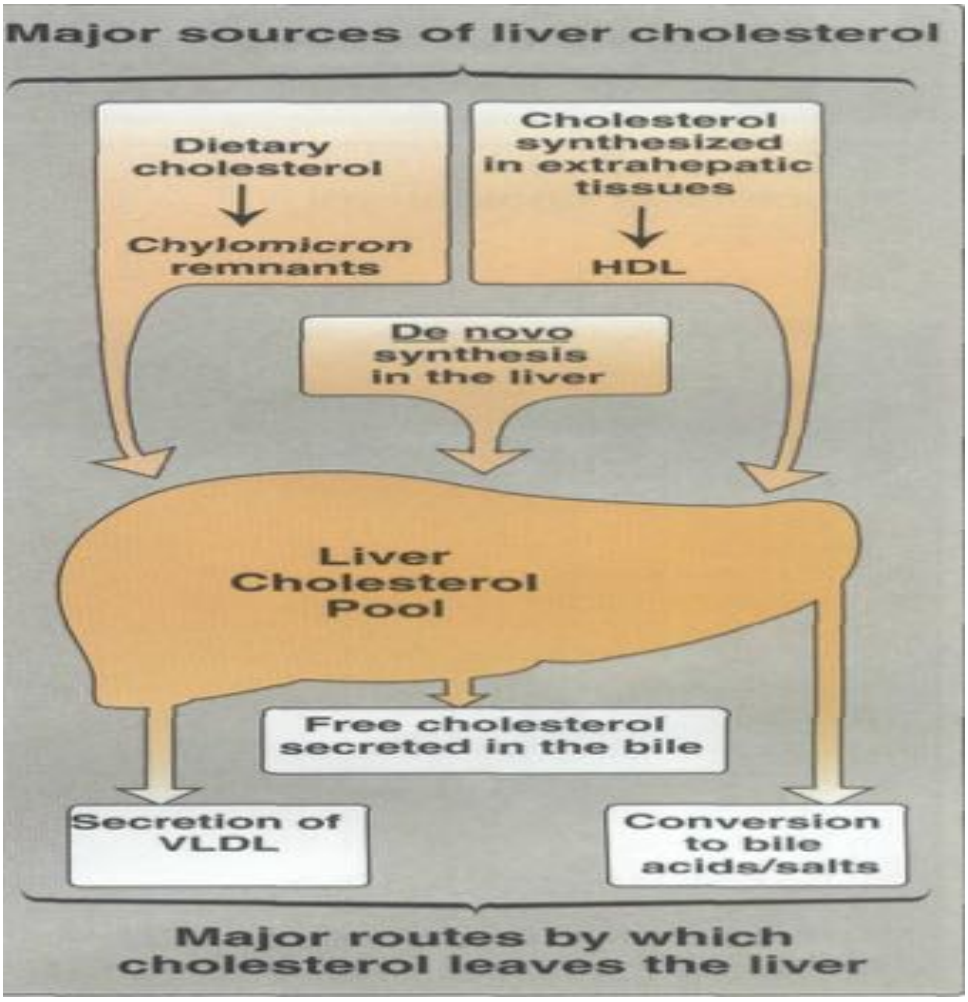
The students are learned to understand the Cholesterol Metabolism including the following points:

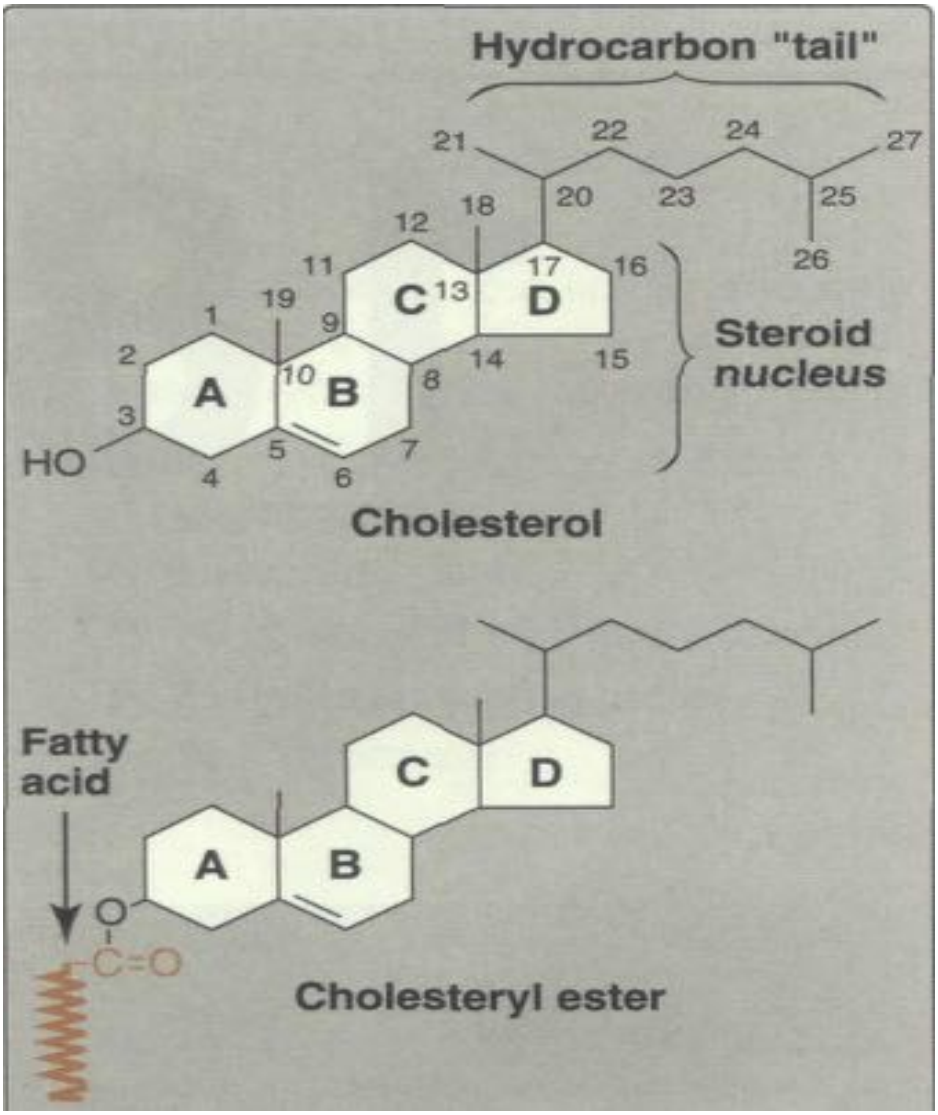
- The Sources of Cholesterol

- The Biosynthesis of Cholesterol

- The Regulation The Cholesterol Biosynthesis

CHOLESTROL METABOLISM





CHOLESTROL BIOSYNTHESIS

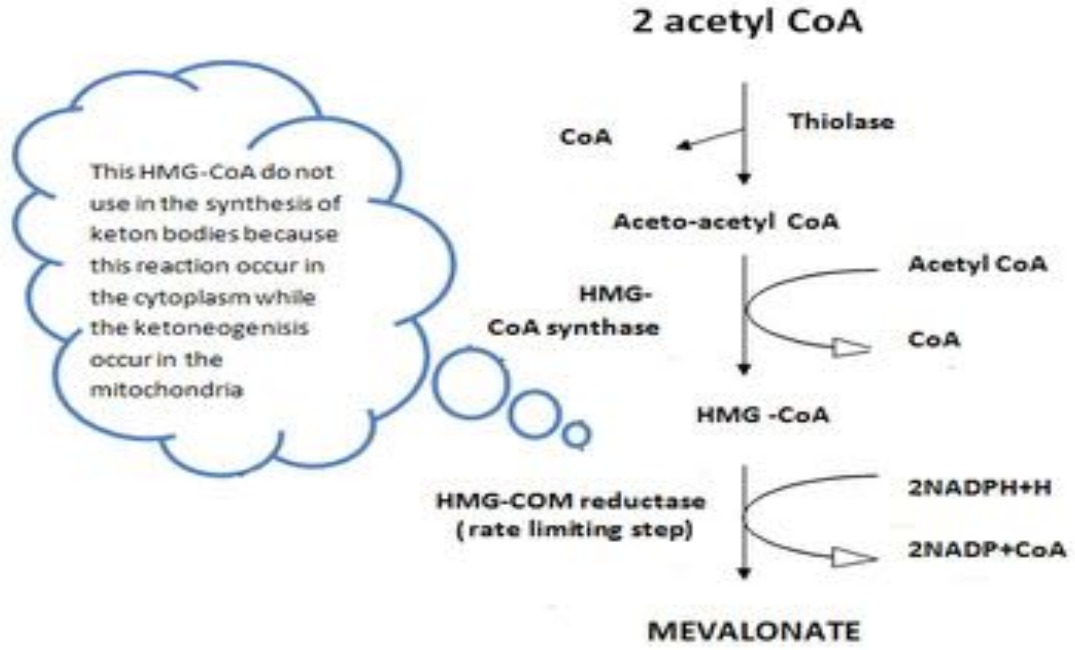
The primary building block is acetyl-CoA. All nucleated cells can synthesize cholesterol principally the liver & intestine, which occur in the cytosol & endoplasmic reticulum.

The body can not break the sterol nucleus (no energy produce from cholesterol).The cholesterol use in the synthesis of vitamin D ,bile acids, steroid hormones ,also the cholesterol inter in the structure of the cell membrane.

Cholesterol biosynthesis may be divided into **five steps** :

