BIOCHEMISTRY

Lec:5 : 2nd stage Dr. Shaimaa S.Mutlak

METABOLISM OF LIPIDS

Biosynthesis of cholesterol:

• **Site of Synthesis**

Essentially all tissues form cholesterol. Liver is the major site of cholesterol biosynthesis; also other tissues are active in this regard, e.g. adrenal cortex, gonads, skin, and intestine are most active.

Low order of synthesis: Adipose tissue, muscle, aorta and neural tissues.

Brain of newborn can synthesize cholesterol while the adult brain cannot synthesize cholesterol.

Tissues Efficiency of cholesterol

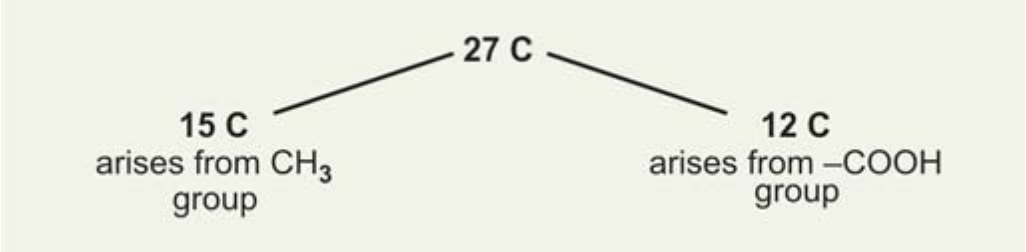
TISSUE	
Formation	(Liver = 100)
Liver	100
• Adult skin	90
• Small intestine	60
• Gonads	31
• Kidney	4
• Adult brain	0
Newborn brain	185

Enzyme system: involved in cholesterol biosynthesis are associated with:

Cytoplasmic particles "microsomes" Soluble fraction—cytosol.

Metabolism:

'Active' acetate (acetyl-CoA) is the starting material and principal precursor. The entire carbon skeleton, all 27 C of cholesterol in humans can be synthesized from active acetate.



Steps of biosynthesis: Cholesterol biosynthesis can be thought of as occurring in Five groups of reactions. They are:

I. Synthesis of mevalonate: A 6-C compound from acetyl-CoA.

II. Formation of "Iso-Prenoid units" (C-5) from Mevalonate:

By successive phosphorylations and followed by loss of CO2.

Note: The isoprenoid units are regarded as the building blocks of the steroid nucleus.

III. Formation of Squalene: A 30-carbon aliphatic chain, formed by condensation of six isoprenoid units.

IV. Cyclisation of Squalene to form Lanosterol.

V. Conversion of Lanosterol → to form cholesterol.

Two-carbon units (acetyl-CoA)

⇩

Acetoacetyl CoA

⇩

3-hydroxy-3-methylglutaryl CoA
(HMG-CoA)

⇩ HMG-CoA REDUCTASE

Mevalonic acid

⇩

Isoprenoids

⇩

Squalene

⇩

Lanosterol

⇩

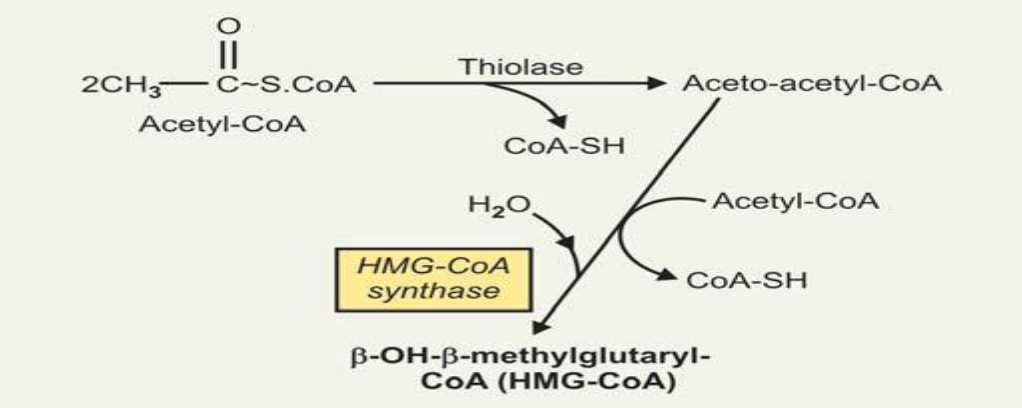
Cholesterol

Figure : Summary of pathways of cholesterol synthesis. from Candlish JK and Crook M. *Notes on Clinical Biochemistry*.

