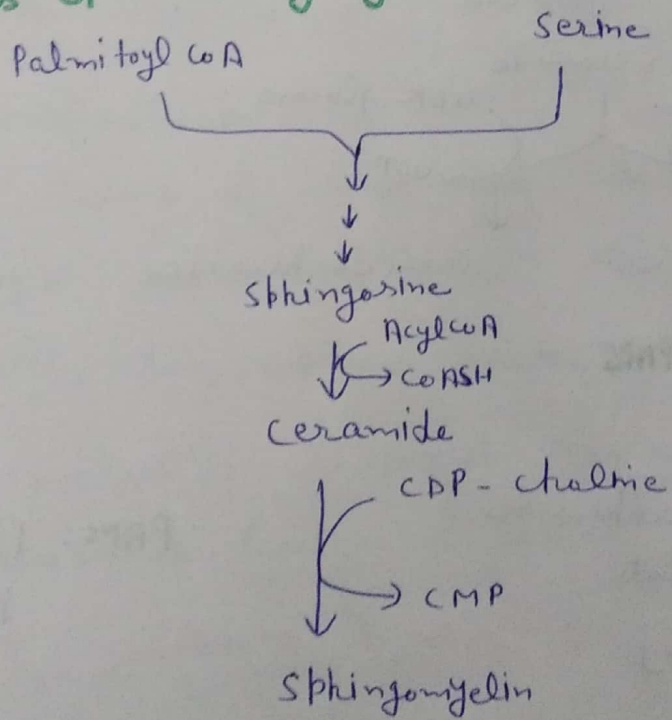
③ Synthesis of Phosphatidylinositol

Phosphatidylinositol is important for signal transmission across the membrane. CDP-diacylglycerol combine with Inositol to form phosphatidylinositol. These reactions are shown in pathway of Phospholipid biosynthesis.

④ Synthesis of phosphatidylglycerol & cardiolipin

CDP-diacylglycerol combines with glycerol-3-phosphate to form phosphatidyl glycerol-3-phosphate, which on release of phosphate group form phosphatidyl glycerol. It combines with ~~glycerol~~ another molecule of phosphatidyl glycerol to finally form diphosphatidyl glycerol (cardiolipin).

⑤ synthesis of sphingomyelins:

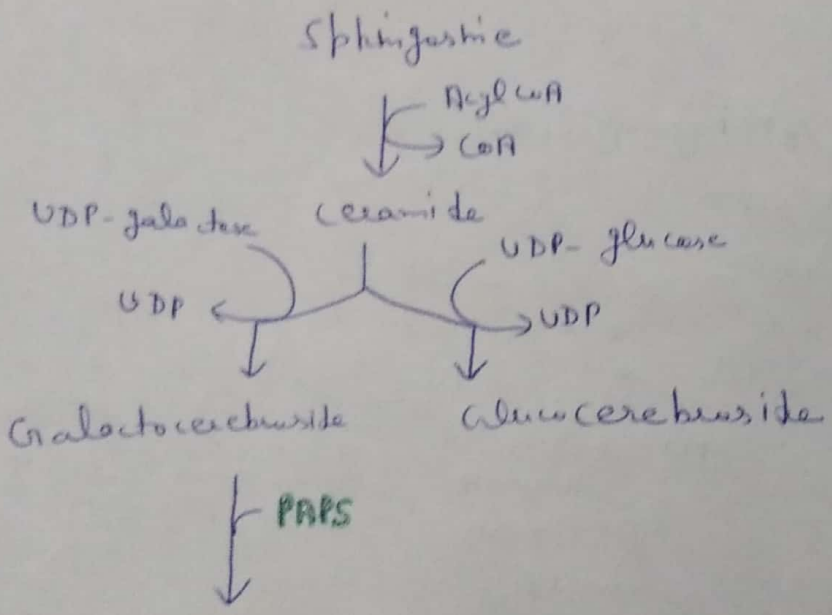


Palmitoyl CoA & serine combine and undergo a sequence of reactions to produce sphingosine which is then acylated to produce ceramide. Ceramide combine with CDP-choline & form sphingomyelin.