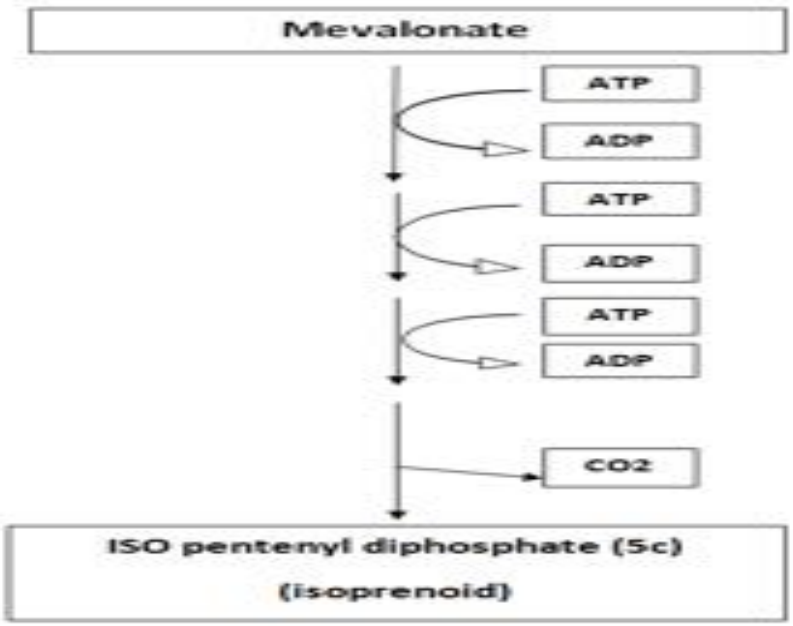
___

— 1- Synthesis of mevalonate



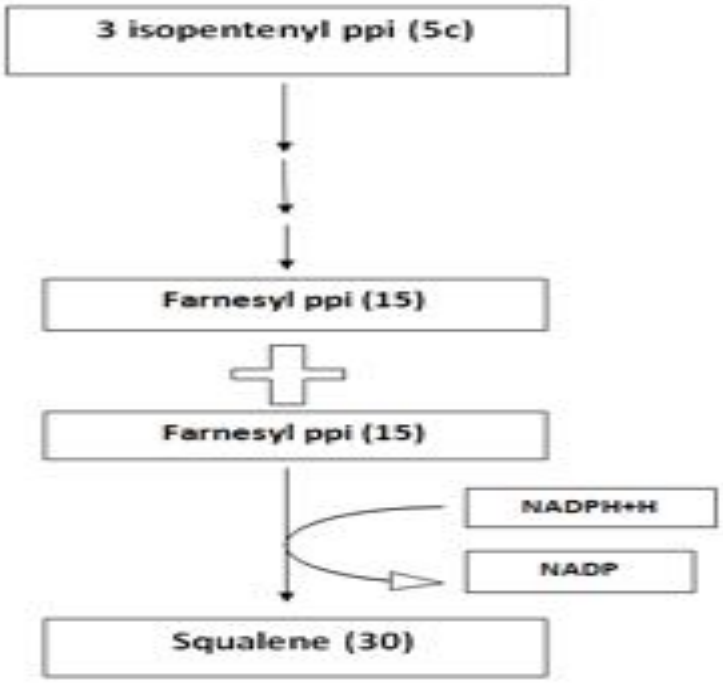
2- formation of isoprenoid (5C) :

Isoprenoid unit formed from mevalonate in several steps, need 3ATP and loss one carbon as Co2 .

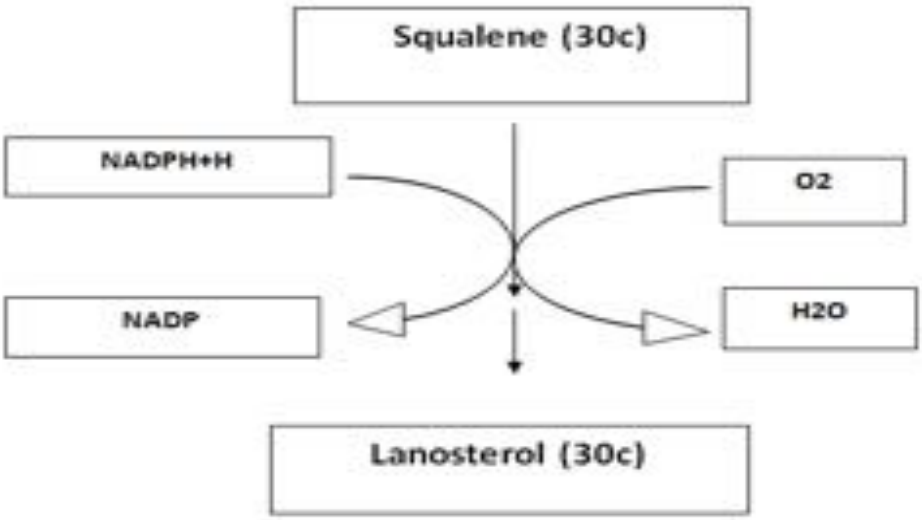


3- formation of squalene (30c):

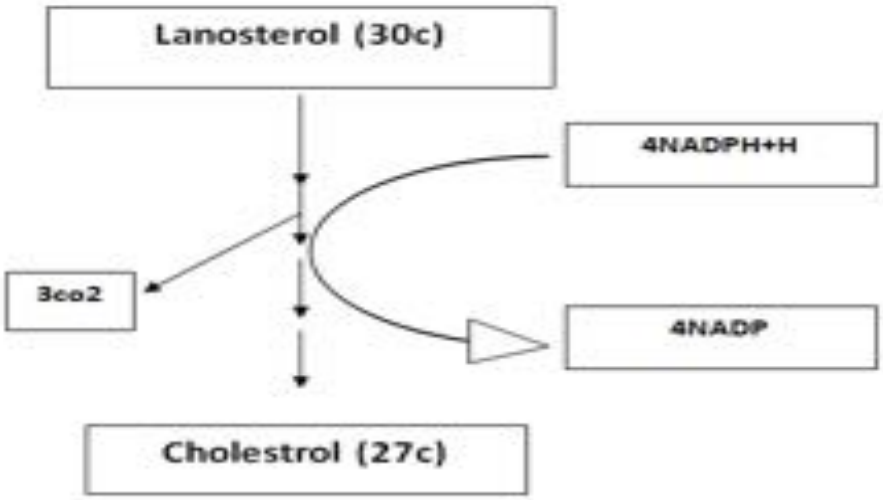
6 isoprenoid units condense to form squalene:



— 4- formation of lanosterol (30c)



5- formation of the cholesterol (27c):



Question : for the synthesis of 1 mole of cholesterol how many mole of acetyl CoA & ATP required and how many mole of co2 liberated?

Answer :

- 18 ATP.
- 18 Acetyl CoA.
- 9 CO2.

