Lipid metabolism - overview

- Dr.S.Sethupathy

Oxidation of Fatty Acids

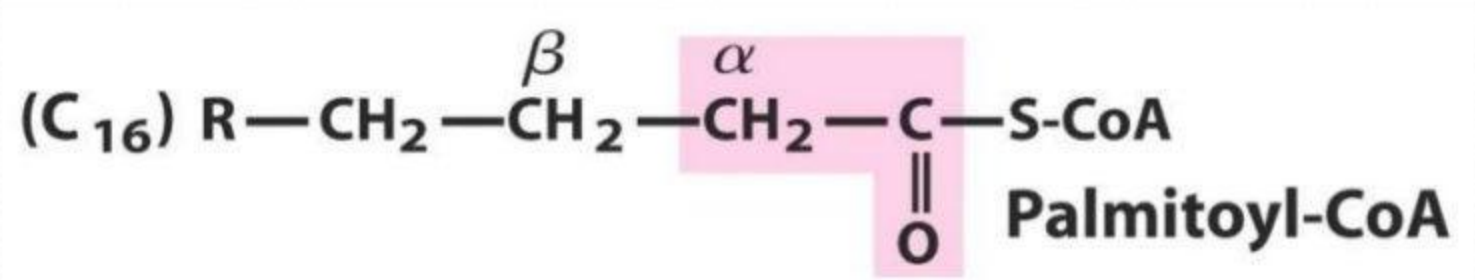
- **Fatty acids** are an important source of energy
- Oxidation is the process where energy is produced by degradation of fatty acids

There are several types of fatty acids oxidation.

(1) β- oxidation of fatty acid
(2) α- oxidation of fatty acids
(3) ω- oxidation of fatty acids

β- oxidation of fatty acid

- **Beta-oxidation** is the process by which fatty acids, in the form of Acyl-CoA molecules, are broken down in mitochondria and/or in peroxisomes to generate Acetyl-CoA – enters TCA cycle
- It occurs in many tissues including liver kidney and heart.
- Fatty acids oxidation doesn't occur in the brain, as fatty acid can't be taken up by that organ.



Stages

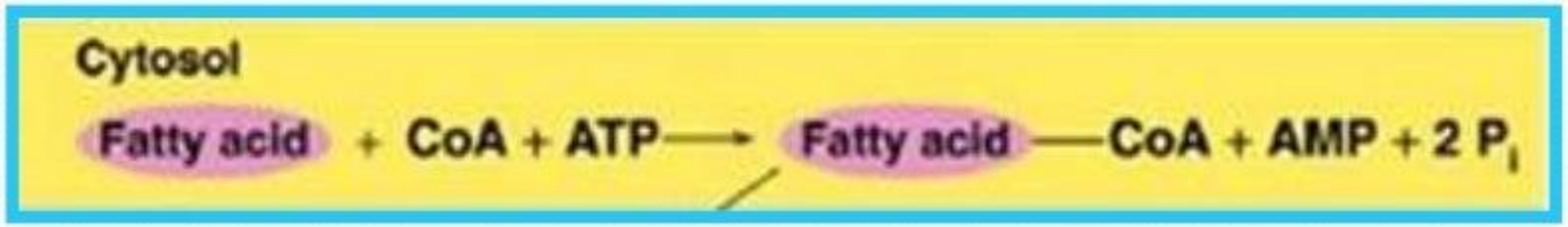
- The beta oxidation of fatty acids involve three stages:

1. Activation of fatty acids in the cytosol
2. Transport of activated fatty acids into mitochondria (**carnitine shuttle**)
3. Beta oxidation proper in the mitochondrial matrix

1) Activation of FA:

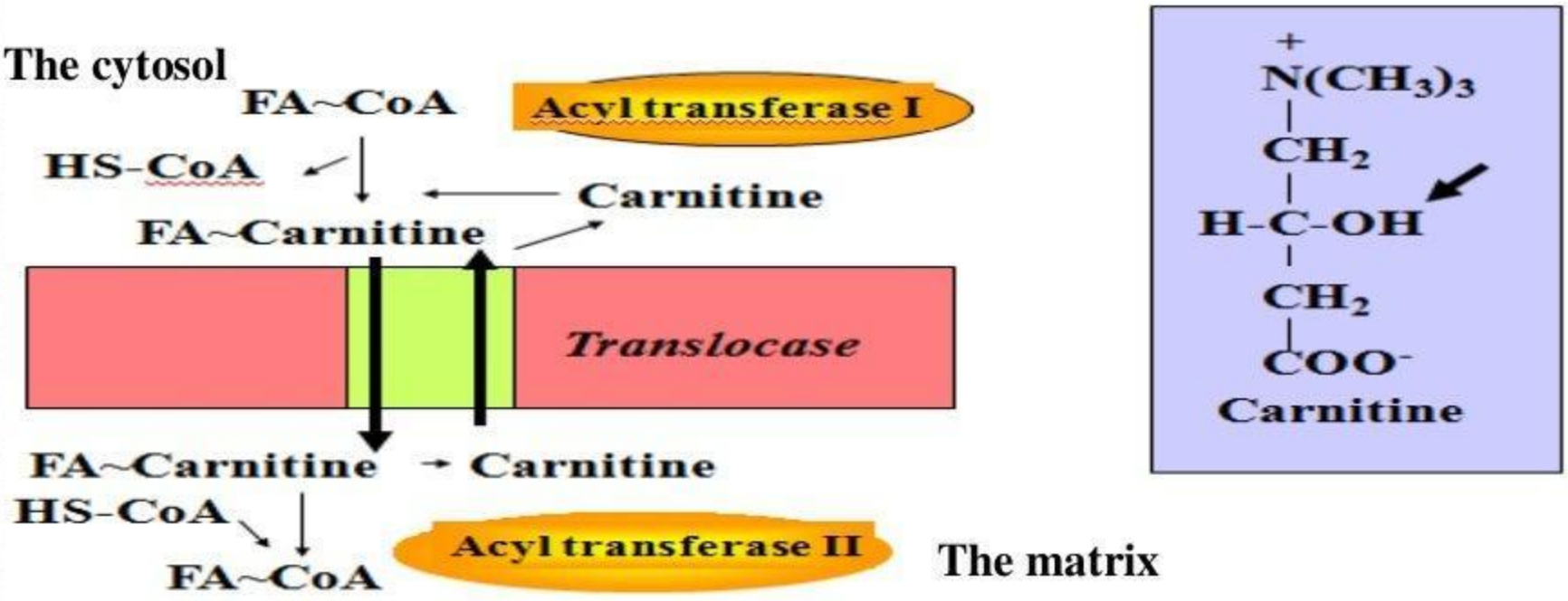
This proceeds by FA thiokinase (acyl COA synthetase) present in cytosol

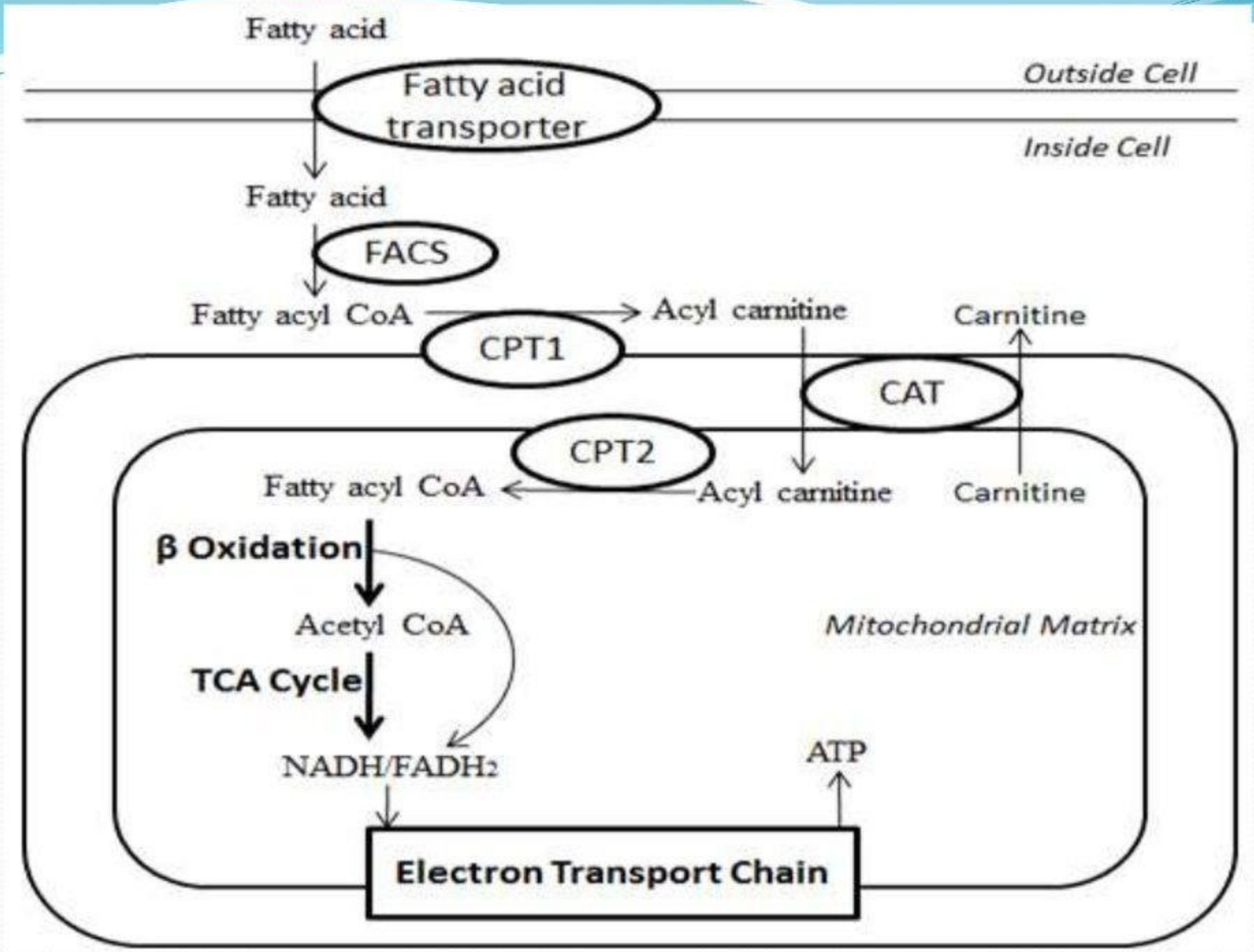
Thiokinase requires ATP, COA SH, Mg^{++}. The product of this reaction is FA acyl COA and water.