Synthesis of ccholesterol:

I. Synthesis of Mevalonate from Acetyl-CoA Consists of two steps:

• Formation of HMG-CoA: (β-OH-β-methyl glutaryl-CoA): HMG-CoA can be formed in the cytosol from acetyl-CoA in two steps catalysed by the enzyme thiolase and HMG-CoA synthase.



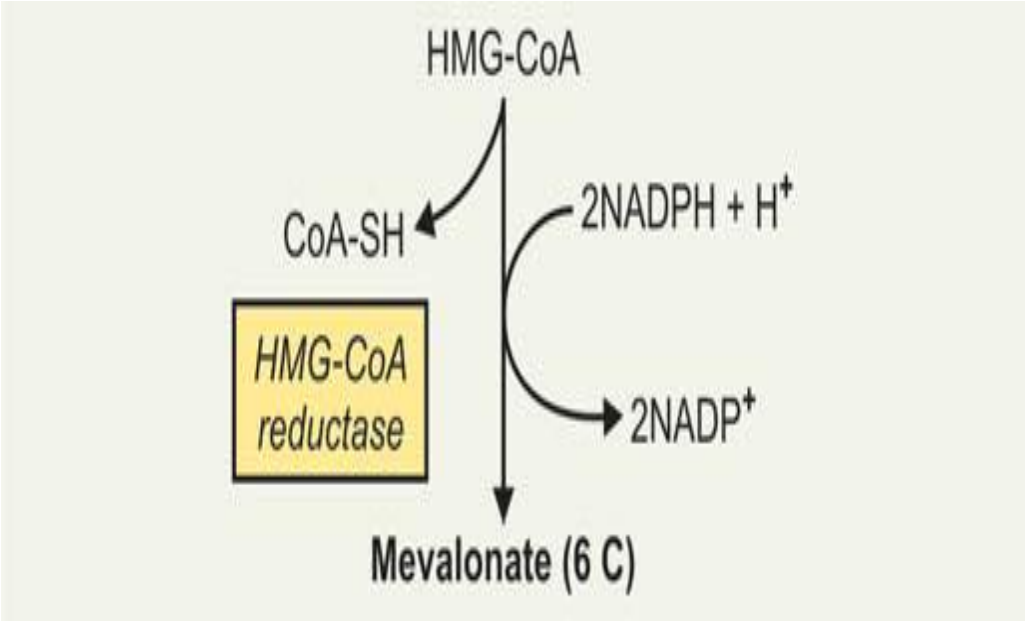
Note

1. HMG-CoA may also be produced as an intermediate in the metabolic degradation of amino acid L-Leucine.

