Cholesterol metabolism

Introduction

- Cholesterol is present in tissues and in plasma either as free cholesterol or combined with a long-chain fatty acid as cholesteryl ester, the storage form.

- In plasma, both forms are transported in lipoproteins.

- It is synthesized in many tissues from acetyl-CoA

- Plasma low-density lipoprotein (LDL) is the vehicle of uptake of cholesterol and cholesteryl ester into many tissues.

- Free cholesterol is removed from tissues by plasma high-density lipoprotein (HDL) and transported to the liver, where it is eliminated from the body either unchanged or after conversion to bile acids in the process known as reverse cholesterol transport.

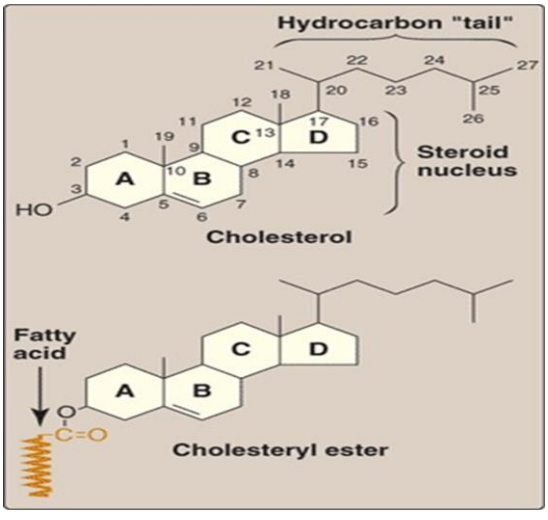
- Cholesterol is the precursor of all other steroids in the body, for example, corticosteroids, sex hormones, bile acids, and vitamin D. It also plays an important structural role in membranes and in the outer layer of lipoproteins.

Sources of cholesterol

- Cholesterol can both be synthesized endogenously about 0.7g\day from (Acetyl CoA) and exogenously about 0.3g\day from (obtained from the diet).
- Significant amounts of cholesterol only occur in meat, eggs, and milk products

Cholesterol structure

Cholesterol is a C27 ($C_{27}H_{46}O$) compound. It has one hydroxyl group at C3 and a double bond between C5 and C6.



Biosynthesis of cholesterol (De novo Synthesis)

- Major sites are liver, adrenal cortex, testes, ovaries & intestine.
- All nucleated cells can synthesize cholesterol, including arterial wall.
- The enzymes involved in the synthesis of cholesterol are partly located in endoplasmic reticulum & partly in cytoplasm.
- Cholesterol synthesized from acetylCoA by a lengthy pathway that may be divided into five steps:

(1) Synthesis of HMG CoA (β-hydroxy β-methylglutaryl CoA)

(2) Synthesis of mevalonate

(3) Formation of isoprenoid units from mevalonate by loss of CO2

(4) Synthesis of squalene

(5) Formation of cholesterol from squalene

Steps of cholesterol biosynthesis

1- Synthesis of HMG CoA (β-hydroxy β-methylglutaryl CoA)