2- Transport of fatty acyl CoA from cytosol into mitochondria (rate-limiting step)

- **Long chain acyl CoA** traverses the inner mitochondria membrane with a special transport mechanism called **Carnitine shuttle**.




Fatty acid
Outside Cell
Fatty acid transporter
Inside Cell
Fatty acid
FACS
Fatty acyl CoA
Acyl carnitine
Carnitine
CPT1
CAT
CPT2
Fatty acyl CoA
Acyl carnitine
Carnitine
β Oxidation
Acetyl CoA
Mitochondrial Matrix
TCA Cycle
NADH/FADH2
ATP
Electron Transport Chain

2-Transport of acyl CoA into the mitochondria (rate-limiting step)

1. Acyl groups from acyl COA is transferred to carnitine to form acyl carnitine catalyzed by **carnitine acyltransferase I,** in the outer mitochondrial membrane.
2. Acylcarnitine is then shuttled across the inner mitochondrial membrane by **a translocase** enzyme.
3. The acyl group is transferred back to CoA in matrix by **carnitine acyl transferase II.**
4. Finally, carnitine is returned to the cytosolic side by translocase, in exchange for an incoming acyl carnitine.

3. Proper of β – oxidation in the mitochondrial matrix

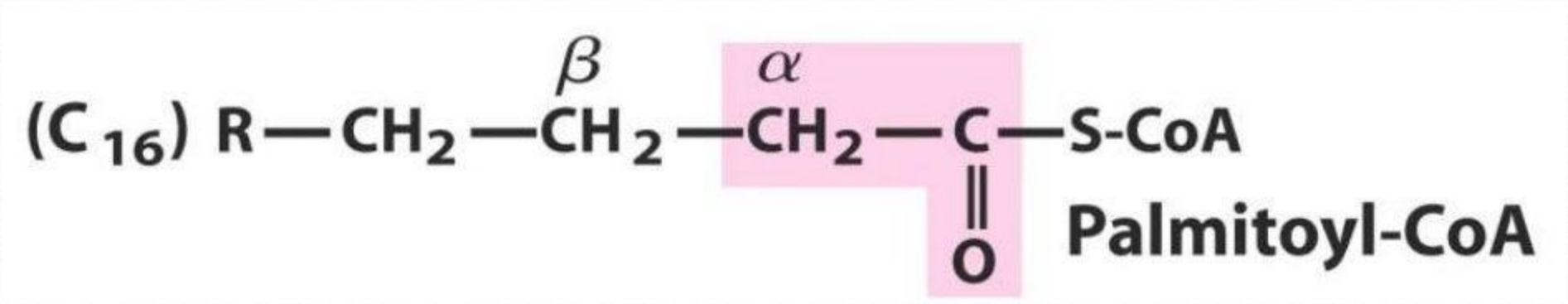
There are 4 steps in β C– oxidation

Step I – Oxidation by ***FAD linked dehydrogenase***

Step II – Hydration by **Hydratase**

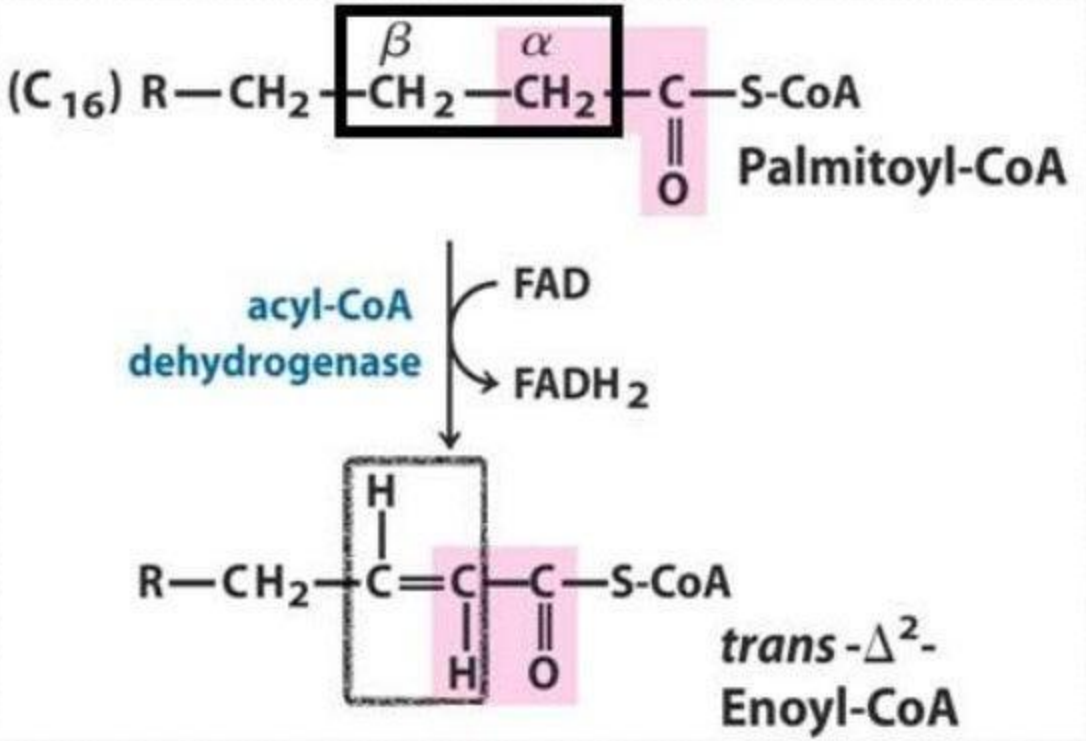
Step III – Oxidation by ***NAD linked dehydrogenase***

Step IV – Thiolytic clevage **Thiolase**

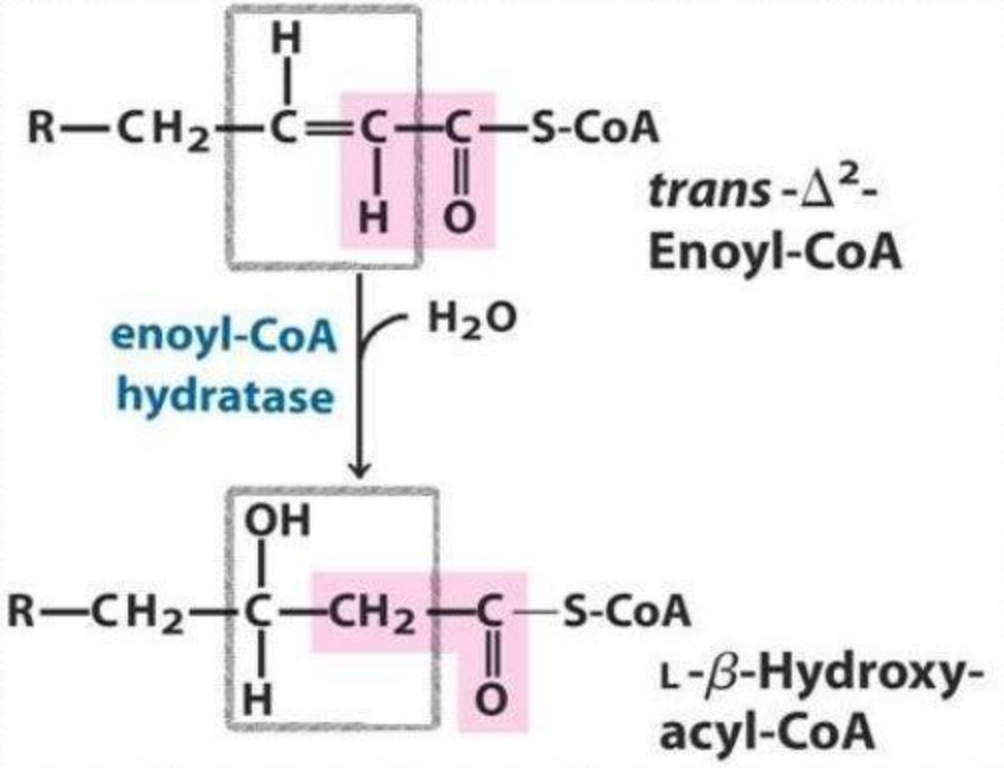


The first reaction is **the oxidation** of acyl CoA by an acyl CoA dehyrogenase to give α-β unsaturarted acyl CoA (enoyl CoA).