Regulation Of Cholesterol Biosynthesis

The enzyme HMG-CoA reductase catalyze the rate limiting step in cholesterol biosynthesis and subjected to various regulatory mechanisms :

1 . Sterol dependent regulation of gene expression :

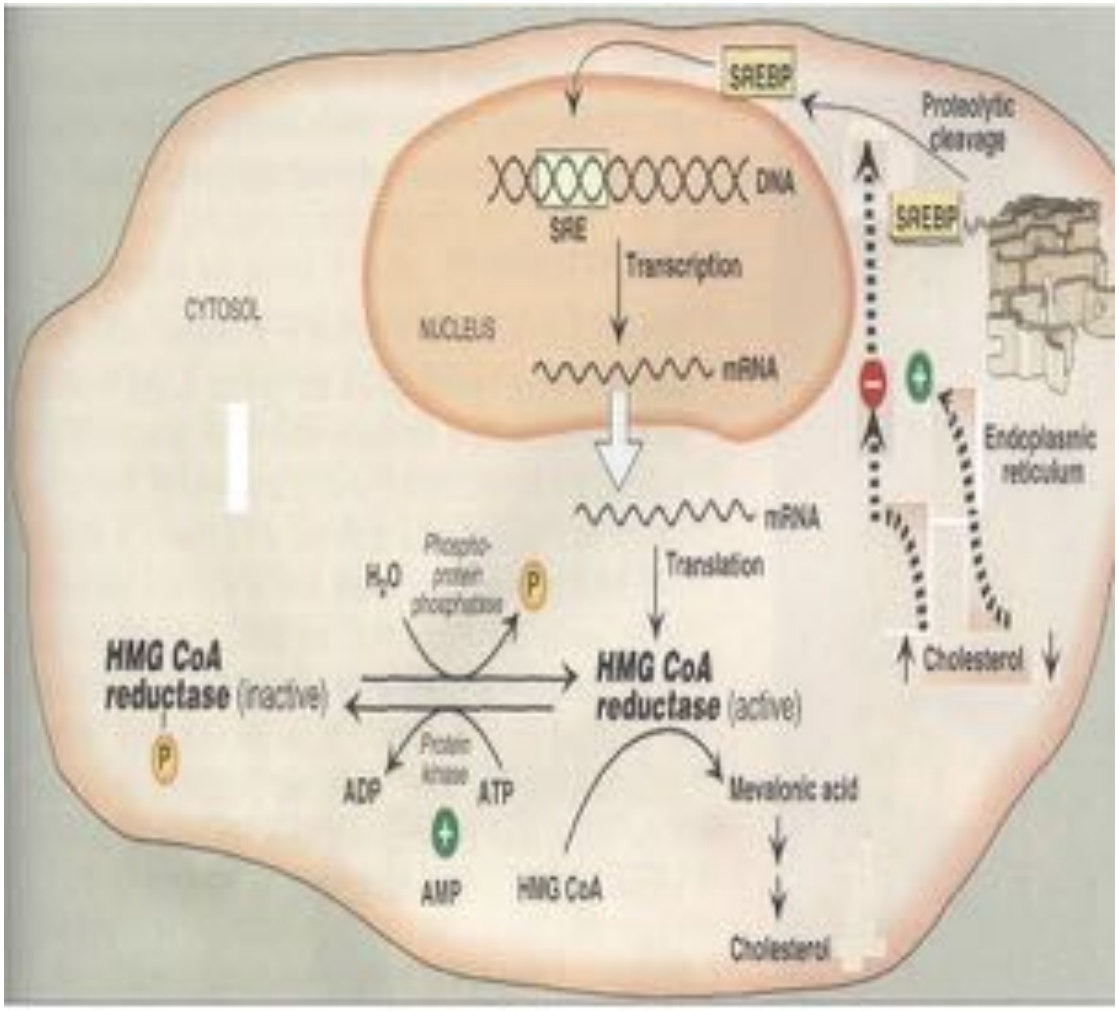
HMG-CoA Reductase gene is controlled by transcription factors called SREBP (sterol regulatory element binding protein).This protein (SREBP) binding initially to the membrane of endoplasmic reticulum which is activated by proteolytic cleavage and the active form travel to the nucleus and stimulate HMG-CoA reductase gene transcription.

When cholesterol levels are low there will be activation of SREBP leading to increase HMG-CoA reductase synthesis and this will lead to increase the cholesterol

biosynthesis. While increase in cholesterol levels prevent the activation of SREBP → low activation of HMG-CoA reductase gene →decrease the cholesterol biosynthesis.

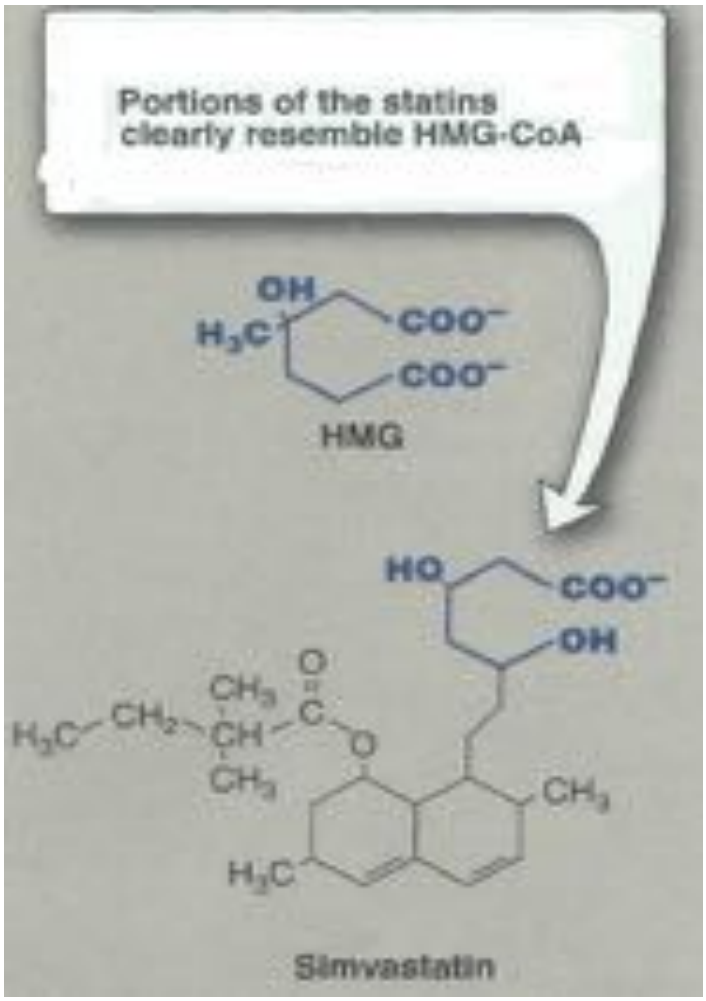
2 . Sterol independent phosphorylation ,dephosphorylation :