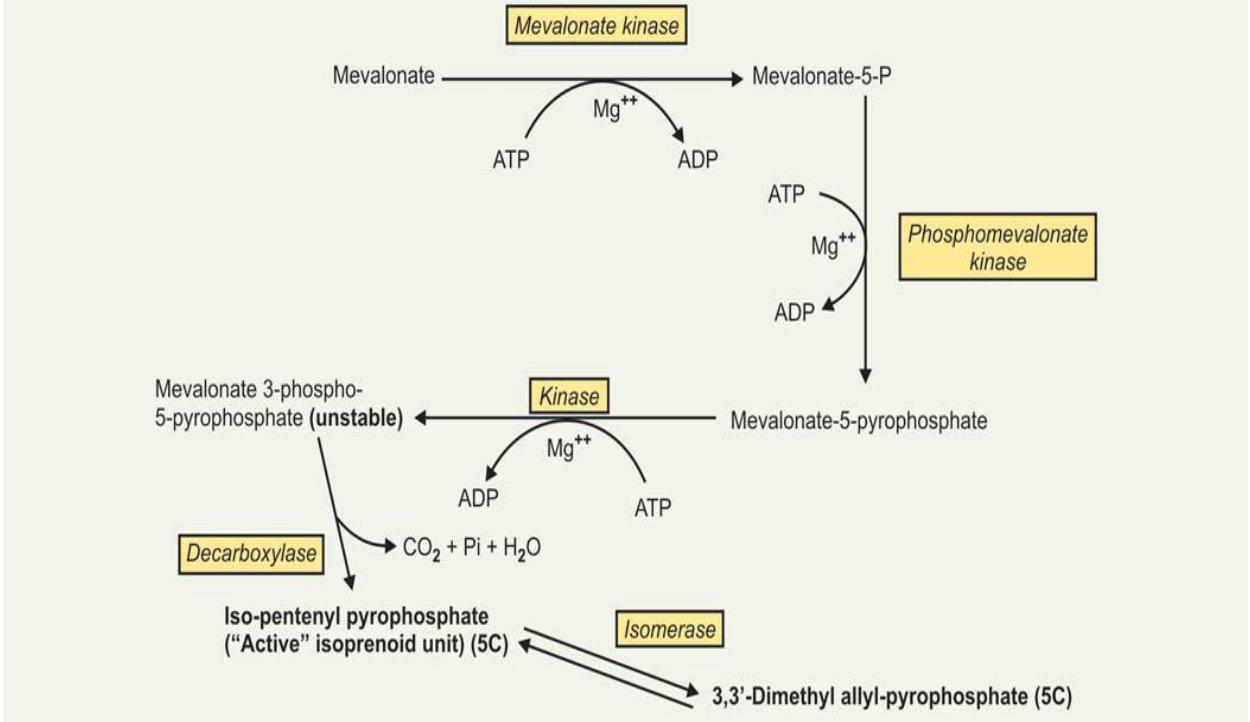
2. There are two pools of HMG-CoA: i. Mitochondrial: Concerned with ketogenesis

ii. Extramitochondrial (cytosolic): Concerned with synthesis of Mevalonate and iso-Prenoid units.

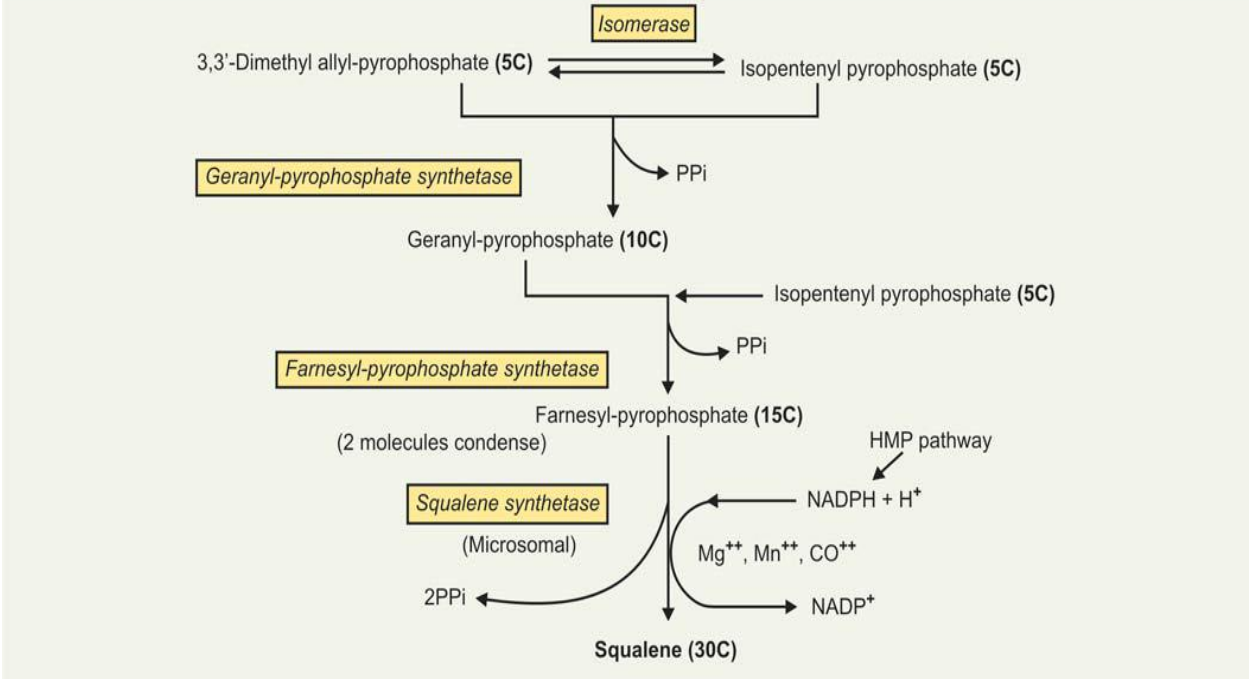
• In the next step, which is the rate-limiting step, HMG-CoA is converted to Mevalonic acid (Mevalonate) catalysed by the enzyme HMG-CoA reductase.



