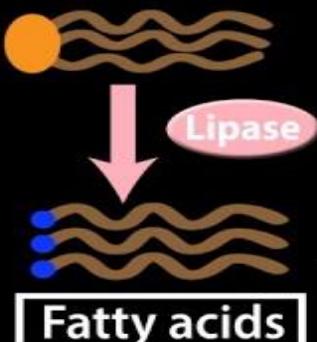
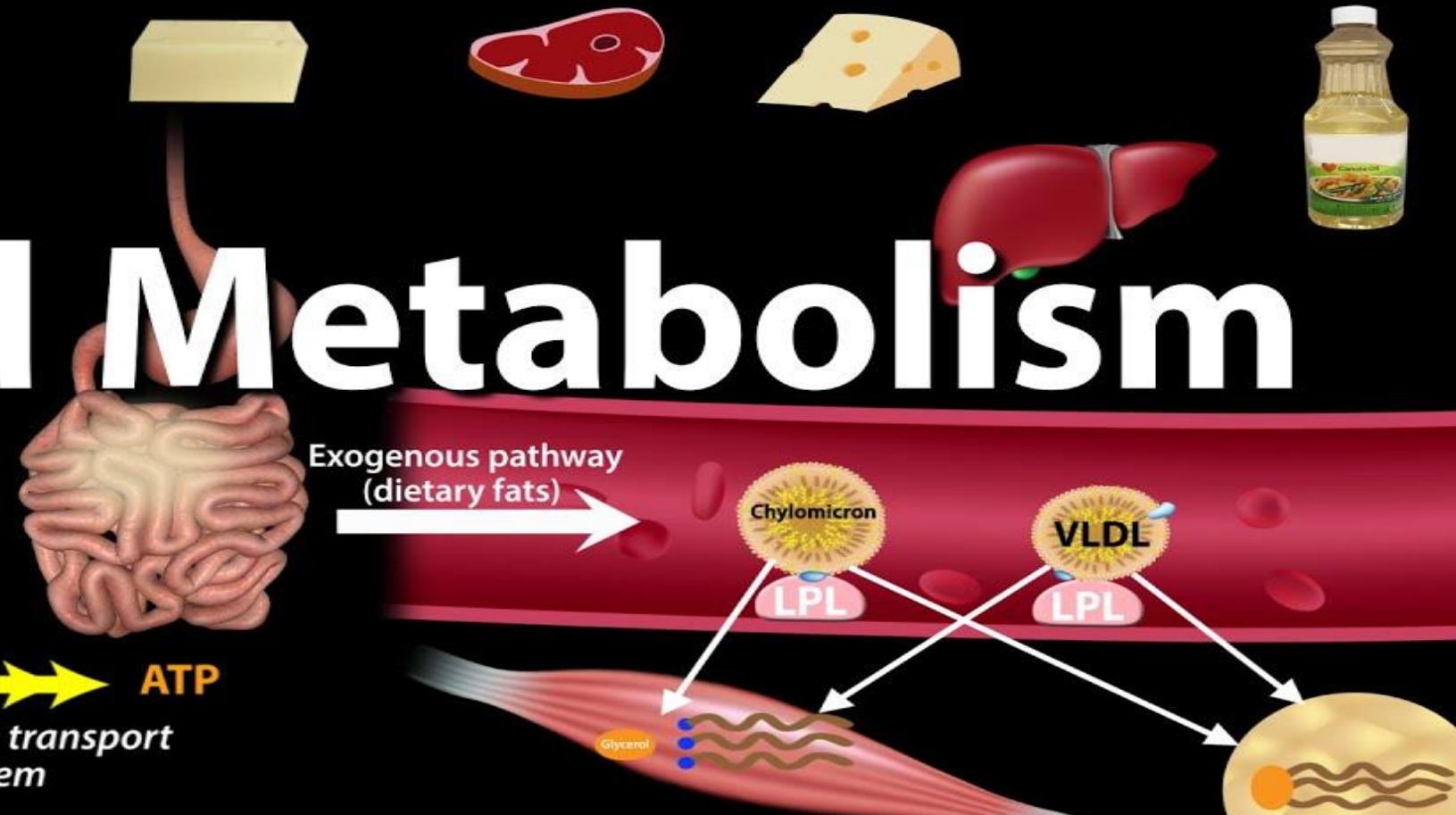
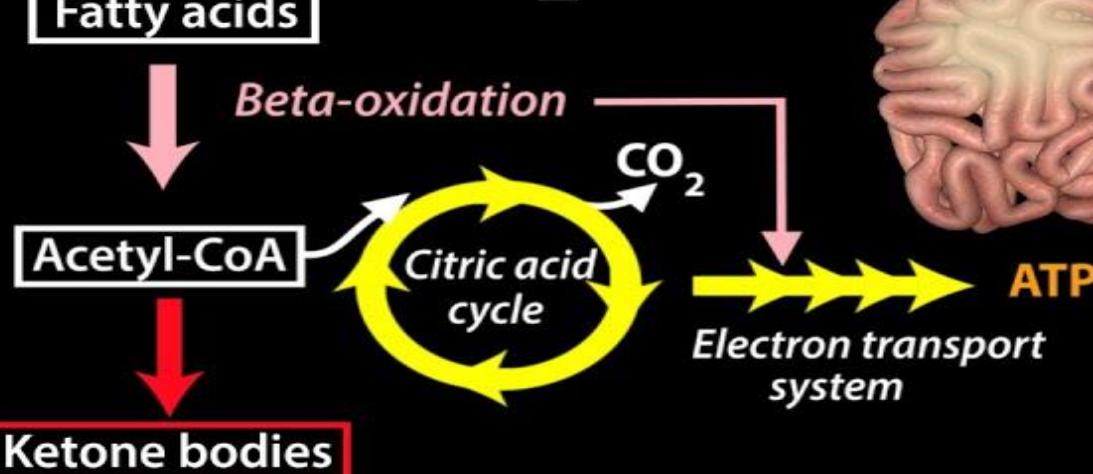


Lipolysis



Lipid Metabolism



LPL = Lipoprotein lipase

Alila
MEDICAL MEDIA

By: Dr. Kalpana Jorasia
Assistant Professor
(VPB)

Why should fat be the fuel reserve of the body?

- Triacylglycerols are the most predominant storage form of energy.
 1. Triacylglycerols (TG) are highly concentrated form of energy, yielding **9 Cal/g**, in contrast to carbohydrates and proteins that produce only 4 Cal/g. This is because fatty acids found in **TG are in the reduced form.**
 2. The triacylglycerols are **non-polar and hydrophobic** in nature, hence stored in pure form with out any association with water (anhydrous form). On the other hand, **glycogen and proteins are polar.** One gram of glycogen combines with 2 g of water for storage

Transport of lipids

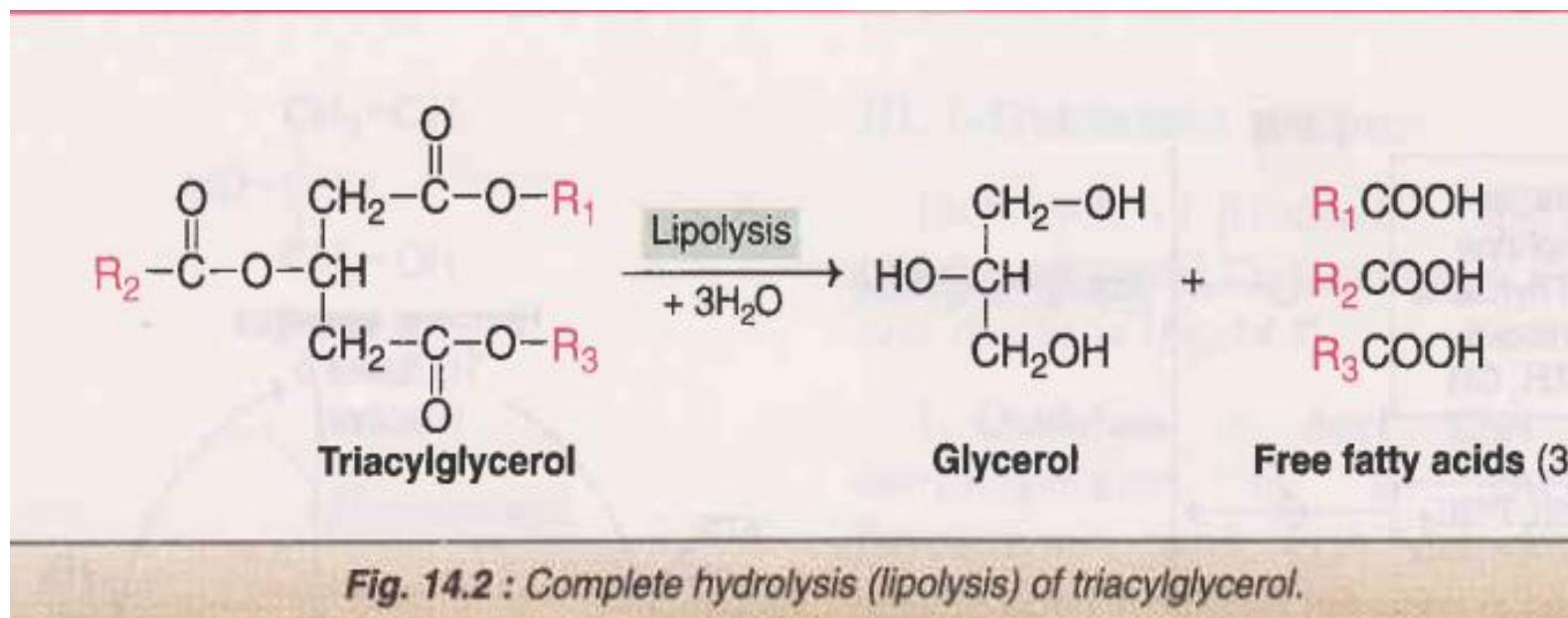
- The insoluble lipids are solubilized in association with proteins to form lipoproteins in which form lipids are transported in the blood stream.
- Free lipids are undetectable in blood.
- Chylomicrons, very low density lipoproteins(VLDL), low density lipoproteins (LDL), high density lipoproteins (HDL) and albumin-free fatty.

Transport of free fatty acids(FFAs):

- FFAs are also called as **non-esterified(NEFAs)** or **unesterified fatty acids (UFAs)** fatty acids. In plasma, long chain FFAs are bound to albumin and in cells they are attached to fatty acid binding protein.

Mobilization of fat from adipose tissues

- Degradation of triacylglycerol in adipocytes is triggered by activation of **hormone sensitive lipase a.**
- The lipase catalyzes hydrolysis of triacylglycerol to produce one molecule of glycerol and three molecules of fatty acid.
- The complete degradation of triacylglycerol to glycerol and free acids is known as **lipolysis**.



Fate of glycerol

- The adipose tissue lacks the enzyme glycerol kinase, hence glycerol produced in lipolysis cannot be phosphorylated here. **It is transported to liver** where it is activated to glycerol 3-phosphate. The latter may be used for the synthesis of triacylglycerols and phospholipids. Glycerol 3-phosphate may also enter glycolysis by getting converted to dihydroxyacetone phosphate.

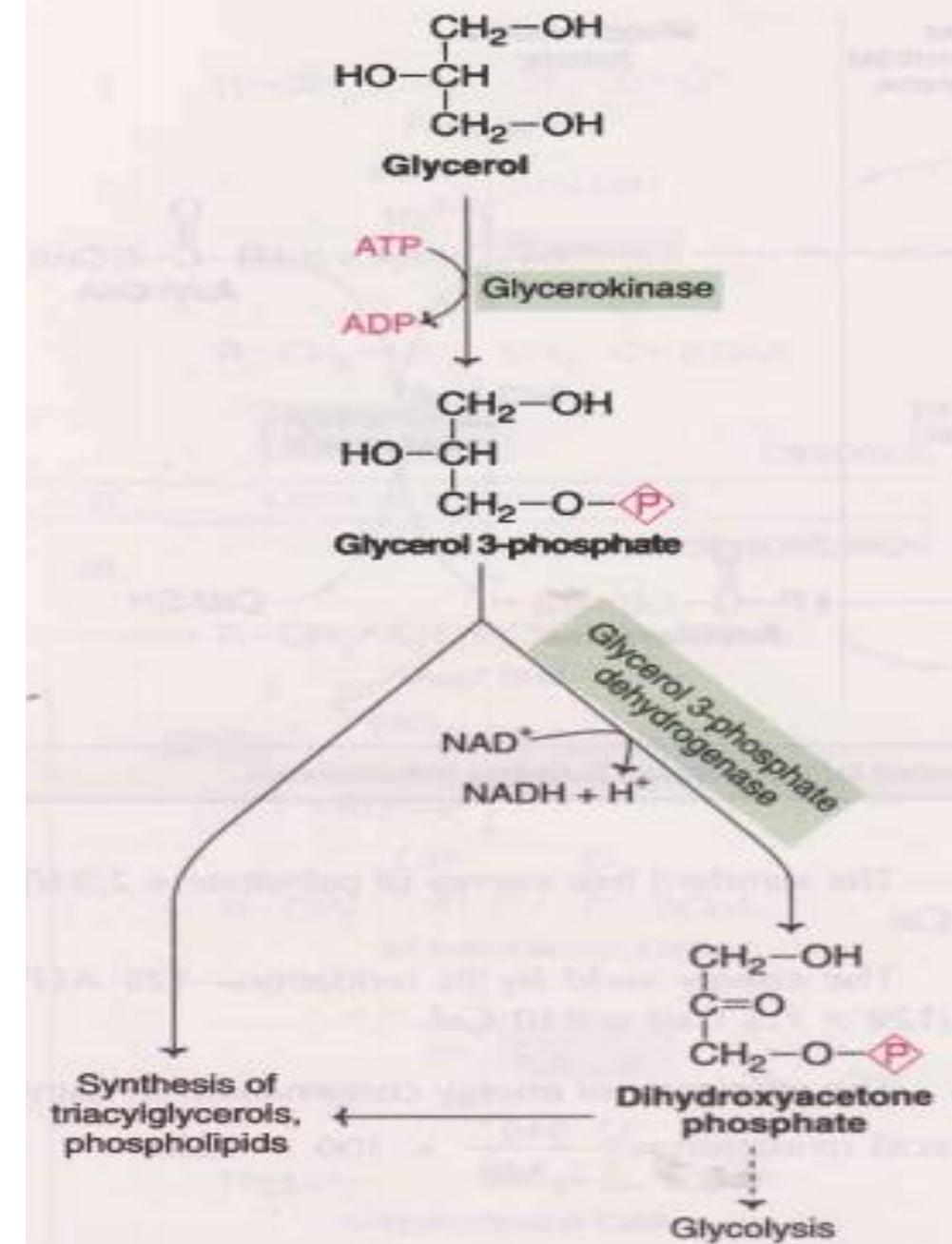


Fig. 14.4 : Fate of glycerol.

Fate of free fatty acids

- The fatty acids released by lipolysis in the adipocytes enter the circulation and are transported in a bound form to albumin.
- The free fatty acids enter various tissues and are utilized for the energy. About **95% of the energy obtained from fat comes from the oxidation of fatty acids.** Certain tissues, however, cannot oxidize fatty acids, e.g. **brain, erythrocytes.**
- **The process of lipolysis of TG and reesterification of FFA to TG is termed as triacylglycerol/fatty acid cycle.**

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.

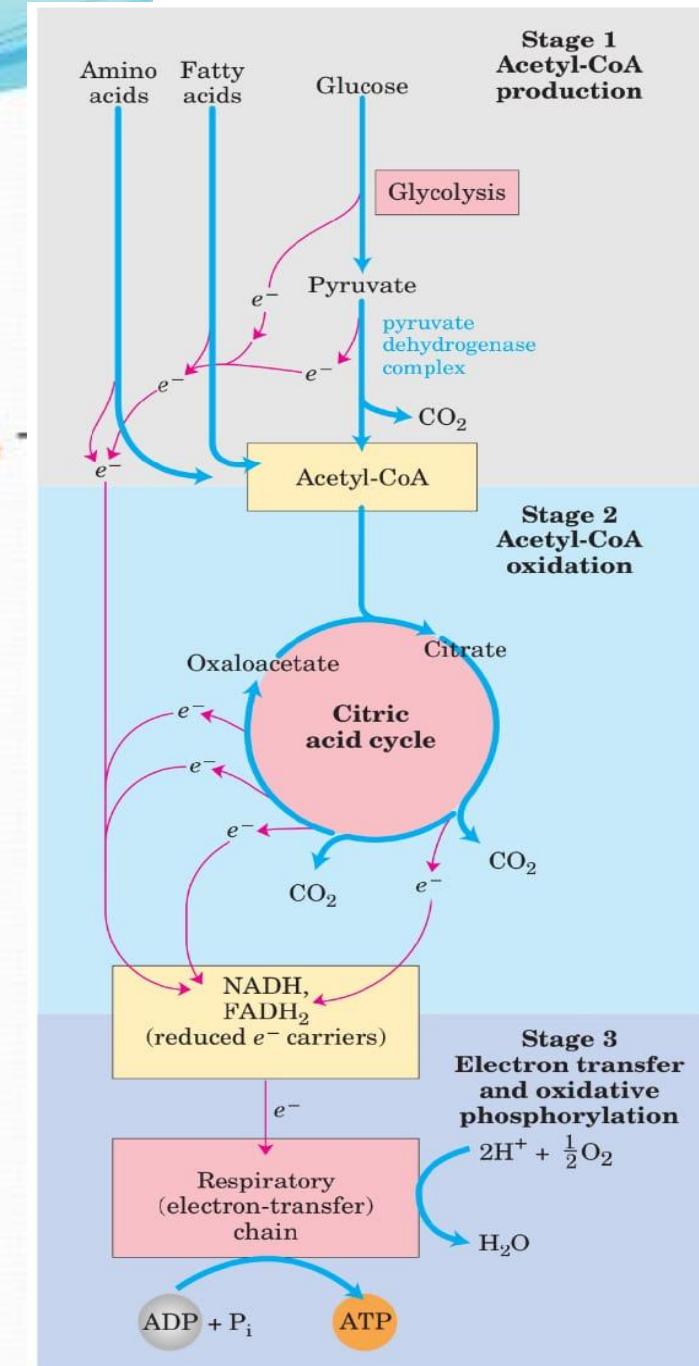
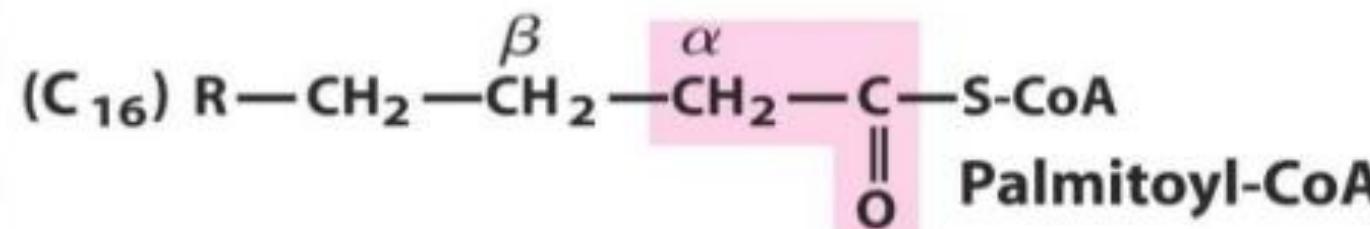
- (1) β - oxidation of fatty acid
- (2) α - oxidation of fatty acids
- (3) ω - oxidation of fatty acids



B- 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**. 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.