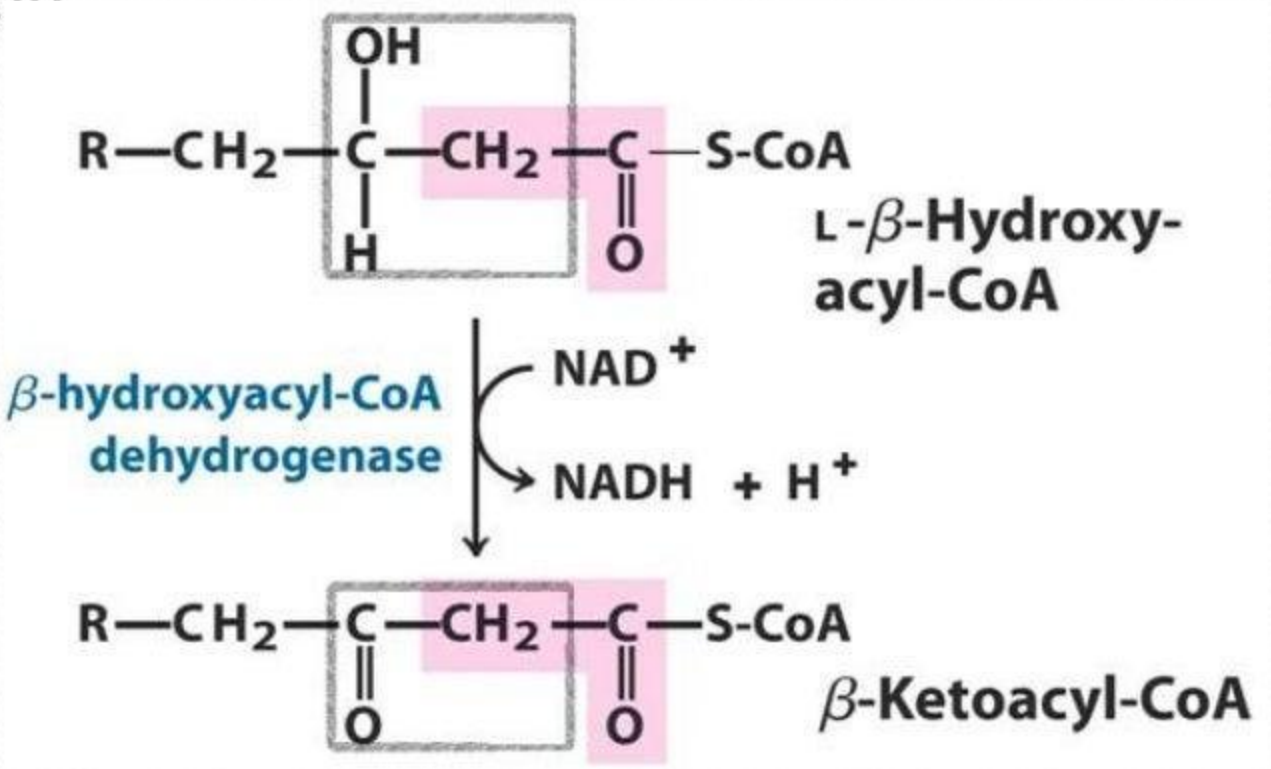
FAD is the hydrogen acceptor.



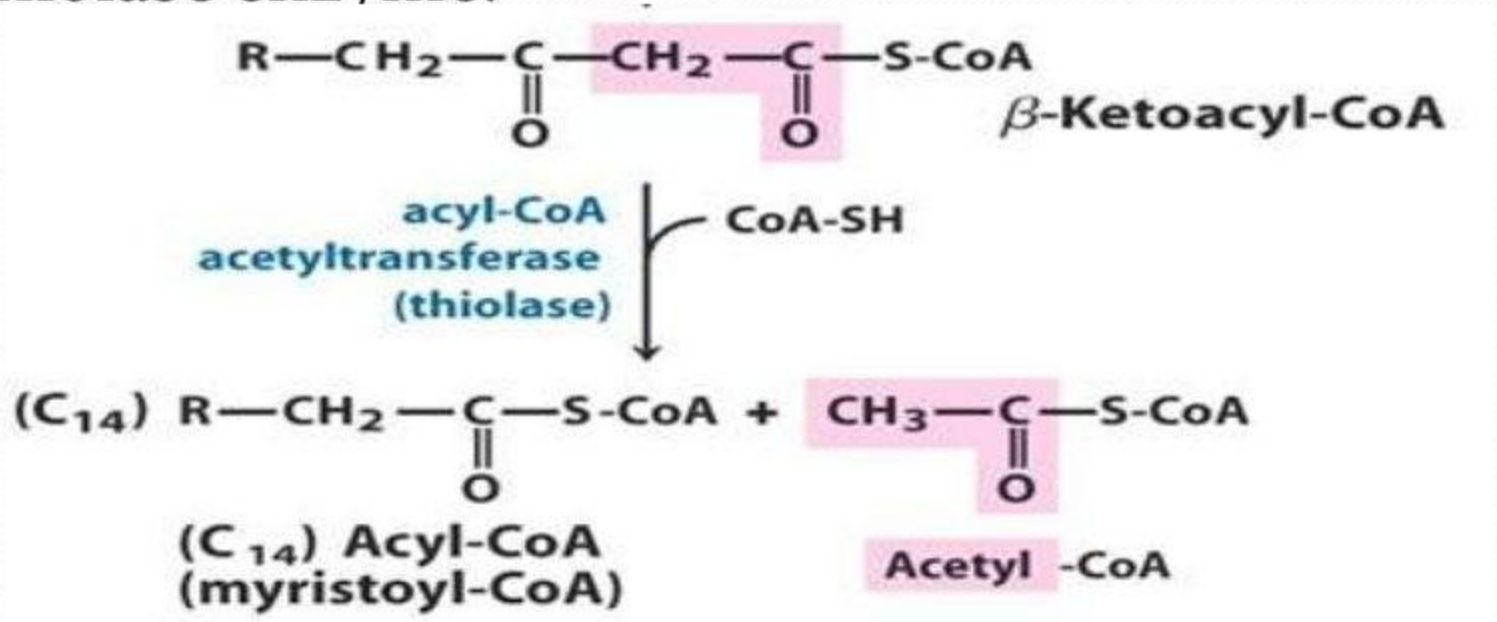
The second reaction is the **hydration** of the double bond to β-hydroxyacyl CoA (p-hydroxyacyl CoA).

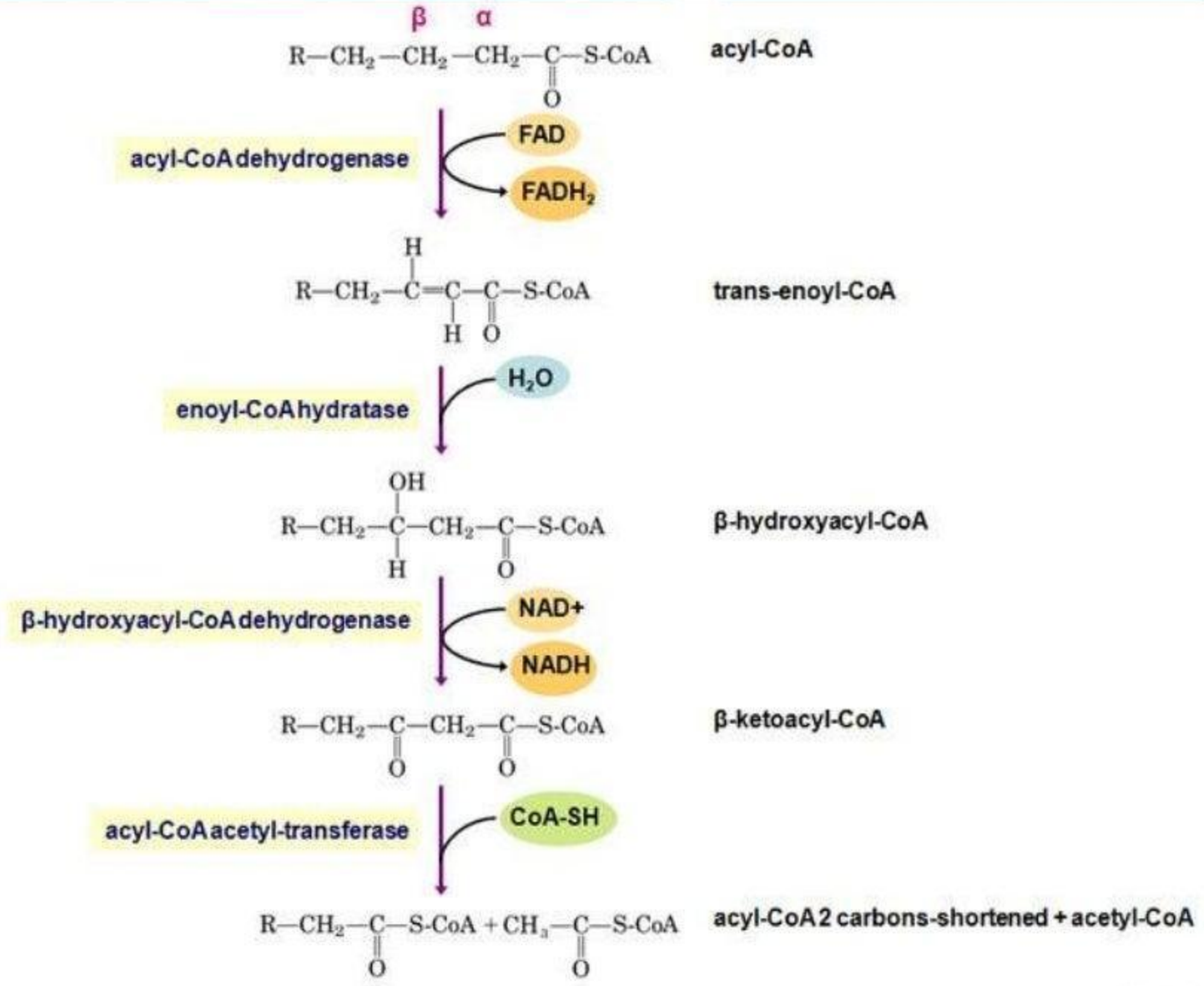


- **The third reaction** is the **oxidation** of β-hydroxyacyl CoA to produce β-Ketoacyl CoA a NAD-dependent reaction



- The fourth reaction is cleavage of the two carbon fragment by splitting the bond between α and β carbons
- By thiolase enzyme.




β α
R—CH2—CH2—CH2—C—S-CoA
O
acyl-CoA
acyl-CoA dehydrogenase
FAD
FADH2
H
R—CH2—C=C—C—S-CoA
H O
trans-enoyl-CoA
enoyl-CoA hydratase
H2O
OH
R—CH2—C—CH2—C—S-CoA
H O
β-hydroxyacyl-CoA
β-hydroxyacyl-CoA dehydrogenase
NAD+
NADH
R—CH2—C—CH2—C—S-CoA
O O
β-ketoacyl-CoA
acyl-CoA acetyl-transferase
CoA-SH
R—CH2—C—S-CoA + CH3—C—S-CoA
O O
acyl-CoA 2 carbons-shortened + acetyl-CoA

energetics

- $FADH_2$ - 1.5 ATP
- $NADH_2$ - 2.5 ATP
- Each cycle 4 ATP
- Palmitic acid – 7 cycles - 7 x 4 = 28
- Acetyl CoA - 8 x 10 ATP – 80
- Activation energy loss – 2 ATP
- Net energy- 108 – 2 = 106 ATP

Regulation

- The availability of fatty acids influences beta oxidation.
- **Glucagon** by activating hormone sensitive lipase **increases FFA** level in blood
- **Insulin inhibits Beta oxidation** by inhibiting this enzyme.
- Malonyl CoA inhibits CAT-1 activity.

