BHARATHIDASAN UNIVERSITY

Tiruchirappalli – 620024

Tamil Nadu, India.

Programme: Biochemistry

Course Title: Intermediary Metabolism

COURSE CODE: BC201CR

Unit: 4

Lipids Metabolism

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BIOSYNTHESIS OF FATTY ACIDS

- The dietary carbohydrates and amino acids,when consumed in excess, can be converted to fatty acids and stored as triacylglycerols.
- Occurs in liver,kidney,adipose tissue,and lactating mammary glands.
- Enzymes for fatty acid synthesis are present in cytosomal fraction.

Three stages of fatty acid synthesis,

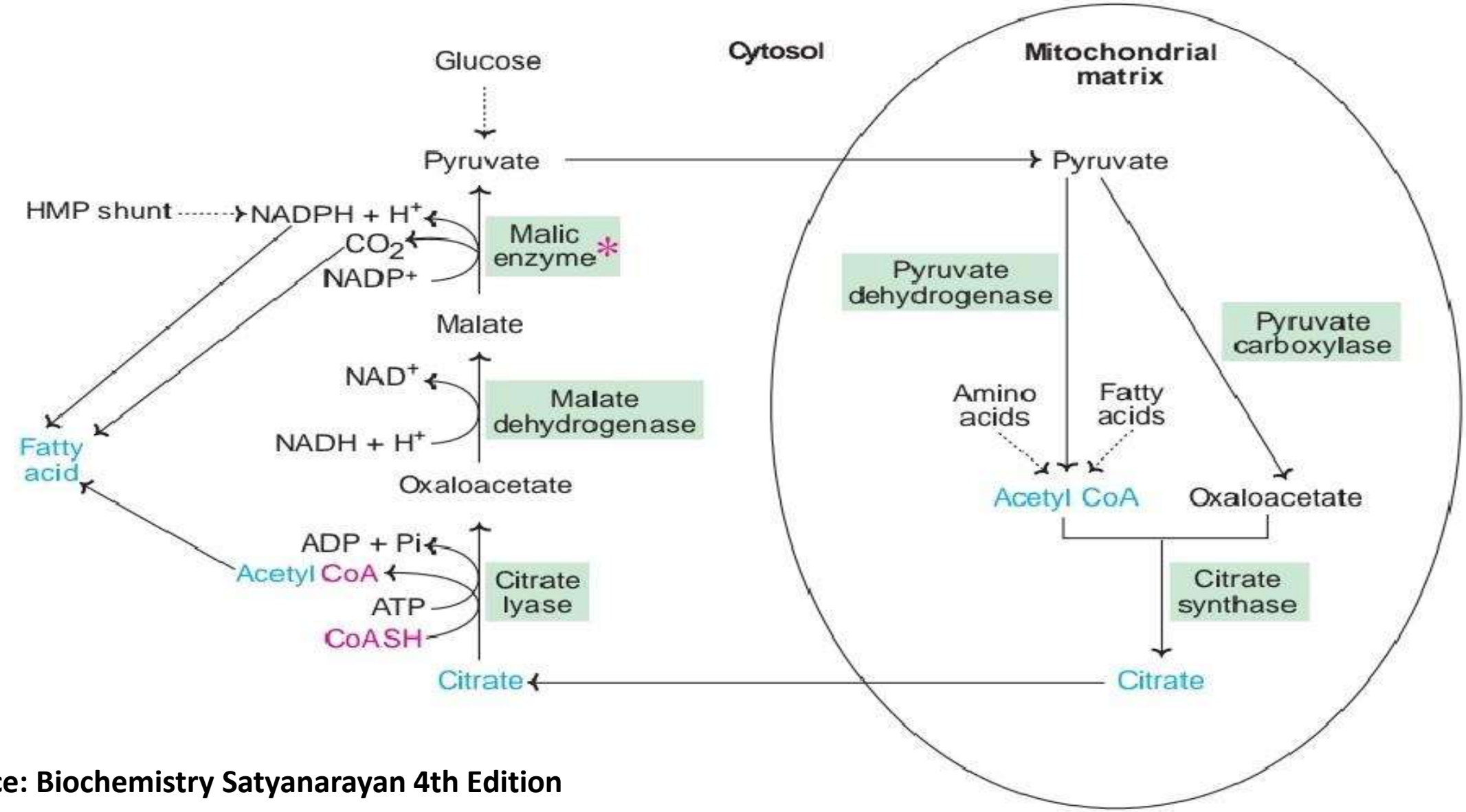
1. **Production of acetyl coA and NADPH**

- Acetyl coA and NADPH are the prequisite for fatty acid synthesis.
- Acetyl coA is produced in mitochondria,which is impermeable to acetyl coA.
- So an alternate or a bypass arrangement is made for the transfer of acetyl coA.
- NADPH and CO2 are also generated in this reaction.

2. **conversion of acetyl coA to malonyl coA**

3.**Reactions of fatty acid synthase complex**

Transfer of acetyl CoA from mitochondria to cytosol



Source: Biochemistry Satyanarayan 4th Edition

2.Conversion of acetyl CoA to malonyl CoA:

- Acetyl coA is converted to malonyl coA by the enzyme acetyl coA carboxylase(a regulatory enzyme in fatty acid synthesis)
- This is an ATP-dependent reactionand requires biotin for CO2 fixation.

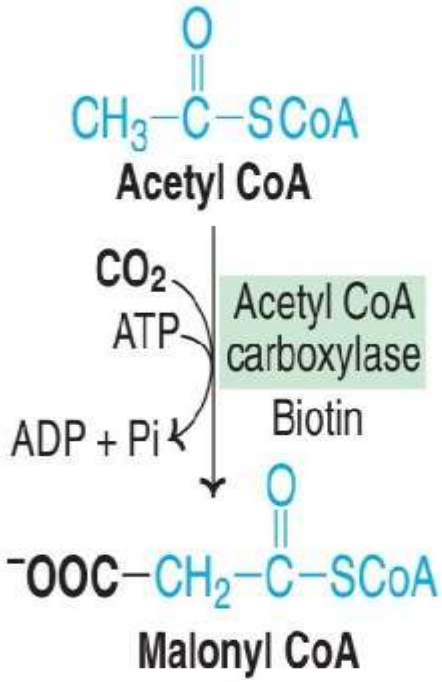


Fig. 14.15 : Conversion of acetyl CoA to malonyl CoA.

Source: Biochemistry Satyanarayan 4th Edition

3.Reactions of fatty acid synthase complex:

Fatty acid synthase complex

- A multifunctional enzyme made up of dimer with two identical subunits.
- Each monomer possesses the activities of seven different enzymes and an acyl carrier protein (ACP).
- The two subunits lie in antiparallel (head-to-tail) orientation.

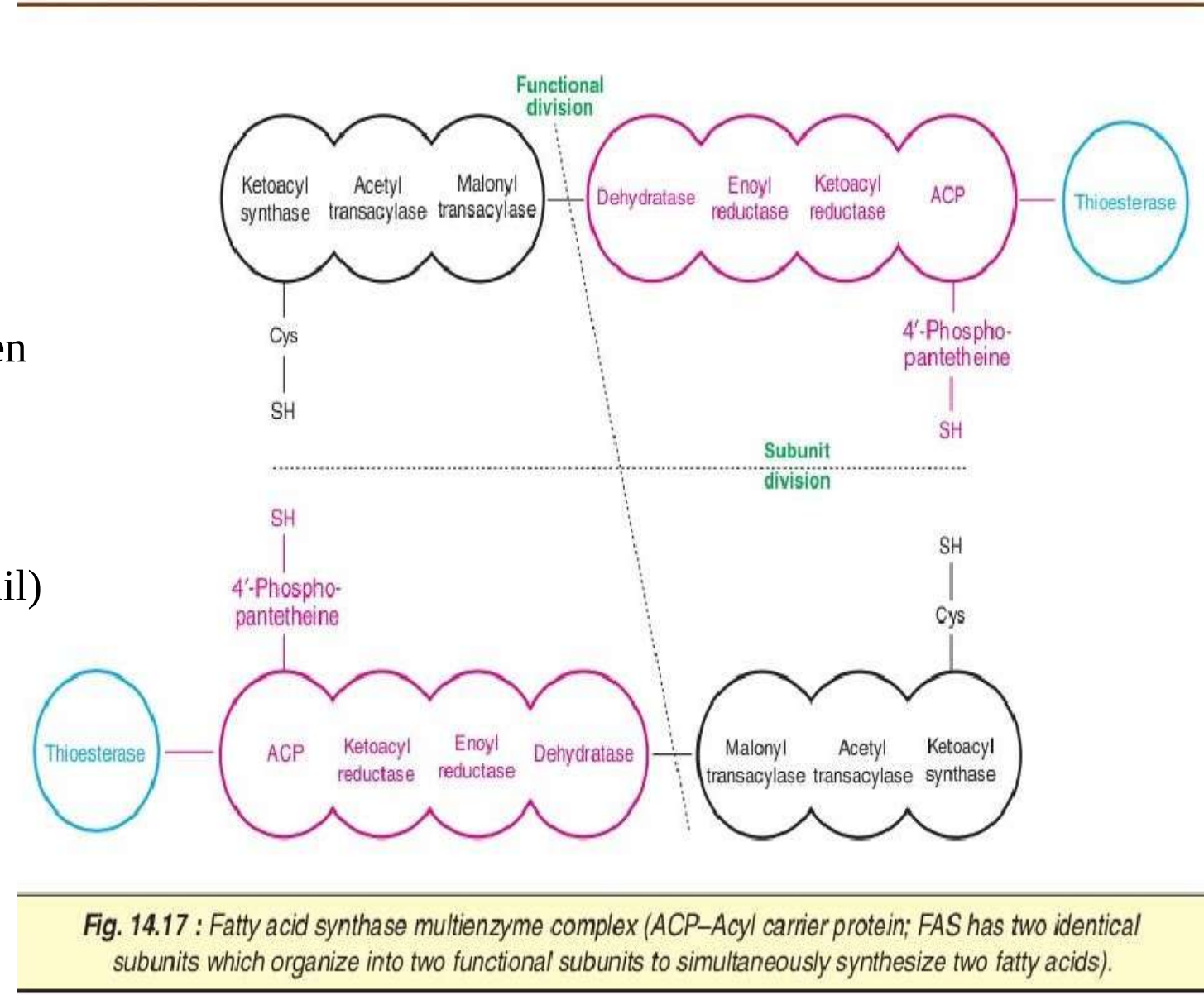


Fig. 14.17 : *Fatty acid synthase multienzyme complex (ACP–Acyl carrier protein; FAS has two identical subunits which organize into two functional subunits to simultaneously synthesize two fatty acids).*