Brain, erythrocytes and adrenal medulla cannot utilize fatty acids for energy requirement



Stages

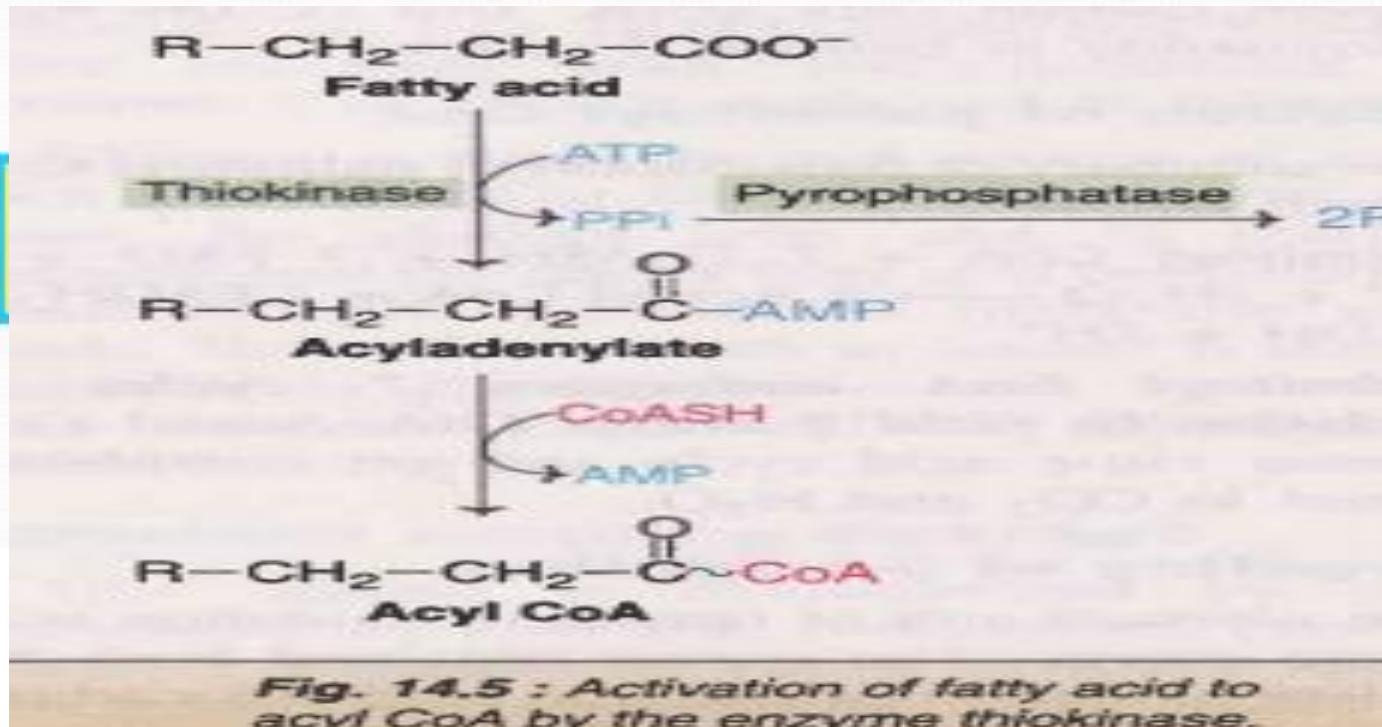
- The beta oxidation of fatty acids involve three stages:
 1. Activation of fatty acids in the cytosol
 2. Transport of activated fatty acids into mitochondria (**carnitine shuttle**)
 3. Beta oxidation proper in the mitochondrial matrix

Beta-Oxidation may be defined as the oxidation of fatty acids on the beta-carbon atom. This results in the sequential removal of a two carbon fragment, acetyl CoA.

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.



✓ In the activation of FFA, two high energy phosphates are utilized.

2.Transfer of activated fatty acids into the mitochondrial matrix

- Short chain fatty acids could cross the inner mitochondrial membrane easily, without the help of any transporter.
- Long chain fatty acids or their acyl-CoA form cannot cross the inner mitochondrial membrane.
- They are transported across the membrane with the help of a transporter called **“carnitine transporter” (β -hydroxy- γ -trimethyl ammonium butyrate.**
- **The cell has two separate pools (cytosolic and mitochondrial) of coenzyme A.**
- **Inhibitor of carnitine shuttle :** Carnitine acyltransferase I is inhibited by **malonyl CoA**, a key metabolite involved in fatty acid synthesis that occurs in cytosol.

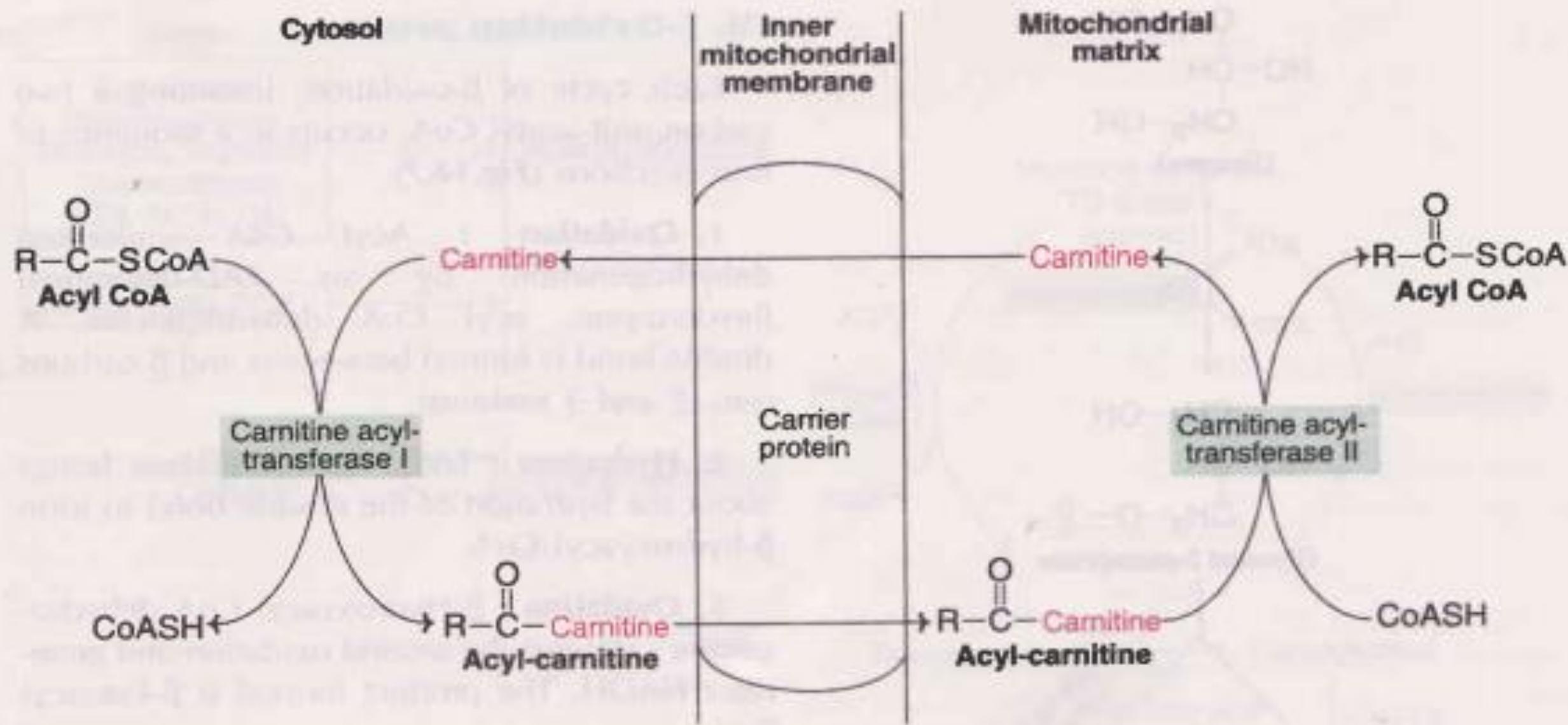


Fig. 14.6 : Carnitine shuttle for transport of activated fatty acid (acyl CoA) into mitochondria.

3. Proper of β – oxidation in the mitochondrial matrix

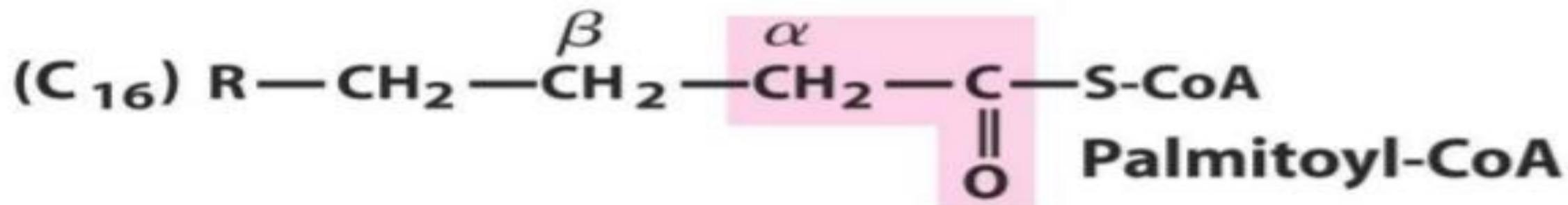
There are 4 steps in β C- oxidation

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

Step II – Hydration by **Hydratase**

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

Step IV – Thiolytic cleavage **Thiolase**



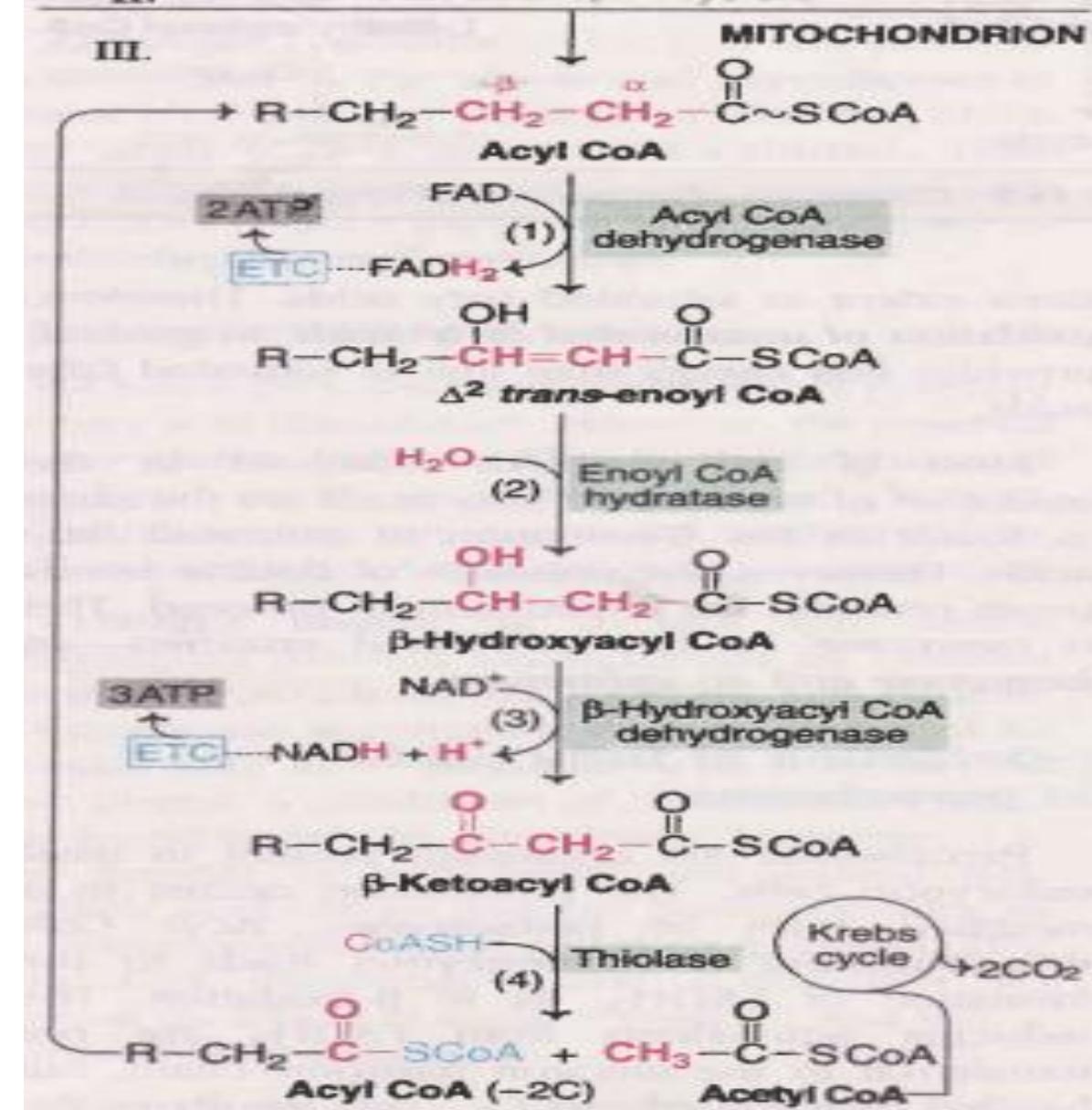
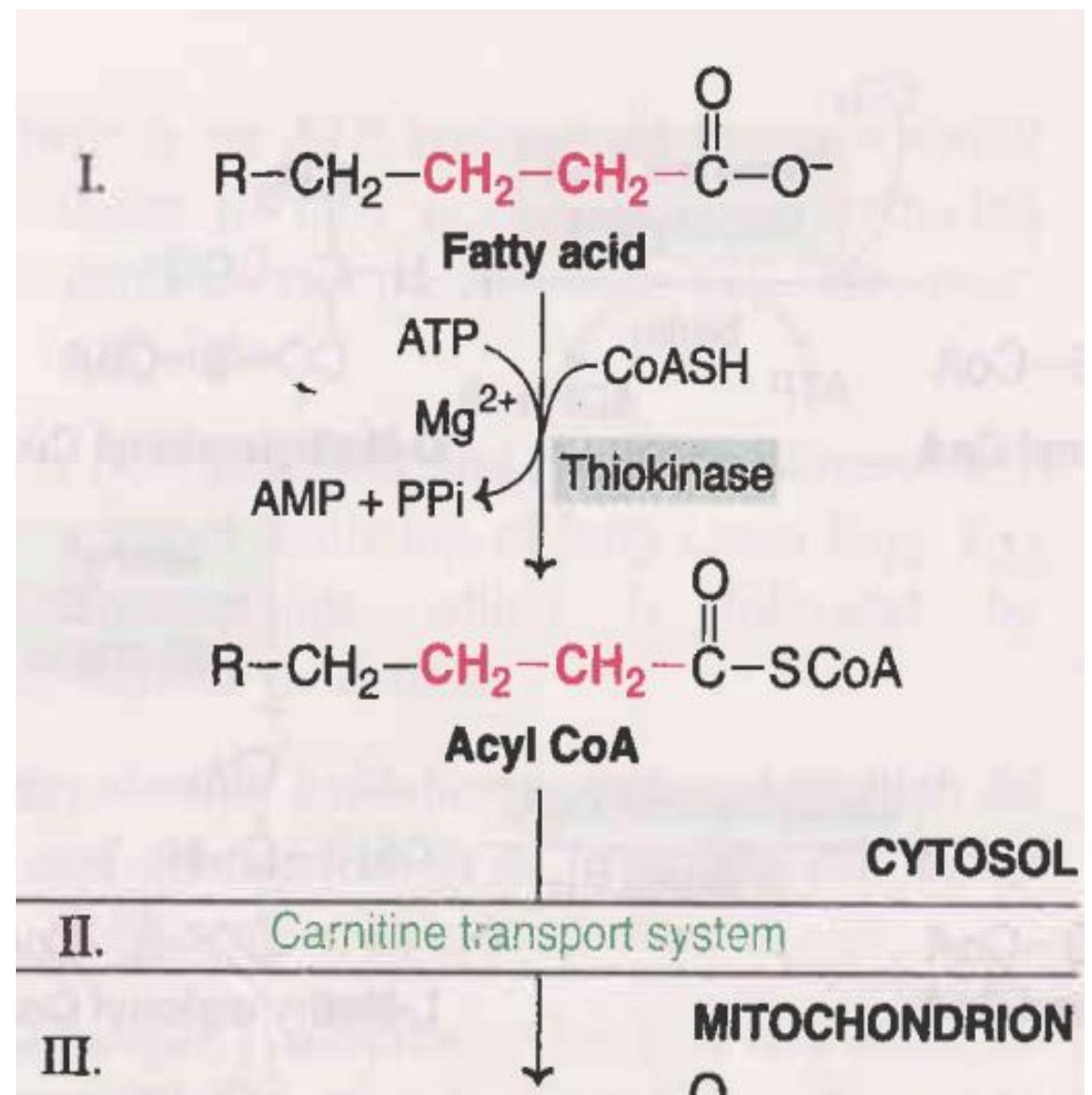


Fig. 14.7 : β -Oxidation of fatty acids : Palmitoyl CoA (16 carbon) undergoes seven cycles to yield 8 acetyl CoA [I—Activation; II—Transport; III— β Oxidation proper—(1) Oxidation, (2) Hydration, (3) Oxidation and (4) Cleavage].

energetics

- FADH₂ - 1.5 ATP
- NADH₂ - 2.5 ATP
- Each cycle 4 ATP
- Palmitic acid - 7 cycles - $7 \times 4 = 28$
- Acetyl CoA - 8×10 ATP - 80
- Activation energy loss - 2 ATP
- Net energy- $108 - 2 = 106$ ATP

Palmitoyl CoA undergoes 7 cycles of beta-oxidation to yield 8 acetyl CoA.