HMG-CoA reductase is activated by dephosphorylation & inhibited by phosphorylation (like acetyl- CoA carboxylase).



3 . Inhibition by drugs :

Statin drugs is structural analogous to HMG-CoA (substrate) & cause competitive inhibition to HMG-CoA reductase.



The Role Of Hormones in Lipid Metabolism

Insulin: enhance the storage of TG in adipose tissue .

1. Moderate the activation of tissue lipase.

2. Promoting the entry of glucose to the cells providing glycerol-3-p (for synthesis of TG)& acetyl CoA (synthesis of F.A).

3.There is also some evidence that the

insulin induce the synthesis of :

- **ATP citrate Lyase.**

-**Acetyl-CoA Carboxylase** (rate limiting step in F.As synthesis).

-Fatty acid synthesis Multienzyme complex.

Epinephrine:

Activate adenyl cyclase→increase the activity of tissue lipase →increase free fatty acids → inhibition of acetyl-CoA carboxylase → decrease the rate of fatty acid synthesis.

Glucagon :

its action similar to epinephrine.

المحاضره الحادية عشر

Objectives:

The students are learned to understand the Disorders of Lipid Metabolism including the following points:

-Factors Effect Serum Cholesterol Levels

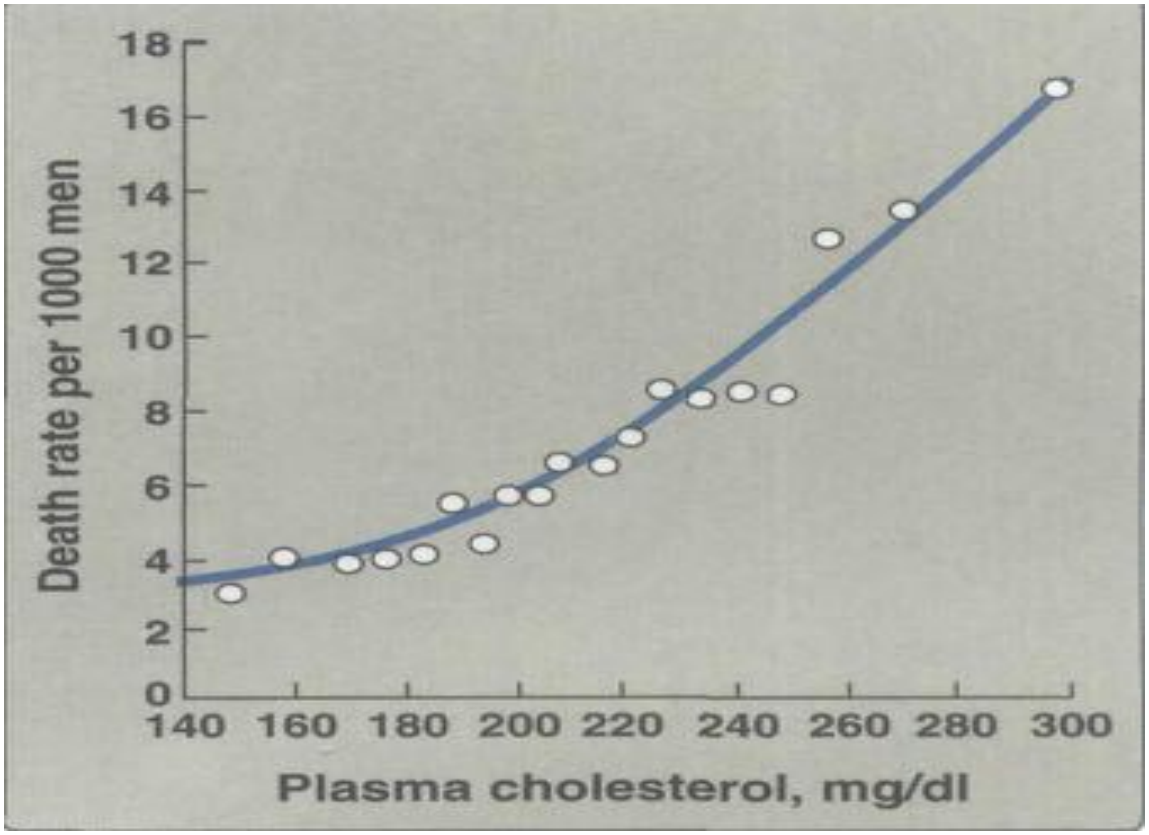
. Dietary factors

. Life style factors

- Hyperlipoproteinaemia

Disorders of Lipid Metabolism

Serum cholesterol levels is correlated with the incidence of atherosclerosis & coronary heart disease (C.H.D) other parameters are also correlated with atherosclerosis such as serum TG level .