Source: Biochemistry Satyanarayan 4th Edition

Biosynthesis of long chain fatty acid-palmitate

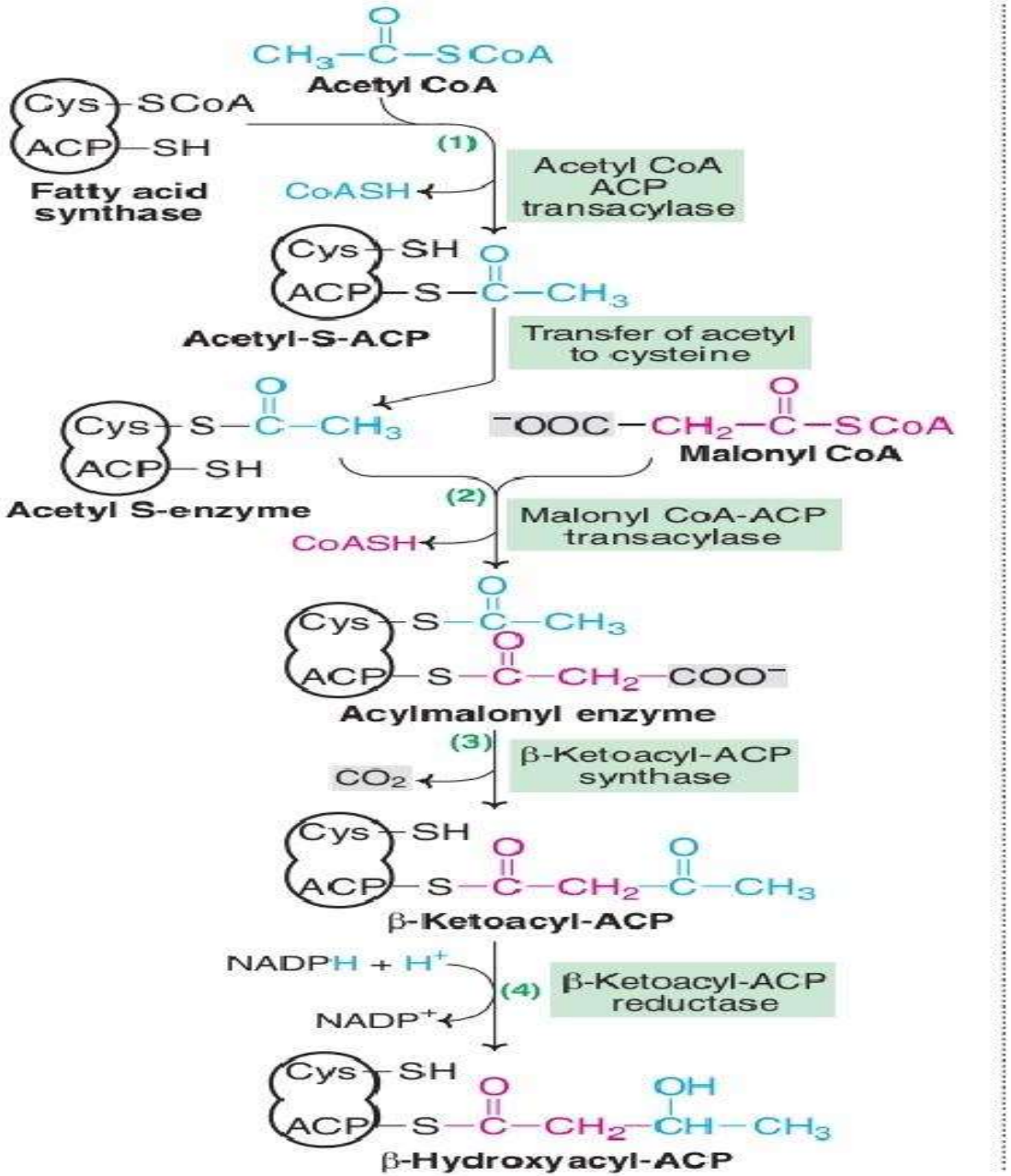
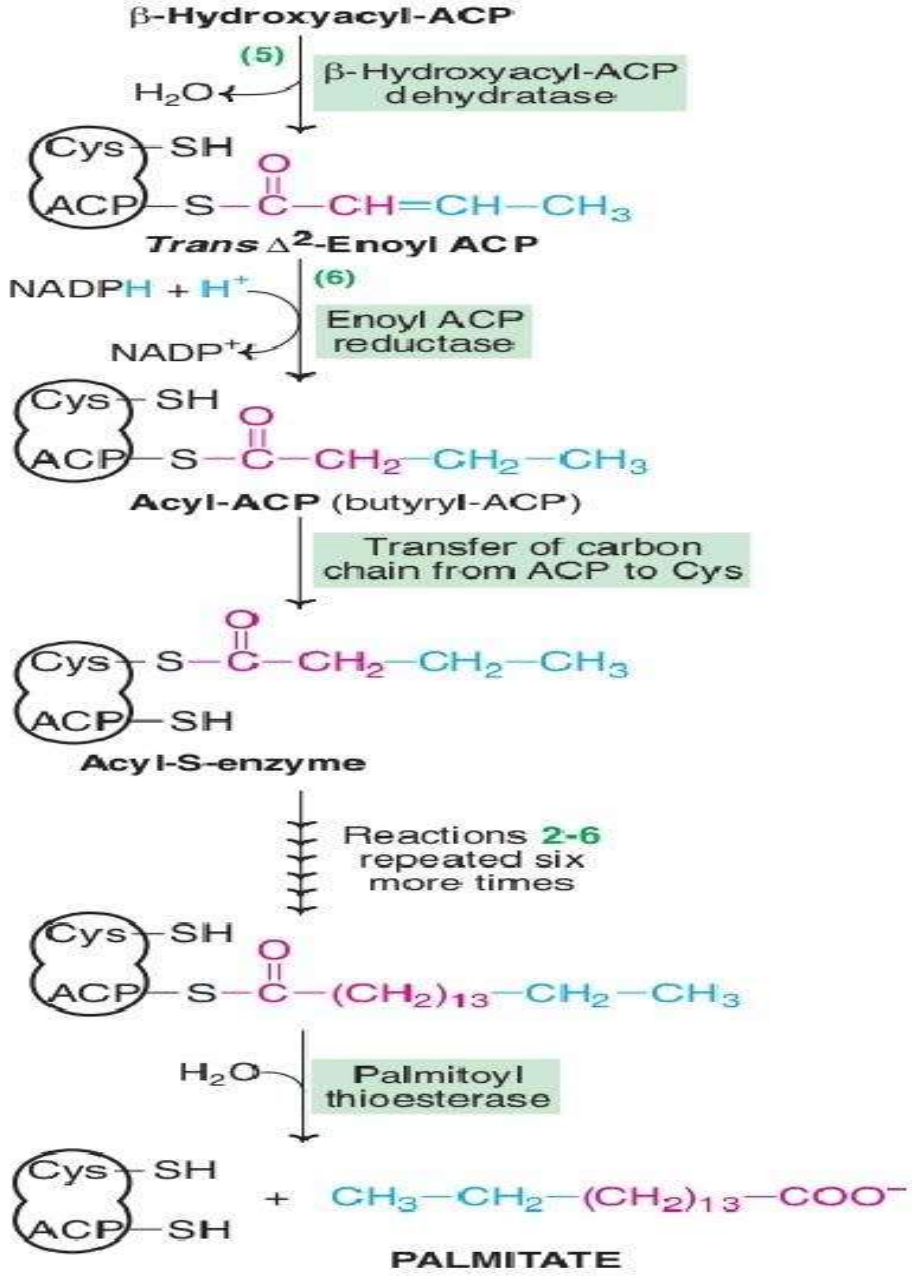


Fig. 14.16 contd. next column



Source: Biochemistry Satyanarayan 4th Edition

Regulation of fatty acid synthesis

1.**Acetyl CoA carboxylase:**

- Availability of citrate promote fatty acid synthesis.
- On the other hand, palmitoyl CoA and malonyl CoA cause inhibit fatty acid synthesis.

2. **Hormonal influence:**

- Insulin promotes fatty acid synthesis while glucagon inhibits.

3.**Dietary regulation:**

- Consumption of high carbohydrate or fat-free diet increases the fatty acid synthesis

4.**Availability of NADPH :**

- NADPH is obtained from HMP shunt, which significantly influences fatty acid synthesis.

TRIACYLGLYCEROLS

- Triacylglycerols or triglycerides are formed by ester linkage of fatty acids to three alcohol groups in glycerol.
- Stored in the form of fats in adipose tissue, to be used later as fuel.

Biosynthesis of TAG:

- TAGs share two precursors; fatty acyl-CoA and L-glycerol 3-phosphate.

Formation of L-glycerol 3-phosphate:

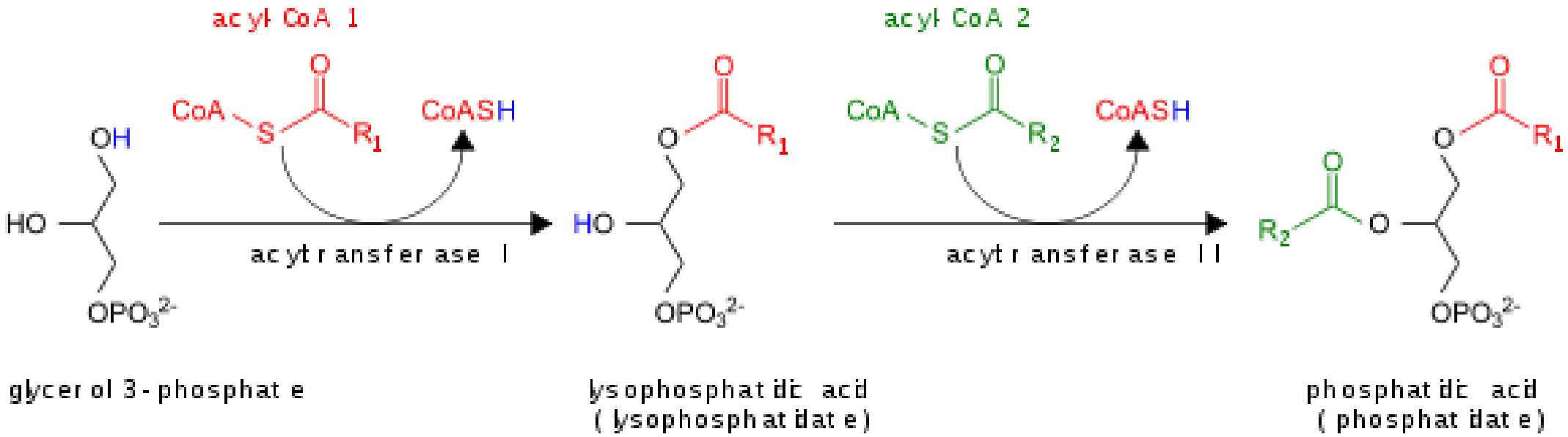
- Majority of the glycerol 3-phosphate is derived from the glycolytic intermediate dihydroxyacetone phosphate (DHAP) by the action of glycerol 3-phosphate dehydrogenase.
- In liver and kidney, it is also formed from glycerol by the action of glycerol kinase.

Formation of fatty acyl-CoAs:

The fatty acyl-CoA sare formed from fatty acids by acyl-CoA synthetases, the same enzymes responsible for the activation of fatty acids for β-oxidation.