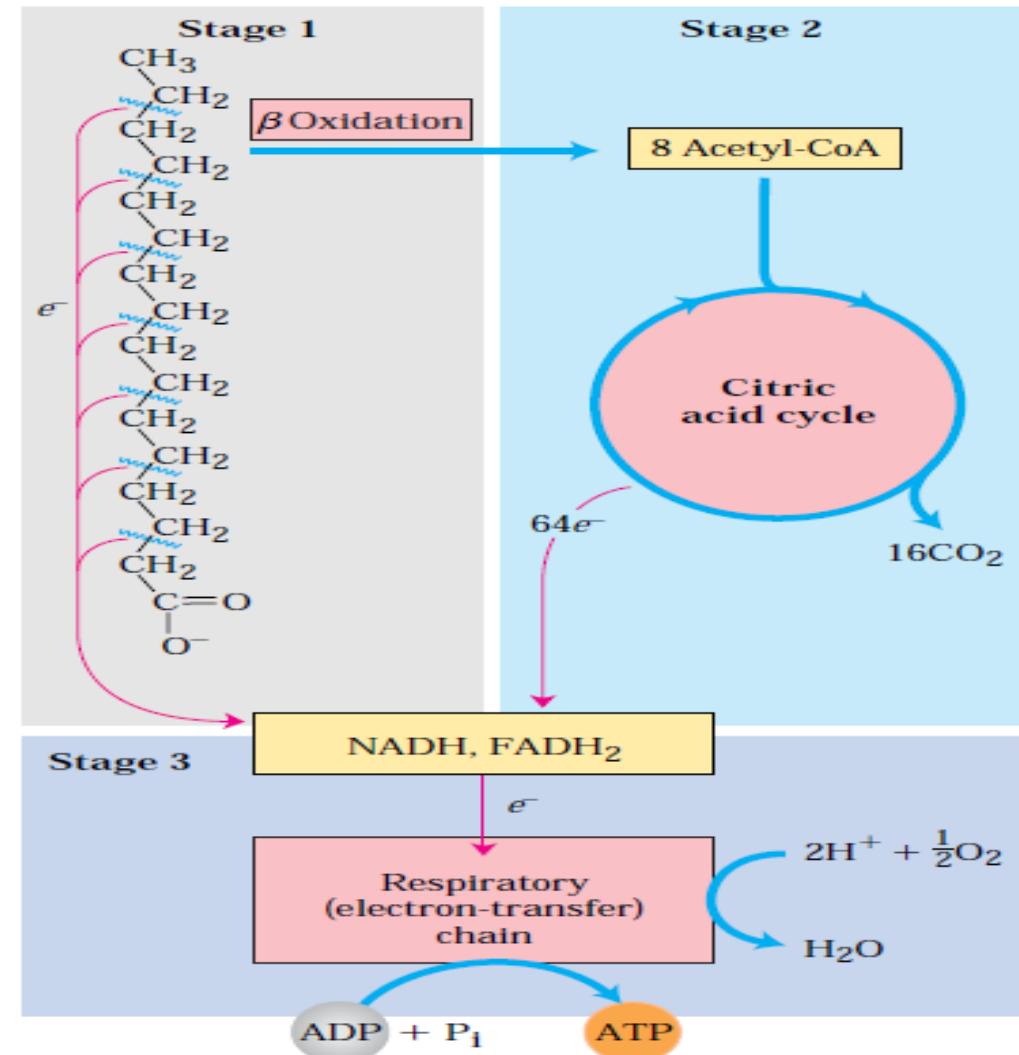


FIGURE 17-7 Stages of fatty acid oxidation. Stage 1: A long-chain fatty acid is oxidized to yield acetyl residues in the form of acetyl-CoA. This process is called β oxidation. Stage 2: The acetyl groups are oxidized to CO₂ via the citric acid cycle. Stage 3: Electrons derived from the oxidations of stages 1 and 2 pass to O₂ via the mitochondrial respiratory chain, providing the energy for ATP synthesis by oxidative phosphorylation.

Oxidation of odd carbon chain fatty acids

- Oxidation of fatty acids with an **odd number** of carbon atoms produces **acetyl CoA** and **one molecule of Propionyl – Co A** as final products.
- This Propionyl-Co A is converted into Succinyl-Co A and **enters TCA cycle**, which can be oxidised or utilized for gluconeogenesis.
- Propionyl CoA is carboxylated in the presence of ATP, CO₂ and **vitamin biotin** to D-methylmalonyl CoA.
- **Methylmalonyl CoA mutase**, is dependent on **vitamin B₁₂** (**deoxyadenosyl cobalamin**)

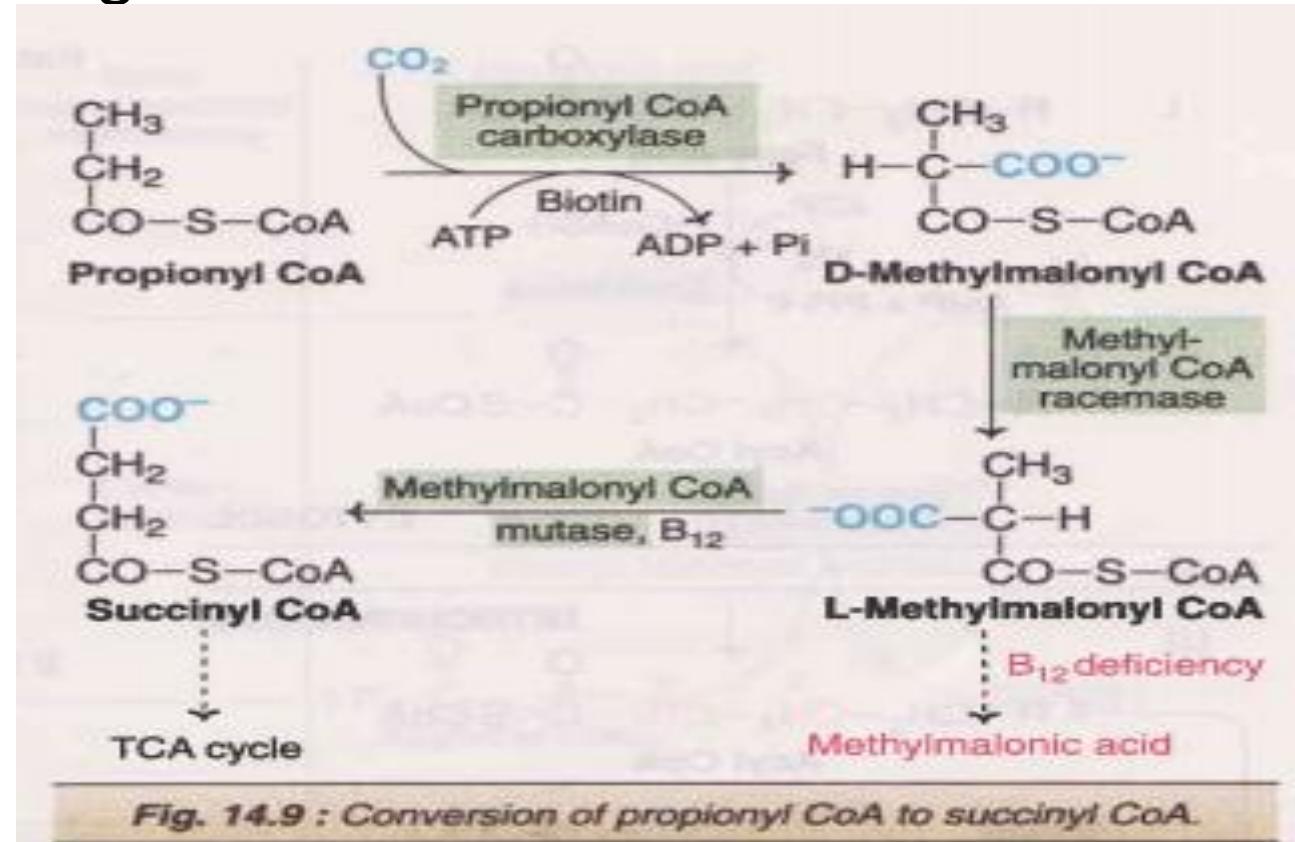


TABLE 17-1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO₂ and H₂O

| <i>Enzyme catalyzing the oxidation step</i> | <i>Number of NADH or FADH₂ formed</i> | <i>Number of ATP ultimately formed*</i> |
|---|--|---|
| Acyl-CoA dehydrogenase | 7 FADH ₂ | 10.5 |
| β-Hydroxyacyl-CoA dehydrogenase | 7 NADH | 17.5 |
| Isocitrate dehydrogenase | 8 NADH | 20 |
| α-Ketoglutarate dehydrogenase | 8 NADH | 20 |
| Succinyl-CoA synthetase | | 8 [†] |
| Succinate dehydrogenase | 8 FADH ₂ | 12 |
| Malate dehydrogenase | 8 NADH | 20 |
| Total | | 108 |

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per FADH₂ oxidized and 2.5 ATP per NADH oxidized.

[†]GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. XXX).

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.

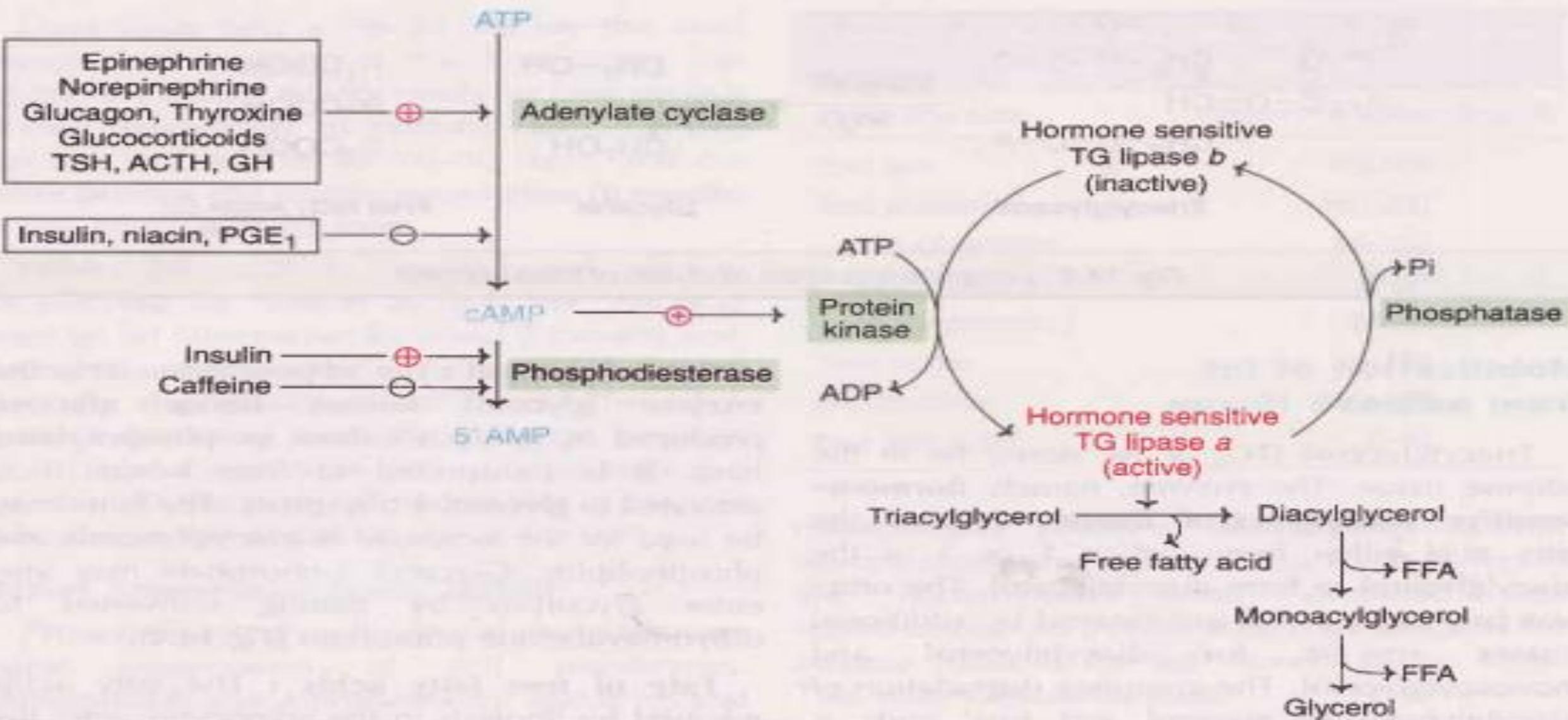
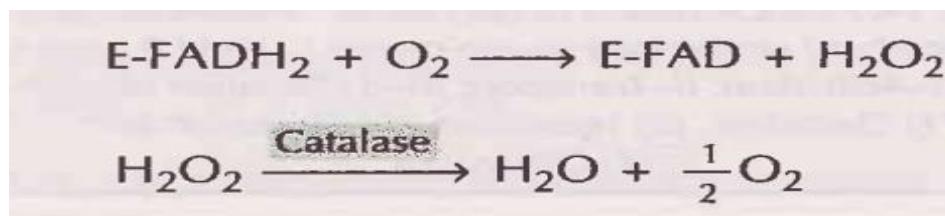


Fig. 14.3 : Control of lipolysis in adipose tissue through cyclic AMP (⊕—Promoting and ⊖—Inhibiting effect; TSH—Thyroid stimulating hormone; ACTH—Adrenocorticotrophic hormone; GH—Growth hormone; PGE₁—Prostaglandin E₁; TG—Triacylglycerol; FFA—Free fatty acid).

Beta-Oxidation of fatty acids in peroxisomes

- Peroxisomes are organelles present in most eukaryotic cells. The beta-oxidation occurs in a modified form in peroxisomes. Acyl CoA dehydrogenase (a flavoenzyme) leads to the formation of FADH₂, as in beta-oxidation.
- The reducing equivalents from FADH₂ are not transferred to the electron transport chain, but handed over directly to O₂. This results in the formation of H₂O₂, which is cleaved by catalase.



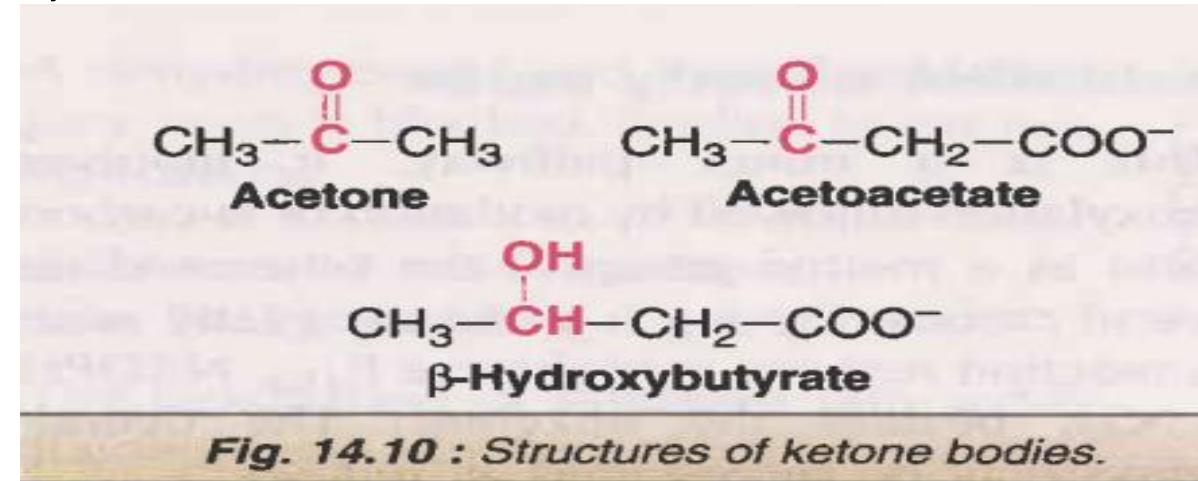
- **There is no ATP synthesized in peroxisomal beta-oxidation of fatty acids,** since the reducing equivalents do not pass through ETC. However, heat is liberated.
- Peroxisomal oxidation is induced by high fat diet and administration of hypolipidemic drugs

OTHER TYPES OF OXIDATION OF FATTY ACIDS

1. **α -oxidation** occurs in brain especially in the **endoplasmic reticulum**. This is involved in the metabolism of methylated fatty acids. First hydroxylation occurs at α - carbon followed by oxidation and decarboxylation releasing CO_2 from the carboxyl terminus, providing the substrate that can be metabolized through β - oxidation. **This type of oxidation does not generate high-energy compounds.**
2. **ω -oxidation** occurs in **endoplasmic reticulum**, which involves hydroxylation and oxidation at the terminal methyl group of fatty acids to form a dicarboxylic acid, which undergoes β - oxidation; **this type of oxidation occurs in peroxisome also**. The end product may be excreted in the urine.
3. Oxidation of unsaturated fatty acids requires two additional enzymes
 - ✓ Enoyl-CoA isomerase, which converts cis-isomer to a trans-isomer
 - ✓ 2, 4-dienoyl-CoA reductase, which is involved in the addition of hydrogen atoms across the double bonds.