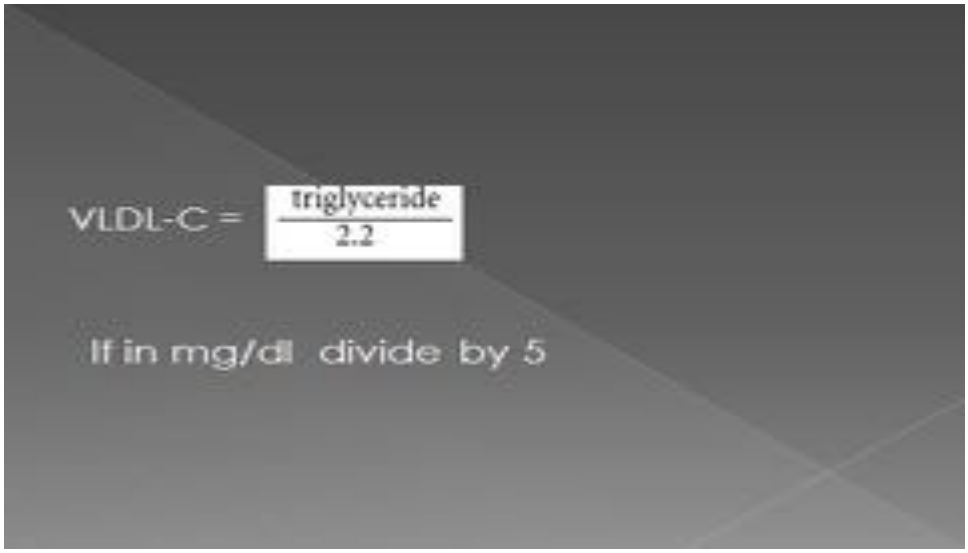
Patient with atherosclerosis can have any of the following abnormalities:

1. Elevated LDL-C with normal VLDL-C.
2. Elevated VLDL-C with normal LDL-C.
3. Elevated of both VLDL-C & LDL-C.

— *C= cholesterol

Lipid profile include

- S.TC (serum total cholesterol)
- S.TG (serum triglyceride)
-S. LDL-C (serum LDL cholesterol)
-S.VLDL-C (serum VLDL cholesterol)
-S.HDL-C (serum HDL cholesterol)



The Friedewald equation enables plasma LDL cholesterol concentration to be calculated and is often used in clinical laboratories:

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \frac{[\text{triglyceride}]}{2.2}$$

If in mg/dl divide by 5

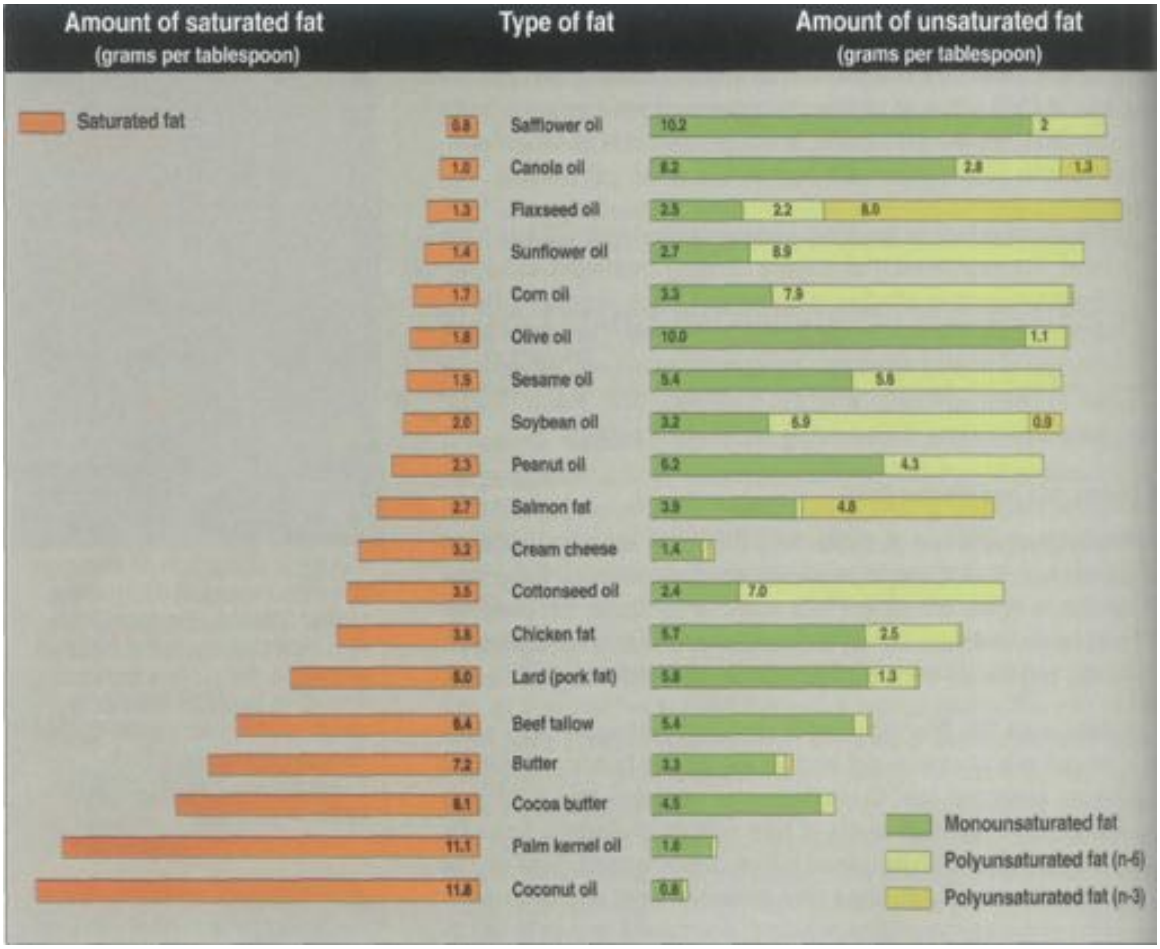
There is also inverse relationship between HDL-C & C.H.D, and it has been considered that the most predictive factor is LDL to HDL cholesterol ratio (if the ratio is high →high risk, if the ratio is low →low risk).