Biosynthesis of Glycolipids

- These are derivatives of ceramide, hence known as glycosphingolipids.
- The simplest form of glycosphingolipids are cerebrosides containing ceramide bound to monosaccharide.
- Galactocerebrosides are major components of membrane lipids in nervous tissue.
- Glucocerebroside is an intermediate in synthesis and degradation of complex glycosphingolipids.

Biosynthesis of cerebrosides & sulfatides:



Galactocerebroside 3-sulfate [sulfatide]

PAPS: Phosphoadenosyl phosphosulfate

Biosynthesis of Cholesterol

- Cholesterol is amphipathic molecule exclusively found in animals hence is often called as Animal sterols.
- It constitute 2g/kg of human body weight.

Functions:

1. It is a structual component of cell membrane
2. Precursor for synthesis of steroid hormones, vitamin D and bile acids.
3. Essential ingredient in structure of lipoproteins.
4. Fatty acids are transported to liver as cholesteryl esters for oxidation.

Cholesterol biosynthesis:

- Almost all tissues of body participate in cholesterol biosynthesis. The lagest contribution is made by liver (50%), Intestine (15%), skin, adrenal cortex & reproductive tissues etc.
- The enzymes involved in cholesterol synthesis are found in cytosol & microsomal fraction of cell.

The cholesterol synthesis involve 5 stages:

1. Synthesis of HMG CoA
2. Formation of mevalonate (6C)
3. Production of isoprenoid units (5C)
4. Synthesis of squalene (30C)
5. Conversion of squalene to cholesterol (27C)

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

Two moles of acetyl coA condense to form acetoacetyl CoA.

Acetoacetyl coA combine with another molecule of acetyl coA to produce HMG CoA.

- Reaction is similar to ketone body formation.

bt cholesterol synthesis
↓ Take Place in
cytosol

ketone body formation
↓ take place in
Mitochondria

so separate Isoenzymes of HMG CoA synthase in Mitochondria & cytosol exist.

2. Formation of Mevalonate:

HMG CoA ⟶ (HMG CoA reductase) Mevalonate

HMG CoA reductase is rate limiting enzyme in cholesterol Biosynthesis

3. Production of Isoprenoid units:

Mevalonate ⟶ (Step 1) 3-phospho 5-pyrophosphomevalonate

↓ Step 2

Isopentenyl pyrophosphate (IPP)

Step 3 ↓ Isomerizes

dimethylallyl pyrophosphate (DPP).

Both IPP & DPP are Isoprenoids.

4. Synthesis of squalene:

IPP & DPP condense to produce 10C Geranyl pyrophosphate (GPP). Another molecule of IPP condenses with GPP to form Farnesyl pyrophosphate (FPP). Two units of Farnesyl pyrophosphate unite & get reduced to produce squalene.

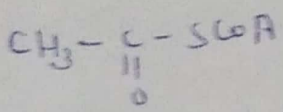
5. Conversion of squalene to cholesterol

Squalene undergoes hydroxylation and cyclization & get converted to **Lanosterol**. This is multistep process (19 Reactions). The important reactions are:

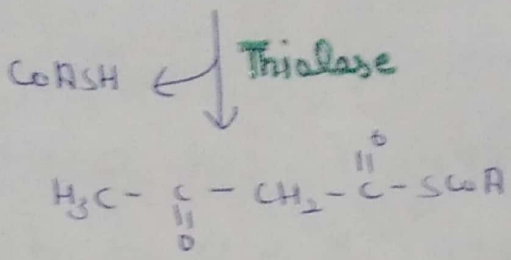
- Reducing the C atoms from 30 to 27
- Removal of two methyl groups from C_4 and one methyl group from C_{14}.
- Shift of double double bond from C_8 to C_5.
- Reduction in double bond present b/w C_{24} and C_{25}.

