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Cholesterol metabolism:

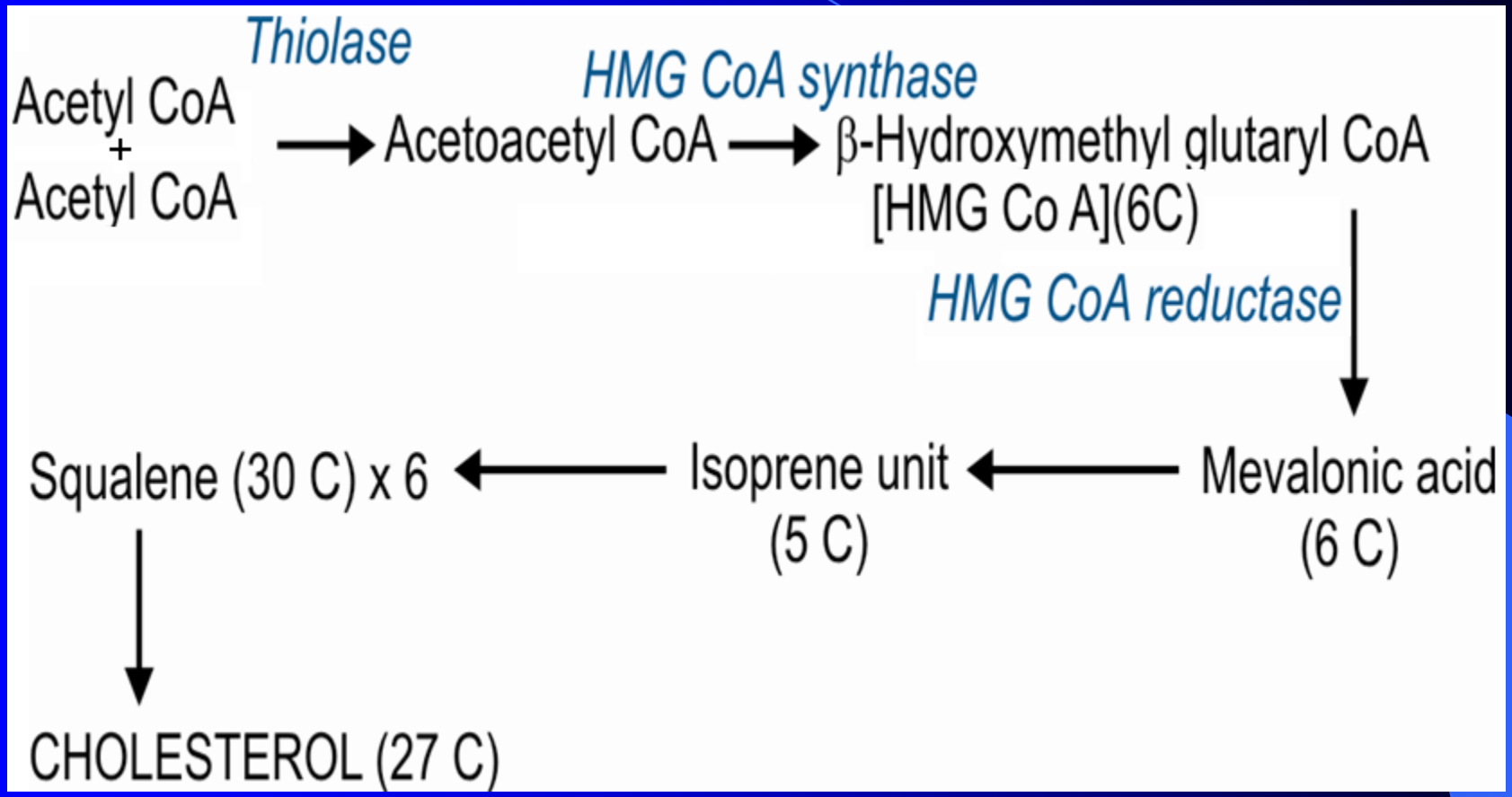
INTRODUCTION

- Cholesterol is a sterol, present in cell membrane, brain and lipoprotein
- It is a precursor for all steroids
- About 1 g of cholesterol is synthesized per day in humans
- It is an amphipathic lipid
- Lipoproteins transports the free cholesterol in the circulation
- Cholesterol ester is a storage form of cholesterol found in most tissues
- 80% of the liver cholesterol converted to bile acids
- Vitamin D_3 formed from 7-dehydrocholesterol.
- All the steroids have cyclopentanoperhydrophenanthrene ring.Made up of three cyclohexane rings, A,B and C and a cyclopentane ring D
- Normal Blood level is 150-200 mg%