Steps in biosynthesis of TAG:

1. Conversion of L-glycerol 3-phosphate to diacylglycerol 3- phosphate (Phosphatidic acid)



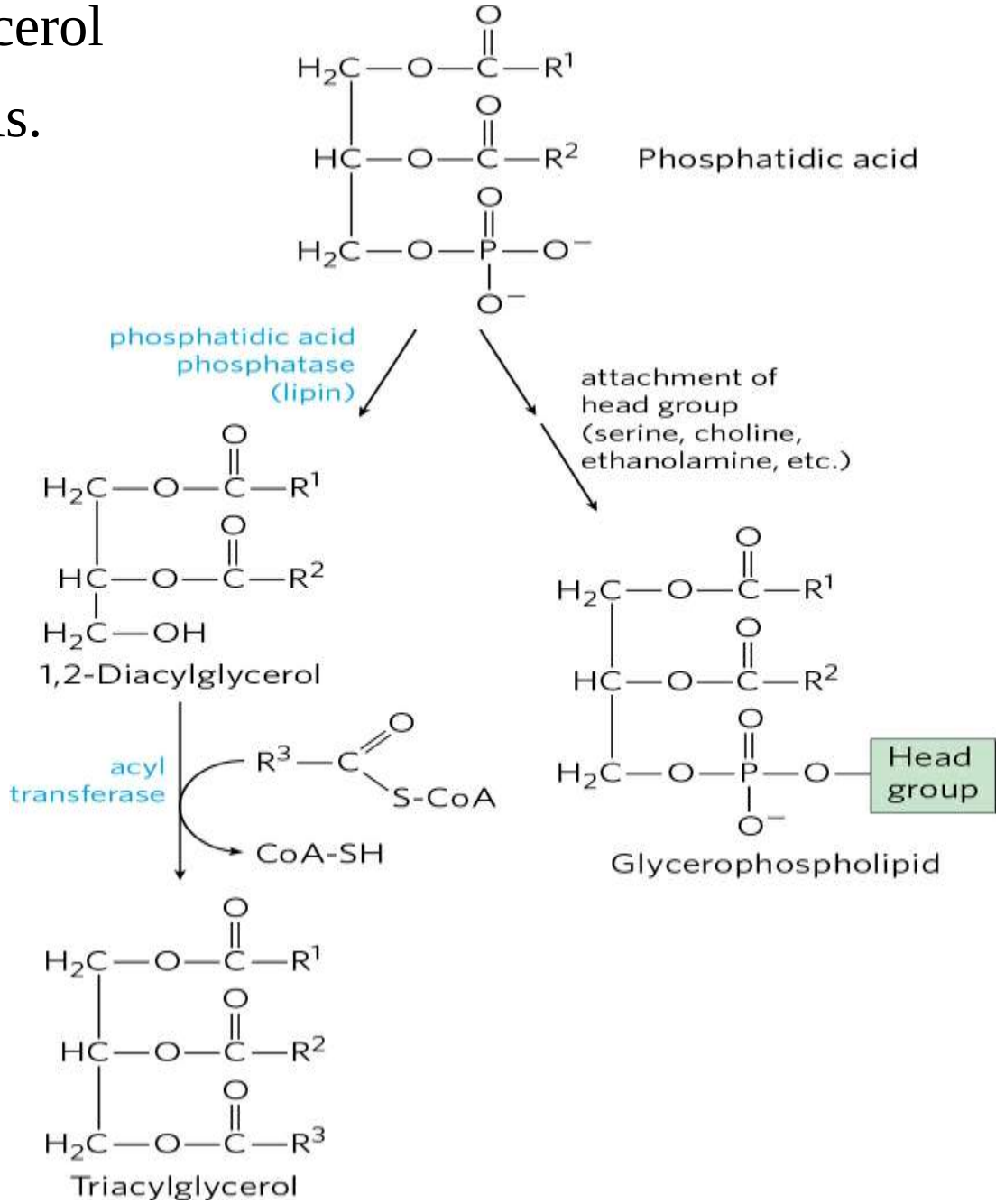
glycerol 3-phosphate

lysophosphatidic acid
(lysophosphatidate)

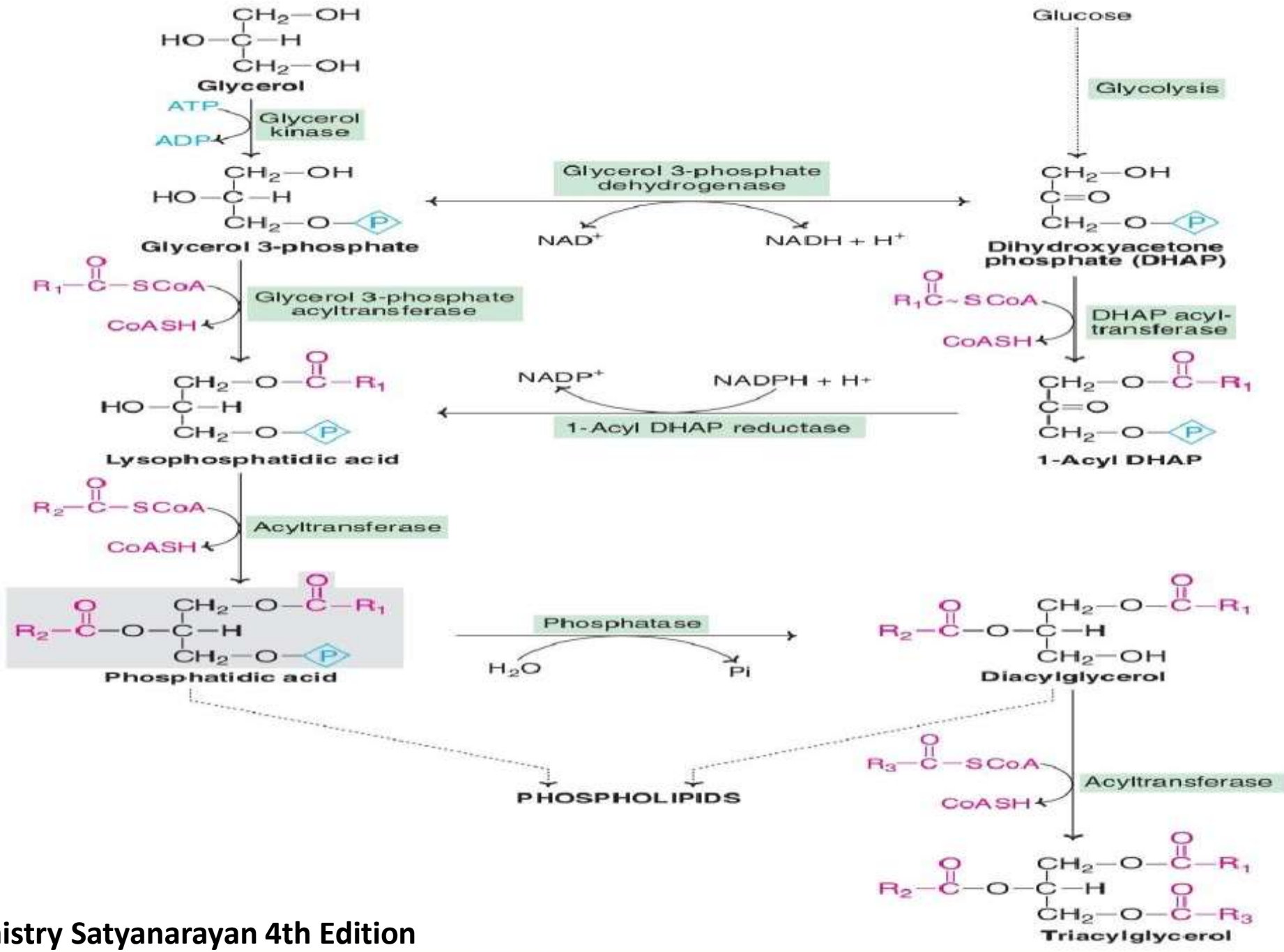
phosphatidic acid
(phosphatidate)

2. Hydrolysis of Phosphatidic acid into 1,2-diacylglycerol
3. Conversion of diacylglycerols into Triacylglycerols.

The intermediates of Triacylglycerol synthesis phosphatidic acid and diacylglycerol are also utilized for phospholipid synthesis.



Source: Biochemistry Satyanarayan 4th Edition

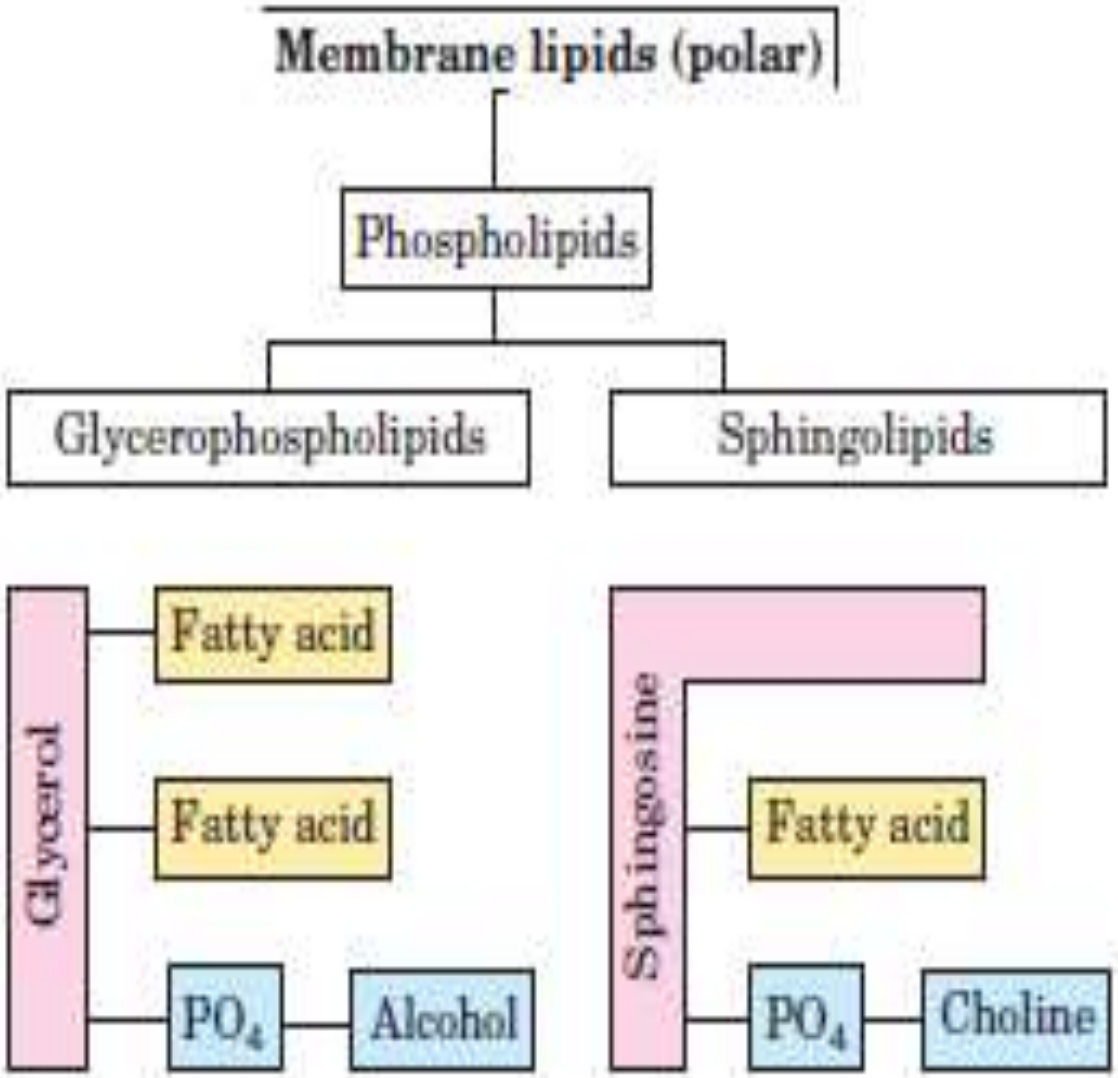


Source: Biochemistry Satyanarayan 4th Edition

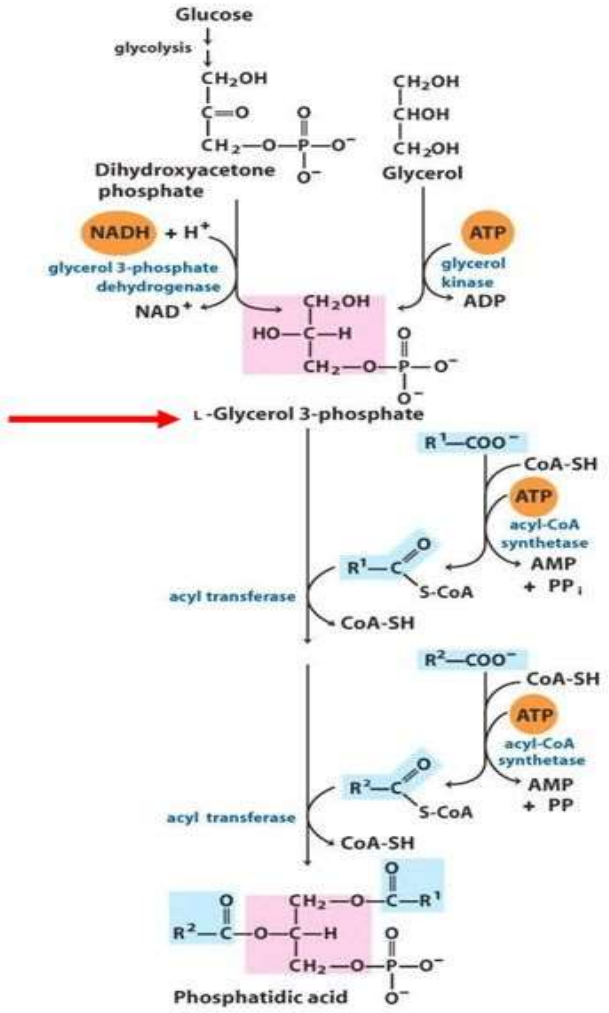
Fig. 14.18 : Synthesis of triacylglycerol.