Penultimate product of these reactions is 7-dehydrocholesterol, which on reduction yield cholesterol

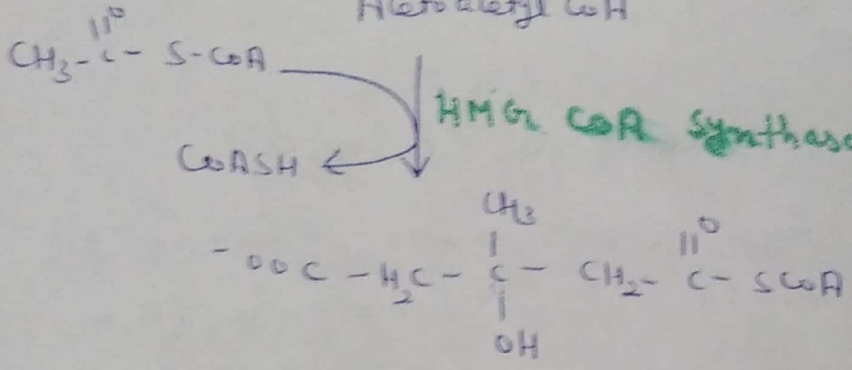
Pathway



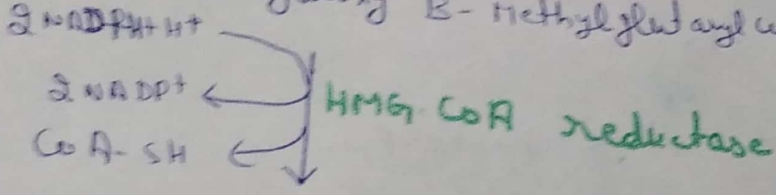
2 Acetyl CoA

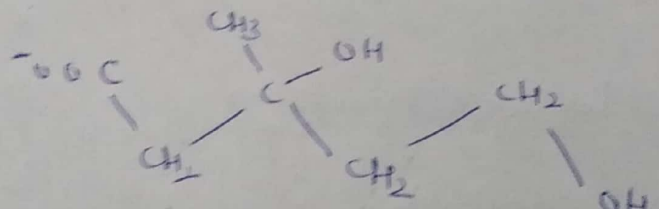


Acetoacetyl CoA

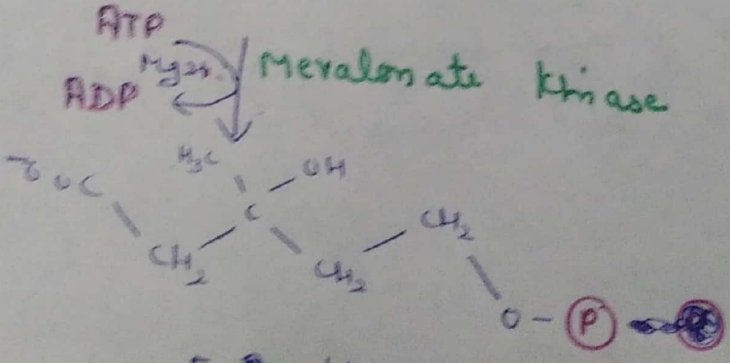


β-hydroxy β-Methylglutaryl CoA (HMG CoA)