Cholesterol biosynthesis

Location of pathway

1. The pathway is located in the cytosol
2. Raw material Acetyl-CoA.
3. Most cells can make cholesterol, but liver is most active.

Stages

1 - Synthesis of mevalonate

2. Synthesis of isopentenyl units

3. Synthesis of squalene

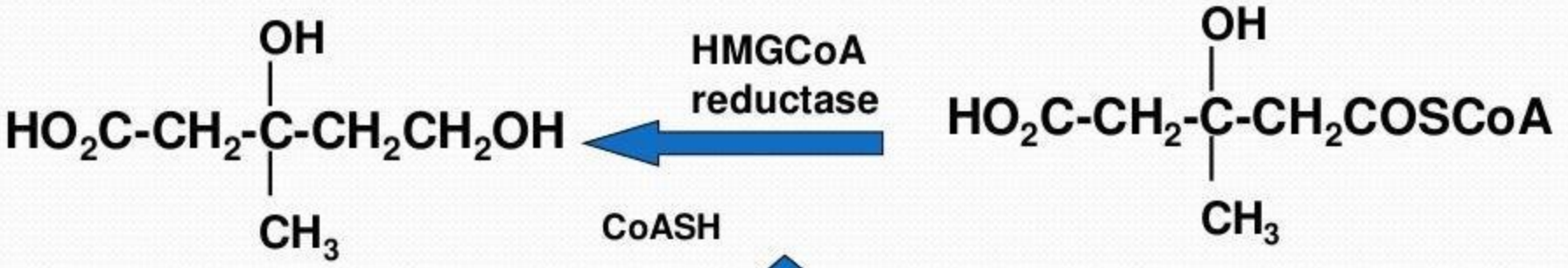
4.Synthesis of lanosterol

5. Synthesis of cholesterol

Cholesterol Biosynthesis: Formation of Mevalonate

Liver is primary site of cholesterol biosynthesis

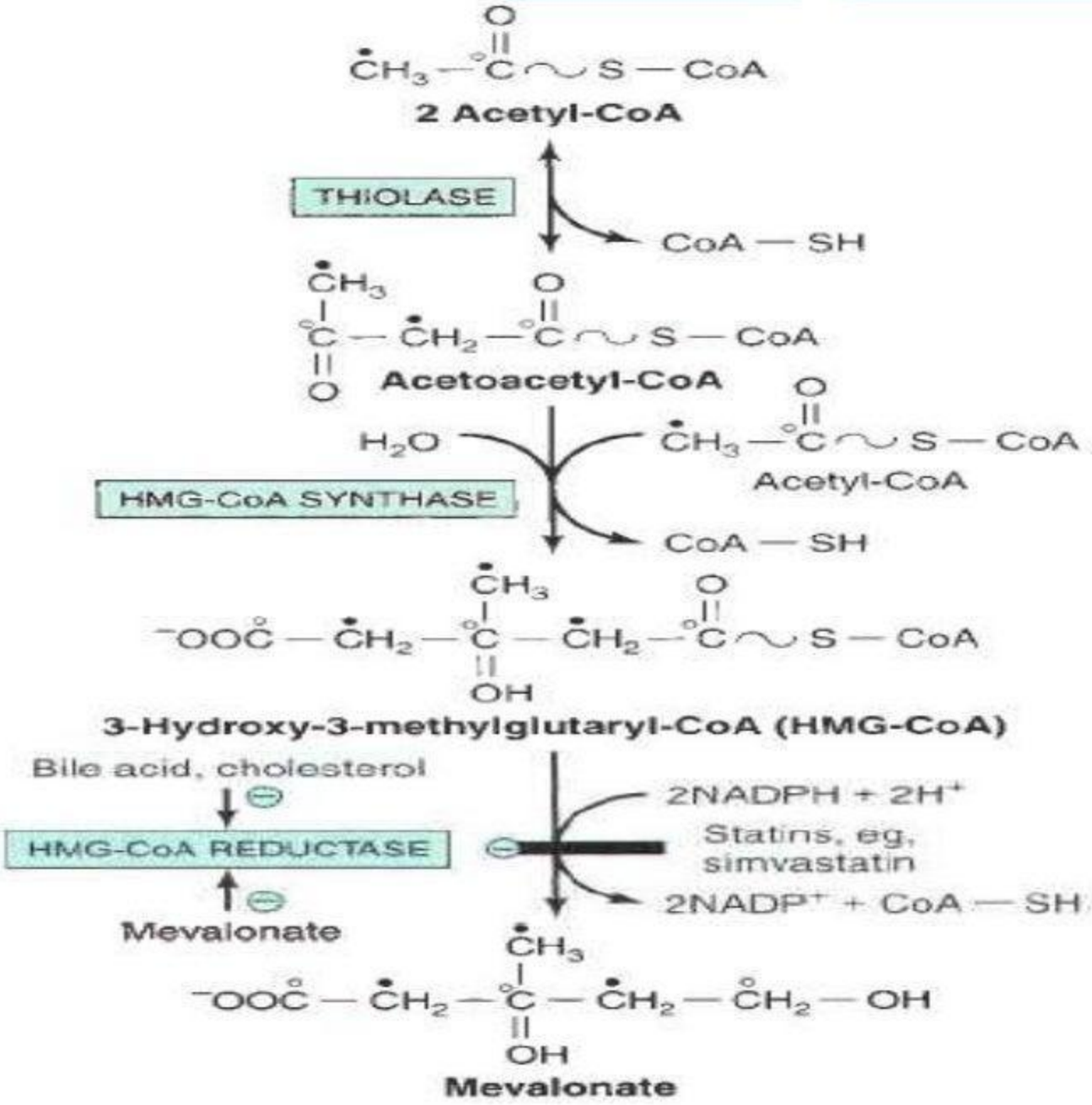
HMG CoA Synthase



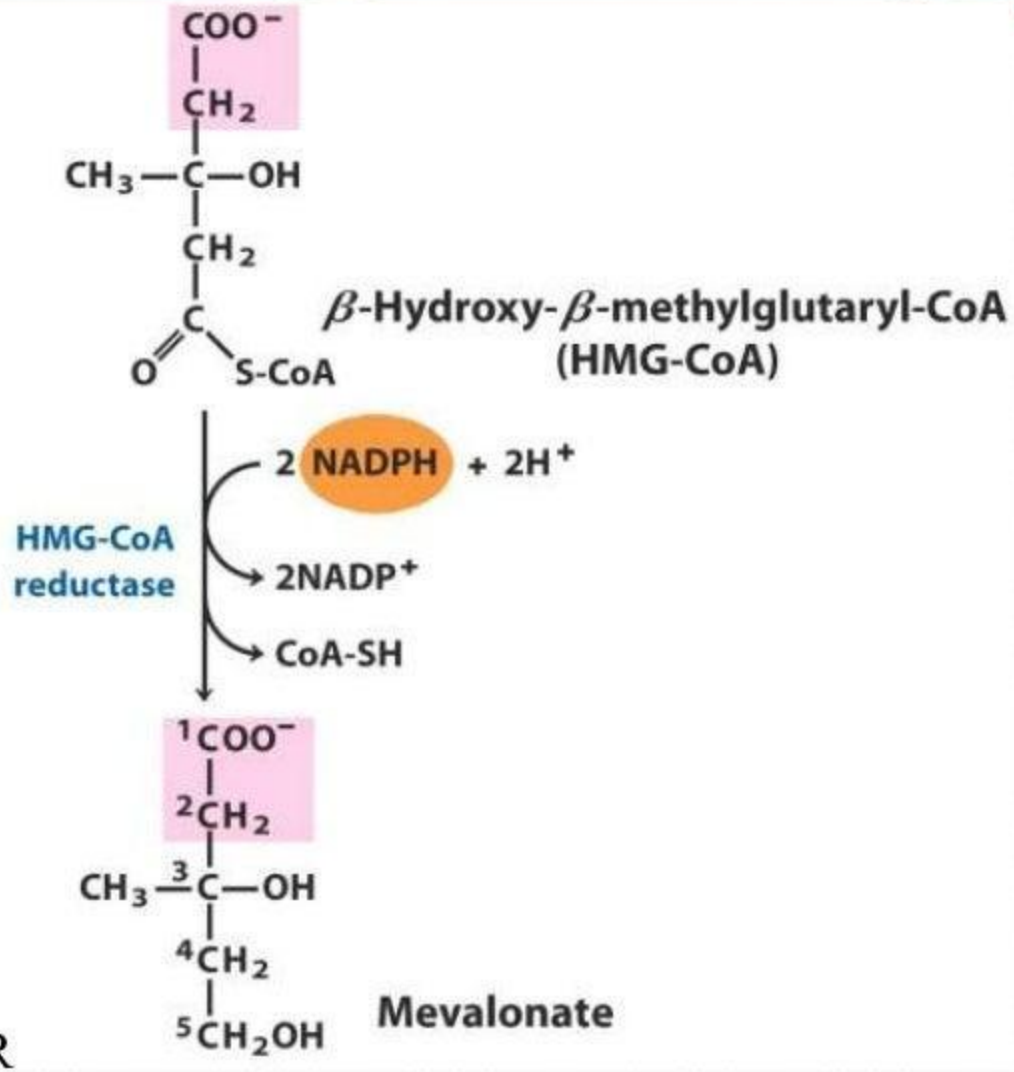
3*R*-Mevalonic acid

Key control step in cholesterol biosynthesis

β-Hydroxy-β-methyl-glutaryl CoA (HMG CoA)


2 Acetyl-CoA
THIOLASE
CoA — SH
Acetoacetyl-CoA
H2O
HMG-CoA SYNTHASE
Acetyl-CoA
CoA — SH
3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA)
Bile acid, cholesterol
HMG-CoA REDUCTASE
Mevalonate
2NADPH + 2H+
Statins, eg, simvastatin
2NADP+ + CoA — SH
Mevalonate