PHOSPHOLIPIDS

- Phospholipids are polar membrane lipids with polar head groups and non-polar tail which are major constituents of membrane lipids.
- There are two classes - glycerophospholipid and sphingolipids.
- If the backbone is glycerol they are called glycerophospholipid and
- if sphingosine it is called as sphingolipids
- **Source : Principles of Biochemistry , Lehninger Nelson & Cox, 4th**



SYNTHESIS OF PHOSPHOLIPIDS



Phosphatidic acid is derived from L-glycerol 3-phosphate and two acyl-CoAs

Source : Principles of Biochemistry , Lehninger Nelson & Cox, 4th

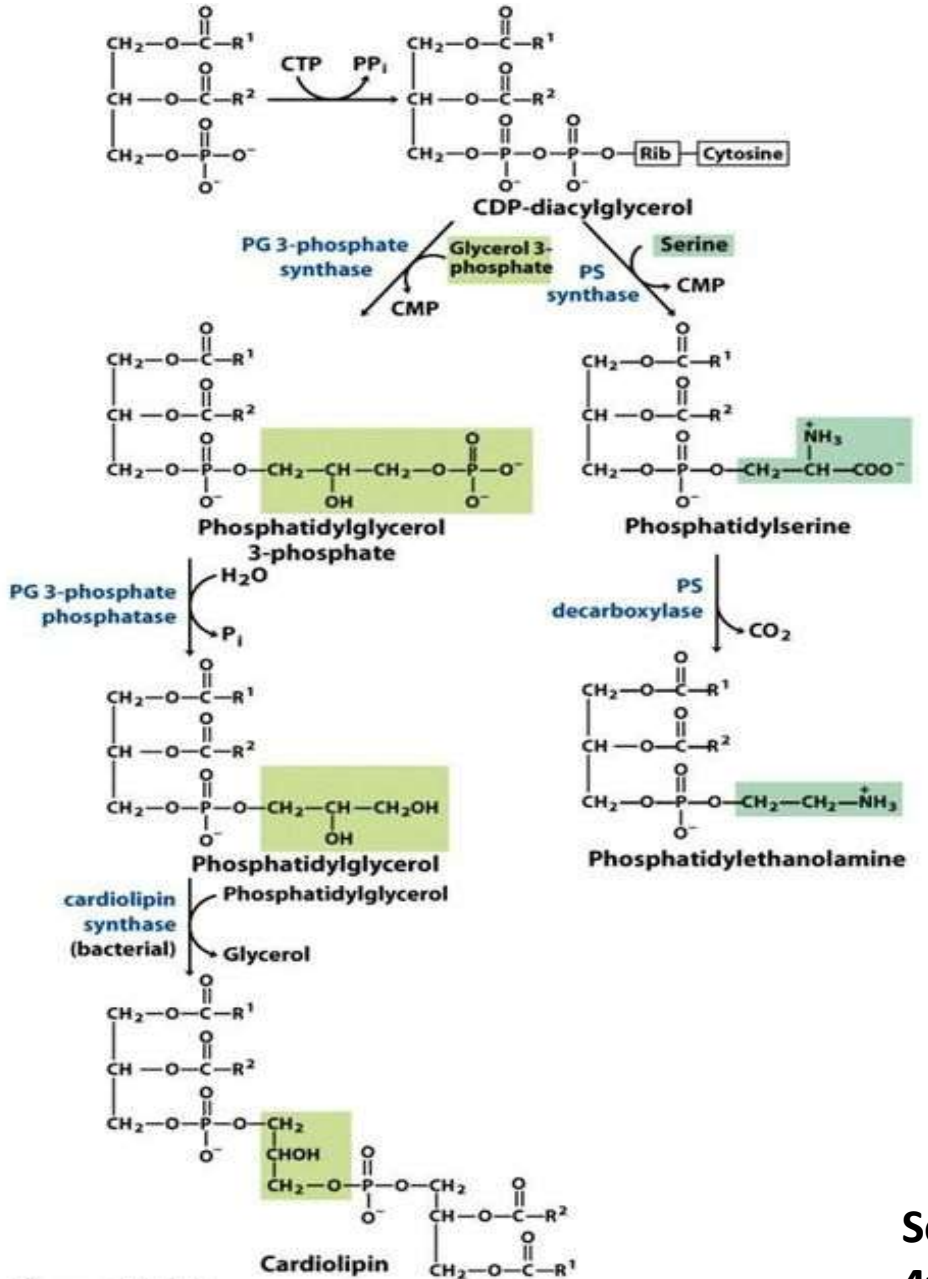


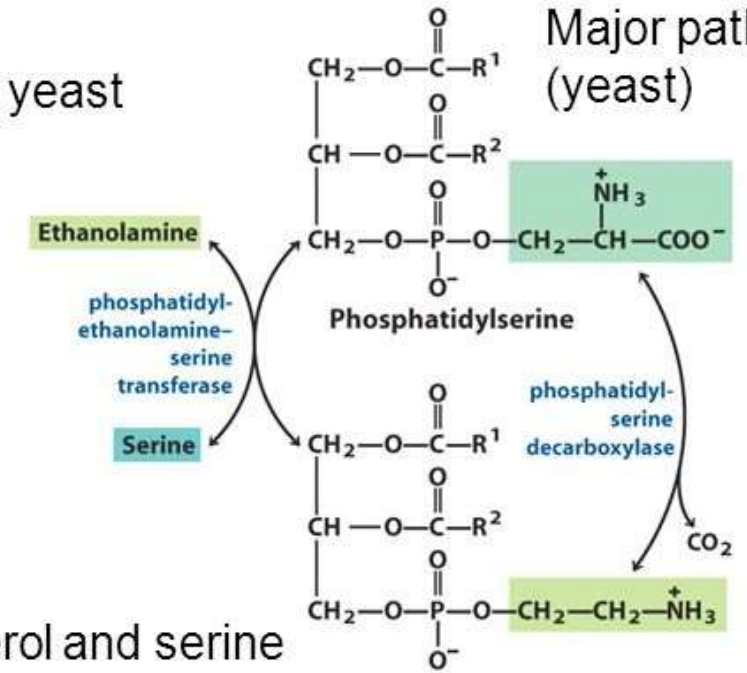
Figure 21-25
Lehninger Principles of Biochemistry, Fifth Edition

Origin of the polar head groups of phospholipids in *E. coli*. Initially, a head group (either serine or glycerol 3-phosphate) is attached via a CDP diacylglycerol intermediate (strategy 1

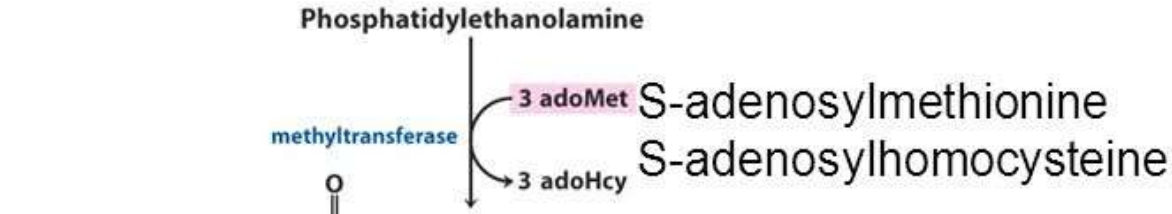
Source : Principles of Biochemistry , Lehninger Nelson & Cox, 4th

Figure, 21-27, 28-a
Salvage pathway in yeast

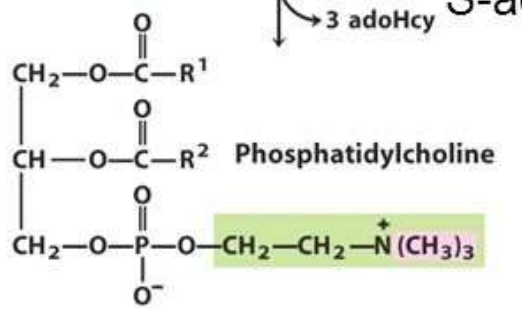
Major pathway in Eukaryotes
(yeast)



In mammals
(no CDP-diacylglycerol and serine to PS)
Head-group exchange
(PC—PS or PE—PS)