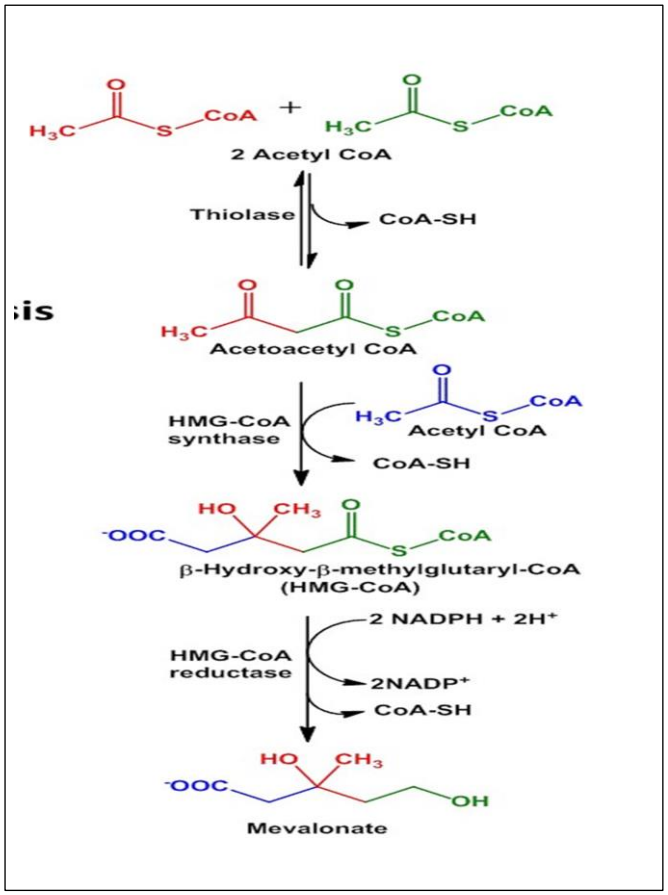
- Two moles of acetyl CoA condense to form acetoacetyl CoA.
- Another molecule of acetyl CoA is then added to produce HMG CoA.
- These reactions are similar to that of ketone body synthesis. The two pathways are distinct. Ketone bodies are produced in mitochondria while cholesterol synthesis occurs in cytosol.
- Two isoenzymes of HMG CoA synthase are known.
- The cytosomal enzyme is involved in cholesterol synthesis whereas the mitochondrial HMG CoA synthase participates in ketone body formation.

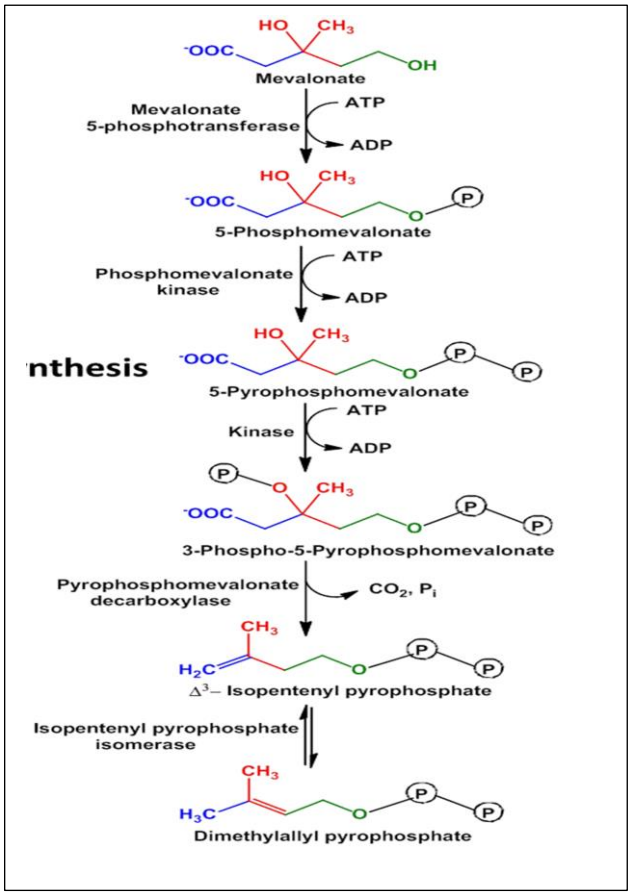
2- Synthesis of mevalonate

- HMG CoA reductase is the rate limiting enzyme in cholesterol biosynthesis. This enzyme is present in endoplasmic reticulum & catalysis the reduction of HMC CoA to Mevalonate.
- The reducing equivalents are supplied by NADPH.

3. Formation of Isoprenoid Units:

- Mevalonate is phosphorylated sequentially using ATP by three kinases, and after decarboxylation of the active isoprenoid unit, (Isopentenyl pyrophosphate (lPP)).
- Isopentenyl pyrophosphate (lPP) is isomerizes to dimethylallylpyrophosphate (DPP).
- IPP & DPP are 5-carbon isoprenoid units.