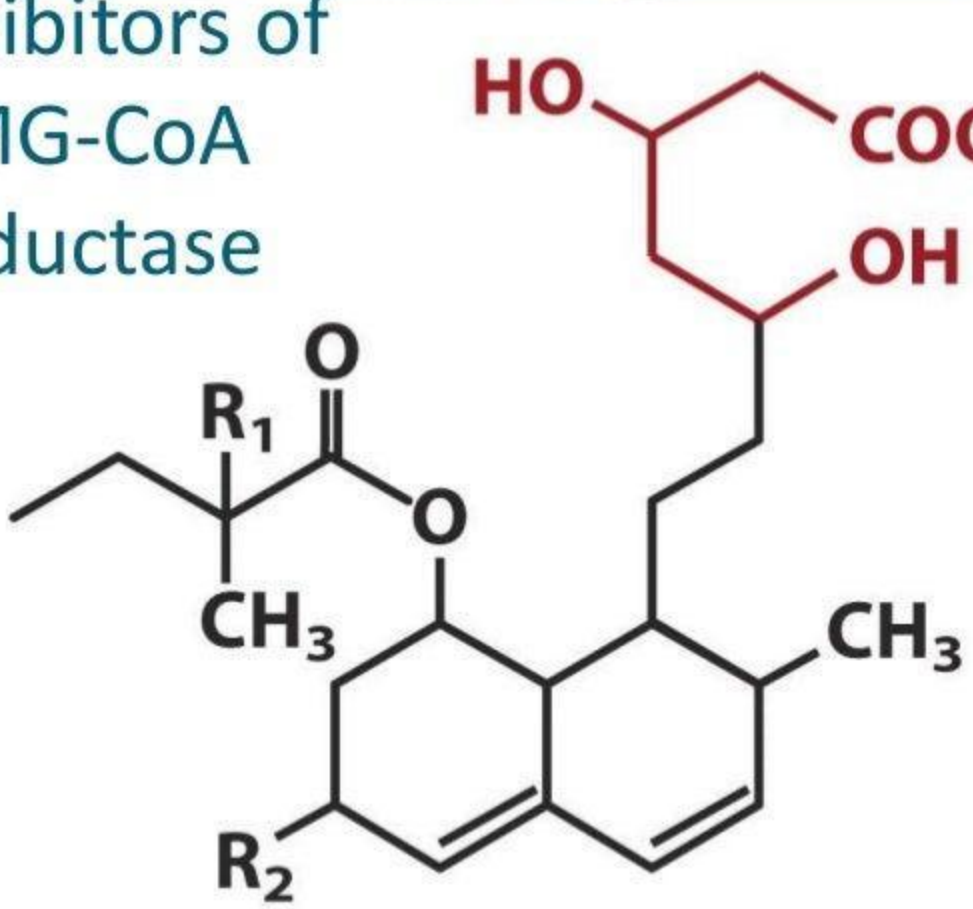
HMG-CoA Reductase

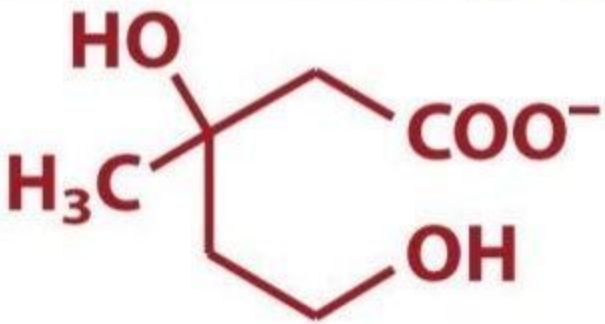


HMG-CoA reductase

1. integral membrane protein in the ER
2. carries out an irreversible reaction
3. is an important regulatory enzyme in cholesterol synthesis