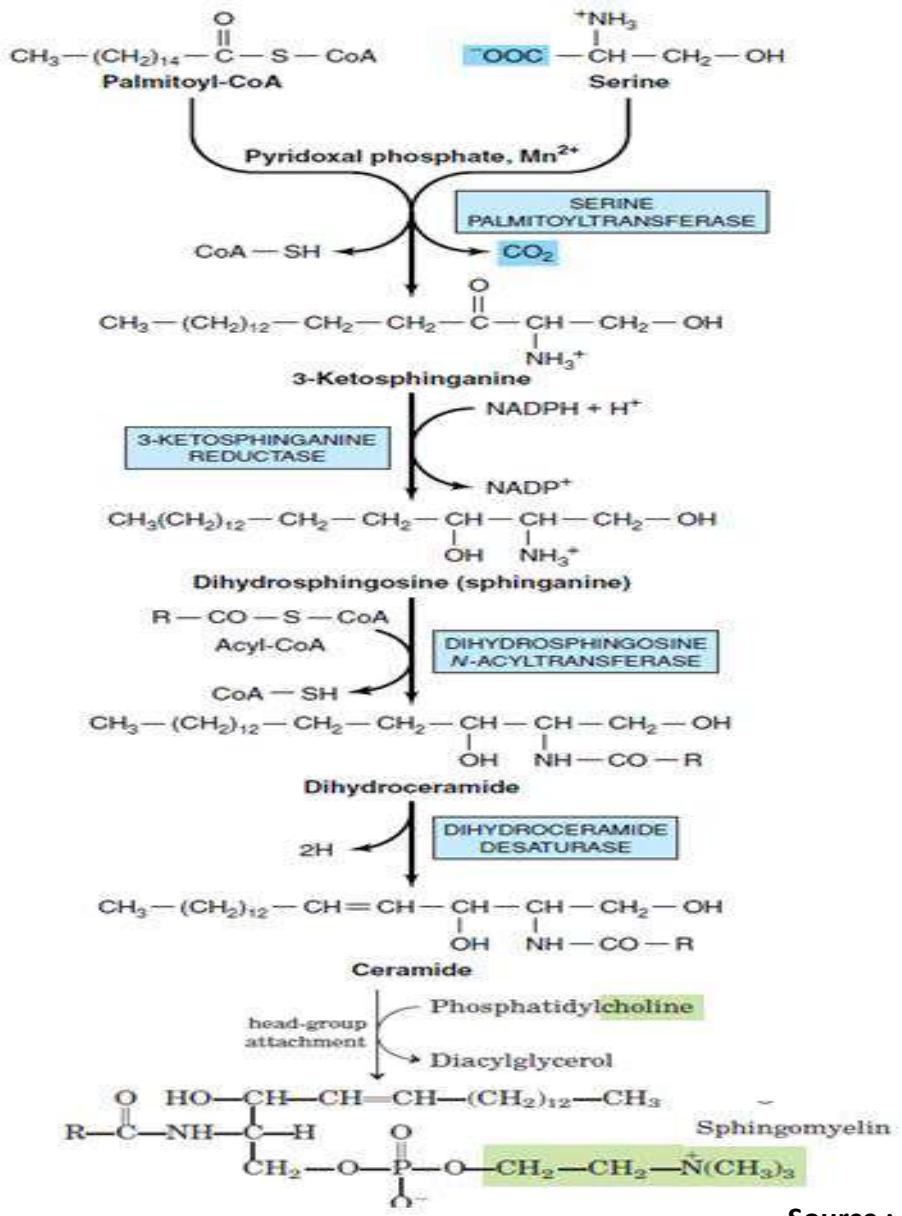


phosphatidylserine ⇌



Source : Principles of Biochemistry , Lehninger Nelson & Cox, 4th

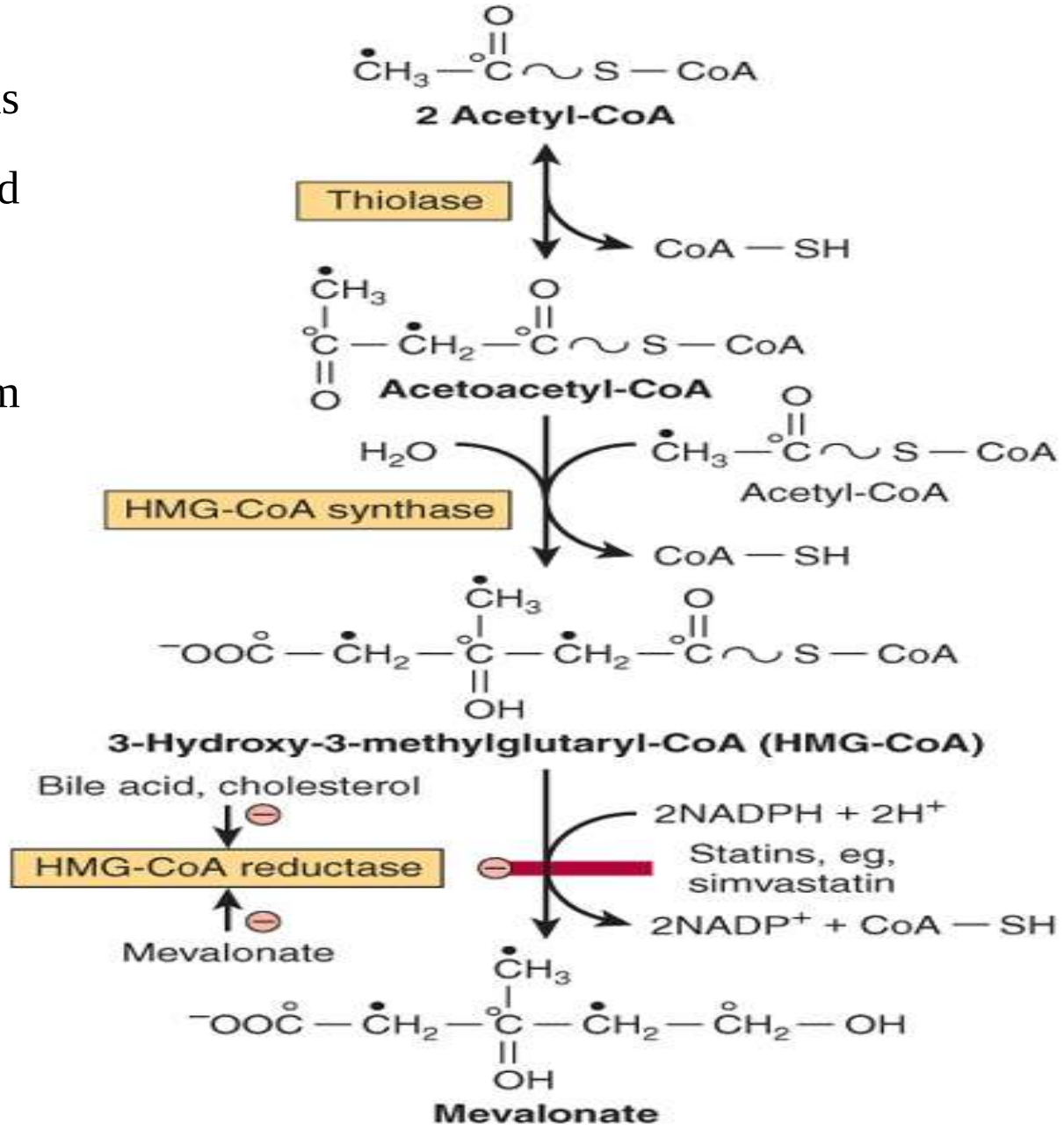
Sphingomyelin Biosynthesis



Source : Harper's Illustrated Biochemistry,26th Edition

BIOSYNTHESIS OF CHOLESTEROL

- Cholesterol is an amphipathic molecule that serves as component of membrane, plasma lipoproteins and precursors of steroid hormones, Vitamin D and bile acids.
- It is present either in free form or in the storage form combined with fatty acid to form cholesterol ester.
- In plasma both are transported in the form of lipoproteins



Source:https://www.google.com/url?sa=i&url=https%3A%2F%2Fslideplayer.com%2Fslide%2F14046192%2F&psig=AOvVaw3nAdwms55

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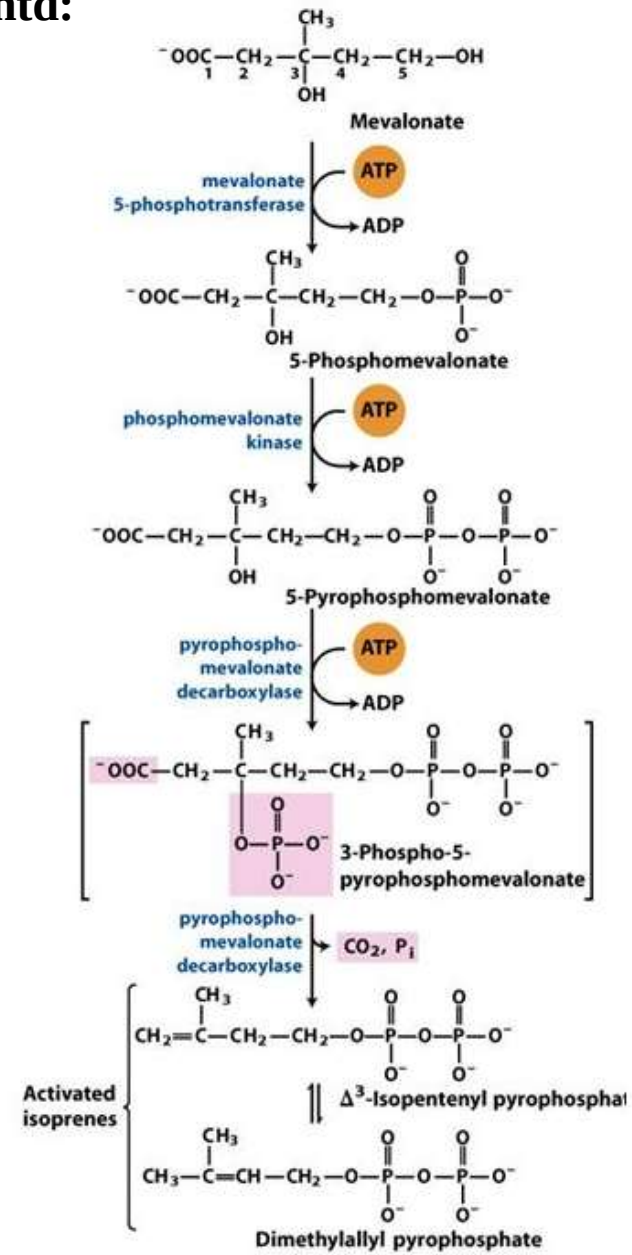
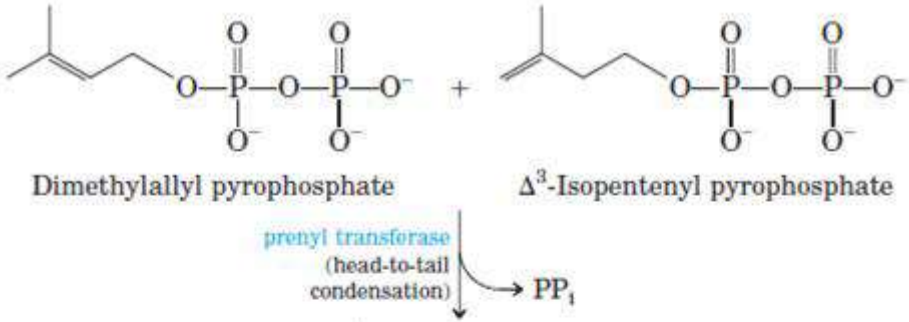
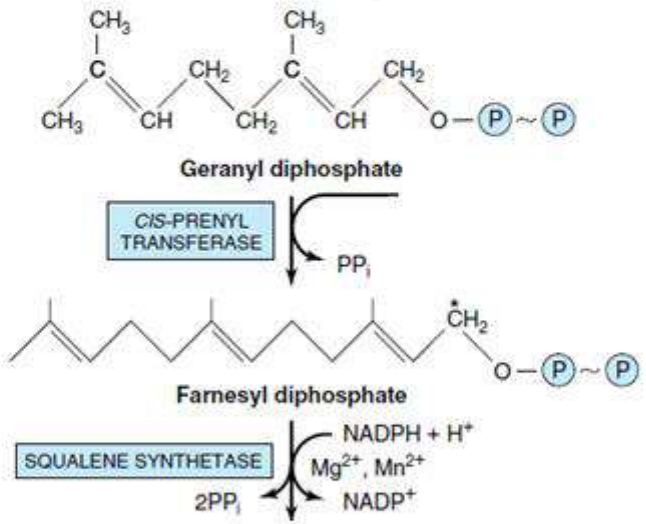
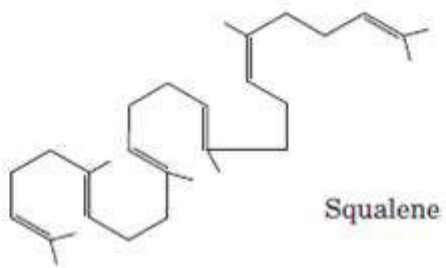
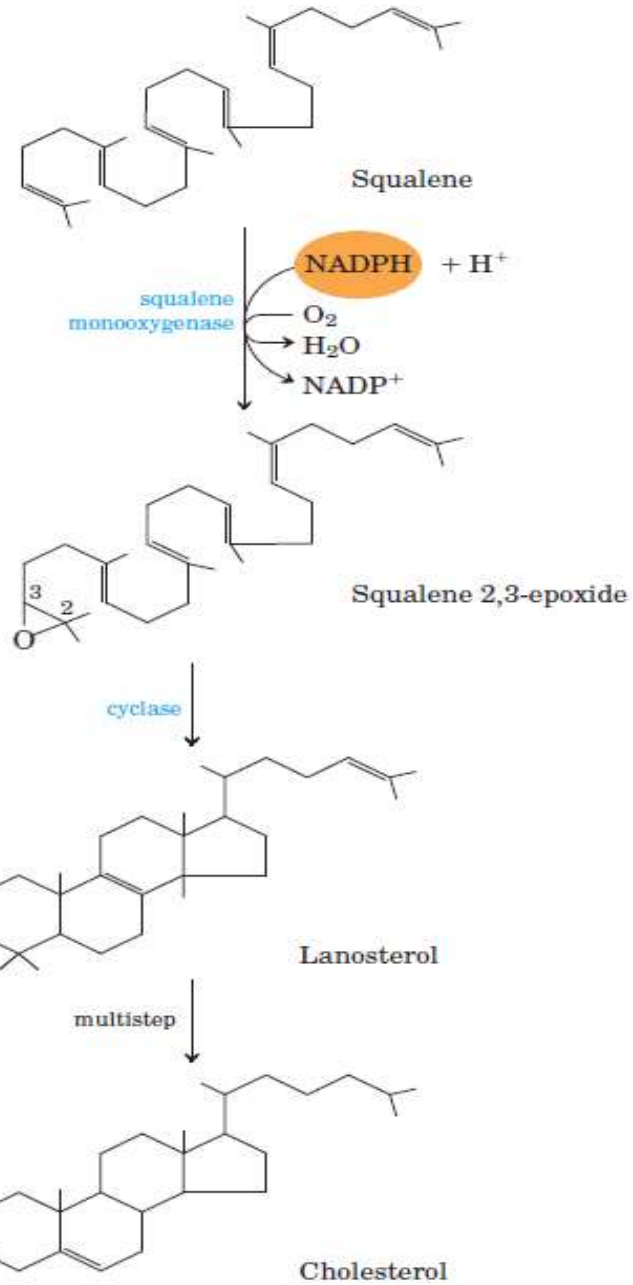