Step 1 &2 **step 3**

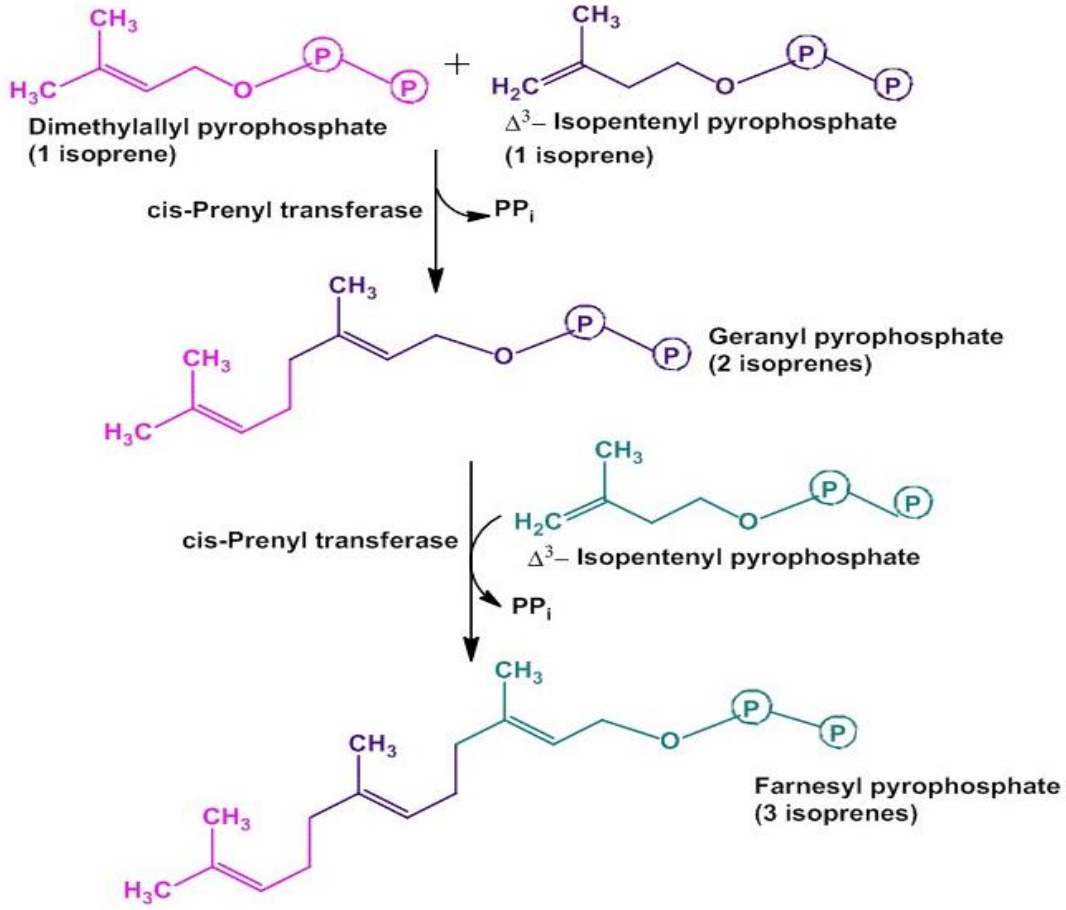
4-Synthesis of Squalene

Squalene (C30) is synthesized from six molecules of Isopentenyl Pyrophosphate (C5) and the reaction sequence is- C5→C10 →C15 →C30.

This stage in the synthesis of cholesterol starts with the isomerization of isopentenyl pyrophosphate (lPP) to dimethylallyl pyrophosphate (DPP). (DPP) then condensed with (lPP) to form the ten-carbon intermediate geranyl diphosphate.

A further condensation with (lPP) forms farnesyl diphosphate C15 .

Two molecules of farnesyl diphosphate condense at the diphosphate end to form squalene.



5- Formation of cholesterol

Squaline, a linear isoprenoid, is cyclized to form lanosterol (C30 sterol). Three methyl groups are cleaved from it in subsequent reactions to yield the endproduct, cholesterol (C27) .