KETONE BODIES

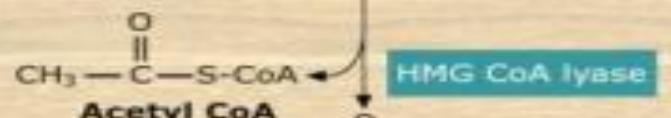
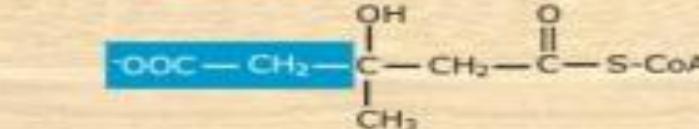
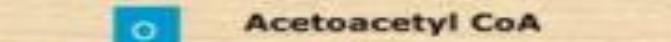
- The compounds namely **acetone, acetoacetate and β -hydroxybutyrate (or 3-hydroxy butyrate)** are known as ketone bodies
- Acetone, acetoacetate**-two are **true ketones**
- β -hydroxybutyrate** does not possess a keto ($C=O$) group.
- Ketone bodies are water-soluble and energy yielding.
- Acetone(volatile waste product which can be excreted via lungs), however, is an exception, since it cannot be metabolized



Ketogenesis (Liver, mitochondrial matrix)

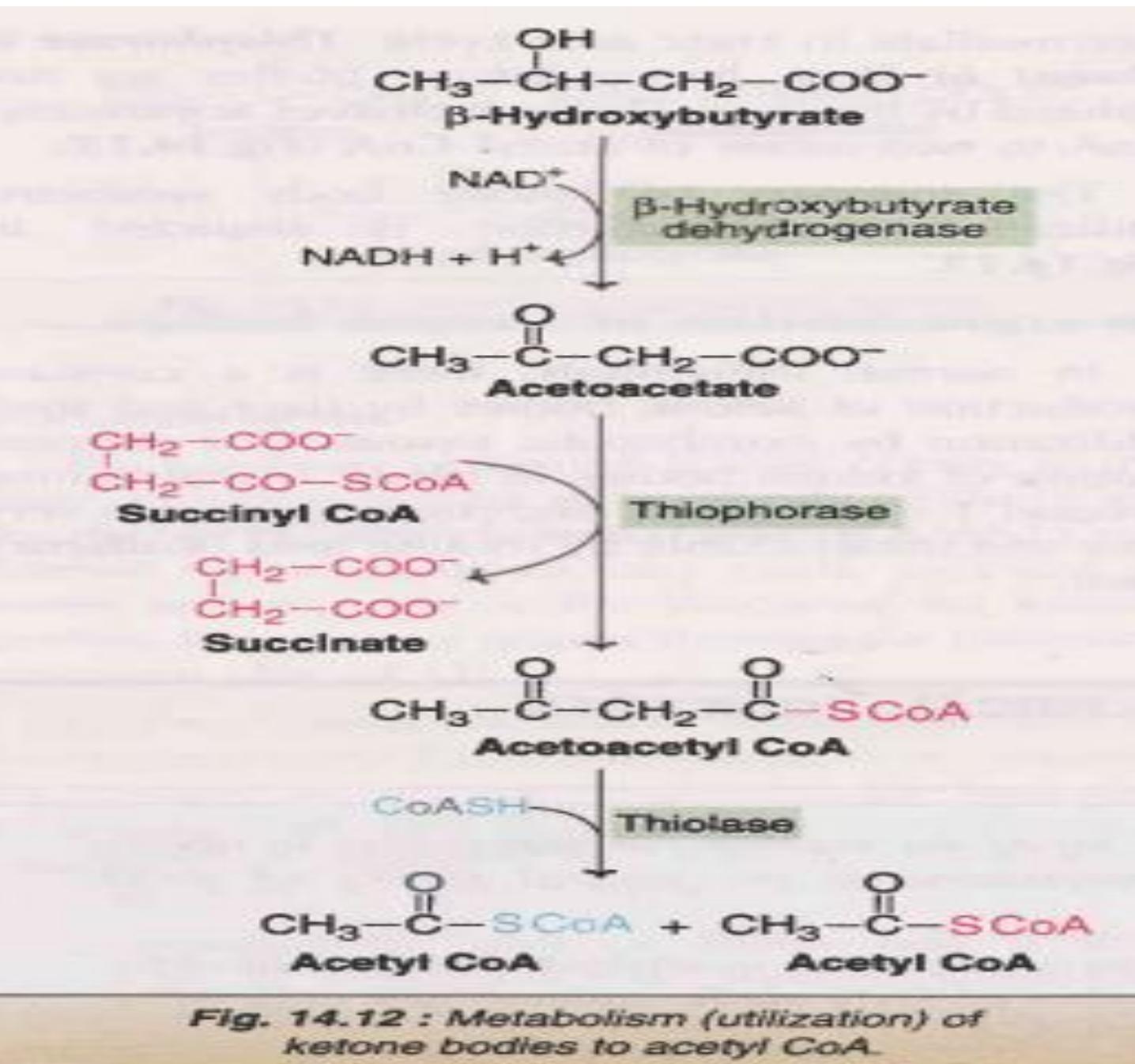
- The synthesis of ketone bodies occurs in the **liver**.
- The enzymes for ketone body synthesis are located in the **mitochondrial matrix**
- Acetyl CoA, formed by oxidation of fatty acids, pyruvate or some amino acids, is the precursor for ketone bodies.
- **HMG CoA synthase**, catalysing this reaction, **regulates the synthesis of ketone bodies**.
- **β -hydroxybutyrate is the most predominant ketone body present in circulation and urine in ketosis**

Ketogenesis



Oxidation/ utilization of ketone bodies

- The **liver lacks** the enzyme called **“thiophorase (Succinyl-CoA: acetoacetyl-CoA transferase)** and therefore cannot use the ketone bodies as fuel.
- As ketone bodies are soluble in water, they could be transported through blood without the involvement of any transporters.
- **Erythrocytes (RBC) -cannot utilize ketone due to lack of mitochondria which lack mitochondria.**
- Excess amount of ketone bodies are produced in starvation and diabetes mellitus.
- During prolonged **starvation**, ketone bodies are the major **fuel source for the brain**.
- **The ketone bodies can meet 50-70% of the brain's energy needs.**
- **In non-ruminants, liver is the sole source of ketone body production. In ruminants,** rumen epithelium and mammary glands are also the sources of ketone bodies.



Overproduction of ketone bodies

- The presence of excessive amount of ketone bodies **in blood** is called as **“ketonemia”**, and it results in the appearance of ketone bodies in **urine** called as **“ketonuria”** and in milk (ketolactia).
- **Ketonemia and ketonuria** is commonly referred to as **ketosis**.
- Smell of acetone in breath is a common feature in ketosis
- **For detection of ketone bodies in urine----Rothera's test.**
- Excess ketone bodies in the blood, decreases blood pH, resulting in **“ketoacidosis”**.
- As ketone bodies complex with Na⁺ and K⁺, urinary loss of ketone bodies result in loss of electrolytes and **polyuria**.

- ❖ **In starvation**, oxaloacetate is drawn out of the citric acid cycle for the synthesis of glucose, thereby decreasing the availability of oxaloacetate, resulting in the accumulation of acetyl-Co A favouring the overproduction of ketone bodies.
- ❖ **In diabetes mellitus**, due to the **deficiency of insulin**, the available glucose is not transported to cells of skeletal muscles and adipocytes. So, to obtain energy, the cell depends on the β -oxidation of fatty acids, resulting in the overproduction of acetyl-CoA, leading to the synthesis of ketone bodies.

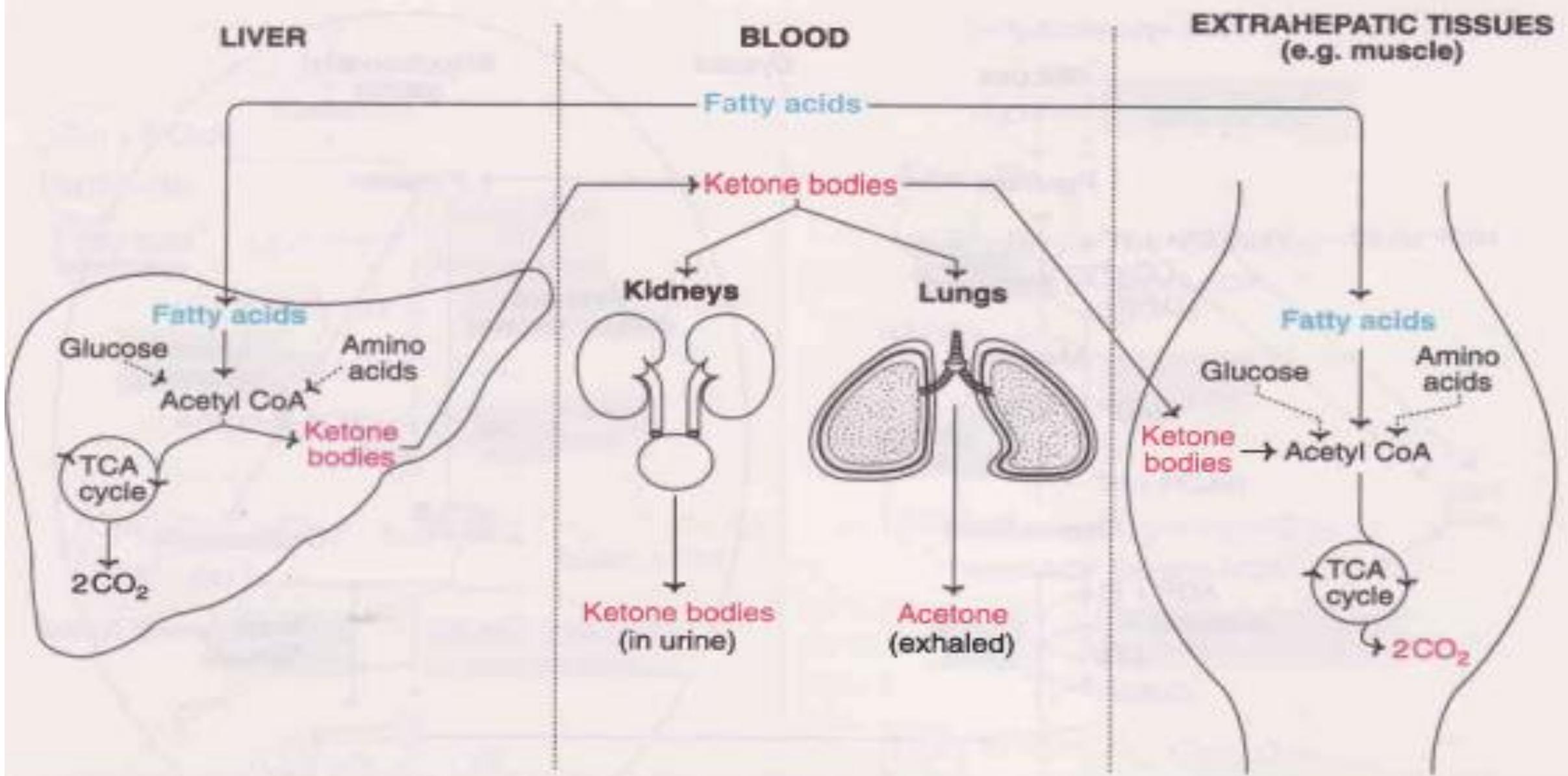


Fig. 14.13 : Summary of ketone body synthesis, utilization and excretion.

FATTY ACID BIOSYNTHESIS

- The synthesis takes place in **cytosol**.
- Fatty acids are synthesized when there is excess nutrient availability (glucose). These will be esterified with glycerol and stored as triacylglycerol or the fatty acids will also be used for the synthesis of phospholipids to form cell membrane.
- Fatty acid synthesis occurs mainly in the **liver** and **adipocytes** and to a lesser extent in mammary gland during lactation.
- **Acetyl CoA and NADPH** are the two important prerequisites for fatty acid synthesis along with **ATP**.
- The **HMP shunt is the major source of NADPH**. The other source is by the action of malic enzyme.

Fatty Acid Synthesis

- **The overall synthesis can be divided into 3 steps**

1. Production of acetyl CoA and NADPH
2. Formation of malonyl CoA from acetyl CoA
3. Reactions of Fatty acid synthase complex

1. PRODUCTION OF ACETYL CoA AND NADPH

- Acetyl CoA and NADPH are the prerequisites for fatty acid synthesis. Acetyl CoA is produced in the mitochondria by the oxidation of pyruvate and fatty acids, degradation of carbon skeleton of certain amino acids, and from ketone bodies.
- Mitochondria, however, are not permeable to acetyl CoA.
- An alternate or a bypass arrangement is made for the transfer of acetyl CoA to cytosol.
- Acetyl CoA condenses with oxaloacetate in mitochondria to form citrate.
- Citrate is freely transported to cytosol where it is cleaved by citrate lyase to liberate acetyl CoA and oxaloacetate. Oxaloacetate in the cytosol is converted to malate.
- Malic enzyme converts malate to pyruvate. NADPH and CO₂ are generated in this reaction. Both of them are utilized for fatty acid synthesis.