Source : Principles of Biochemistry , Lehninger Nelson & Cox, 4th

Degradation of Cholesterol

- Cholesterol is converted to coprostanol by the bacterial action in the small intestine
- Cholesterol in small amount is incorporated in to the membrane of the hepatocytes.
- Free cholesterol is converted to ester form by the action of acyl-CoA – cholesterol acyl transferase (ACAT) which transfers the acyl group from CoA.

Beta oxidation of fatty acid

- Beta-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA
- Acetyl-CoA enters the citric acid cycle while NADH and FADH2, which are co- enzymes, are used in the electron transport chain.
- It is referred as "beta oxidation" because the beta carbon of the fatty acid undergoes oxidation to a carbonyl group.

Role of Carnitine in Beta oxidation

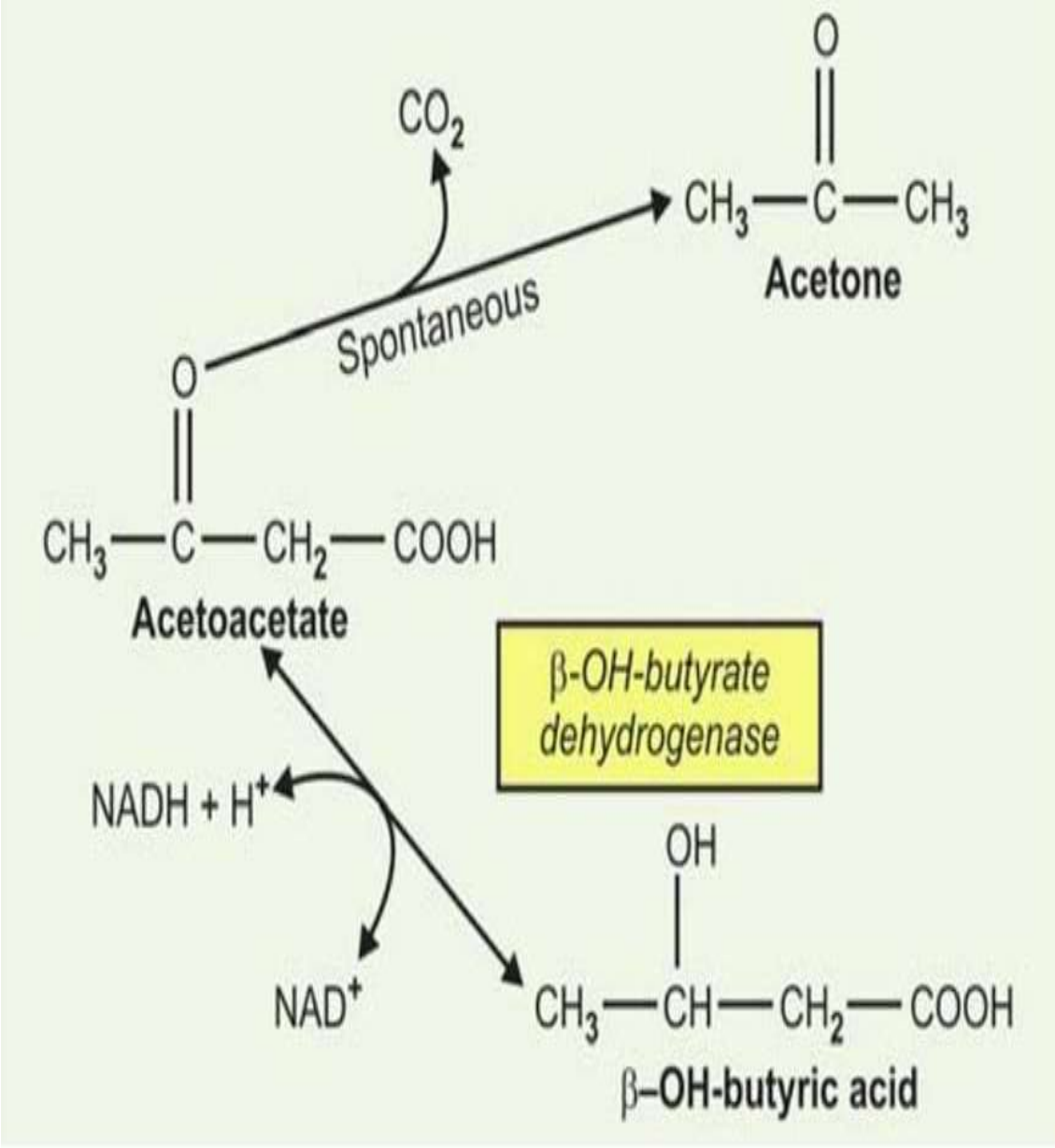
- Inner membrane is impermeable to fatty acyl CoA
- Activated long chain fatty acyl CoA are carried across the inner- mitochondrial membrane by Carnitine.
- The acyl group is transferred from the Sulfur atoms of fatty acyl Co A to the hydroxyl group
- Reaction carried out by the enzyme Carnitine acyl transferase located on the outer surface of inner mitochondrial membrane
- This modification is sufficient to cross the inner mitochondrial membrane
- Fatty acyl carnitine then enters the mitochondrial matrix facilitated diffusion through Carnitine transporter of the inner mitochondrial membrane.
- The acyl group is transferred back to CoA on the matrix side of the membrane
- Free carnitine re-enters intermembrane space through carnitine transporter

Regulation of Beta-Oxidation of Fatty Acids

- B-Oxidation is regulated by the mechanisms that control oxidative phosphorylation
- **Activators:** Epinephrine stimulates ß-oxidation by activating a cAMP-dependent protein kinase, which leads to the phosphorylation and thus activation of HSL. When activated, HSL releases fatty acids and glycerol from adipose tissue for ß-oxidation.
- **Inhibitors:** Insulin inhibits ß-oxidation by dephosphorylating HSL and thus inhibiting the release of fatty acids from adipose tissue.
- Fatty acids, which are the major source of energy in the human body, are oxidized mainly by ß-oxidation.

ketogenesis:

- Ketone bodies are water-soluble molecules or compounds that contain the ketone groups produced from fatty acids by the liver (ketogenesis).
- Three substances are collectively known as “ketone bodies” (or “acetone bodies”).
- Acetoacetate, acetone and β-OH butyric acid are metabolic products that are produced in excess during excessive breakdown of fatty acid.
- Acetoacetate continually undergoes spontaneous decarboxylation to produce acetone



Source: Medical Biochem 8th edition-MN Chatterjee,Rana shinde

Regulation of ketogenesis

Ketogenesis speeds up or slows down depending on three important factors:

- **The level of circulating Free FattyAcids:** Ketosis does not occur in vivo unless there is a rise in the level of circulating free fattyacids that arises from lipolysis of triglycerides in adipose tissues. Therefore, conditions that affect mobilization of free fattyacids from adipose tissues are important in controlling ketogenesis.

Lipoprotein

- Lipoprotein is a carrier protein which carries the dietary lipids to transfer into our cells through out the blood stream.
- Lipoproteins are made up of lipid and protein molecule. The purpose of protein is transfer the hydrophobic compounds through the polar components.
- Lipoproteins are further classified by their density, amount of cholesterol. There are 5 main types of lipoproteins are present, they are ;

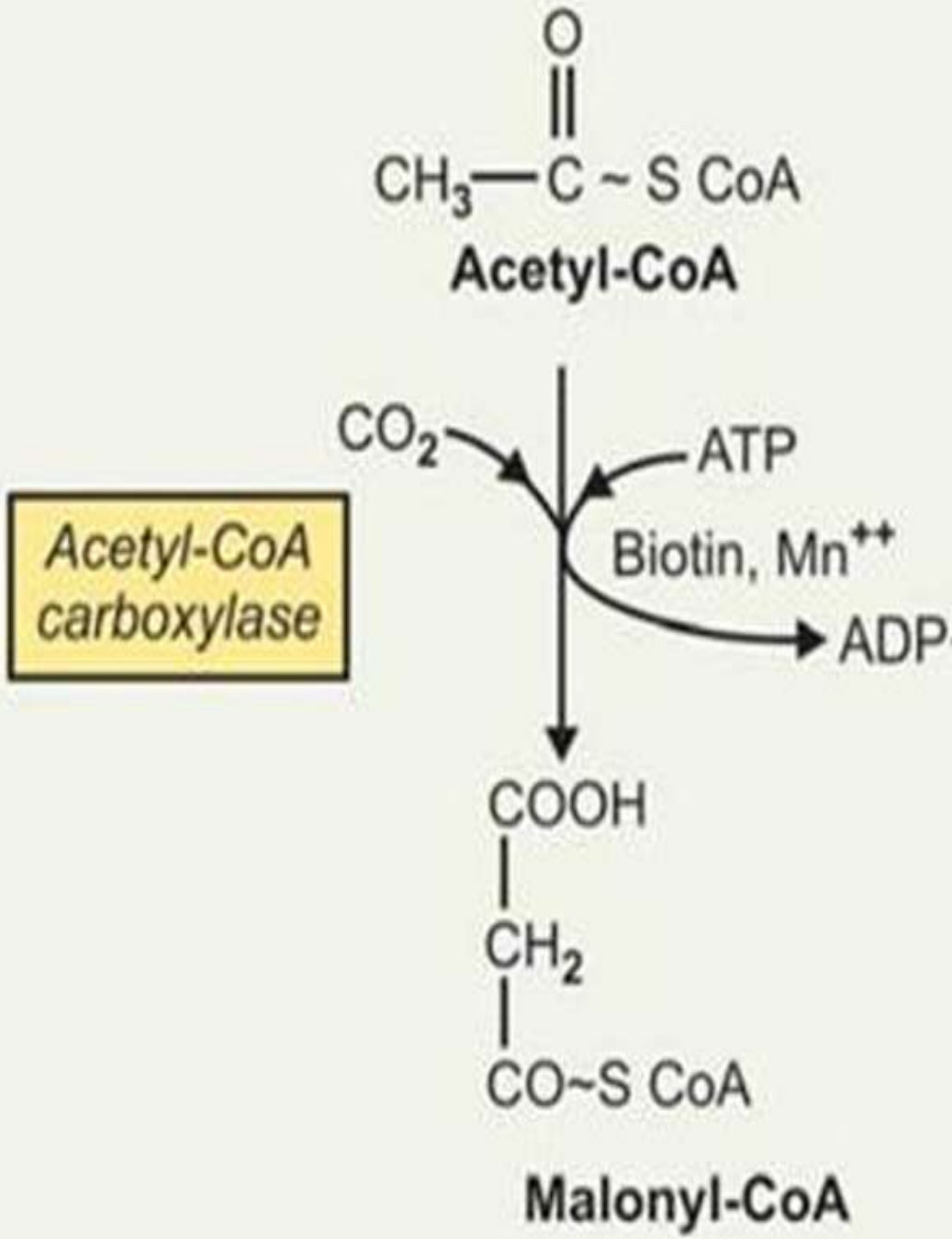
1. Chylomicron
2. VLDL
3. LDL
4. HDL

- Lipoprotein can transfer the dietary lipids and the hepatic cholesterol by two major pathways

1. Exogenous pathway
2. Endogenous pathway

- **Rate of entry of F.F.As into the liver:** If F.F.As are entering the liver cells in low concentrations, they will nearly all esterified into triglycerides and transported out of the liver in very low density lipoproteins (VLDL). However, when high concentrations of F.F.As enter the liver such as in starvation, the acetyl CoA carboxylase (gate-keeper enzyme) is inhibited and malonyl CoA decreases.