- Hypercholesterolemia seen in nephrosis, diabetes mellitus, hypothyroidism and obstructive jaundice
- Increased cholesterol level leads to atherosclerosis
- The OH group in the 3rd position can get esterified to fatty acids to form cholesterol esters. This esterification occurs in the body by transfer of PUFA moiety by Lecithin cholesterol acyl transferase. This step is important in the regulation of cholesterol level.
- It is a poor conductor of electricity

SYNTHESIS

- Site: Extra Mitochondrial. The enzymes involved are found in cytosol and microsomal fractions of the cell.
- Synthesis takes place in liver, skin and intestine and also in adrenal cortex & testis.
- All the 27 carbon atoms are derived from acetyl CoA
- 18 acetyl Co A are required
- Acetyl CoA formed in glycolysis and β-Oxidation of fatty acid are the precursors for the cholesterol synthesis


Thiolase
HMG CoA synthase
Acetyl CoA
+
Acetyl CoA
Acetoacetyl CoA
β-Hydroxymethyl glutaryl CoA
[HMG Co A](6C)
HMG CoA reductase
Mevalonic acid
(6 C)
Isoprene unit
(5 C)
Squalene (30 C) x 6
CHOLESTEROL (27 C)

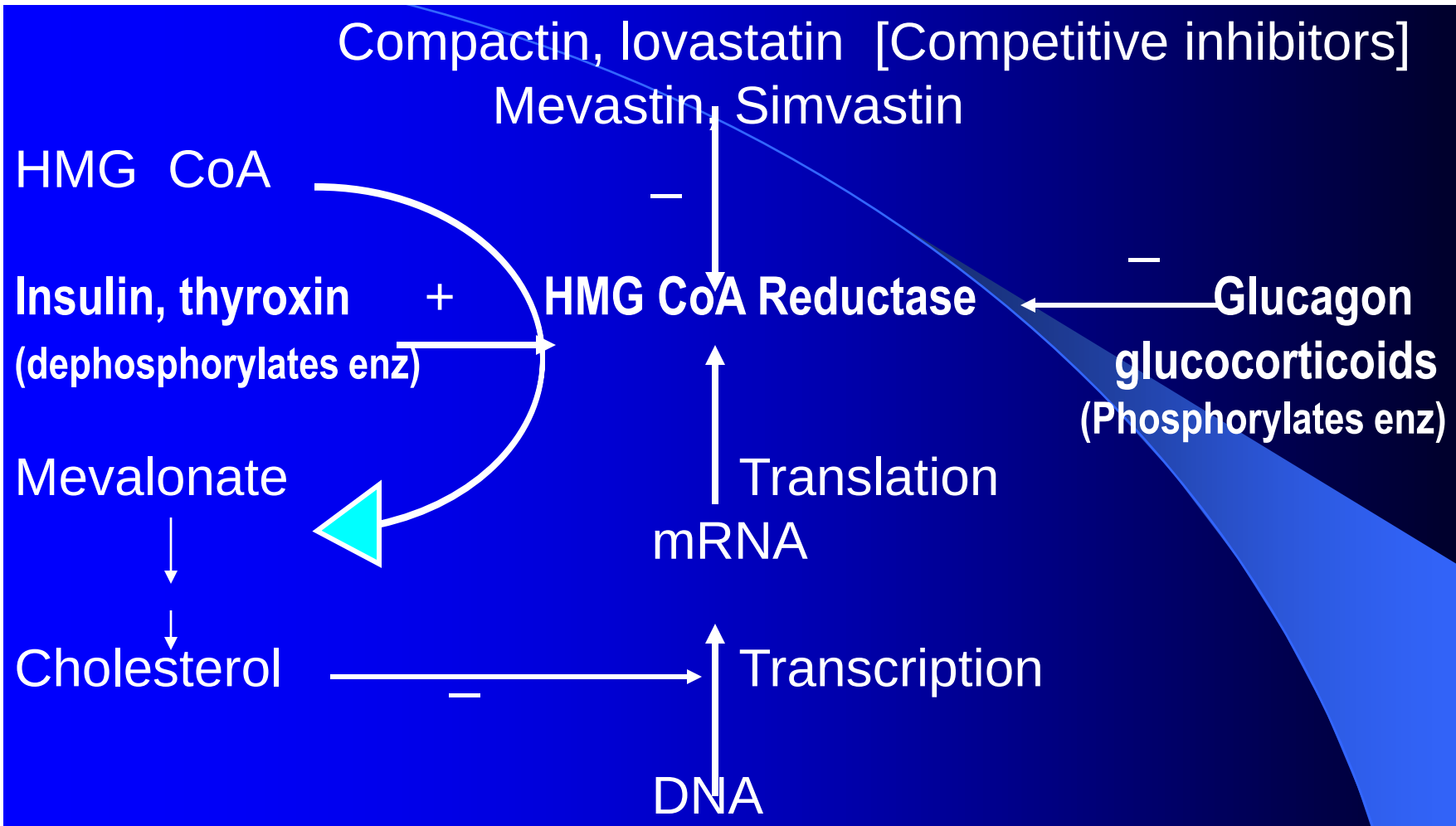
Regulation of Cholesterol synthesis

- Cholesterol biosynthesis is controlled by the rate limiting enzyme **HMG-CO A reductase**

1. **Feedback control**: The end product cholesterol controls its own synthesis of the enzyme by a feedback mechanism. Increase in the cellualar 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. **Hormonal regulation**: The HMG CoA reductase exists in two interconvertible forms.
   Insulin and thyroid hormones **Increase** HMG CoA reductase activity
   The dephosphorylated form of the enzyme is more active, phosphorylated is less active. Hormones exert their influence through cAMP