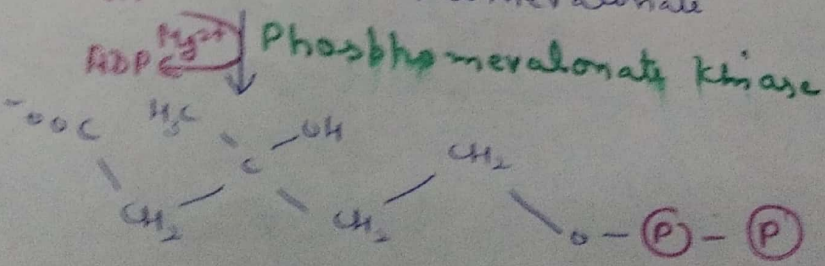




Mevalonate

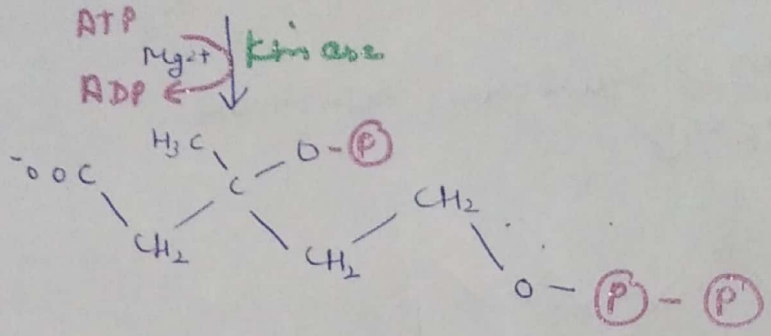


5-Phosphomevalonate

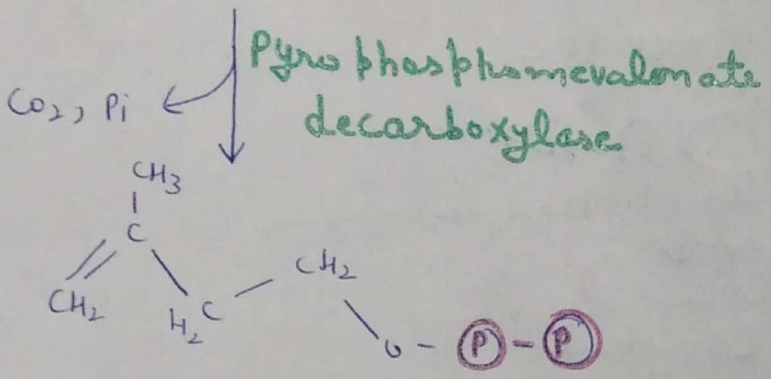


5-Pyrophosphomevalonate

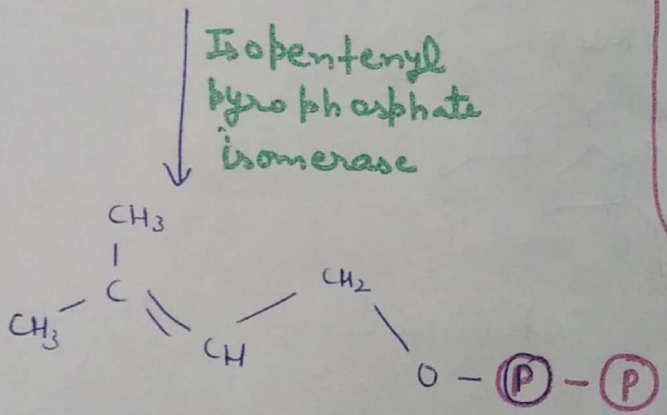
5- pyrophosphomevalonate



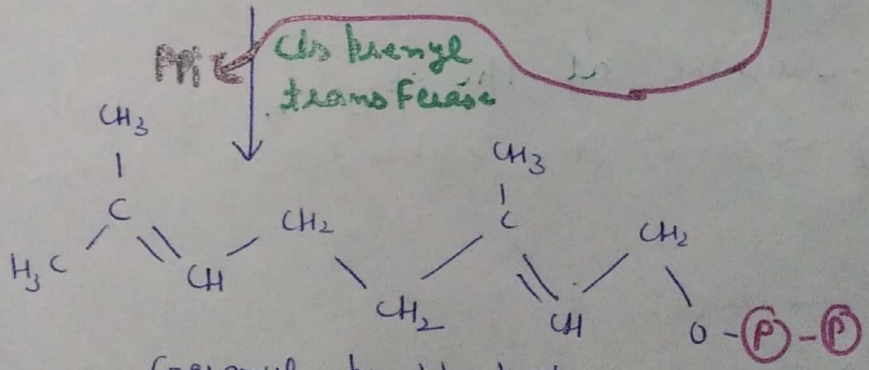
3- phospho 5- pyrophosphomevalonate



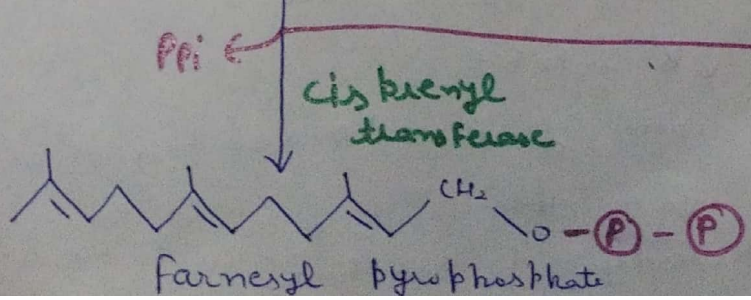
Isopentenyl pyrophosphate (5C)



Dimethyl allyl pyrophosphate