This relation can be explained by the fact that the role of LDL is transport of cholesterol to peripheral tissue & HDL act as scavenger of cholesterol from the tissue.

Factors Effect Serum Cholesterol

1 . Diet :

substitution in the diet of polyunsaturated & monounsaturated ,is beneficial for lowering serum cholesterol. Plant oil such as corn oil ,sunflower, seed oil contain a high proportion of polyunsaturated fatty acid while olive oil contain high proportion of monounsaturated.



Sucrose and fructose have a greater effect in raising blood lipids particularly TG than other CHO.

The reason of cholesterol lowering effect of unsaturated F.A is not fully understood however the following mechanism have been postulated:

* Up regulation of LDL receptors → increase in the catabolic rate of LDL.

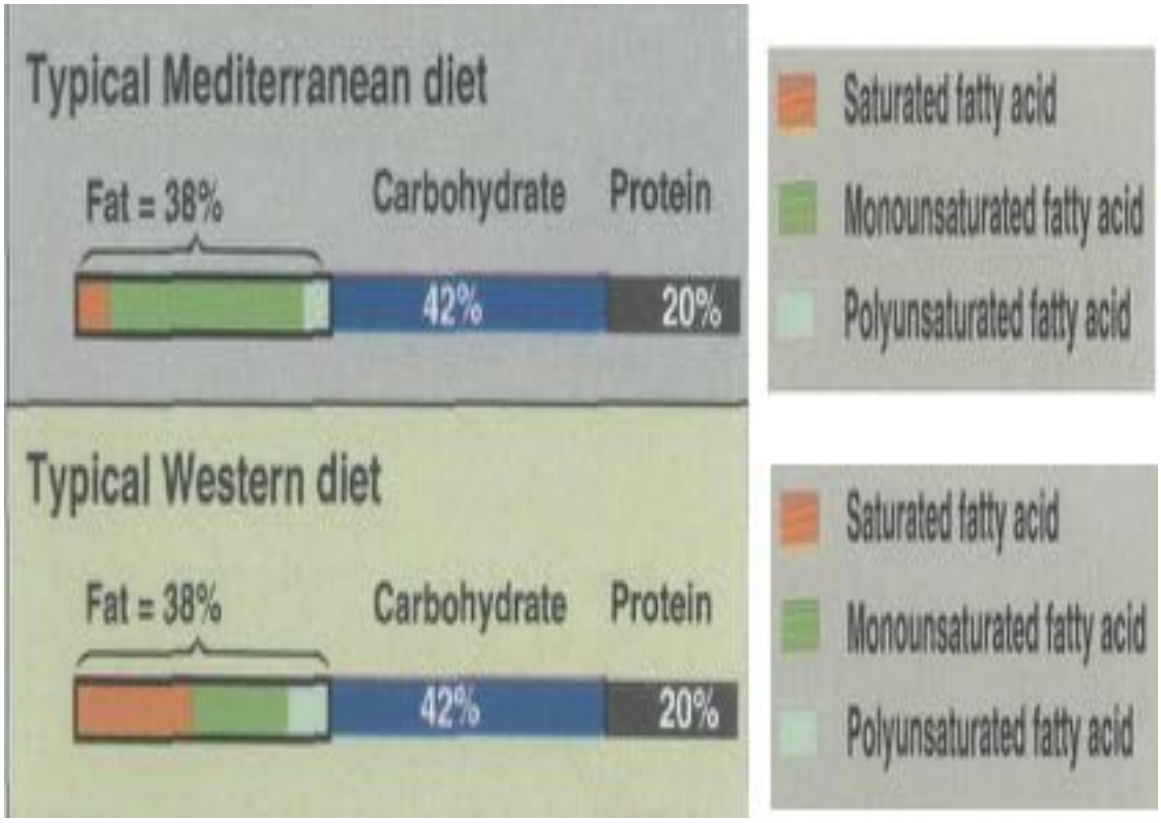
* Stimulation of cholesterol excretion in bile.