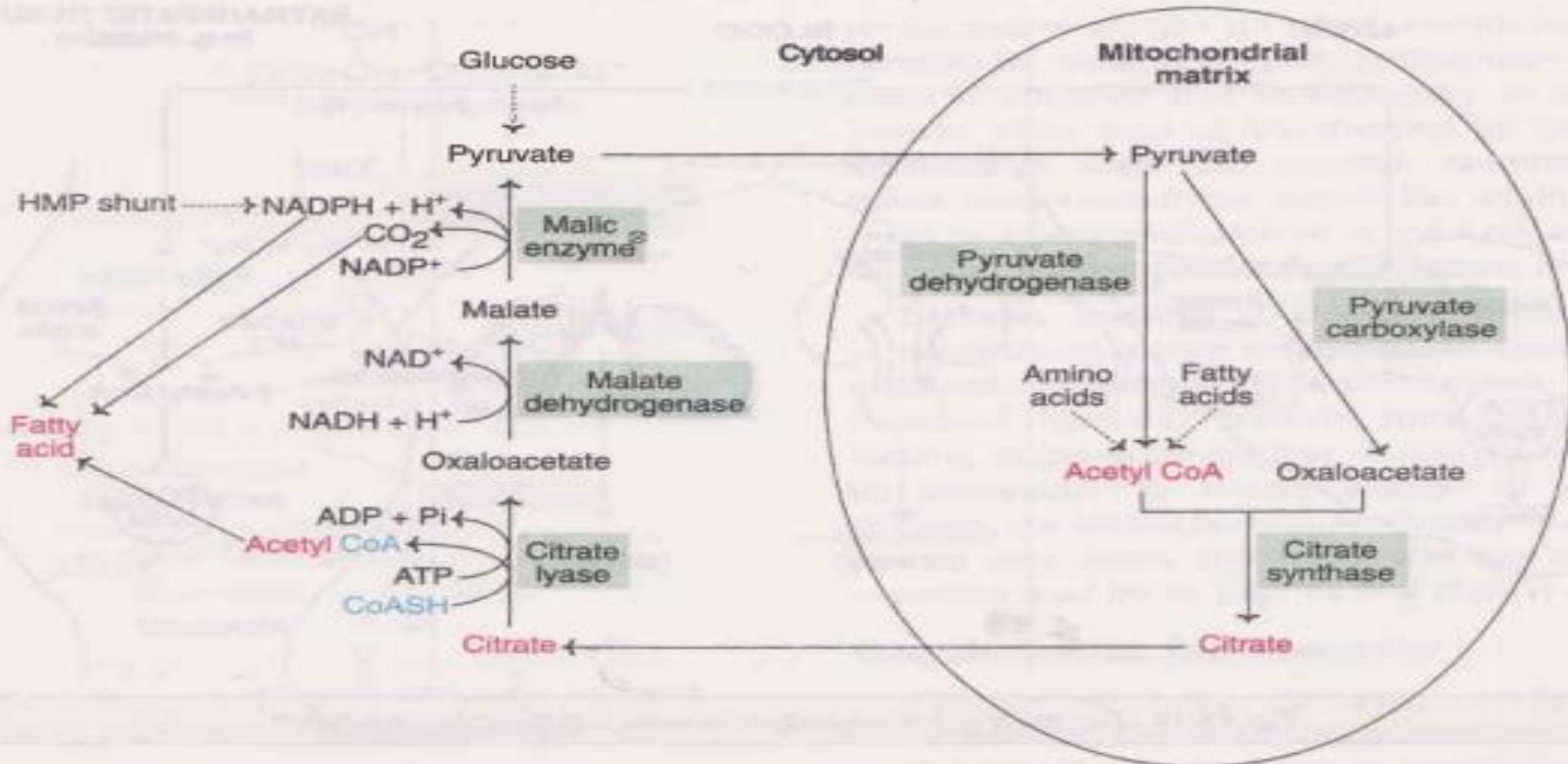


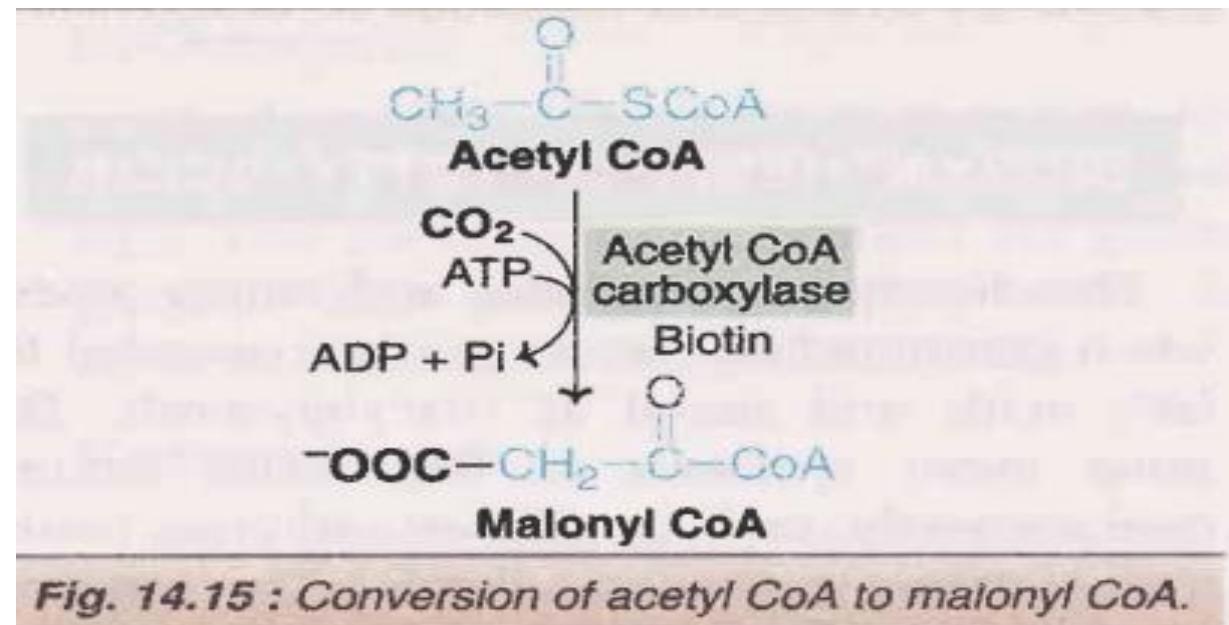
Fig. 14.14 : Transfer of acetyl CoA from mitochondria to cytosol

(HMP shunt—Hexose monophosphate shunt; ⊗—also known as malate dehydrogenase).

2. FORMATION OF MALONYL CoA FROM ACETYL CoA

- The acetyl-CoA is carboxylated to form malonyl-CoA, catalyzed by **acetyl-CoA carboxylase**, a **biotin** dependent enzyme. This enzyme is the **regulatory enzyme** in the synthesis of fatty acids.

Regulatory enzyme in
the synthesis of fatty
acids: **acetyl-CoA**
carboxylase



3. REACTION OF FATTY ACID SYNTHASE COMPLEX

(Fatty acid complex) FAS COMPLEX

- ✓ The remaining reactions of fatty acid synthesis are catalyzed by a multifunctional enzyme known as **fatty acid synthase (FAS) complex**.
- ✓ Fatty acid synthase (FAS) is a multienzyme complex possessing **7 different enzyme activities**.
- ✓ The fatty acid synthase of mammals is a **dimer composed** of two identical subunits. The complex has **two thiol groups**.
 1. –SH group of **cysteine residue**
 2. –SH group of **ACP (acyl carrier protein) containing 4-phosphopantetheine**.

Fatty acid complex (FAS)

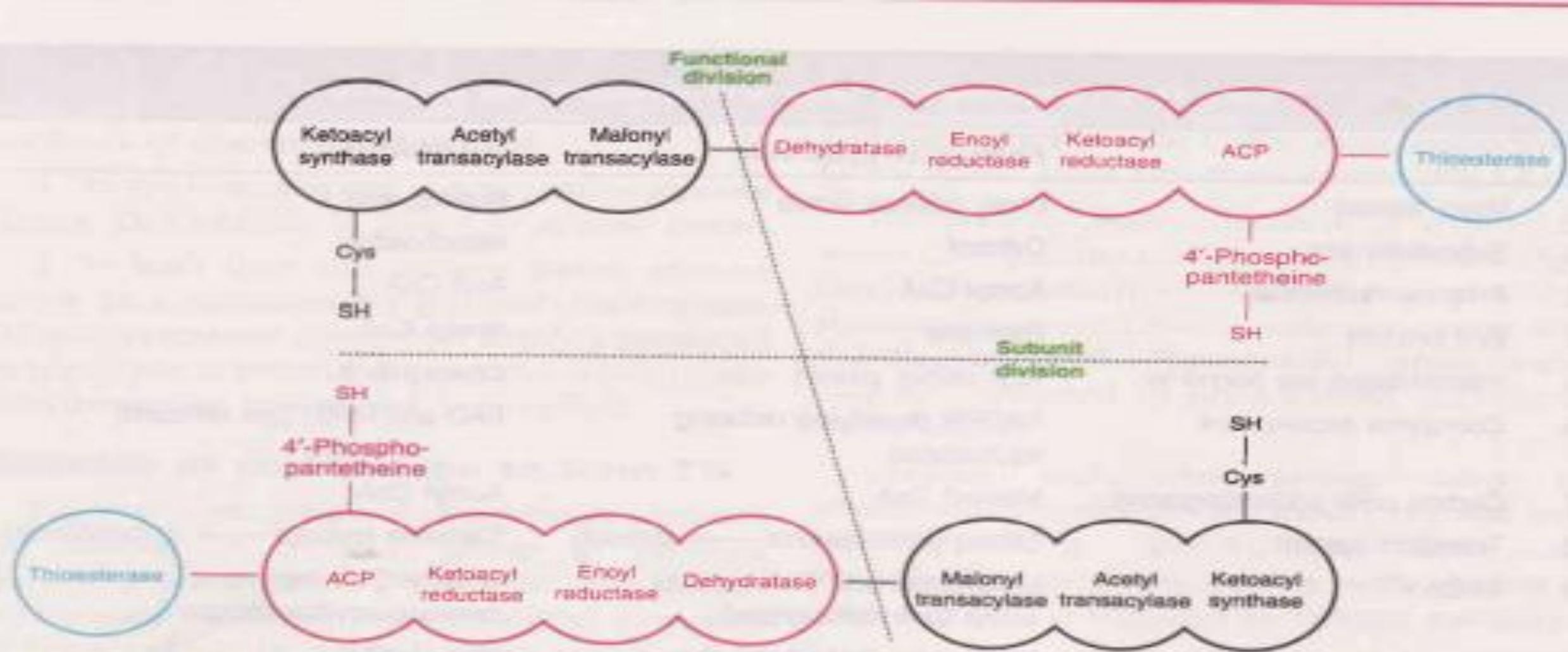


Fig. 14.17 : Fatty acid synthase multienzyme complex (ACP-Acyl carrier protein; FAS has two identical subunits which organize into two functional subunits to simultaneously synthesize two fatty acids).

1. The two carbon fragment of acetyl CoA is transferred to ACP of fatty acid synthase, catalysed by the enzyme, **acetyl CoA-ACP transacylase**.
 - The acetyl unit is then transferred from ACP to cysteine residue of the enzyme.
 - Thus ACP site falls vacant.
2. The enzyme **malonyl CoA-ACP transacylase** transfers malonate from malonyl CoA to bind to ACP.
3. The acetyl unit attached to cysteine is transferred to malonyl group (bound to ACP). The malonyl moiety loses CO₂ which was added by acetyl CoA carboxylase. Thus, **CO₂ is never incorporated into fatty acid carbon chain.** The decarboxylation is accompanied by loss of free energy which allows the reaction to proceed forward. This reaction is catalyzed by **β-ketoacyl ACP synthase**

- 4.** β -Ketoacyl ACP reductase **reduces** ketoacyl group to hydroxyacyl group. The reducing equivalents are supplied by NADPH.
- 5.** β -Hydroxyacyl ACP undergoes **dehydration**. A molecule of water is eliminated and a double bond is introduced between α and β carbons.
- 6.** A second NADPH-dependent **reduction**, catalysed by **enoyl-ACP reductase** occurs to produce acyl-ACP. The four-carbon unit attached to ACP is butyryl group.
- ✓ **The reduction, dehydration and reduction are repeated until the chain is 16 carbon in length.** At this point **hydrolysis** (palmitoyl thioesterase) occurs and **the palmitate is released.**

❖ **Note:** The two functional subunits of FAS independently operate and synthesize two fatty acids simultaneous

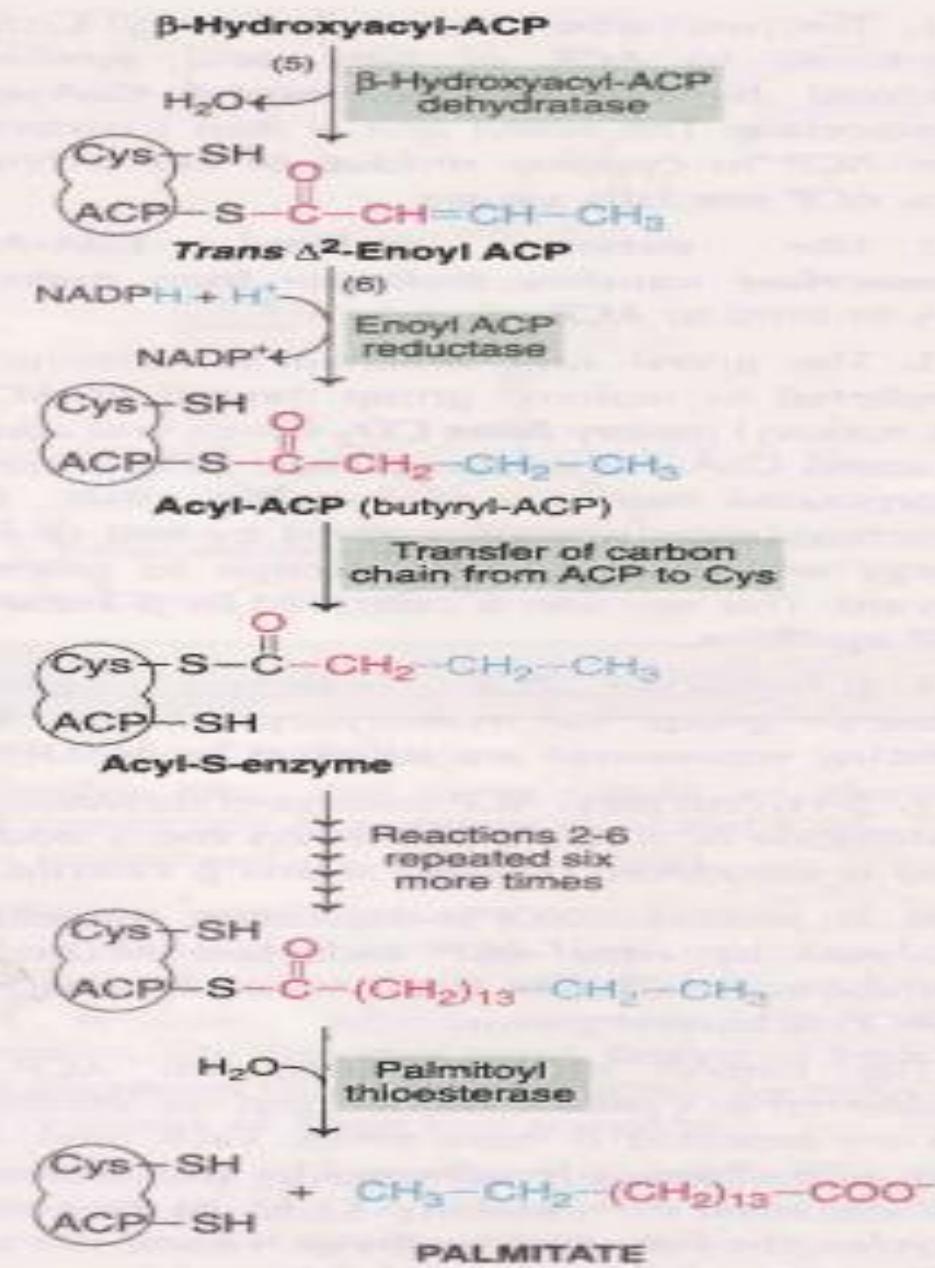
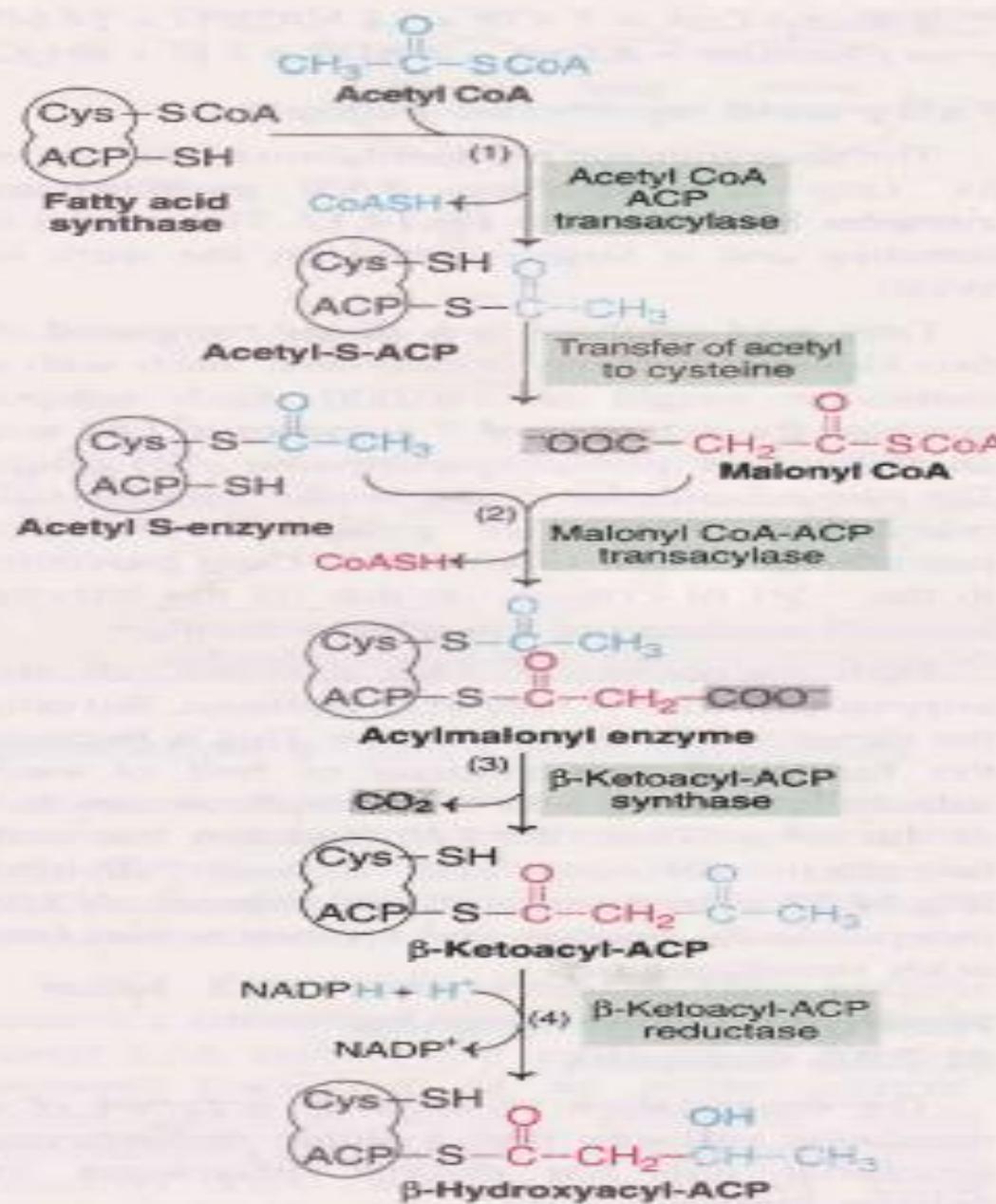


Fig. 14.16 contd. next column

BIOENERGETICS OF FATTY ACID SYNTHESIS

For the synthesis of one molecule of palmitate

| Reactions | ATP utilized |
|--|--------------|
| 1 ATP / molecule of acetyl CoA from citrate. Therefore, for 8 molecules of acetyl CoA (to form one molecule of palmitate) | 8 |
| 1 ATP / molecule malonyl CoA. | 7 |
| Therefore for 7 malonyl CoA | |
| Total ATP utilized | 15 |

- In addition 14 molecules of NADPH are needed to synthesize one molecule of palmitate from citrate.