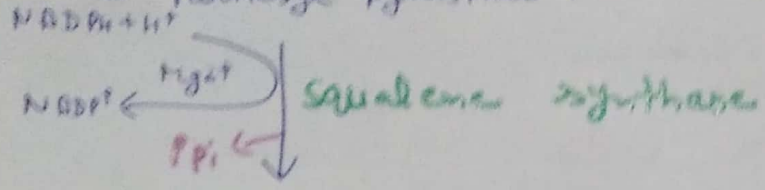


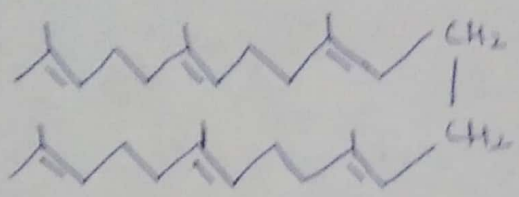
Geranyl pyrophosphate



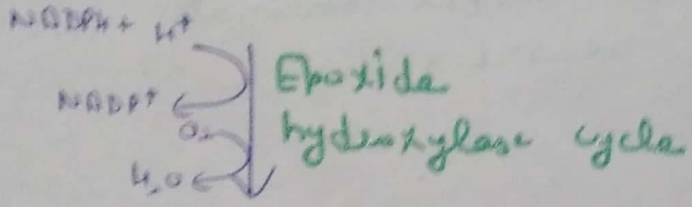
Farnesyl pyrophosphate

2 Farnesyl bisphosphate /

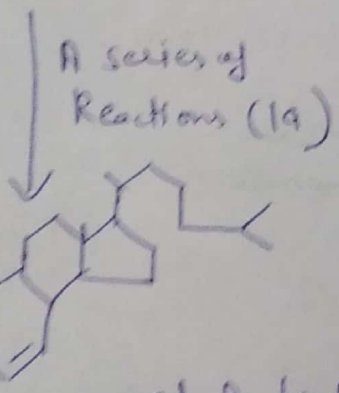




Squalene



Lanosterol



Cholesterol

Regulation of Cholesterol Synthesis:

HMG CoA reductase at the begning of pathway is rate limiting enzyme. It is subjected to different metabolic controls.