Regulation of Cholesterol synthesis

- HMG CoA reductase, the rate limiting enzyme, is the major control point for cholesterol biosynthesis.
- Regulation of this enzyme by

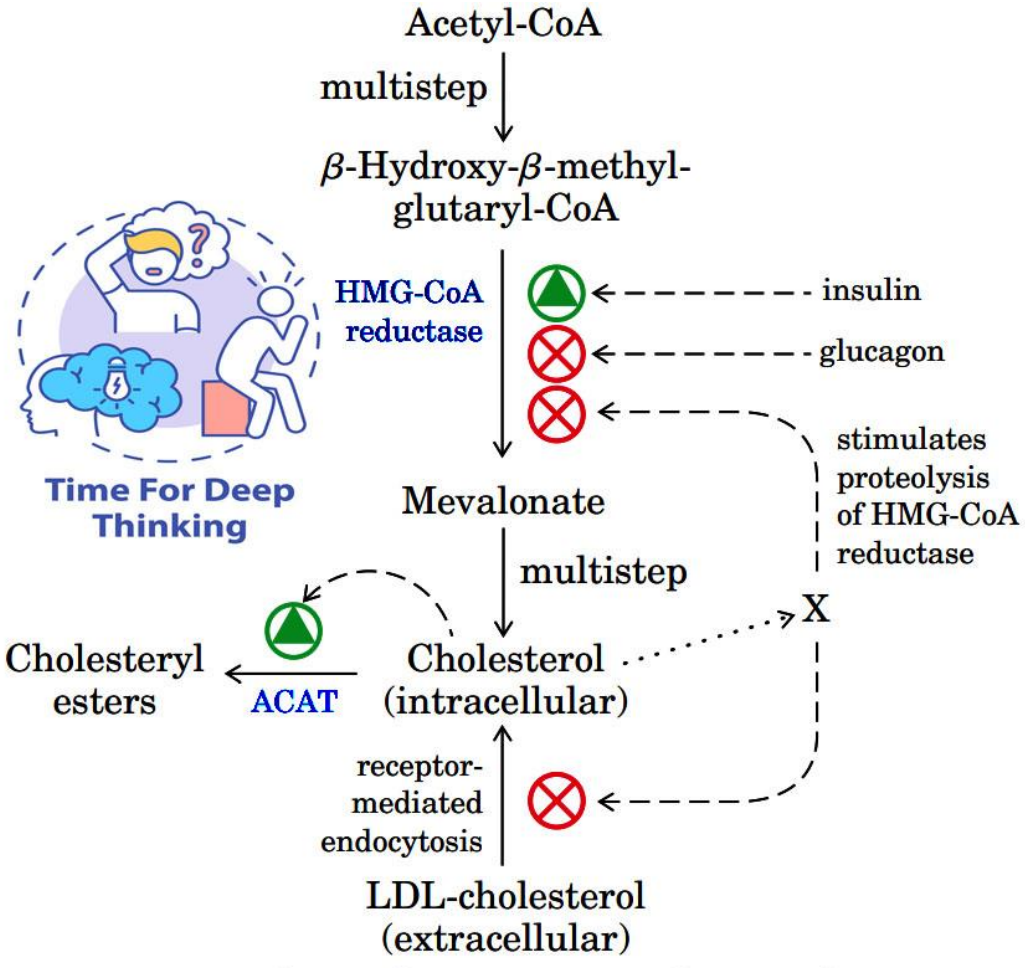
1- **Feedback control**: The end product cholesterol controls its own synthesis of the enzyme by a feedback mechanism.

- Increase in the cellular concentration of cholesterol reduces the synthesis of the enzyme by decreasing the transcription of the gene responsible for the production of HMG CoA reductase.

2- Interconversion: Activation and inactivation of proteins through phosphorylation/dephosphorylation is referred to as interconversion. Effector hormones such as insulin and thyroxine stimulate HMG CoA reductase by dephosphorylation while glucagon inhibits the enzyme through cAMP- dependent phosphorylation.