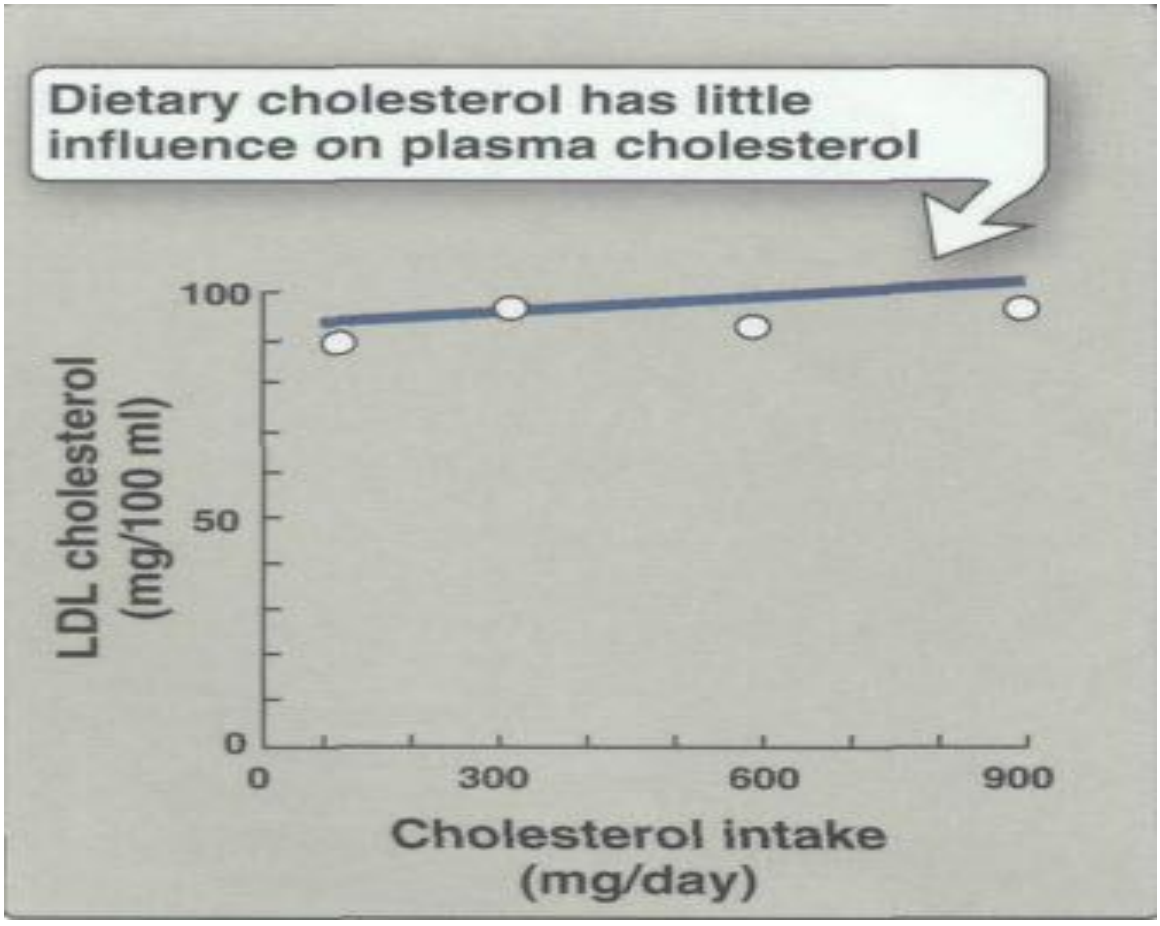
* Stimulation of cholesterol oxidation to bile acids.

ž **Monounsat.F.As:** ↓TC ↓LDL-C ↑HDL-C

ž **Omega 6:** ↓TC ↓LDL-C ↓HDL -C

ž **Omega 3:**↓ TG and act as antiarrhythmic and as antithrombotic


Typical Mediterranean diet
Fat = 38%
Carbohydrate
Protein
42%
20%
Saturated fatty acid
Monounsaturated fatty acid
Polyunsaturated fatty acid
Typical Western diet
Fat = 38%
Carbohydrate
Protein
42%
20%
Saturated fatty acid
Monounsaturated fatty acid
Polyunsaturated fatty acid


Dietary cholesterol has little influence on plasma cholesterol
LDL cholesterol (mg/100 ml)
100
50
0
0
300
600
900
Cholesterol intake (mg/day)

— 2 . Life style factors:

- ž 1-Hypertension.
- ž 2-Smoking.
- ž 3-Male gender.
- ž 4-Obesity,particulary abdominal obesity.
- ž 5-Lack of exercise , regular exercise associated with
  - — a- ↓LDL
  - — b- ↑HDL.
  - — c- ↓TG.
- — 6- drinking hard water is better than the pure water.
- — 7- emmotional stress.
- — 8- coffee drinking
- ž 9- premenopausal women appear to be protected
- ž (beneficial effect of estrogen).
- Ž 10-moderate alcohol consumption → ↑HDL-C.

Hyperlipoproteinaemia

according to the electrophoresis pattern there are five types :

1. Familial LPL deficiency (Type 1)
2. Familial hyper cholestrolemia (Type 2)
3. Broad β disease(Type 3)
4. Hypertriglyceridemia (Type 4)
5. Familial lipoproteinemia (Type 5)

Fredrickson's classification of hyperlipidaemias

Type	Electrophoretic	Increased lipoprotein
I	Increased chylomicrons	Chylomicrons
IIa	Increased β-lipoproteins	LDL
IIb	Increased β and pre-β-lipoproteins	LDL and VLDL
III	Broad β-lipoproteins	IDL
IV	Increased pre-β-lipoproteins	VLDL
V	Increased chylomicrons and pre-β-lipoproteins	Chylomicrons and VLDL

Familial LPL deficiency (Type 1):

Deficiency of lipoprotein lipase or deficiency of Apo C2 ,result in slow clearance of chylomicron & VLDL from the serum leading to hypertriglyceridemia.

Familial hyper cholestrolemia (Type 2) :

Defective in Apo B receptors or mutation in ligand region of Apo B.

1. Type IIa : increase in LDL →increase cholesterol.
2. Type II b : increase LDL & VLDL → increase cholesterol & TG.

Type II may arise secondary to hypothyroidism.

Broad β disease (Type 3):

Due to abnormality in Apo E leading to increase chylomicron remnant & VLDL remnant which appear as broad band on electrophoresis.

hypertriglyceridemia (Type 4):

Over production of VLDL by the liver, it may also arise secondary to diabetes type 2 ,obesity ,alcoholism & taking progestational hormones.

familial lipoproteinemia (Type 5)

Increase in chylomicron (not remnant) & VLDL also it may arise secondary to diabetes & obesity.