Inhibitors of HMG-CoA Reductase

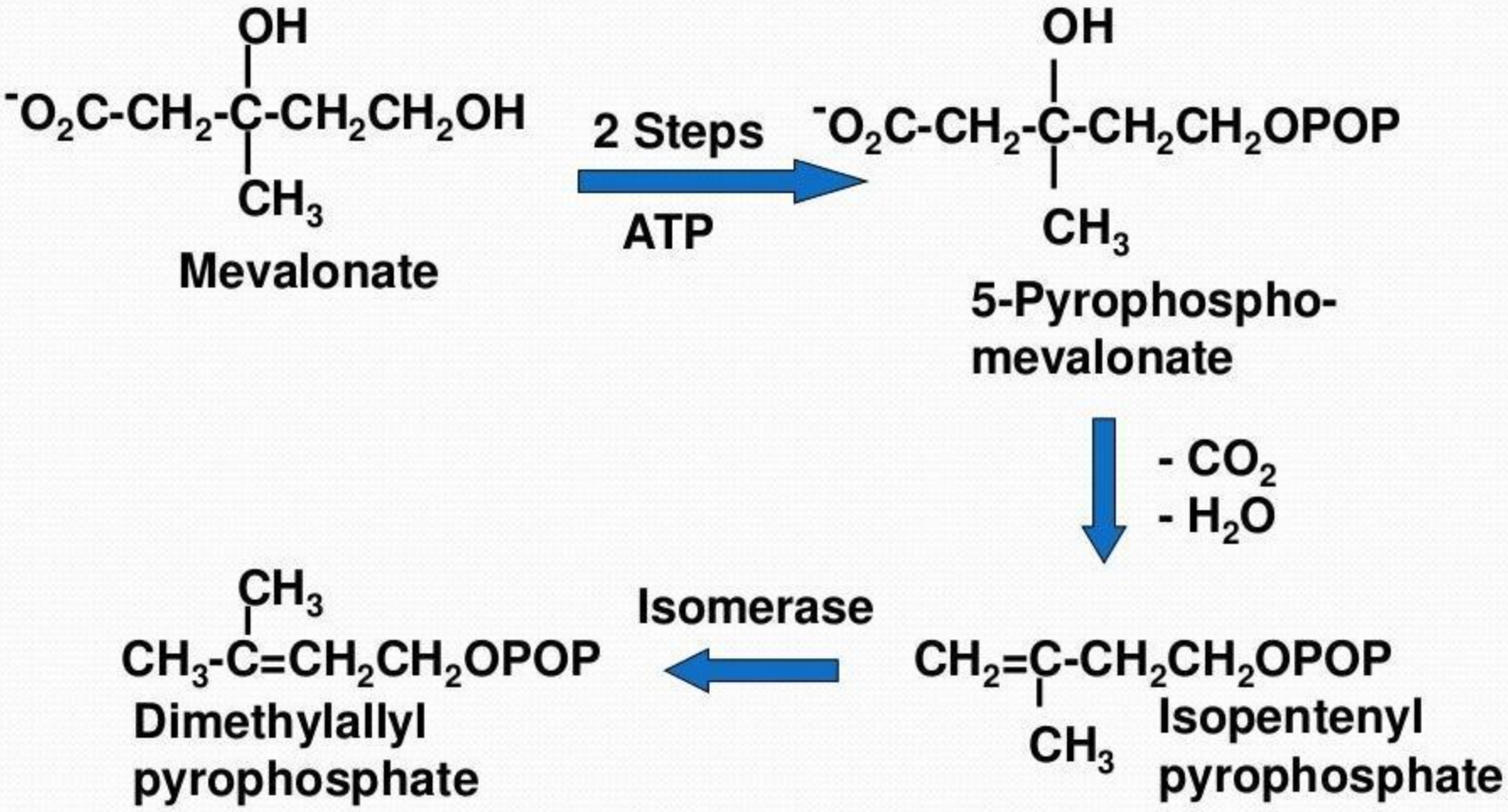




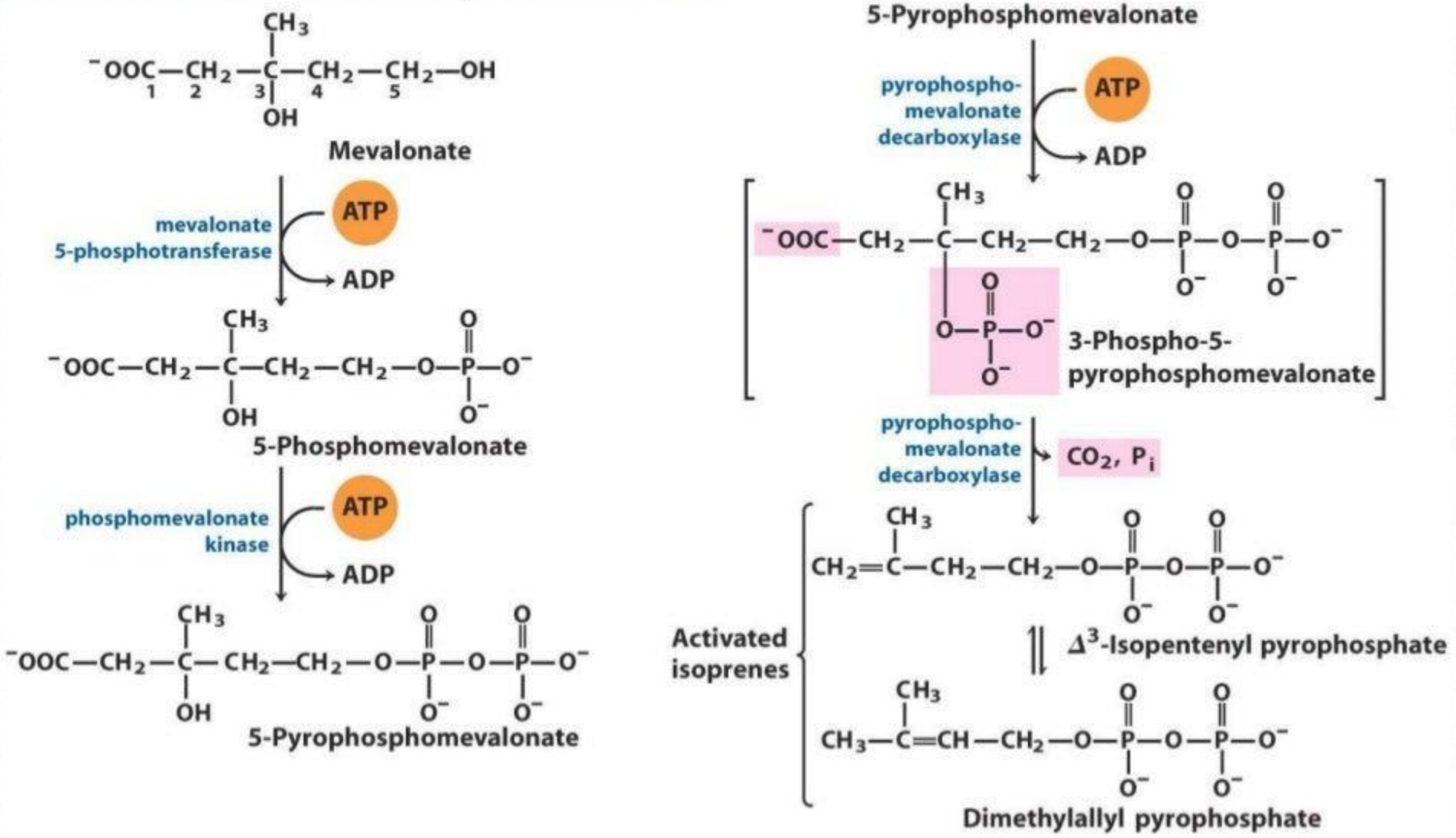
Mevalonate

$R_1 = H$	$R_2 = H$	**Compactin**
$R_1 = CH_3$	$R_2 = CH_3$	**Simvastatin (Zocor)**
$R_1 = H$	$R_2 = OH$	**Pravastatin (Pravachol)**
$R_1 = H$	$R_2 = CH_3$	**Lovastatin (Mevacor)**

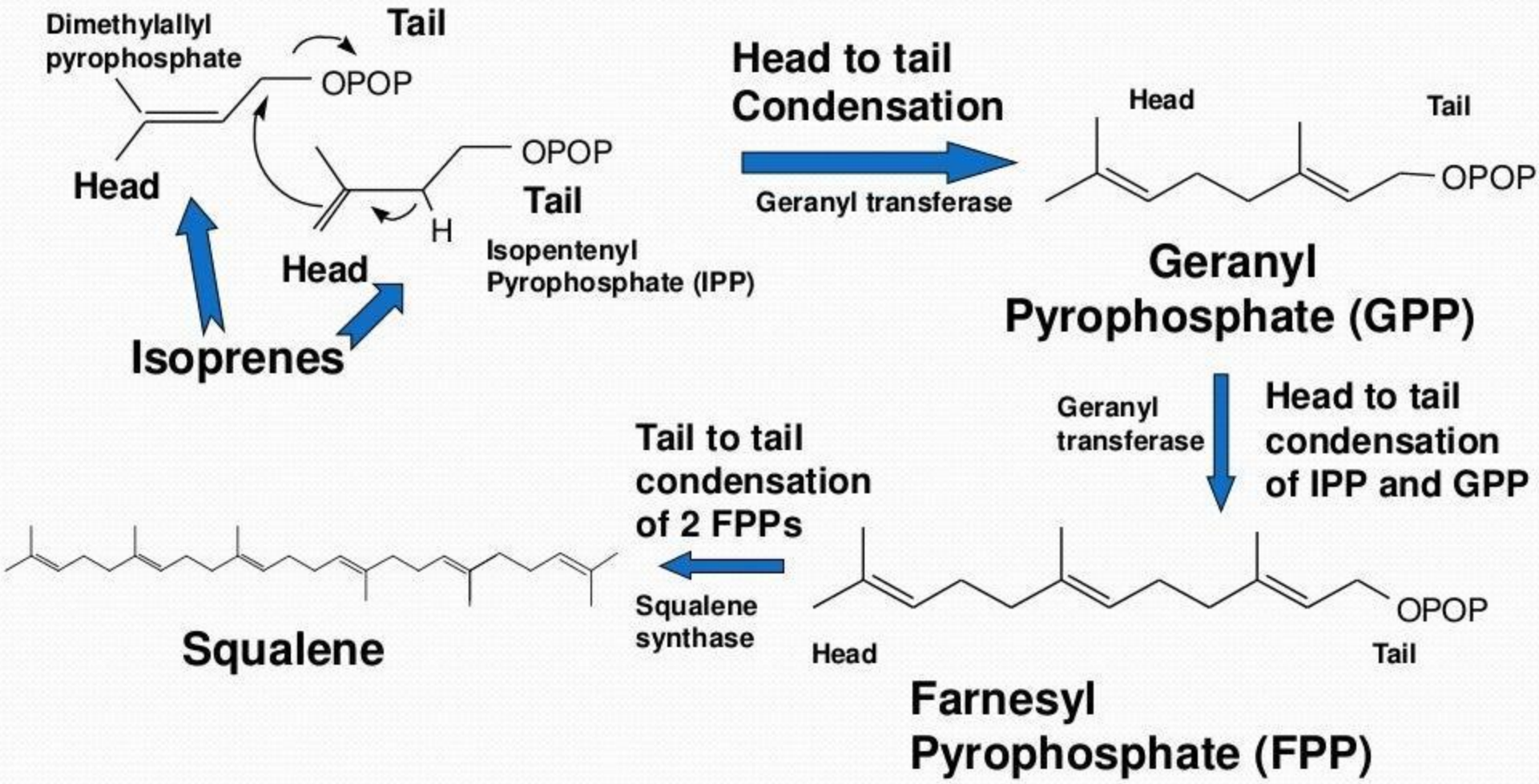
Cholesterol Biosynthesis: Processing of Mevalonate



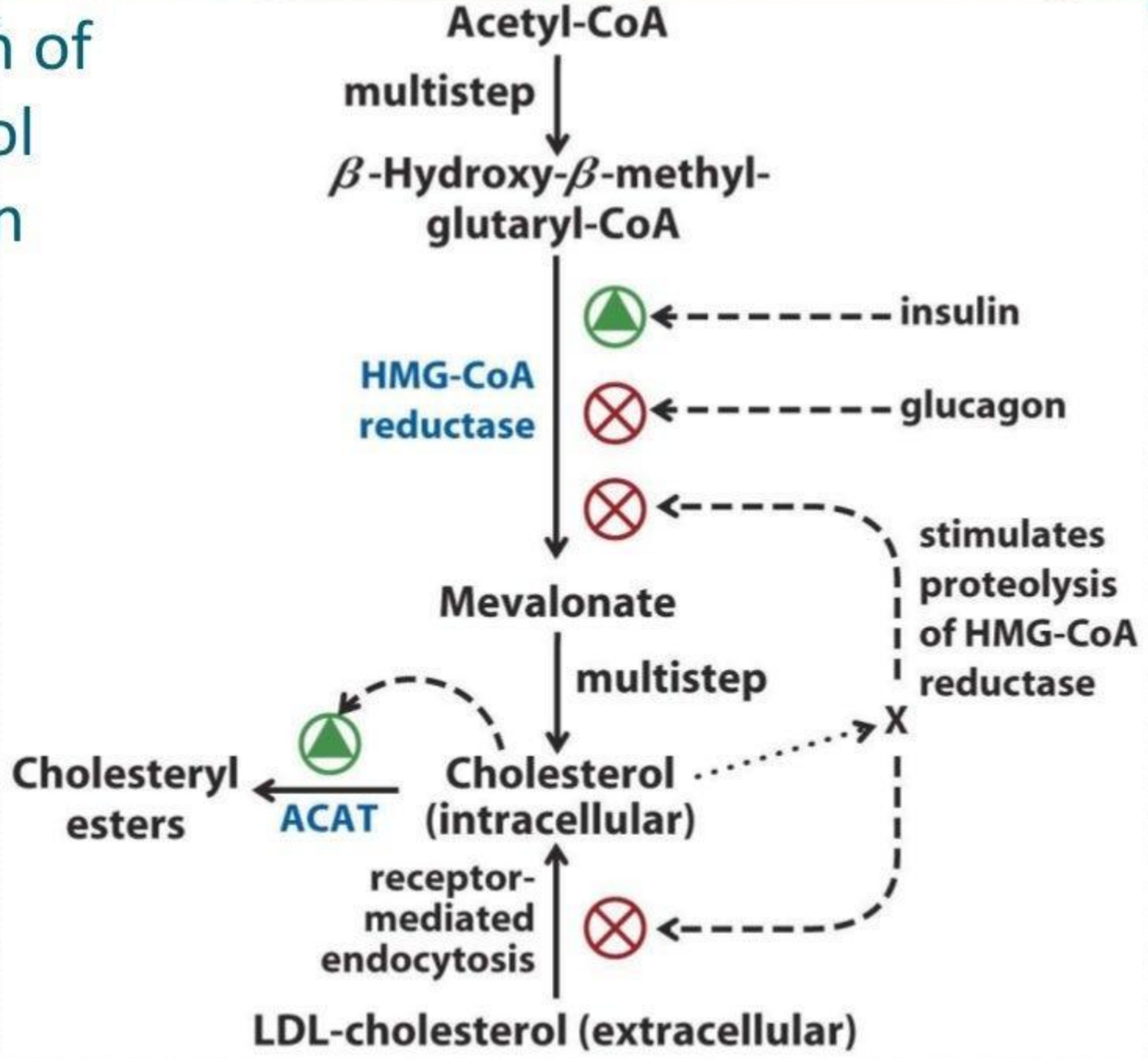
Cholesterol Synthesis:



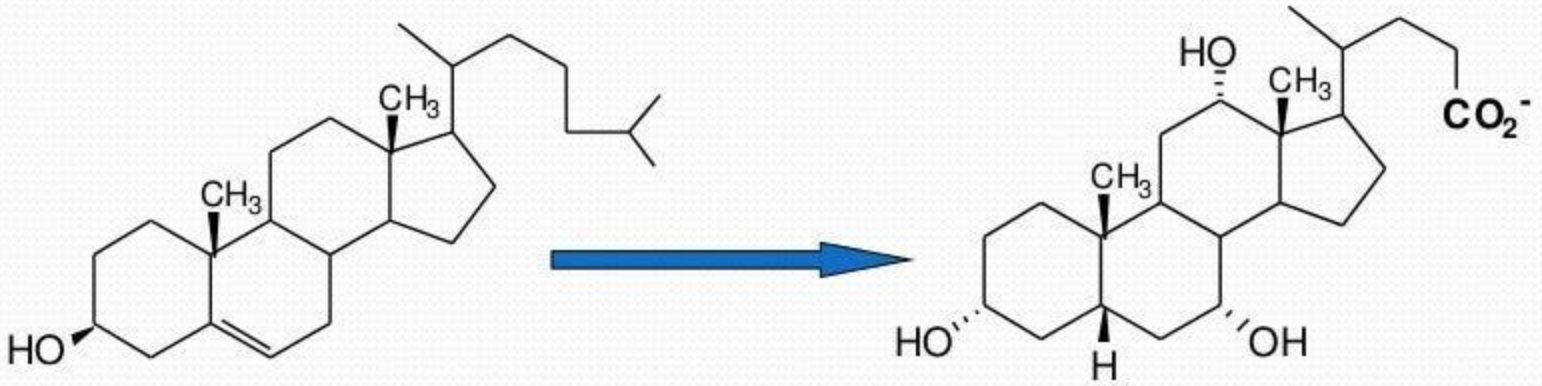
Cholesterol Biosynthesis: Isoprenoid Condensation



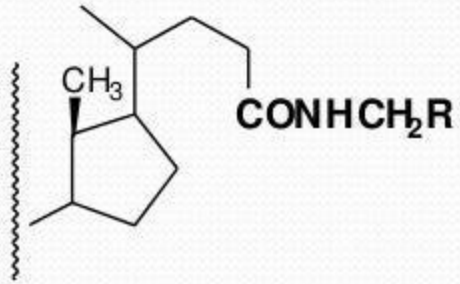
Regulation of Cholesterol Production



Transformations of Cholesterol: Bile Salts



Cholesterol **Cholic acid**

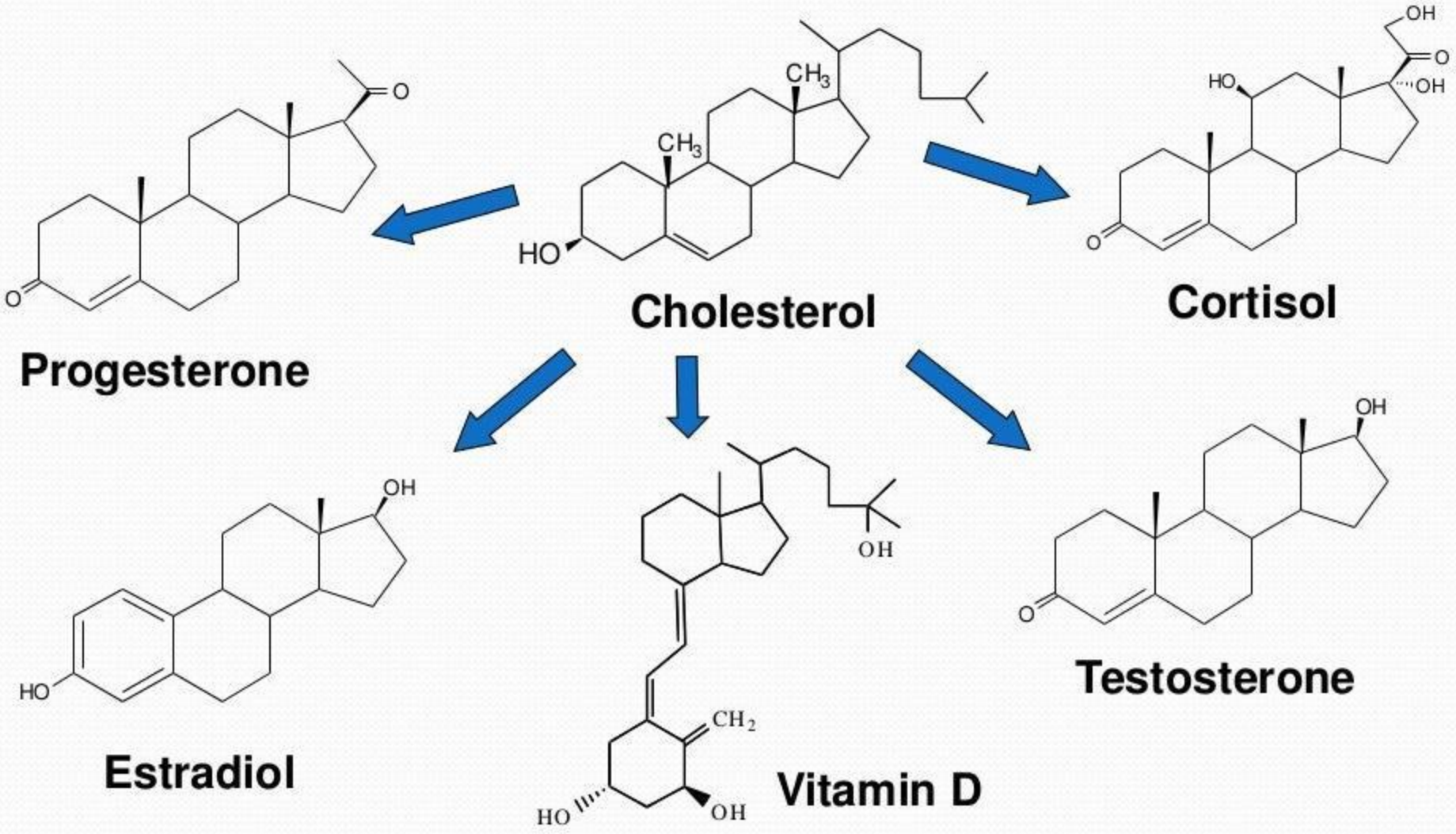


R = $CH_2SO_3^-$ Taurocholate

R = CO_2^- Glycocholate

Detergents

Transformations of Cholesterol: Steroid Hormones



Factors affecting serum cholesterol

- **Role of Fatty acids**
- **Effect of high fructose intake on blood lipids**
- Hypercholesterolemia occurs in **diabetes mellitus, Hypothyroidism, Obstructive jaundice, Familial hypercholesterolemia.**

- Hereditary factor -In familial hypercholesterolemia, due to LDL receptor defect, LDL cholesterol uptake is reduced

- **Hypolipidemic drugs**
- **Statins** - competitive inhibitors of HMG CoA-reductase.

- **Clofibrate** It enhances fecal excretion of cholesterol and bile acids and also increases the peroxisomal oxidation of fatty acids in liver.

- **Cholestyramine** This increases their excretion bile acids in the stools.

- **Clofibrates, gemfibrosil** lower plasma TGL by decreasing VLDL .Activate lipoprotein lipase.

- **Probucol** increases the catabolism of LDL. It also has antioxidant properties

- **Nicotinic acid** reduces lipolysis and inhibits VLDL production.

Ketogenesis

- Acetoacetate, beta hydroxy butyrate and acetone
- In the liver mitochondria.

- Two molecules of acetyl CoA condense to form acatoacetyl CoA by thiolase or acetoacetyl CoA synthase .

- **Step two:** Acetoacetyl CoA condenses with another molecule of acetyl CoA to form 3-Hydroxy-3-methyl-glutaryl CoA (HMG-CoA) by HMG-CoA synthase enzyme.

- **Step three:** HMG-CoA lyase cleaves HMG - CoA to acetoacetate and acetyl CoA.

- **Step four:** Acetoacetate is the primary ketone body.
- It is reduced to beta hydroxy butyrate by beta-hydroxy butyrate dehydrogenase using $NADH+H^+$ as coenzyme.

- Acetoacetate undergoes non enzymatic spontaneous decarboxylation to acetone.

Fate of ketone bodies

- 3-hydroxy butyrate is the predominant ketone body present in blood and urine in ketosis.
- Liver cannot utilize ketone bodies
- It lacks the particular enzyme- the CoA – transferase or thiophorase.
- Peripheral tissues utilize them.- Succinyl CoA – acetoacetate CoA transferase or thiophorase
- Succinyl CoA + acetoacetate – succinate + acetacetyl CoA

Regulation

- If there is increase of lipolysis, there is increase of ketogenesis.
- Insulin inhibits ketogenesis
- Glucagon and norepinephrine promotes .
- In diabetes mellitus , due to insulin deficiency, ketosis occurs.
- Starvation – increase of ketogenesis

Chylomicrons

- Dietary lipid absorbed in the small intestine is incorporated into chylomicrons which reach systemic circulation via lymphatics, thoracic duct .
- In circulation , by the action of lipoprotein lipase (LPL) , chylomicrons on releasing fatty acids and glycerol become smaller in size known as chylomciron remnants.
- The remnants are removed in the liver by receptor mediated endocytosis.
- Insulin increases LPL activity
- In type I hyperlipoproteinemia , there is a defect in LPL leading to fasting chylomicronemia . VLDL is also increased
- Hepatomegaly, eruptive xanthoma, lipemia retinalis and abdominal pain are characteristic features

Treatment

- Fat diet containing short and medium chain fatty acids
- High carbohydrates diet will induce VLDL synthesis and it is to be limited
- When fasting serum kept in fridge for 24 hrs, a creamy layer on top due to chylomicrons appear and on electrophoresis, a band at the point of application is seen.

VLDL Very low density lipoproteins

- They are involved in the transport of triacyglcyerol, cholesterol produced in the liver.
- LPL acts on it and releases fatty acids and glycerol on hydrolysis of TGL
- VLDL becomes IDL that contain apo B100 & apo E
- Part of IDL is taken up liver via Apo B100, E receptor
- Part of IDL releases TGL, apo E and becomes LDL-a cholesterol rich, apo B100 containing lipoprotein.