3. A large supply of cholesterol from food inhibits the HMG CoA reductase directly.

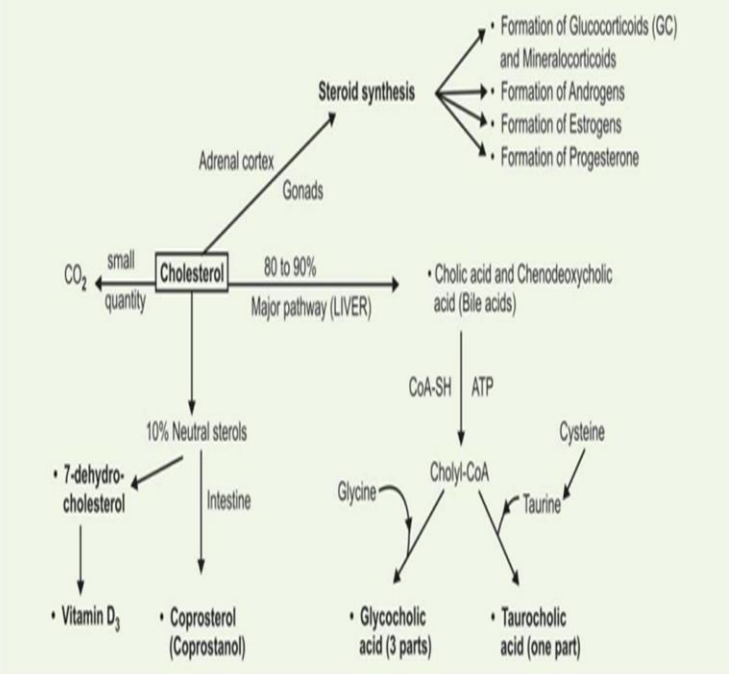
4. Inhibition by drugs: The statin drugs, including lovastatin (mevinolin), simvastatin, and mevastatin are competitive inhibitors of HMG CoA reductase since they are structural analogues of HMG CoA , the substrate of the enzyme . They can effectively block cholesterol synthesis and are used to lower the plasma cholesterol level in patients with hyper-cholesterolemia.



Regulation of cholesterol formation

FATE OF CHOLESTEROL

. Degradation to CO2: In human tissues—conversion to CO2 does not occur.
• Conversion to Bile Acids: Major pathway, more than 50 percent is converted to bile acids and excreted in faeces
• Conversion to Neutral Sterols: 10 percent of cholesterol is converted to neutral sterols, called as coprosterol (coprostanol), which is formed in lower part of intestine by the bacterial flora and excreted in faeces.
• Conversion to 7-Dehydrocholesterol: In skin, by UV light of Sun's rays, 7-dehydrocholesterol is converted to vit. D3 (cholecalciferol).
• Formation of Adrenocortical Hormones: Glucocorticoids and mineralocorticoids are formed from cholesterol in adrenal cortex.
• Formation of Androgens
• Formation of Estrogens
• Formation of Progesterone



Cholesterol excretion

- Cholesterol is excreted from the body via the bile either in the unesterified form or after conversion into bile acids in the liver.

- **Coprostanol** is the principal sterol in the feces; it is formed from cholesterol by the bacteria in the lower intestine.

Bile Acids Are Formed from Cholesterol

The primary bile acids are synthesized in the liver from cholesterol. These are cholic acid (found in the largest amount in most mammals) and chenodeoxycholic acid. The secondary bile acids, deoxycholic acid, and lithocholic acid