TABLE 14.3 Comparison of fatty acid synthesis and oxidation

| | <i>Fatty acid synthesis</i> | β - <i>Oxidation</i> |
|-----------------------------------|---|--|
| 1. Major tissues | Liver, adipose tissue | Muscle, liver |
| 2. Subcellular site | Cytosol | Mitochondria |
| 3. Precursor/substrate | Acetyl CoA | Acyl CoA |
| 4. End product | Palmitate | Acetyl CoA |
| 5. Intermediates are bound to | Acyl carrier protein | Coenzyme A |
| 6. Coenzyme requirement | NADPH (supplying reducing equivalents) | FAD and NAD ⁺ (get reduced) |
| 7. Carbon units added/degraded | Malonyl CoA | Acetyl CoA |
| 8. Transport system | Citrate (mitochondria \longrightarrow cytosol) | Carnitine (cytosol \longrightarrow mitochondria) |
| 9. Inhibitor | Long chain acyl CoA (inhibits acetyl CoA carboxylase) | Malonyl CoA (inhibits carnitine acyltransferase I) |
| 10. The pathway increased | After rich carbohydrate diet | In starvation |
| 11. Hormonal status that promotes | High ratio of insulin/glucagon | Low ratio of insulin/glucagon |
| 12. Status of enzyme(s) | Multifunctional enzyme complex | Individual enzymes |

Regulation of fatty acid synthesis

- **Acetyl CoA carboxylase** : This enzyme controls a committed step in fatty acid synthesis.
- **Hormonal influence** : **Insulin** promotes fatty acid synthesis
glucagon inhibits.
- **Dietary regulation:**
 - 1) high carbohydrate or fat-free diet **increases** the synthesis of acetyl CoA carboxylase and fatty acid synthase, which **promote fatty acid formation**.
 - 2) fasting or high fat diet **decreases** fatty acid production by reducing the synthesis of acetyl CoA carboxylase and fatty acid synthase (FAS).
- **Availability of NADPH**: About 50-60% of required NADPH is obtained from HMP shunt, which significantly influences fatty acid synthesis

Desaturation of fatty acid chains

- A microsomal enzyme system called **fatty acyl CoA desaturase** is responsible for the formation of unsaturated fatty acids.

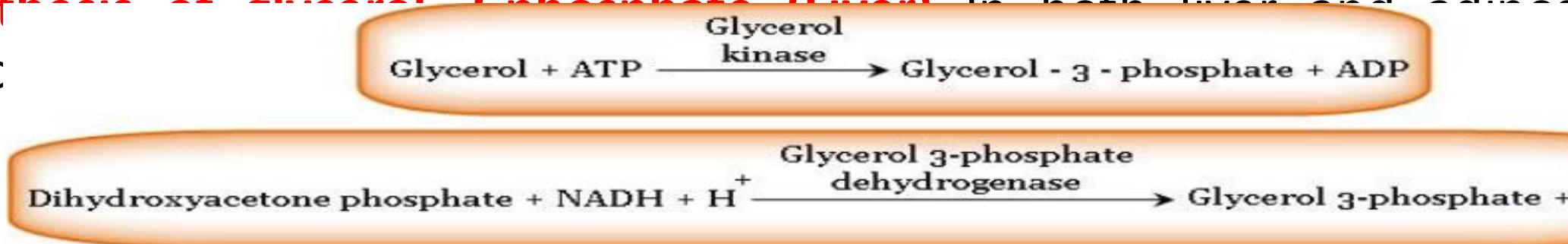
SYNTHESIS (Elongation) OF LONG CHAIN FATTY ACIDS FROM PALMITATE

- The end product of the fatty acid synthesis is palmitic acid.
- In cells fatty acids having chain length of C18, C20,C22 and C24 are commonly seen.
- The synthesis of these fatty acids occurs mainly in the **endoplasmic reticulum** using malonyl CoA and NADPH.
- The palmitate participates as CoA derivative instead of fatty acyl ACP

BIOSYNTHESIS OF TRIACYLGLYCEROL

- Synthesis of TAG occurs in **adipose tissue and liver**.
- **Smooth endoplasmic reticulum** is the site of synthesis.
- Fatty acids and glycerol must be activated prior to the synthesis of triacylglycerols. Conversion of fatty acids to acyl CoA by thiokinase is already described (see Fig.14.6).

Synthesis of glycerol 3-phosphate (G3P) in both liver and adipose tissue, glucose



Dihydroxyacetone phosphate (DHAP) produced in glycolysis is reduced by glycerol 3-phosphate dehydrogenase to glycerol 3-phosphate

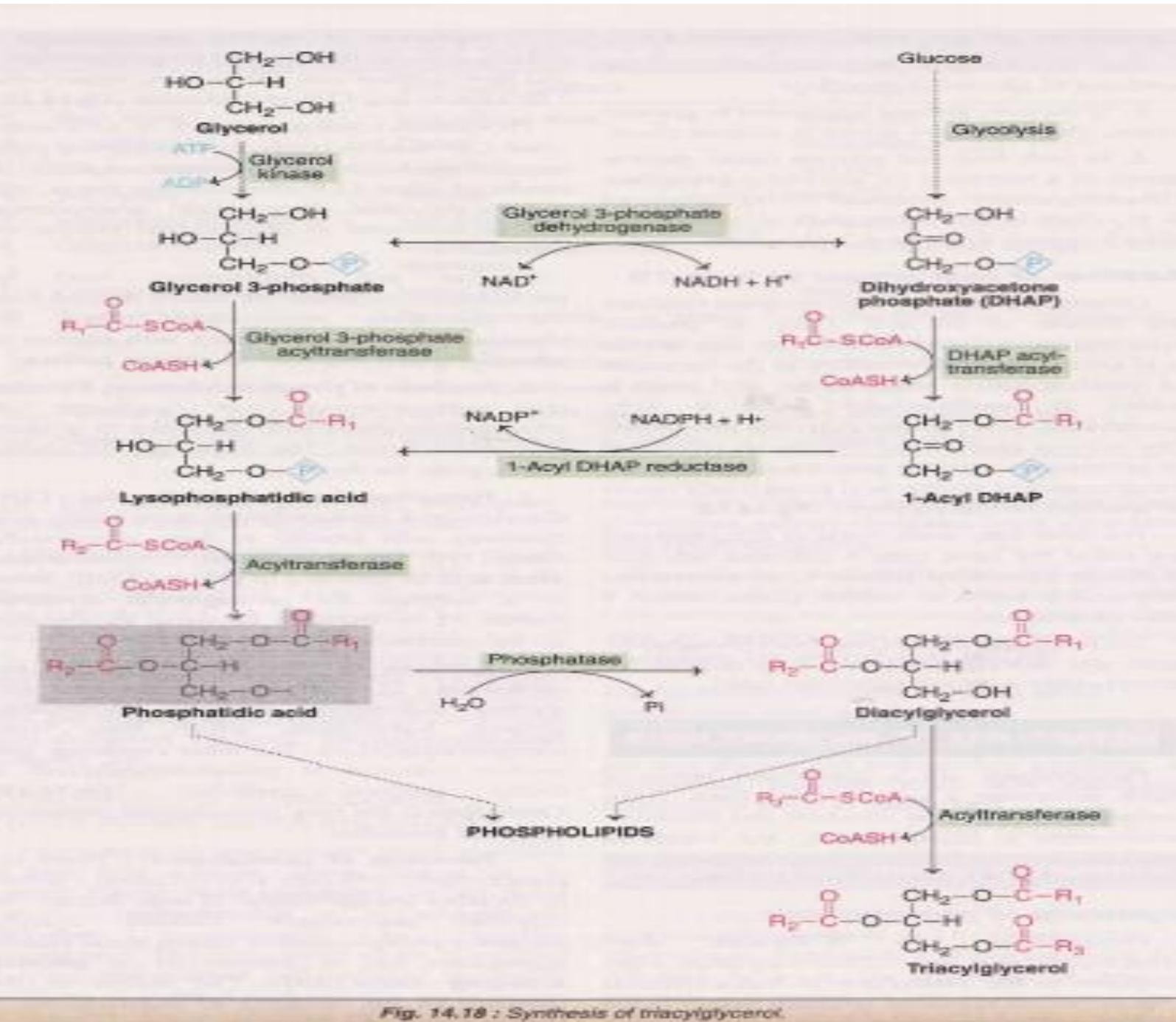
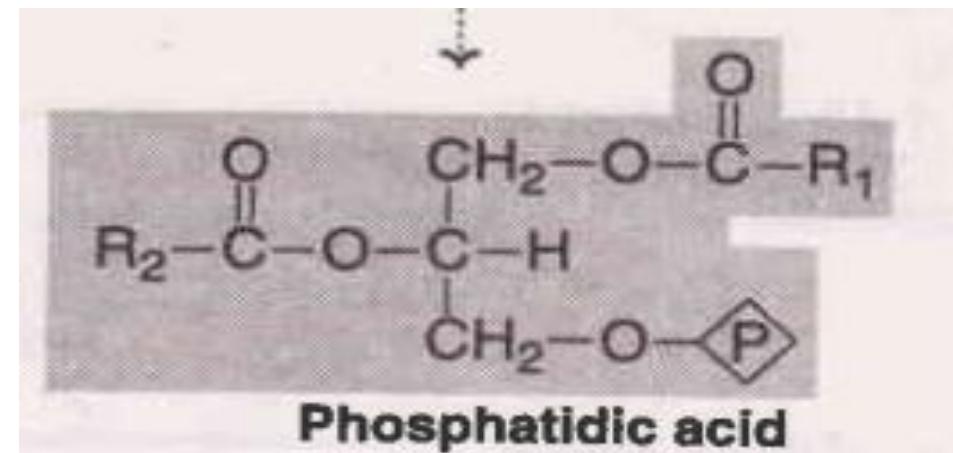


Fig. 14.18 : Synthesis of triacylglycerol.

BIOSYNTHESIS OF PHOSPHOLIPIDS

- Phosphatidic acid is the **precursor** for the synthesis of various phospholipids.
- The compound that may bind to the phosphoric acid group of phosphatidic acid may be **choline, ethanolamine, serine, inositol, or glycerol**, resulting in different phospholipids.



- Generally the fatty acid at **C 1 is saturated** and that at **C 2 is unsaturated**

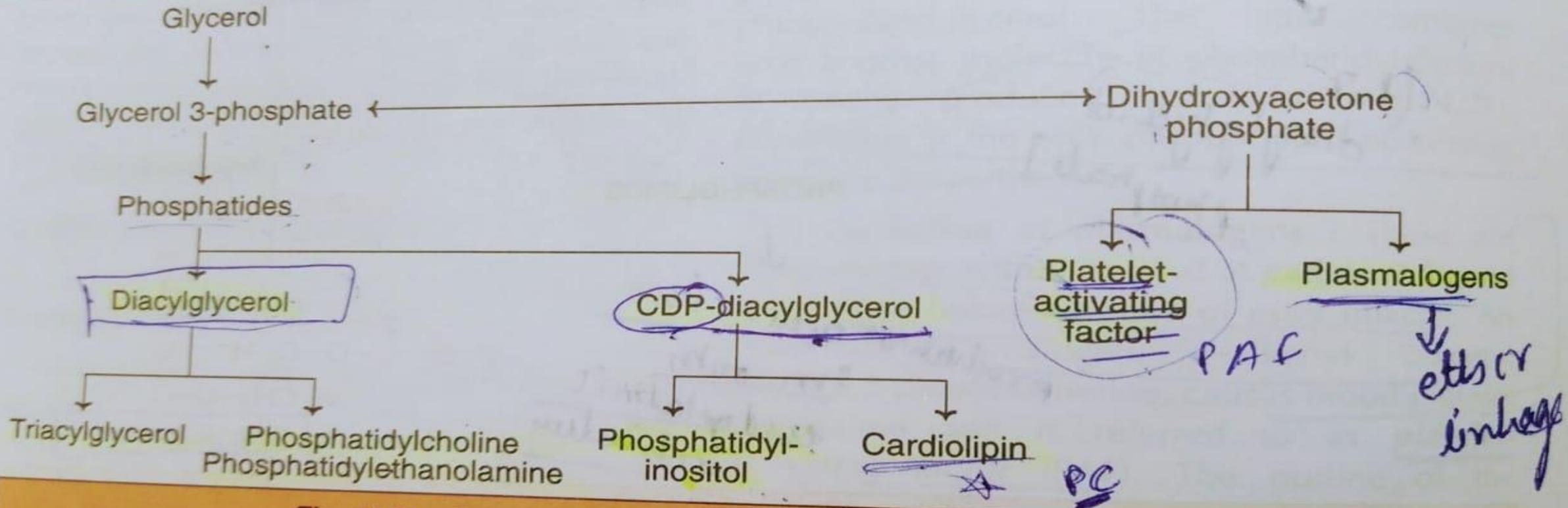


Fig. 14.20 : Overview of acylglycerol and phospholipid synthesis.

*cardiolipin → diphosphatidylglycerol **

- **PFA (platelet activating factor)** is also known as **1-Alkenyl 2-acetylglycerol 3-phosphocholine**

- In mammals, **phosphatidyl serine** is not synthesized from CDP-diacyl glycerol, instead it is derived from phosphatidyl ethanolamine via the head-group exchange reaction

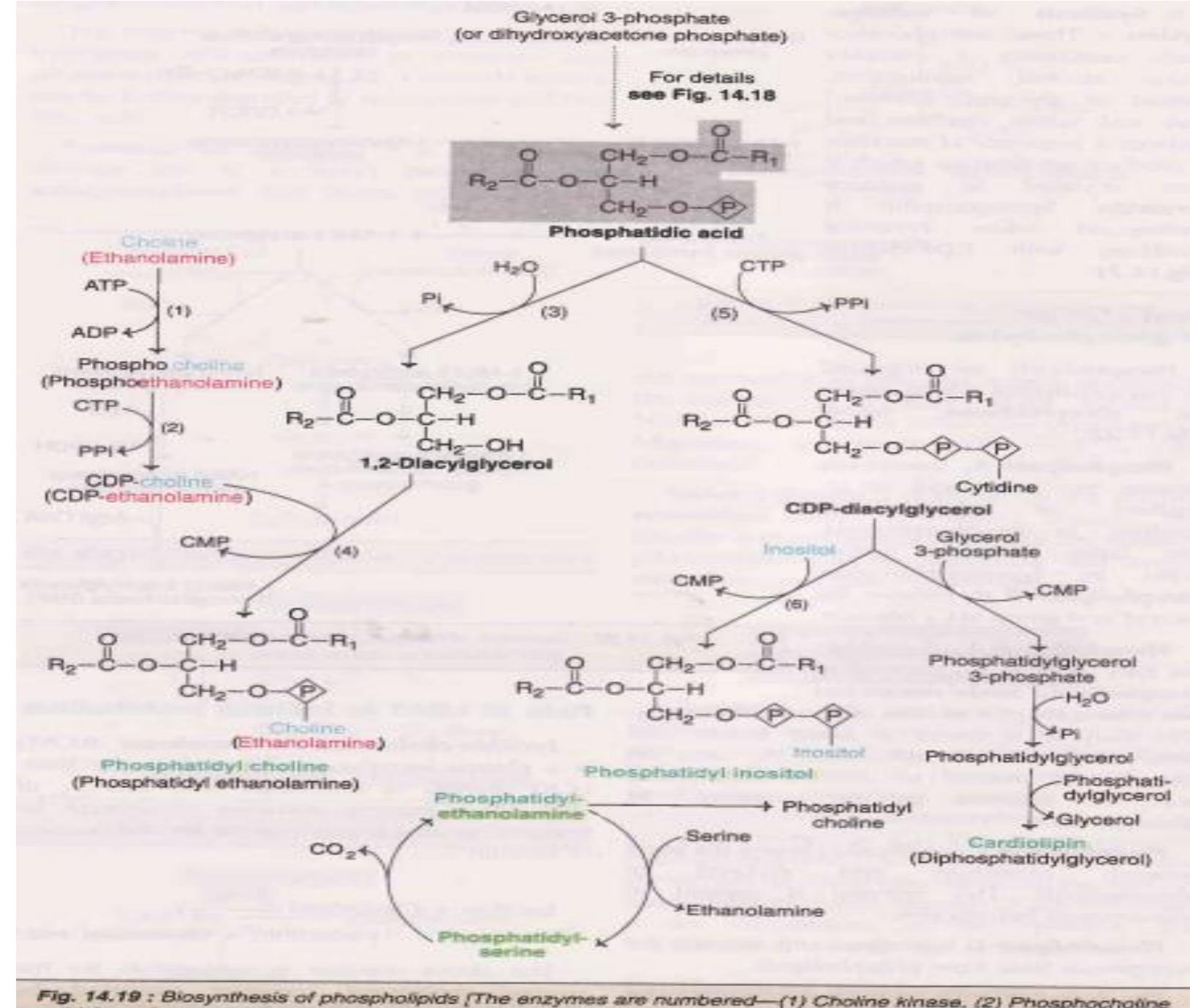
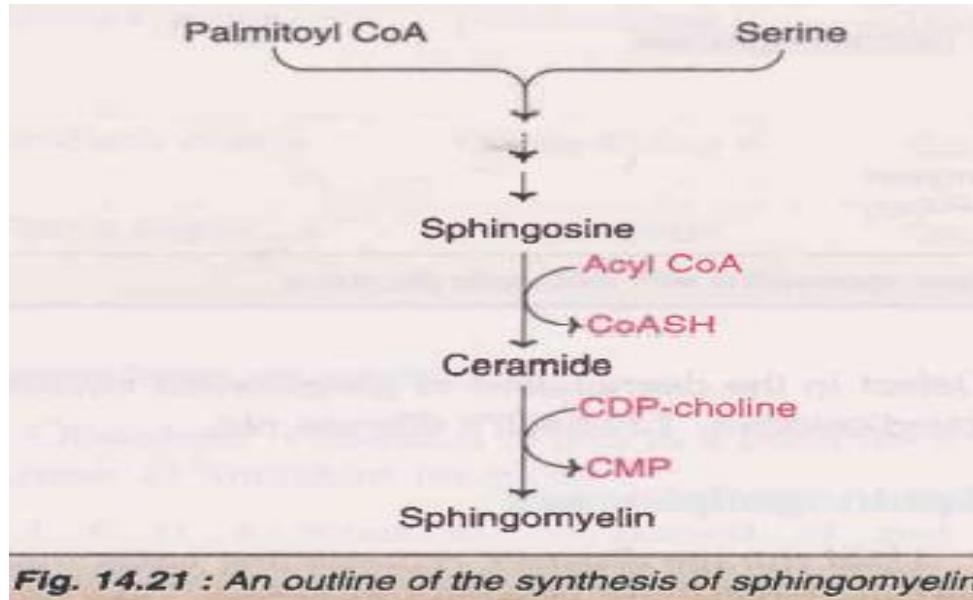