- Decrease malonyl CoA result in increased beta oxidation of fatty acid activation of carnitine palmitoyl transferase I and allow more fatty acyl CoA to be oxidized.



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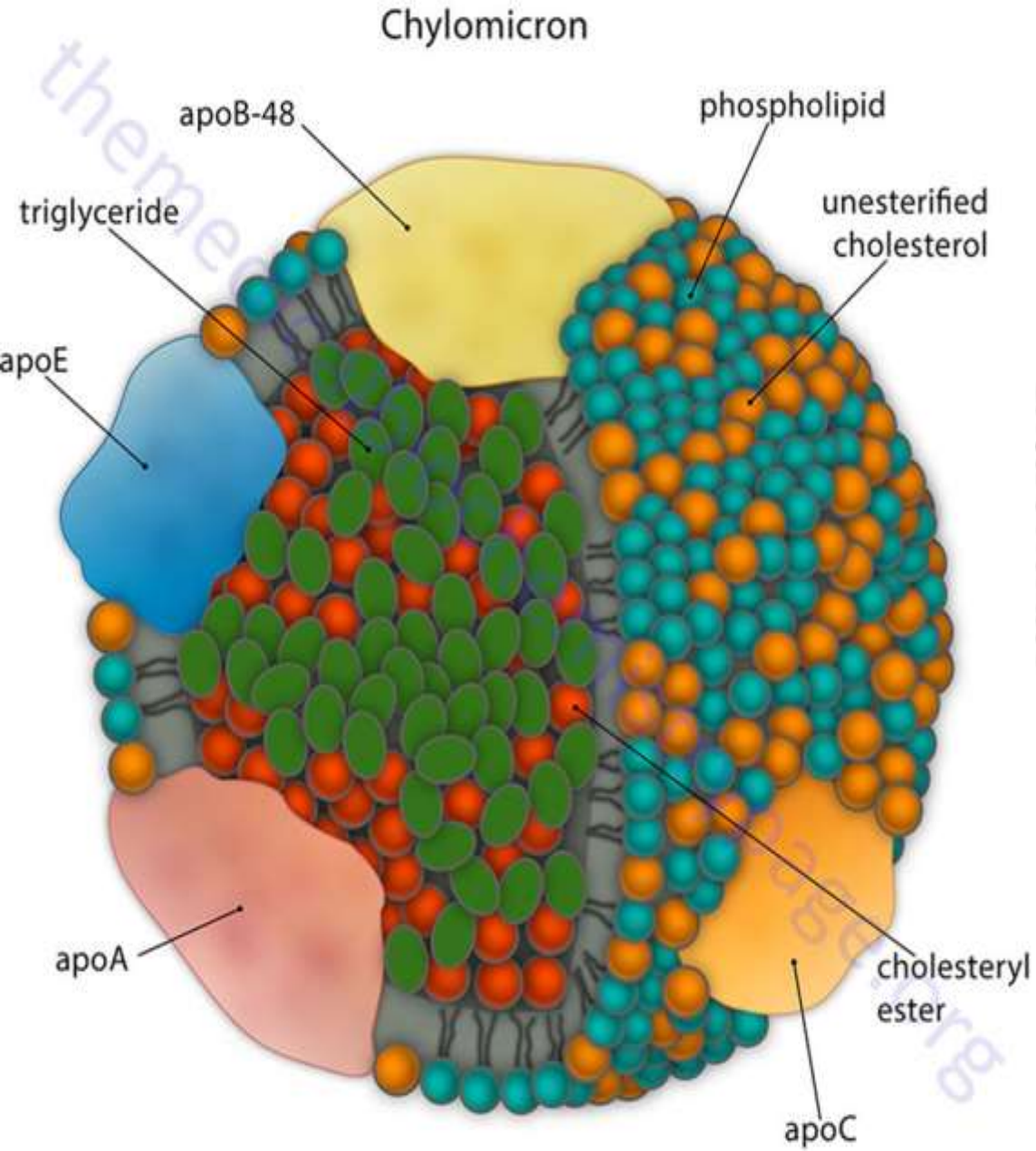
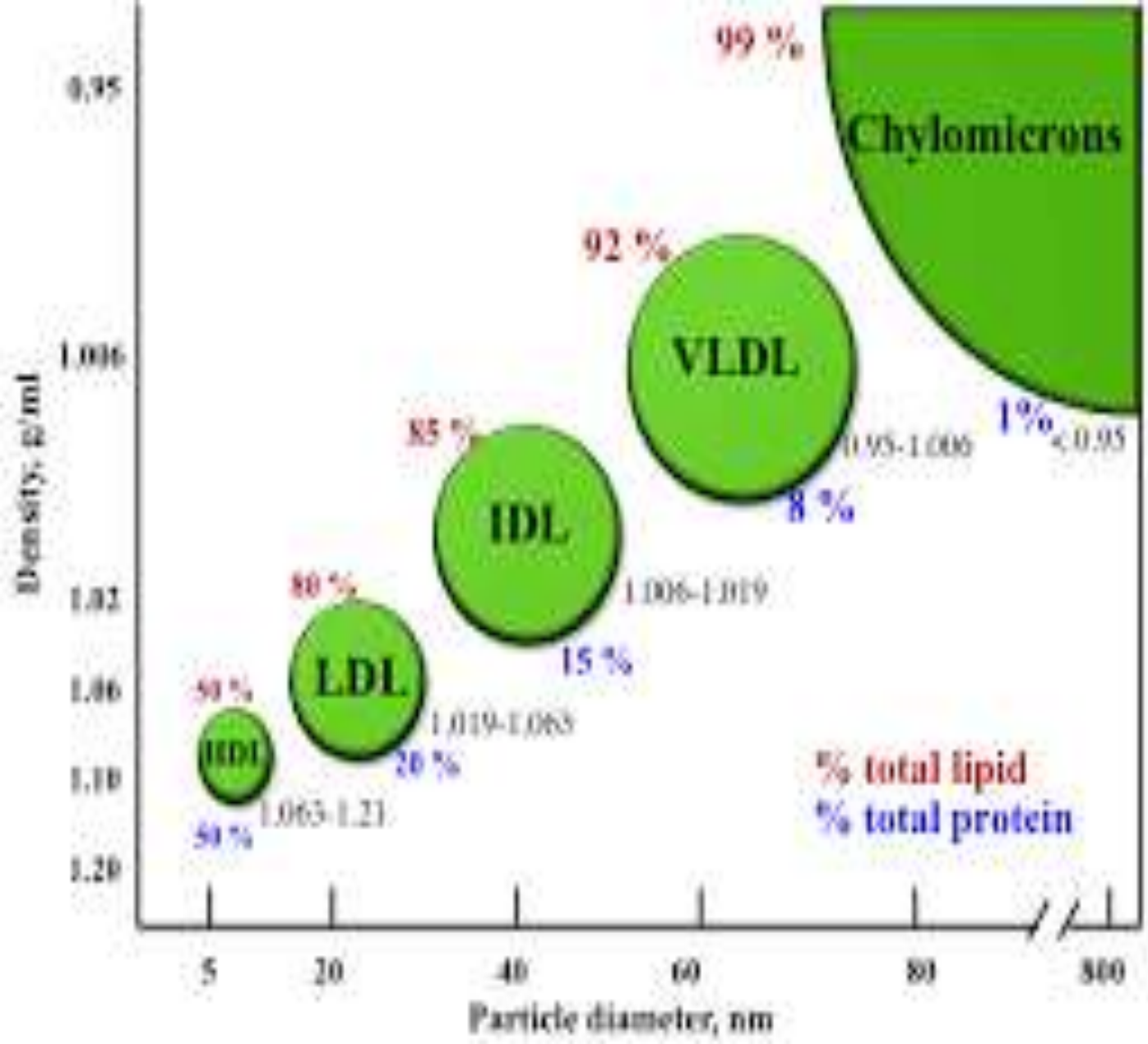




Source:https://themedicalbiochemistrypage.org/lipoproteins-blood-lipids-and-lipoprotein-metabolism/

Apolipoprotein:

- Apolipoproteins are present in the outer membrane of the lipoprotein.
- Apolipoproteins are mainly used for the identification of site and it can solubilize the lipids in aqueous solution.
- And it can act as a activator of some enzymes which are required for the lipoprotein metabolism.
- Every lipoprotein has individual apolipoprotein.
- There are 4 types of apolipoprotein they are

1. Apo A-[1,II,III]
2. Apo B-[48;100]
3. Apo C-[I,II,III]
4. Apo E

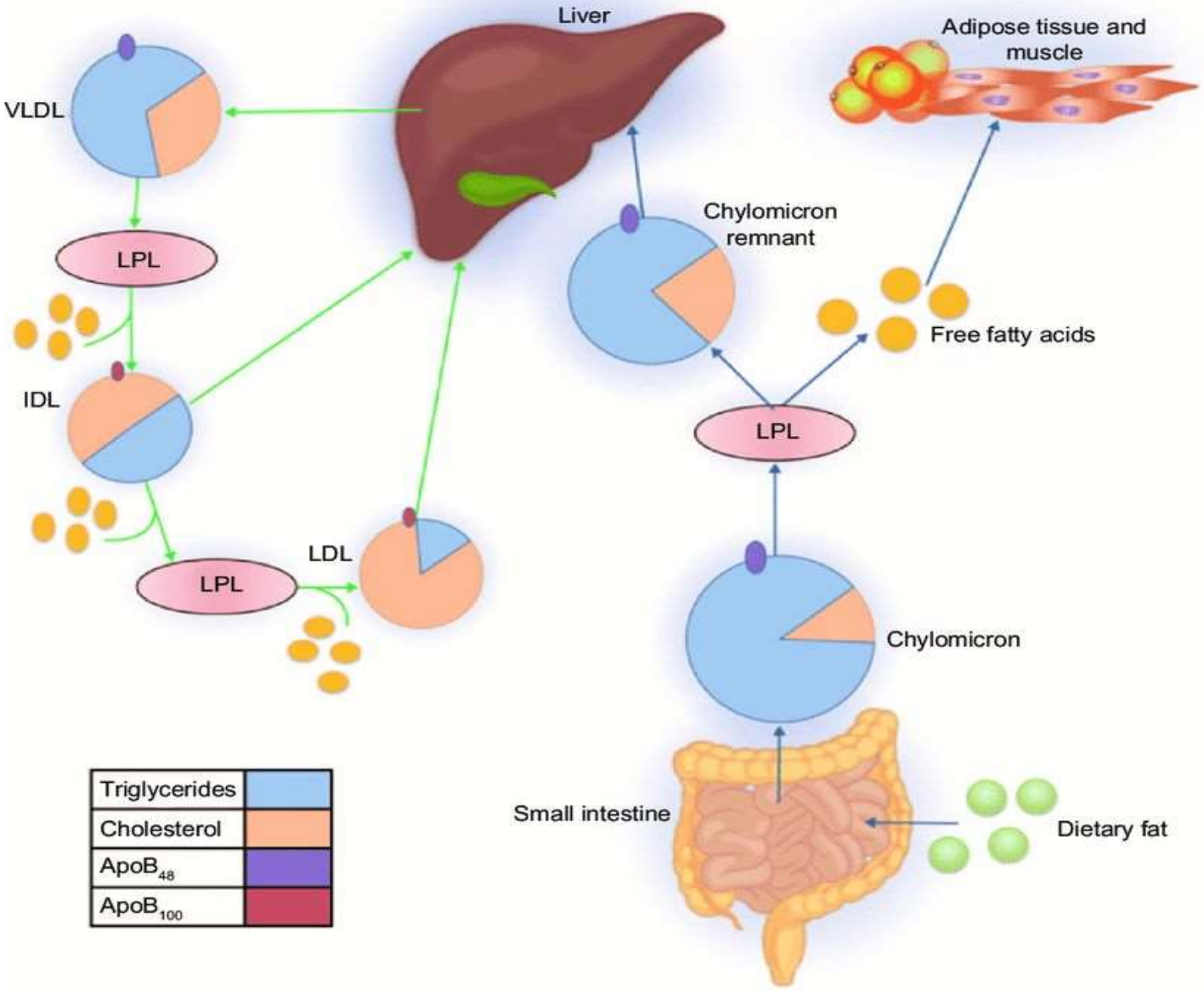
Exogenous pathway:

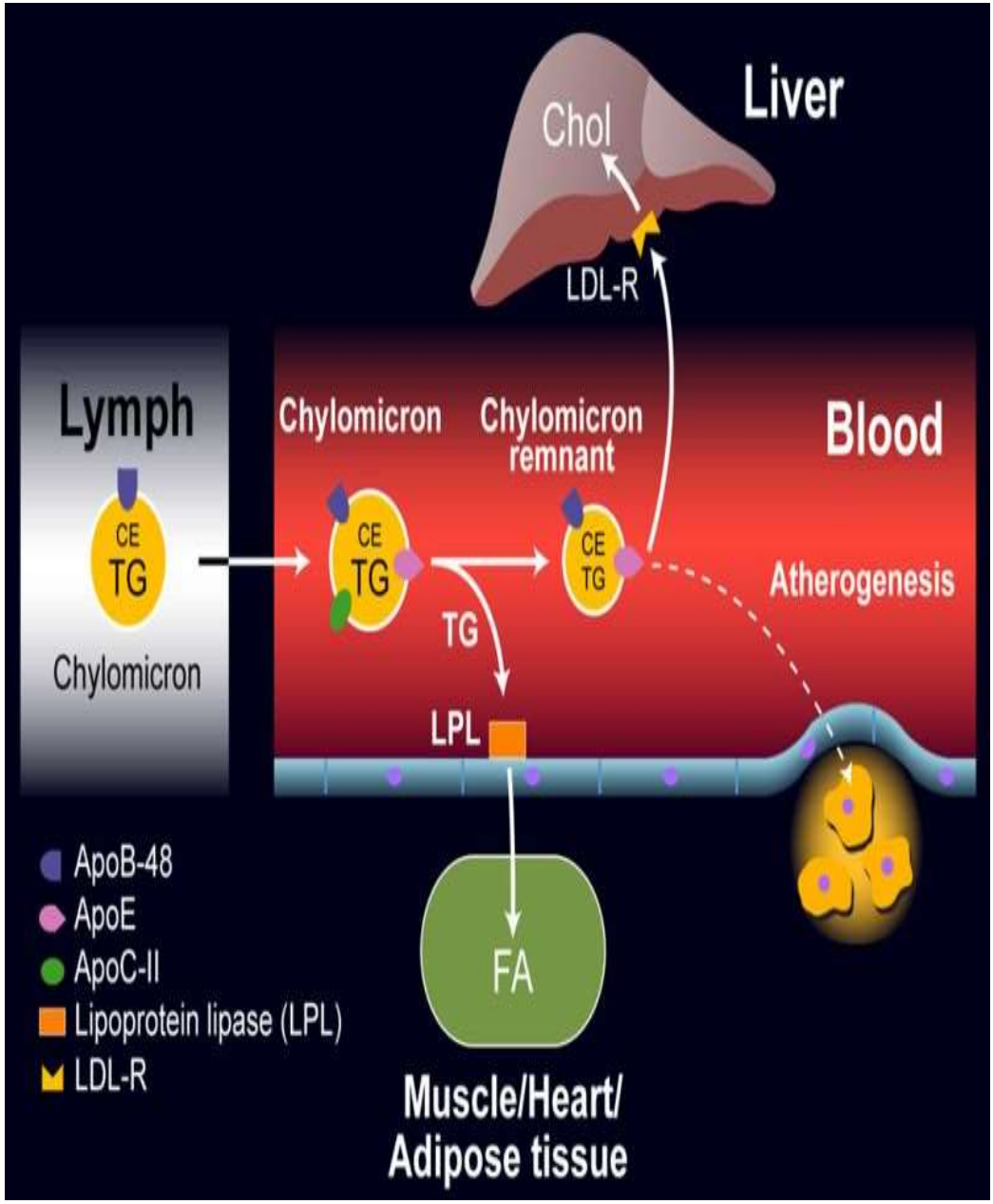
- In this pathway the lipids are gained from over the intake of diet.
- The lipids are then transferred to the intestine and the lipids are stored in intestine in the form of triglycerides.
- The intestinal triglycerides are transferred to our peripheral tissues for storage and energy purpose .
- The free lipids are then transferred to the liver.

chylomicron:

- It carry the triglycerides [glycerol + free fatty acid] from the intestine.
- Specifically attach to apolipoprotein[B-48].
- Chylomicron pass through the lymph system and then diffuse into the blood stream further it hydrolysed by the enzyme namely lipoprotein lipase ,which cleaves the triglycerides into monoacylglycerol and fatty acids.
- The free fatty acids are then transferred to the peripheral tissue such as [adipose tissue, muscle tissue].

- After removal of free fatty acids the chylomicron reduced their size into smaller, and it contain only cholesterol the reduced state of chylomicron is called as chylomicron remnant.
- The chylomicron remnant then bind to the receptor of LDL. The LDL-Receptor recognised by the apo B-48.
- At last the dietary cholesterol can transfer to the hepatic tissue. After its synthesised in the liver and secreted a liver cholesterol.
- It furtherly go for the endogenous pathway such as VLDL,LDL,IDL&HDL synthesis and transfer of liver cholesterol to other body tissues.





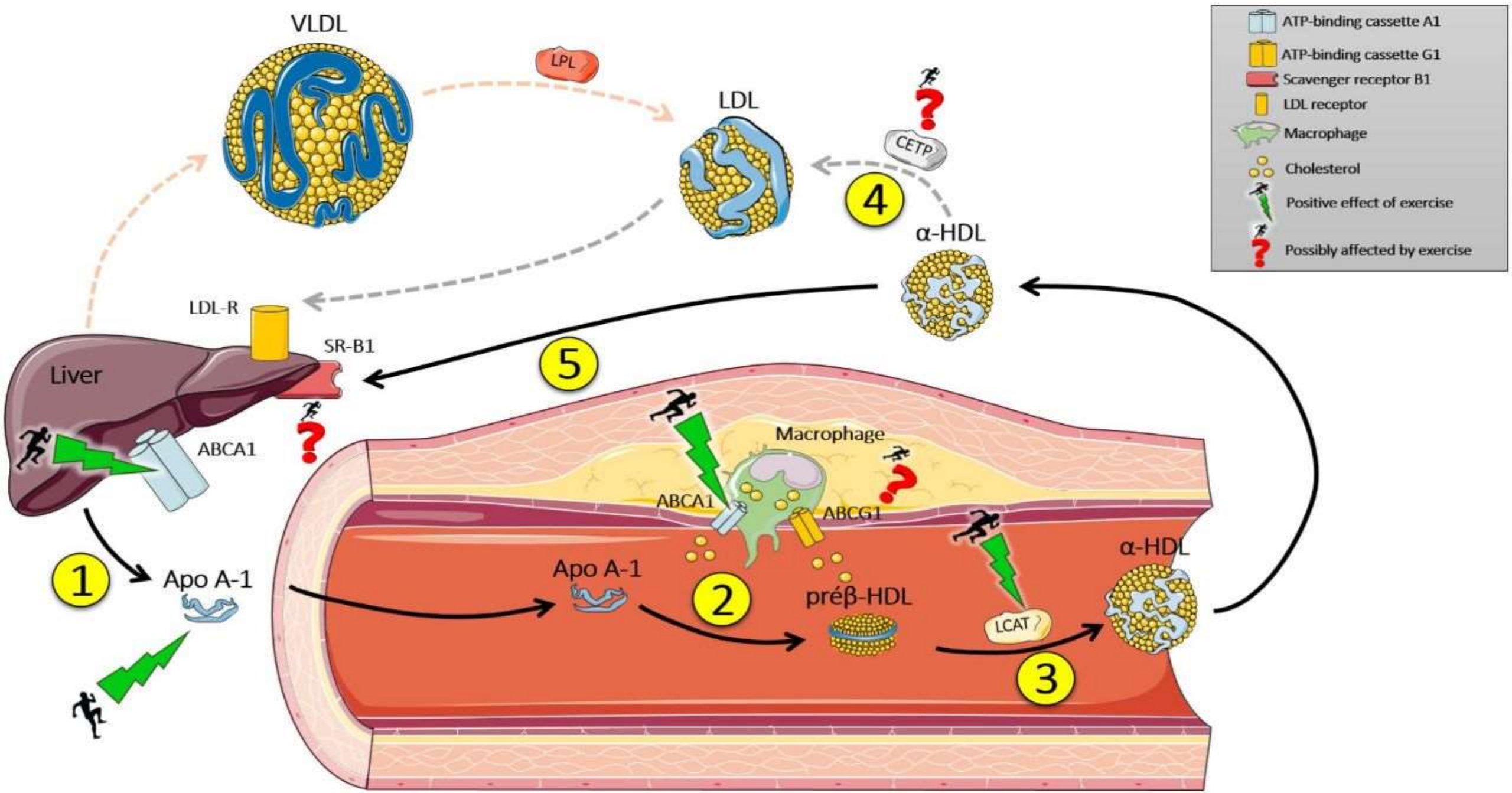
Source:https://www.ncbi.nlm.nih.gov/books/NBK305896/

HDL or good cholesterol

- The HDL was synthesised in the liver and intestine. Its otherwise called as [APO A-1].
- There are 2 types of HDL was formed they are pre βHDL or nascent HDL. The APO A-1 HDL can interact with the enterocyte hepatocyte receptors to forms pre HDL.
- it is disc shaped HDL and then interact with the cell receptors and incorporate with the cholesterol to form the matured HDL.
- The mature HDL is spherical in shape.
- All this transformations are supervised by the enzyme LCAT.

Reverse cholesterol transport

- In this transport the excess free cholesterols are carried from other peripheral tissues by the help of lipoprotein HDL-C.
- The HDL carry the free cholesterol and it can esterified the free cholesterol to form cholesterol esters.
- The cholesterol esters are then transferred into liver by the HDL Receptor named [SR-BI].SCAVENGERS RECEPTOR TYPE B1.
- The SR-B1 is presented in the surface of hepatic cell. The distributed cholesterol can redistributed to our body or excreted by the gall bladder.



Source:https://www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2018.00526/full