Synthesis Bile acids

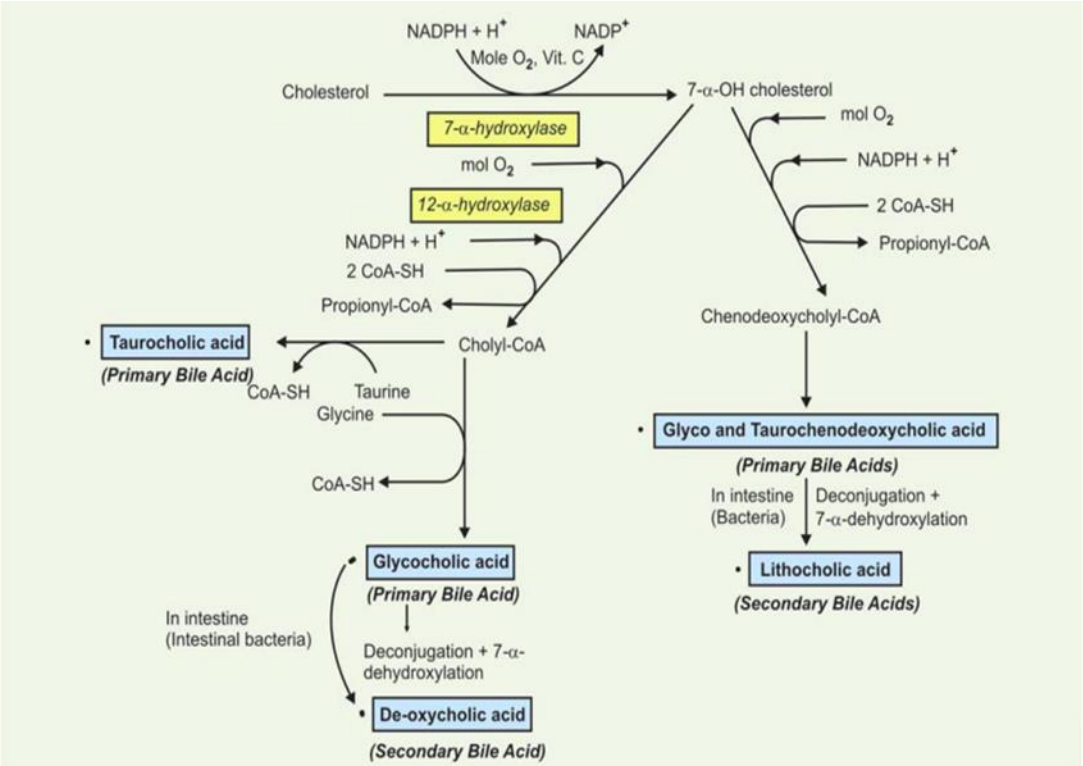
- Bile acids are steroids consisting of 24 carbon atoms carrying one carboxylate group and several hydroxyl groups.
- Bile acids are synthesized from cholesterol through several steps:

1- The double bond in cholesterol is removed by reduction.

2- Mono-oxygenases then introduce one or two additional –OH groups into the steroid nucleus. The slowest step is hydroxylation at position 7 by an 7-α- hydroxylase.
3- The side chain of cholesterol is shortened by three carbon atoms and the terminal carbon atom is oxidized to a carboxylate group.

- Cholic acid and chenodeoxycholic acid are formed at the end of these steps and are known as the primary bile acids.

- After being biosynthesized, they are mostly activated with Coenzyme A and then conjugated with (glycine) or the non-proteinogenic amino acid (taurine). The acid amides formed in this way are known as the conjugated bile acids or bile salts.



- The other bile acids, deoxycholic acid and lithocholic acid are only formed in intestine by the enzymatic cleavage of the –OH group at C7 by intestinal bacteria. They are therefore referred to as secondary bile acids. The acid amide bond in the salt is also cleaved by intestinal bacteria (deconjugation).

- Bile salts are composed of the salts of four different kinds of free bile acids when interact with strong base producing a Na and K ions of these acids.

- The salts are large, negatively charged ions that are not readily absorbed by the upper region of the small intestine; consequently, they remain in the small intestine until most of the fat is digested.

Functions of bile salts:

1- Emulsification of fats that aids in digestion and absorption of fat.
2- Activate pancreatic lipase.
3- Aid in absorption of fat – soluble vitamins and cholesterol by forming water-soluble micelles.
4- Keeps cholesterol in solution helping to prevent the formation of gallstones.
5- Buffer action: Bile salts contribute to the neutralization of any HCl escaped from the stomach to the intestine thus keeping the pH of intestine within normal.
6- Anti-putrifactive action: Bile salts inhibit the growth of harmful bacteria in large intestine.

Gallstones:

Stones of the gall bladder and biliary ducts can be composed of:
1- Cholesterol (90 – 98 %)
2- Bile pigments.
3- Calcium carbonate and calcium salts of bile acids.

Formation of gallstones may be due to the following factors:

1- A change in the relative composition of bile that results in supersaturation or precipitation of cholesterol.

2- Presence of foreign substances such as bacterial infection in the Gallbladder.

3- High concentration of blood cholesterol.