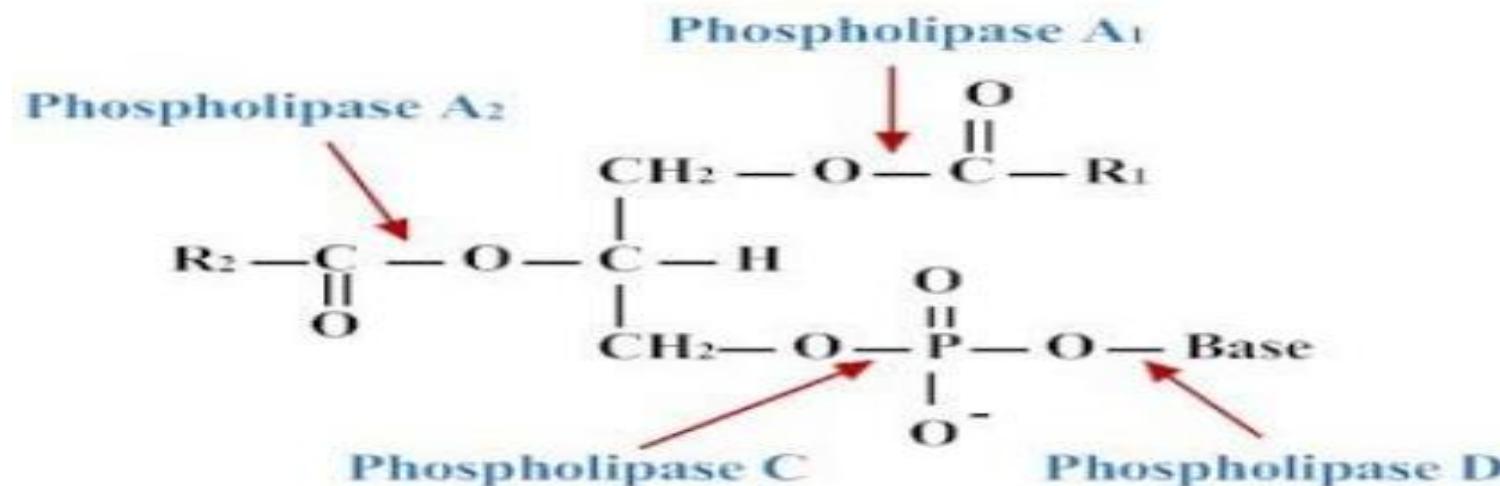
Fig. 14.19 : Biosynthesis of phospholipids (The enzymes are numbered—(1) Choline kinase, (2) Phosphocholine

- **Synthesis of sphingomyelins** : These are **phospholipids** containing a complex **amino alcohol, sphingosine**, instead of glycerol. Palmitoyl CoA and serine combine and undergo a sequence of reactions to produce sphingosine which is then acylated to produce ceramide. Sphingomyelin is synthesized when ceramide combines with CDP-choline.



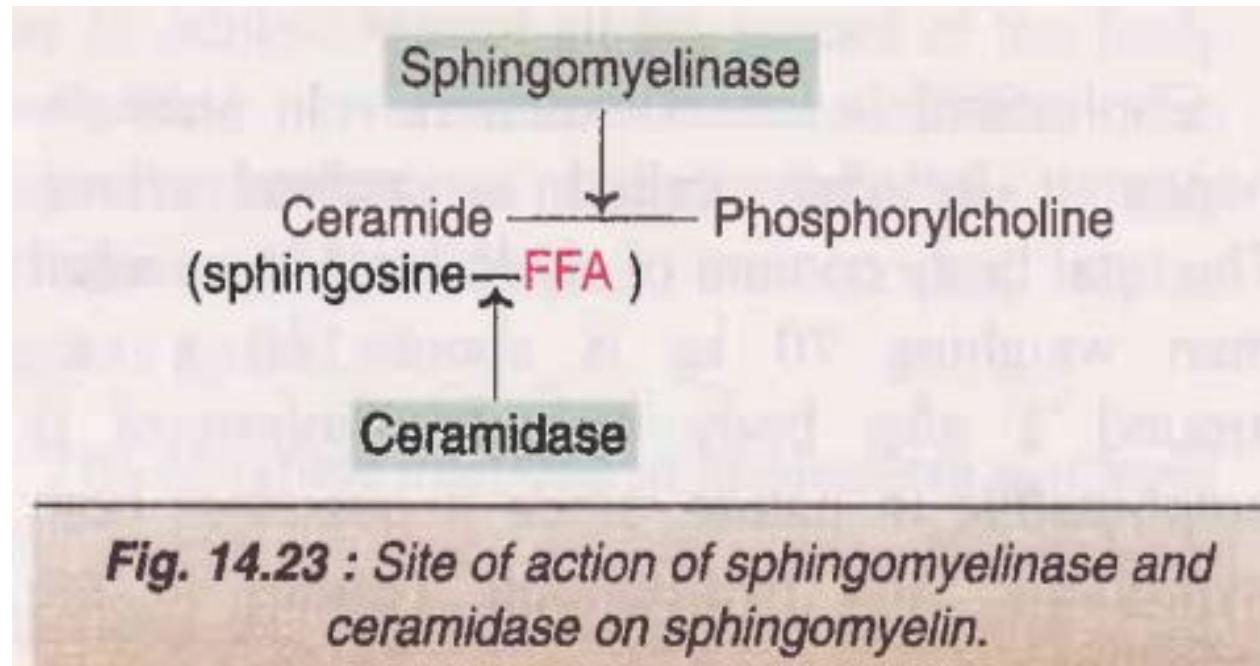
Degradation of phospholipids/Action of phospholipase

- **Phospholipase A₁** removes the acyl group from carbon 1 of phospholipid.
- **Phospholipase A₂** also releases acyl group from carbon 2 of phospholipid.
- **Phospholipase B** acts on the lysophospholipid, after the action of A2.
- **Phospholipase C** liberates diacylglycerol from phospholipids.
- **Phospholipase D** produces phosphatidic acid from various phospholipids



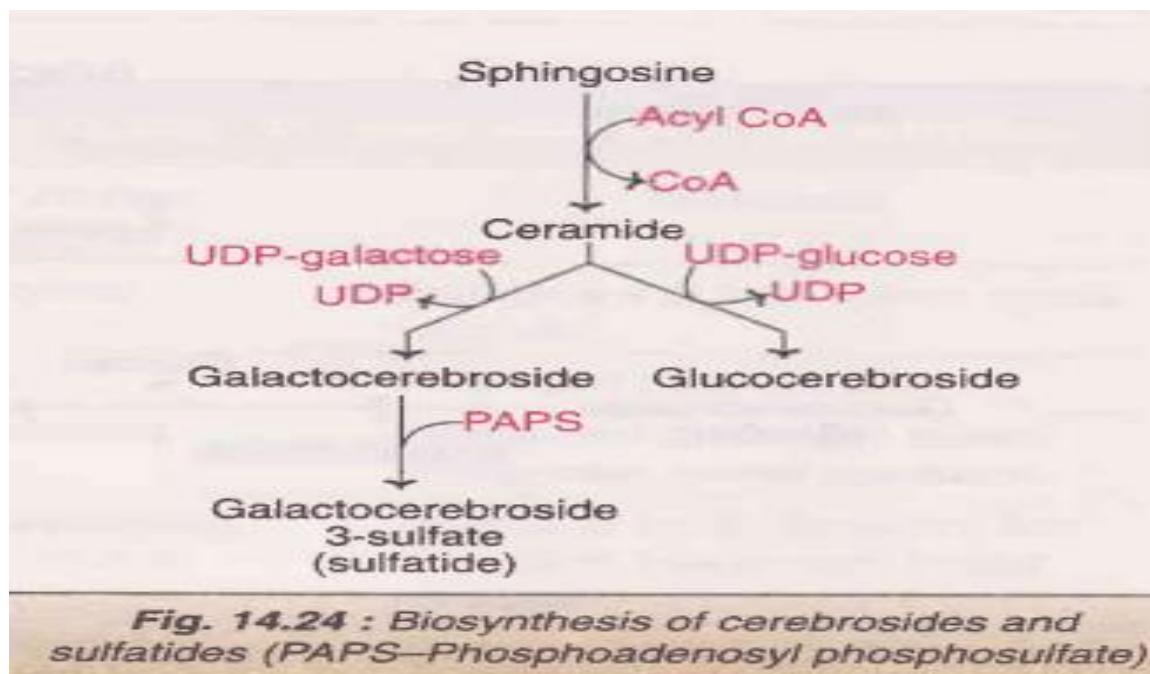
Degradation of sphingomyelins

- The enzyme **sphingomyelinase** of lysosomes hydrolyses **sphingomyelins** to ceramide and phosphorylcholine.
- Ceramide formed further degraded to sphingosine and free fatty acid by **ceramidase**.



Metabolism of Glycolipids

- Glycolipids are derivatives of ceramide (sphingosine bound to fatty acid), and they are known as **glycosphingolipids**.
- The simplest form of glycosphingolipids are **cerebrosides (ceramide + monosaccharides)**.
- Galactocerebroside (Gal-Cer) and glucocerebroside (Glu-Cer) are the common glycosphingolipids.



Lipid storage disease/Sphinogolipidoses

- Lipid storage diseases, representing lysosomal storage defects, are inherited disorders. They are characterized by the accumulation of complex lipids.
- The term sphingolipidoses is often used to collectively refer to the genetic disorders that lead to the accumulation of any one of the sphingolipids (glycosphingolipids and sphingomyelins).

Lipid storage diseases

TABLE 14.4 Some examples of sphingolipidoses (lipid storage diseases) with their characteristics

| Disease | Missing/defective enzyme | Major storage compound | Symptoms |
|----------------------|--------------------------|-----------------------------|--|
| Niemann-Pick disease | Sphingomyelinase | Sphingomyelins | Enlargement of liver, spleen, mental retardation. |
| Farber's disease | Ceramidase | Ceramide | Painful and deformed joints. |
| Gaucher's disease | β -Glucosidase | Glucocerebroside | Enlargement of liver and spleen, osteoporosis, mental retardation. |
| Krabbe's disease | β -Galactosidase | Galactocerebrosides | Absence of myelin formation, liver and spleen enlargement, mental retardation. |
| Tay-Sachs disease | Hexosaminidase A | Ganglioside GM ₂ | Blindness, mental retardation, death within 2-3 years. |
| Fabry's disease | α -Galactosidase | Ceramide trihexoside | Renal failure, skin rash, pain in lower extremities. |

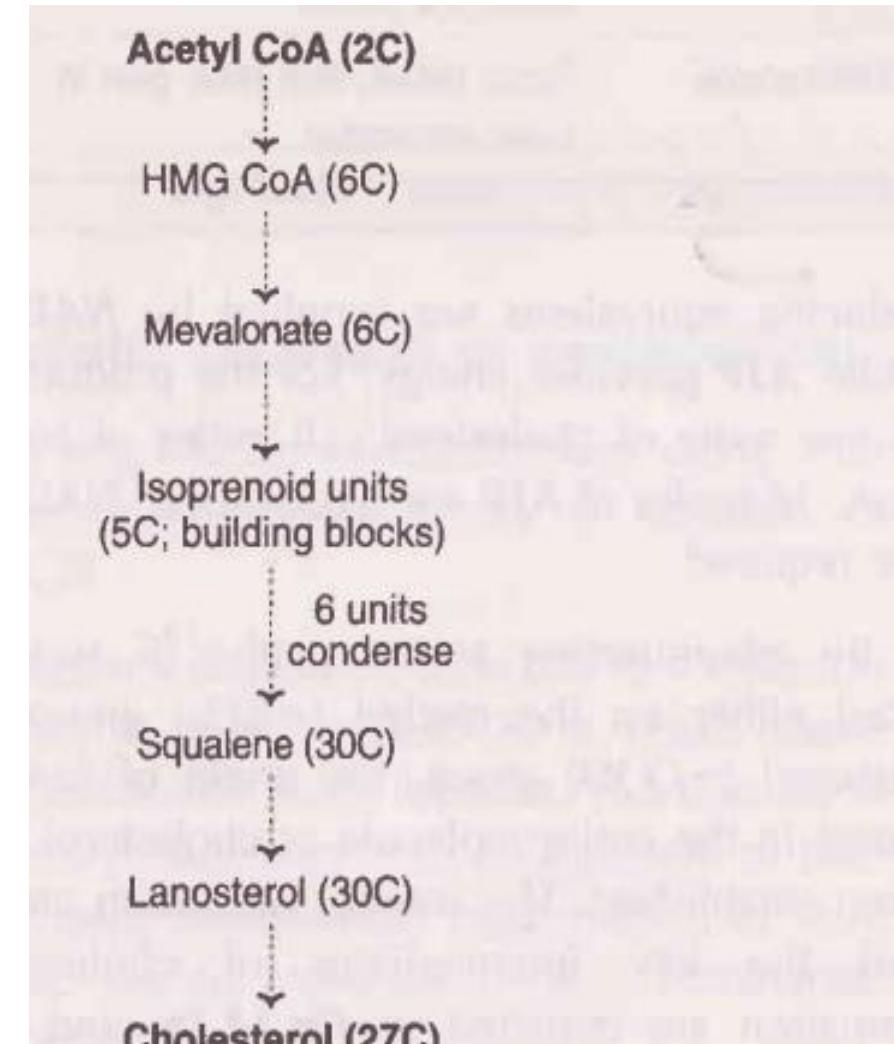
CHOLESTEROL BIOSYNTHESIS

- Almost all the tissues of the body participate in cholesterol biosynthesis. The largest contribution is made by **liver (50%)**, **intestine (15%)**, skin, adrenal cortex, reproductive tissue etc.
- The enzymes involved in cholesterol synthesis are found in the **cytosol** and **microsomal fractions** of the cell.
- **Acetate of acetyl CoA** provides all the carbon atoms in cholesterol.
- The reducing equivalents are supplied by **NADPH** while **ATP** provides energy.

The synthesis of cholesterol (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)

HMG CoA reductase is the rate limiting enzyme in cholesterol biosynthesis



**Fig. 14.26 : Outline of cholesterol biosynthesis—
(A) Derivation of carbon atoms from acetate,
(B) Key intermediates with the carbon atoms.**

- The penultimate product is **7-dehydrocholesterol** which, on **reduction, finally yields cholesterol.**
- Cholesterol biosynthesis is now believed to be a part of a major metabolic pathway concerned with the synthesis of several other **isoprenoid** compounds. These include

-ubiquinone (coenzyme Q of electron transport chain)

-dolichol (found in glycoprotein).

Both of them are derived from **farnesyl pyrophosphate.**

Regulation of cholesterol biosynthesis (by HMG CoA reductase)

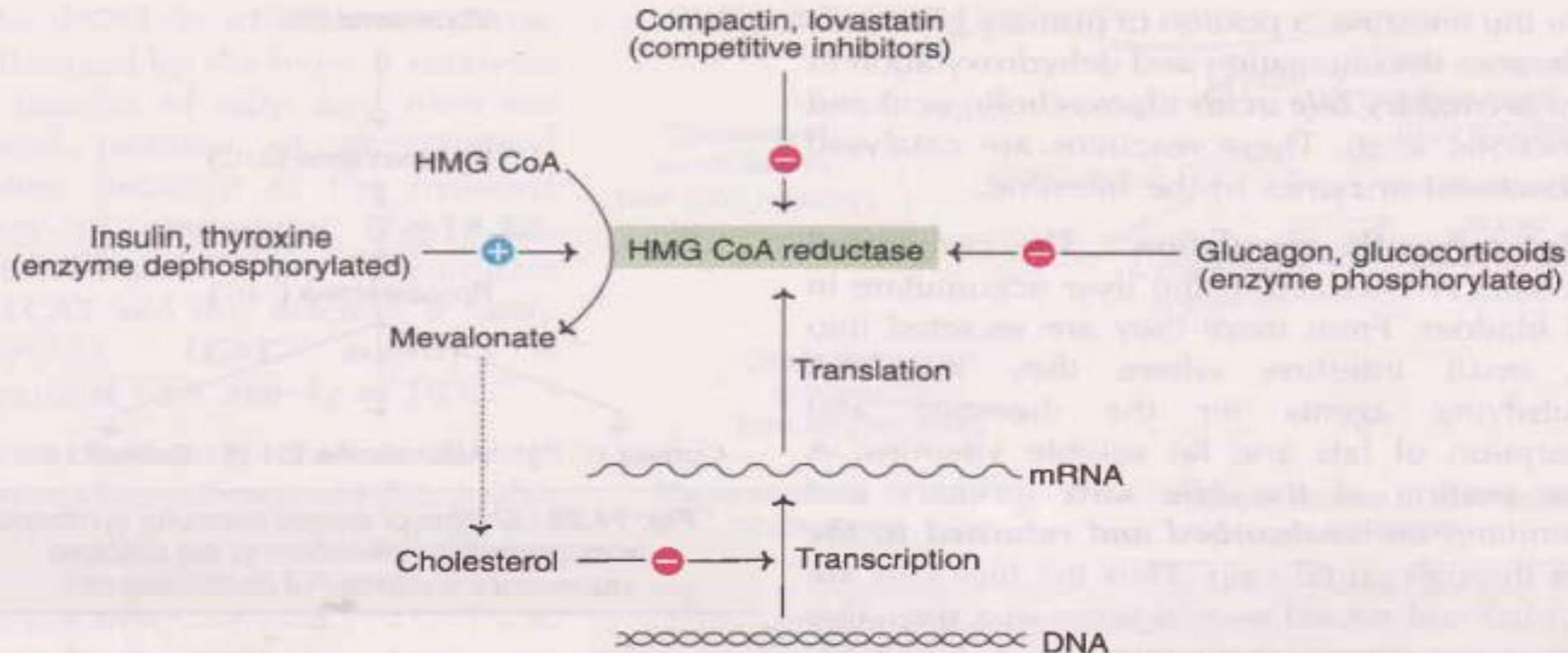


Fig. 14.28 : Regulation of cholesterol biosynthesis by HMG CoA reductase (+—Promoting effect; -—Inhibitory effect).