① Feedback Control:

↑ cholesterol level in cell

↓ ⊗ Inhibit

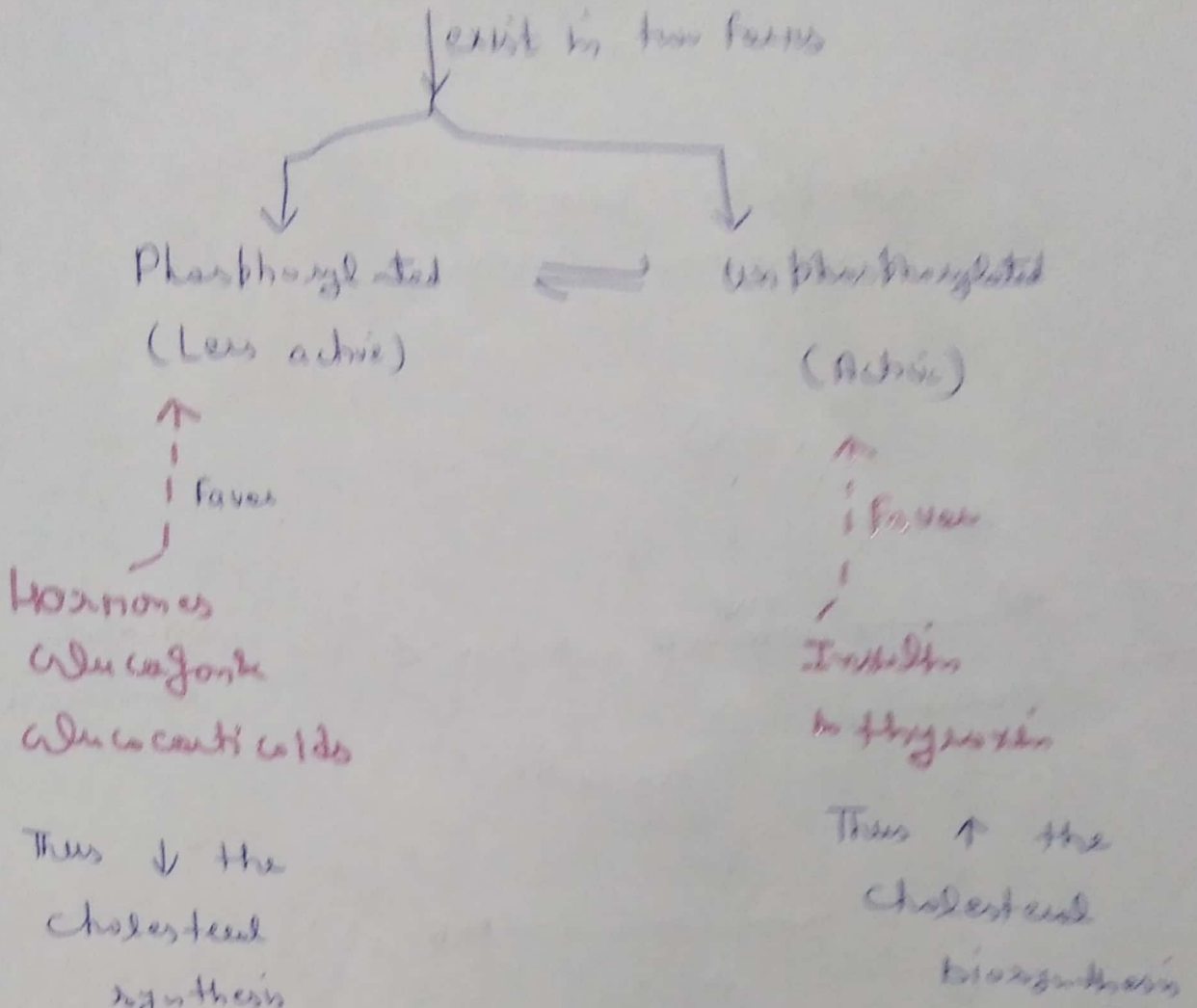
Transcription of HMG CoA reductase gene

↓ Inhibit

cholesterol biosynthesis

② Hormonal Regulation

HMG CoA reductase exist in two forms



③ Inhibition by drugs

Drugs Compactin & Lovastatin

↓are competitive Inhibitors of HMG CoA reductase

↓ Thus

Inhibit cholesterol biosynthesis & reduce cholesterol level.

④ Bile acids also inhibit activity of HMG CoA reductase.

Summary of cholesterol Biosynthesis:

Regulation