Low density lipoprotein (LDL)

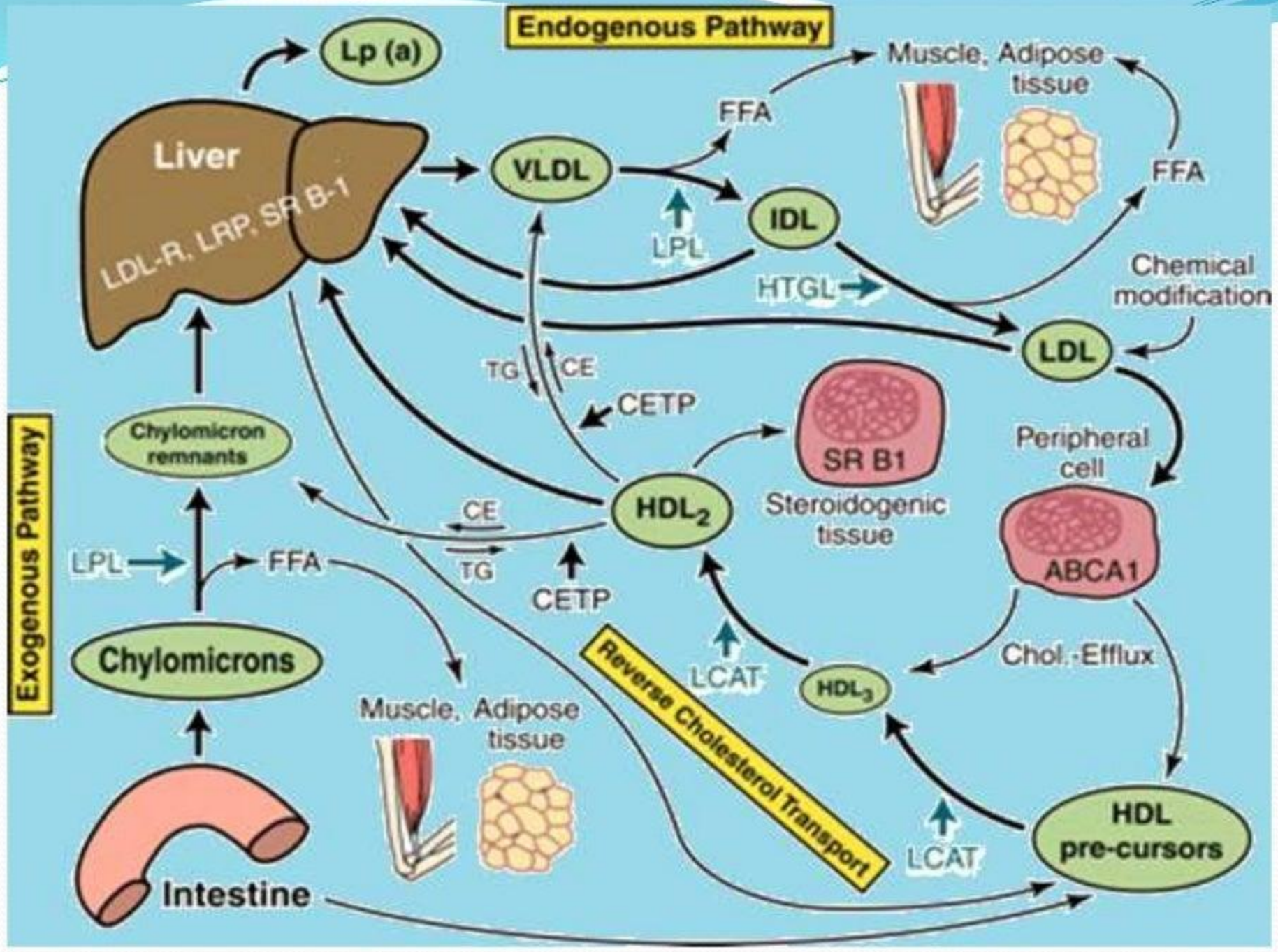
- LDL transports cholesterol from liver to extra hepatic tissues. LDL concentration positively correlates with cardiovascular disease
- LDL is taken up by LDL receptors mainly present in liver, adrenal cortex and extra hepatic tissues .

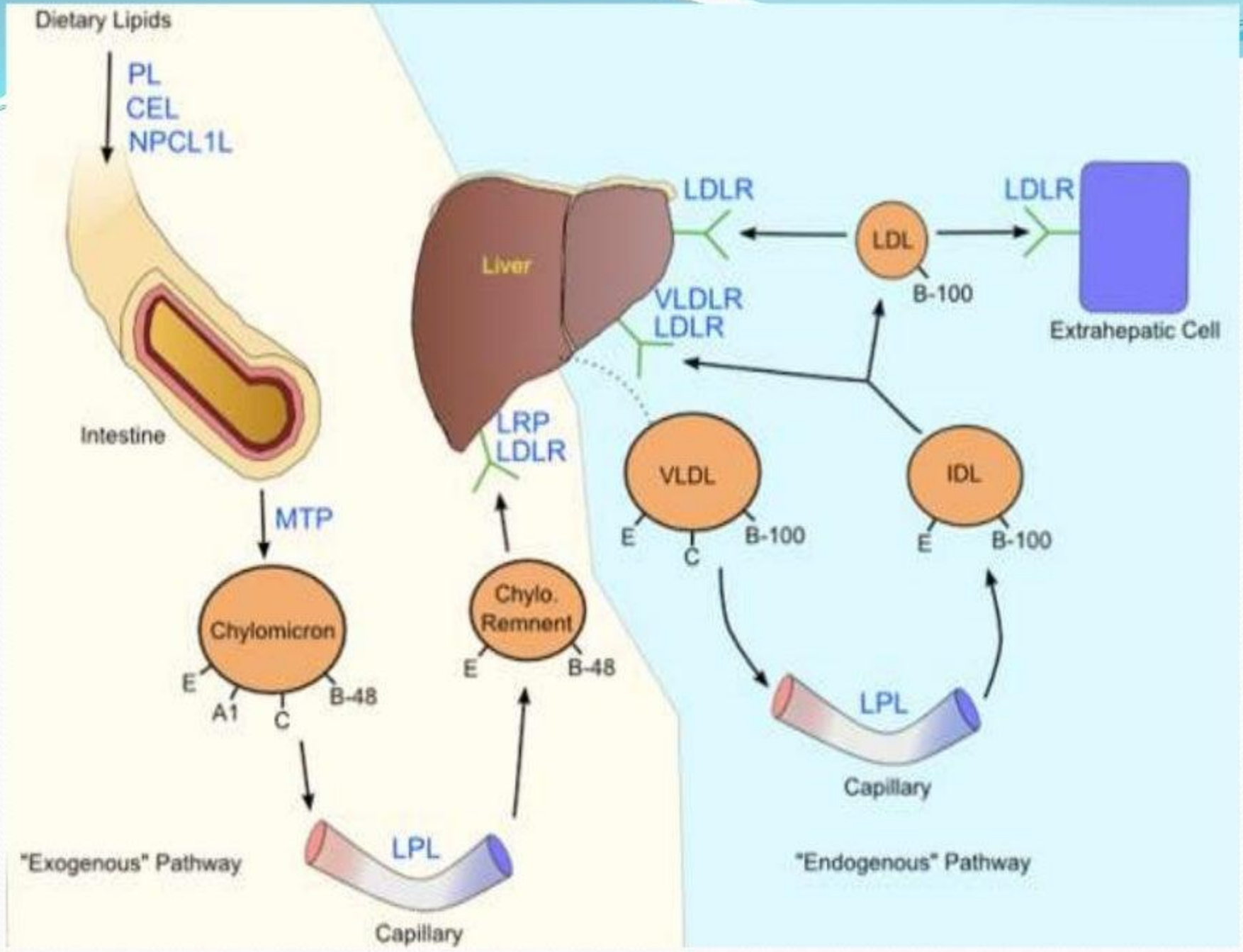
Familial hypercholesterolemia

- Type II a-hyperlipoproteinemia
- It is due to LDL receptor defect
- Serum cholesterol and LDL cholesterol are increased where as TGL is normal on electrophoresis, beta-band is increased
- Tuberous xanthoma, atherosclerosis and early CAD. Low cholesterol high PUFA diet and drugs such as HMG CoA **reductase** inhibitors ,bile acid binding resin are given.

High density lipoprotein

- It is synthesized and secreted from both liver and intestine.
- Nascent HDL is discoid, phospholipid bilayer containing apo A and free cholesterol.
- Plasma enzyme LCAT (Lecithin cholesterol acyl transferase) by activator Apo A1 bind to the disk and esterifies cholesterol.
- Non-polar cholesteryl ester forms the core and HDL becomes spherical .


Endogenous Pathway
Lp (a)
Liver
LDL-R, LRP, SR B-1
VLDL
FFA
Muscle, Adipose tissue
FFA
IDL
LPL
HTGL
Chemical modification
LDL
TG
CE
CETP
SR B1
Steroidogenic tissue
Peripheral cell
ABCA1
Exogenous Pathway
Chylomicron remnants
HDL2
CE
TG
CETP
LPL
FFA
Chylomicrons
LCAT
HDL3
Chol.-Efflux
Reverse Cholesterol Transport
Muscle, Adipose tissue
LCAT
HDL pre-cursors
Intestine


Dietary Lipids
PL
CEL
NPCL1L
Intestine
MTP
Chylomicron
E
A1
C
B-48
Capillary
LPL
"Exogenous" Pathway
Chylo. Remnent
E
B-48
LRP
LDLR
Liver
LDLR
VLDLR
LDLR
LDL
B-100
LDLR
Extrahepatic Cell
VLDL
E
C
B-100
IDL
E
B-100
LPL
Capillary
"Endogenous" Pathway

- **Lipid profile (Reference range)**

- Total serum cholesterol : 140 – 200 mg/dL

- Serum LDL cholesterol – less than 100mg/dl

- Serum triglycerides - 50- 150 mg/dL (Less than 100 mg/dL is optimal)

- Serum HDL cholesterol - 40- 70 mg/dL

- HDL Less than 40 mg/dL in men and less than 50 mg/dL in women increases the risk of heart disease.
- HDL more than 60 mg/dl decreases the risk of heart disease.

- LDL/HDL ratio – less than 3 is cardio protective and more than 5 increases the risk.

- Total cholesterol/ HDL ratio should be less than 5:1 . Ideal is 3.5:1.

Thank you