DEGRADATION OF CHOLESTEROL

1. Synthesis of bile acids:

- The synthesis of **primary bile acids (Cholic acid and chenodeoxycholic acid)** takes place in the **liver**.
- The step catalysed by **7 α -hydroxylase** is inhibited by bile acids and this is **the rate limiting reaction**.
- In the intestine, a portion of primary bile acids undergoes deconjugation and dehydroxylation to form **secondary bile acids (deoxycholic acid and lithocholic acid)**

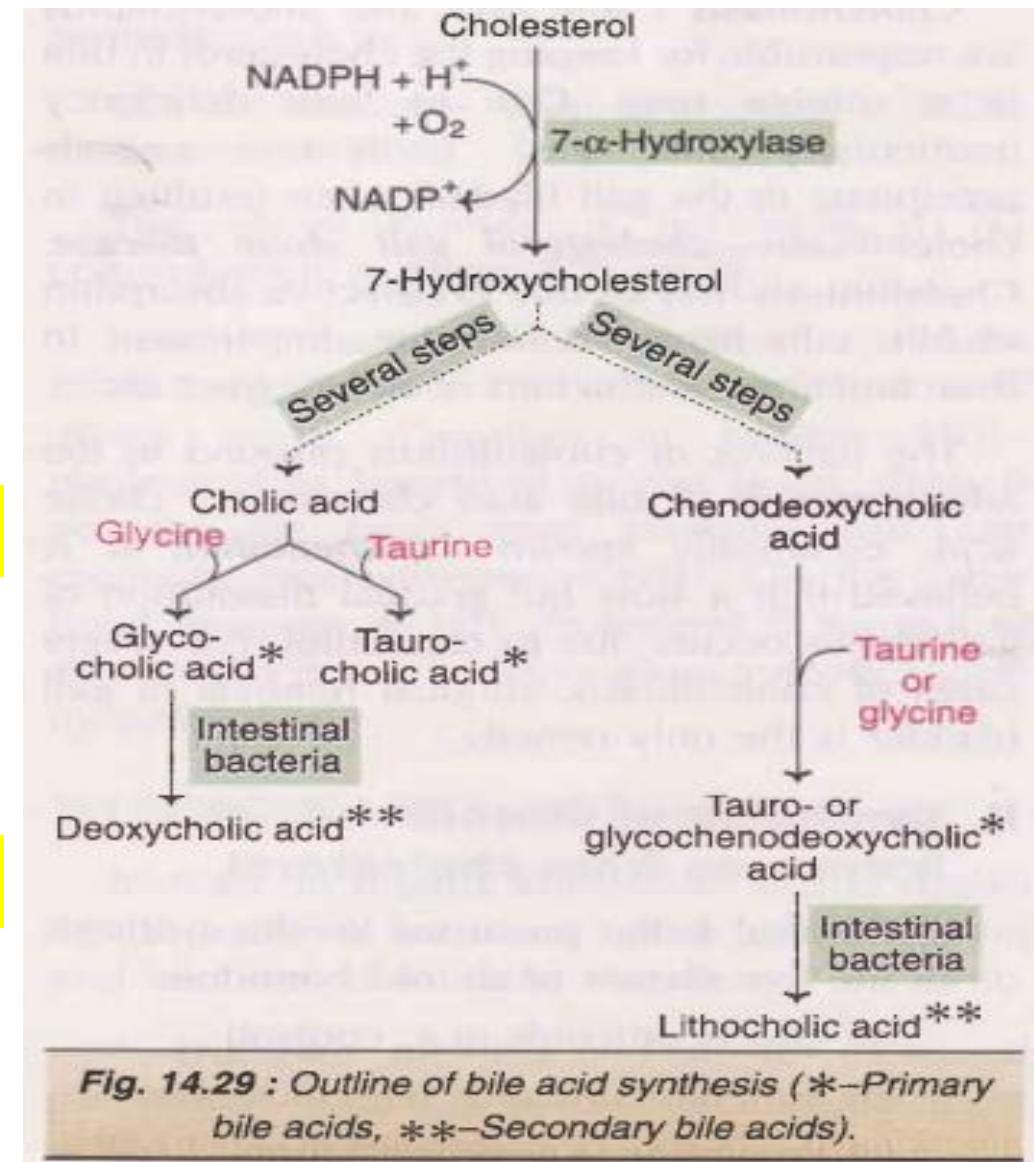


Fig. 14.29 : Outline of bile acid synthesis (*—Primary bile acids, **—Secondary bile acids).

- Fecal excretion of bile salts is the only route for the removal of cholesterol from the body.
- **Cholelithiasis**-cholesterol gall stone disease.

2. Synthesis of steroid from cholesterol

Cholesterol is the precursor for the synthesis of all the **five classes** of steroid hormones

- (a) Glucocorticoids (e.g. cortisol)
- (b) Mineralocorticoids (e.g. aldosterone)
- (c) Progestins (e.g. progesterone)
- (d) Androgens (e.g. testosterone)
- (e) Estrogens (e.g. estradiol).

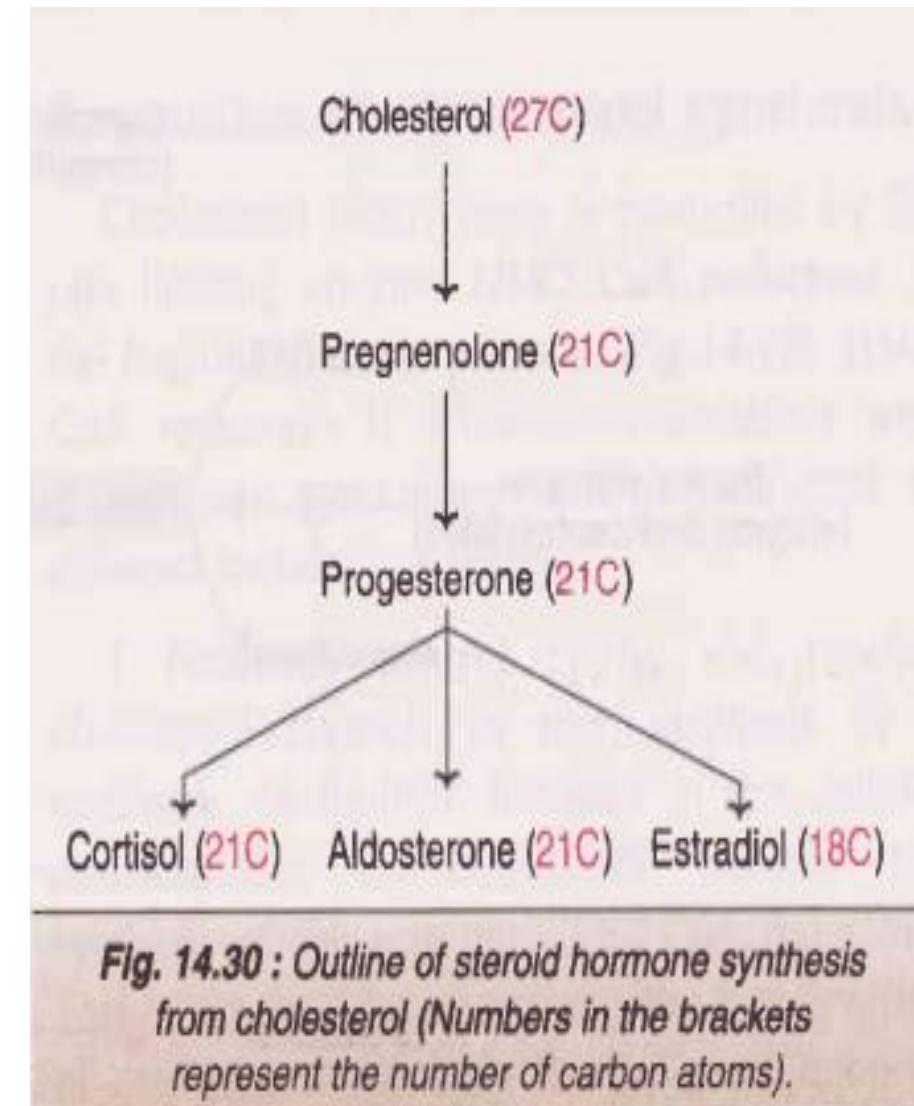


Fig. 14.30 : Outline of steroid hormone synthesis from cholesterol (Numbers in the brackets represent the number of carbon atoms).

3. Synthesis of vitamin D

7-Dehydrocholesterol, an intermediate in the synthesis of cholesterol, is converted to **cholecalciferol (vitamin D₃)** UV ultraviolet rays in the skin.

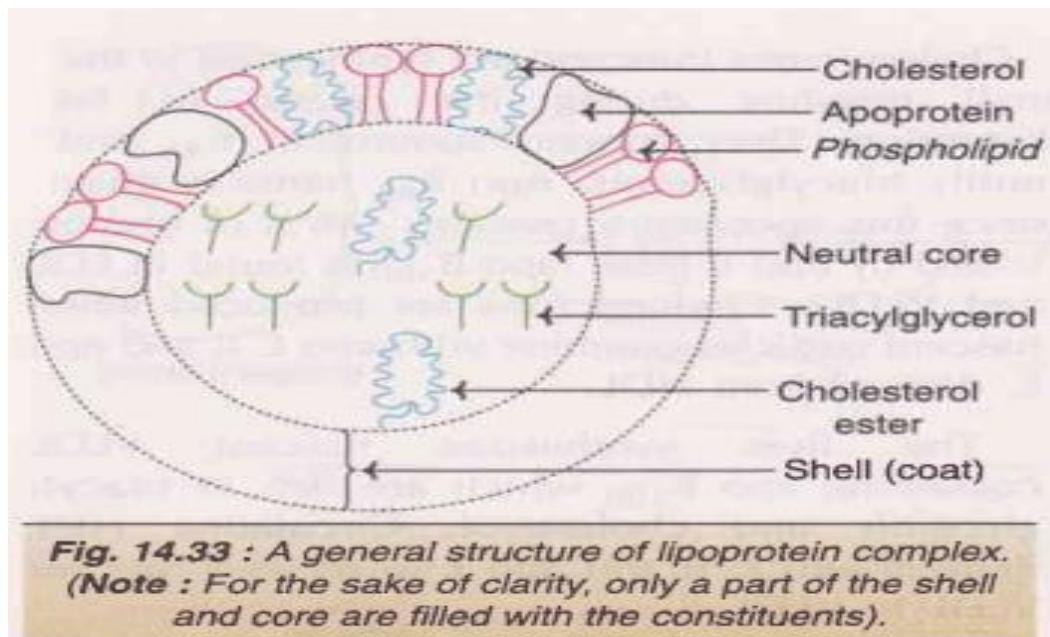
Hypercholesterolemia

Increase in plasma cholesterol (> 200 mg/dl) concentration is known as hypercholesterolemia and is observed in many disorders:

- ✓ Diabetes mellitus
- ✓ Hypothyroidism (myxoedema)
- ✓ Obstructive Jaundice
- ✓ Nephrotic syndrome

Lipoproteins

- Lipoproteins are molecular complexes that consist of **lipids and proteins** (conjugated proteins).
- They function as transport vehicles for lipids in blood plasma.
Lipoproteins deliver the lipid components (cholesterol, triacylglycerol etc.) to various tissues for utilization.



Classification of lipoproteins

1. **Chylomicrons** : They are synthesized in the intestine
2. **Very low density lipoproteins (VLDL)** : They are produced in liver and intestine.
3. **Low density lipoproteins (LDL)** : They are formed from VLDL in the blood circulation.
4. **High density lipoproteins (HDL)** : They are mostly synthesized in liver
5. **Free fatty acids-albumin** : Free fatty acids in the circulation are in a bound form to albumin

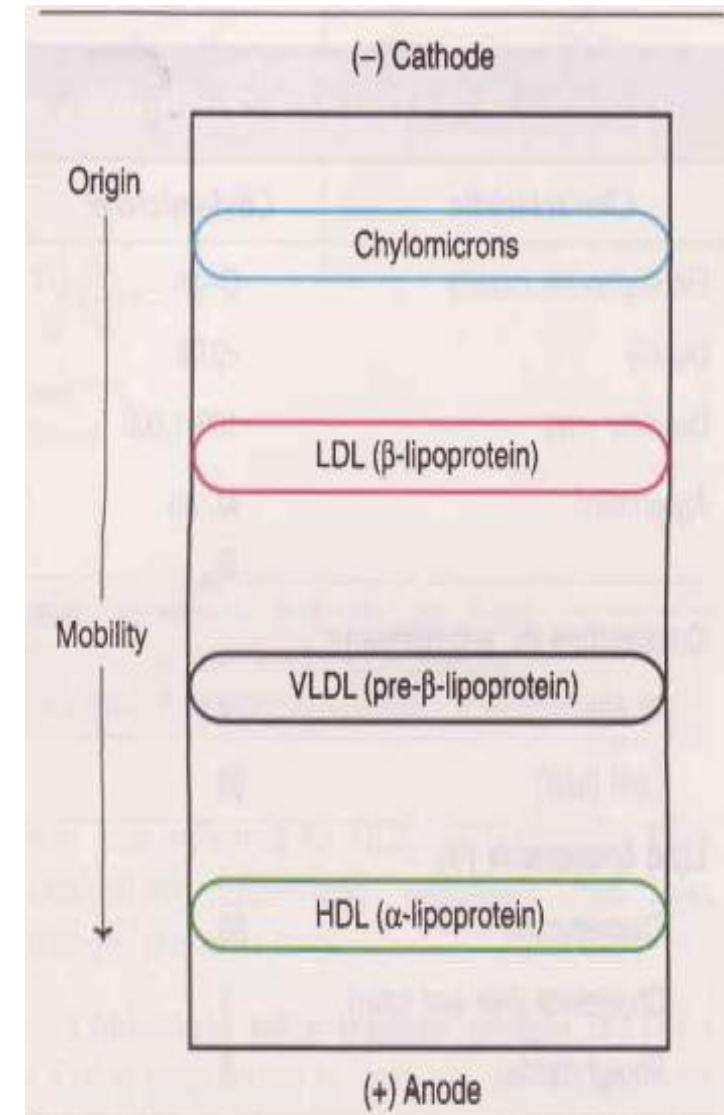


Fig. 14.34 : Electrophoresis of plasma (serum) lipoproteins.

Apolipoproteins

- The protein components of lipoproteins are known as apolipoproteins or, simply, apoproteins. They perform the following functions
 - 1 . Act as structural components of lipoproteins.
 2. Recognize the cell membrane surface receptors.
 3. Activate enzymes involved in lipoprotein metabolism

Hyperlipoproteinemia

TABLE 14.6 Classification and characteristics of hyperlipoproteinemias (hyperlipidemias)

| <i>Hyperlipoproteinemia Type</i> | <i>Increased plasma lipoprotein(s)</i> | <i>Increased plasma lipid (most)</i> | <i>Probable metabolic defect</i> | <i>Risk of atherosclerosis</i> | <i>Suggested treatment</i> |
|----------------------------------|--|--------------------------------------|----------------------------------|--|--|
| I | Chylomicrons | Triacylglycerols | Deficiency of lipoprotein lipase | May increase | Low fat diet |
| IIa | LDL | Cholesterol | Deficiency of LDL receptors | Very high (mostly in coronary artery) | Low cholesterol fat diet; cholestyramine |
| IIb | LDL and VLDL | Triacylglycerols and cholesterol | Overproduction of apo-B | — do — | — do — |
| III | IDL | Triacylglycerols and cholesterol | Abnormality in apo-E | Very high (mostly in peripheral vessels) | Low fat and low caloric diet; clofibrate |
| IV | VLDL | Triacylglycerols | Overproduction of TG | May or may not increase | Low fat and low caloric diet; niacin |
| V | Chylomicrons and VLDL | Triacylglycerols | — | — do — | — do — |

Atherosclerosis

- Atherosclerosis (Greek: athere-mush) is a complex disease characterized by thickening or hardening of arteries due to the accumulation of lipids (particularly cholesterol, free, and esterified) collagen, fibrous tissue, proteoglycans, calcium deposits etc. in the inner arterial wall.
- Atherosclerosis is a progressive disorder that narrows and ultimately blocks the arteries.
- Infarction is the term used to indicate the stoppage of blood flow resulting in the death of affected tissue.
- **Coronary arteries**--the arteries supplying blood to heart--are the most commonly affected leading to myocardial infarction or heart attacks.

thank you