- **Glucagon and glucocorticoids decrease HMG-CoA reductase activity**
- **Inhibition by drugs: The drugs Compactin and lovastatin, mevastatin, simvastin are competitive inhibitors used to decrease the cholesterol.**
- **HMG CoA reductase is inhibited by bile acids.**
- **LDL transports cholesterol from the liver to peripheral tissues.**
- **HDL transports cholesterol from tissues to liver**



- Glucagon and glucocorticoids inactivate the enzyme through phosphorylation
- **Insulin, thyroxin activate the enzyme through dephosphorylation**

METABOLIC FATE OF CHOLESTEROL

Cholesterol is converted into following compounds as shown below.
Cholesterol is mainly excreted in the form of bile salts in stool.

Acetyl CoA ⟶ Cholesterol →
- Steroid hormone (Testosterone, estrogens progesterone,glucocorticoids mineralocorticoids)
- Vitamin D_3
- Bile acids [salts]

Increased plasma cholesterol results in the accumulation of cholesterol under the tunica intima الغلالة البطانية of the arteries causing atherosclerosis. The progression of the disease process leads to narrowing of the blood vessels. Dietary intake of polyunsaturated fatty acid (PUFA) helps in transport and metabolism of cholesterol and prevents atherosclerosis

Role of LCAT:

High density lipoprotein (HDL) and the enzyme lecithin-cholesterol acyl transferase (LCAT) are responsible for the transport and elimination of cholesterol from the body.

LCAT is a plasma enzyme, synthesized by the liver.

LCAT catalyses the transfer of fatty acid from the second position of phosphatidyl choline (lecithin) to the OH group of cholesterol.

HDL cholesterol is the real substrate for LCAT and this reaction is freely reversible.

LCAT activity is associated with apo-A_1 of HDL.