Synthesis of Isoprenoid Units



Synthesis of Squalene



TRANSPORT OF CHOLESTEROL

1. Cholesterol in the diet is absorbed from the intestine, and in company with other lipids, the cholesterol absorbed, 80 to 90 per cent in the lymph is esterified with long-chain FA.

Esterification may occur in the intestinal mucosa. In man, the total plasma cholesterol varies from 150 to 250 mg% (average 200 mg%), rising with age, although there are wide variations between individuals.

2. The greater part is found in the 'esterified' form and is transported as "lipoproteins" in plasma.
3. Highest proportion of circulating cholesterol is found in LDL (β-lipoproteins) which carry cholesterol to tissues and also in HDL, which takes cholesterol to liver from tissues for degradation (scavenging action).
4. Dietary cholesterol takes several days to equilibrate with cholesterol in plasma, and several weeks to equilibrate w cholesterol in tissues. Free cholesterol in plasma and liver equilibrates in matter of hours.
5. In general, free cholesterol exchanges readily between tissues and lipoproteins, whereas cholesterol esters do not exchange freely. Some plasma cholesterol ester may be formed in HDL as a result of transesterification reaction in plasma between cholesterol and FA in position-2 of lecithin which is catalysed by the enzyme lecithin cholesterol acyl transferase (LCAT).

Cholesterol balance in tissues:

Many factors will determine the cholesterol balance at the cellular level.

(**a) Increase of cholesterol in cells**:

1. Increased synthesis of cholesterol.
2. Hydrolysis of cholesterol ester by the enzyme "cholesterol ester hydrolyase".
3. Uptake and delivery of cholesterol in cells by circulating LDL (uptake by specific receptors).
4. Uptake of cholesterol containing lipoproteins by 'non-receptor' mediated pathway.
5. Uptake of free cholesterol by cell membranes.

(**b) Decrease of cholesterol in cells:**

1. Efflux of cholesterol from cells to HDL (scavenging action).
2. Esterification of cholesterol by the enzyme Acyl-CoA-cholesterol acyl transferase (ACAT).
3. Utilisation of cholesterol for synthesis of steroid hormones, viz. glucocorticoids, mineralo-corticoids,Gonadal hormones.
4. In liver cells: formation of cholic acid.
5. Formation of vit D3.

FATE OF CHOLESTEROL

About 1.0 gm of cholesterol is eliminated from the body per day. Fate of cholesterol has been studied in rats by giving labelled C14 cholesterol and H3 cholesterol.

Fate of Cholesterol

1. **Degradation to CO2:** In human tissues—conversion to CO2 does not occur.

2. **Conversion to Bile Acids**: Major pathway, more than 50 per cent is converted to bile acids and excreted in faeces
3. **Conversion to Neutral Sterols:** 10 per cent 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.
4. **Conversion to 7-Dehydrocholesterol:** In skin, by UV light of Sun's rays, 7-dehydrocholesterol is converted to vit. D3(cholecalciferol).
5. **Formation of Adrenocortical Hormones:** Glucocorticoids and mineralocorticoids are formed from cholesterol in adrenal cortex.
6. **Formation of Androgens**
7. **Formation of Estrogens**
8. **Formation of Progesterone.**