Ketone bodies (ketogenesis and ketolysis)

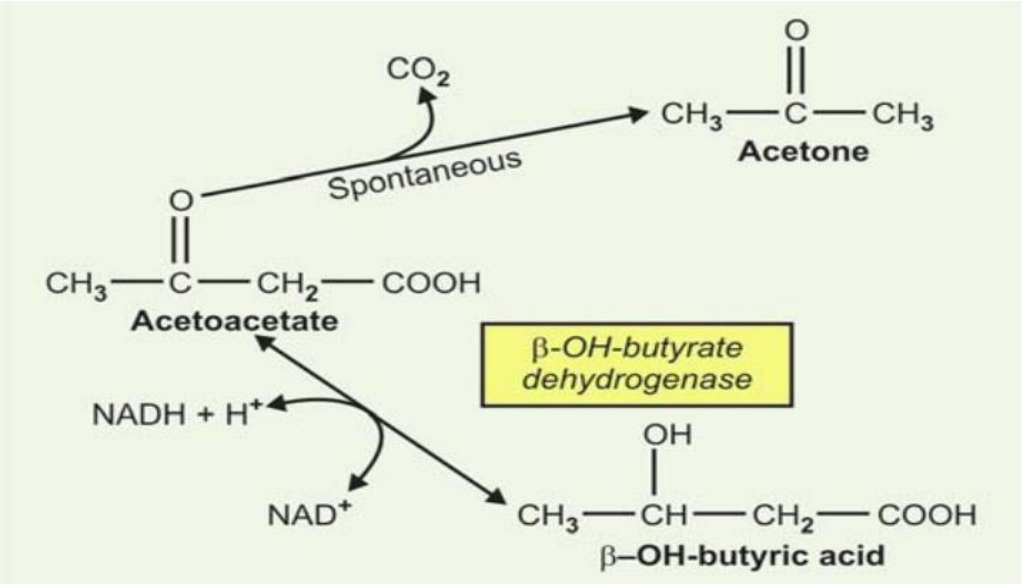
Introduction

1- Ketone bodies are water-soluble molecules or compounds that contain the ketone groups produced from fatty acids by the liver (ketogenesis).

2- Three substances are collectively known as "ketone bodies" (or "acetone bodies").

3- Acetoacetate, acetone and β-OH butyric acid are metabolic products that are produced in excess during excessive breakdown of fatty acid.

4- Acetoacetate continually undergoes spontaneous decarboxylation to produce acetone



- **Ketonaemia**: Rise of ketone bodies in blood above normal level is known as ketonaemia.

- Ketonuria: When the blood level of ketone bodies rises above the renal threshold, they are excreted in urine and are called as ketonuria.

- Ketosis: Accumulation of abnormal amount of ketone bodies in tissues and body fluids is termed as ketosis

-Ketoacidosis: Acetoacetic acid and β-OH-butyric acid are moderately strong acids. They are buffered when present in blood and tissues, loss of buffer cations, which progressively depletes the alkali reserve↓ causing ketoacidosis.
Note: This may be fatal in uncontrolled diabetes mellitus.

Causes of ketoacidosis

1. non- pathological state
   a. Prolonged Starvation
   b. Carbohydrate poor diet
   c. High fat diet
   d. After severe exercise in the post-absorptive state.
2. In Pathologic States
   a. In Diabetes mellitus: In uncontrolled diabetes mellitus, there could be a pathological state of ketosis (or ketoacidosis or even ketoacidotic coma) that may be fatal. In diabetic ketosis, the ketonuria causes loss of sodium and potassium salts of the keto acids leading to severe dehydration.

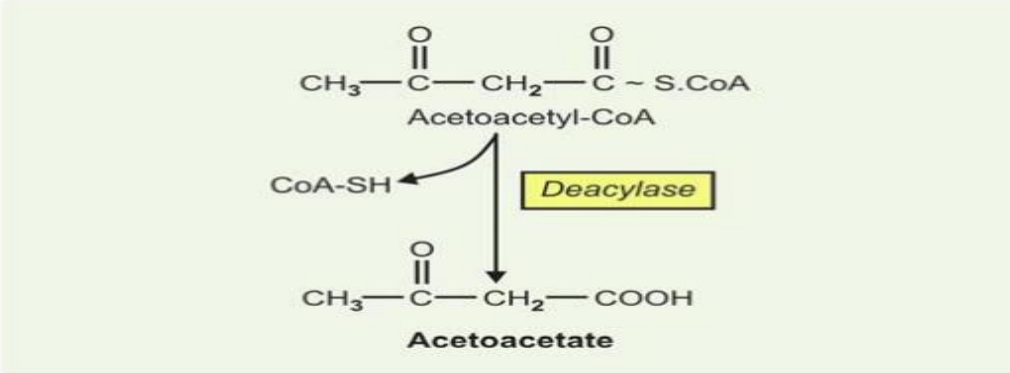
KETONE BODY FORMATION IN LIVER (KETOGENESIS)

Liver appears to be the only organ which produces ketone bodies, the synthetic reaction occur in mitochondria and add to the blood. Extrahepatic tissues can pick up ketone bodies from the circulating blood and utilize them as respiratory substrates.

Steps

1. Formation of Aceto-acetyl-CoA: is the starting material for ketogenesis.
- Two molecules of acetyl-CoA condensed to form Aceto-acetyl-CoA
- This reaction is catalyzed by thiolase enzyme.

2. Formation of Acetoacetate: Acetoacetate is the first ketone body to be formed. This can occur in two ways:



(a) By deacylation: Acetoacetate can be formed from aceto-acetyl-CoA by simple deacylation catalysed by the enzyme aceto-acetyl-CoA deacylase and this pathway dose not seems to be the major pathway (minor pathway)

(b) Second pathway (The HMG-CoA pathway): Formation of acetoacetate via intermediate production of "β-OH-β-methyl glutaryl CoA" (HMG-CoA). Represent the major route of ketone body formation.

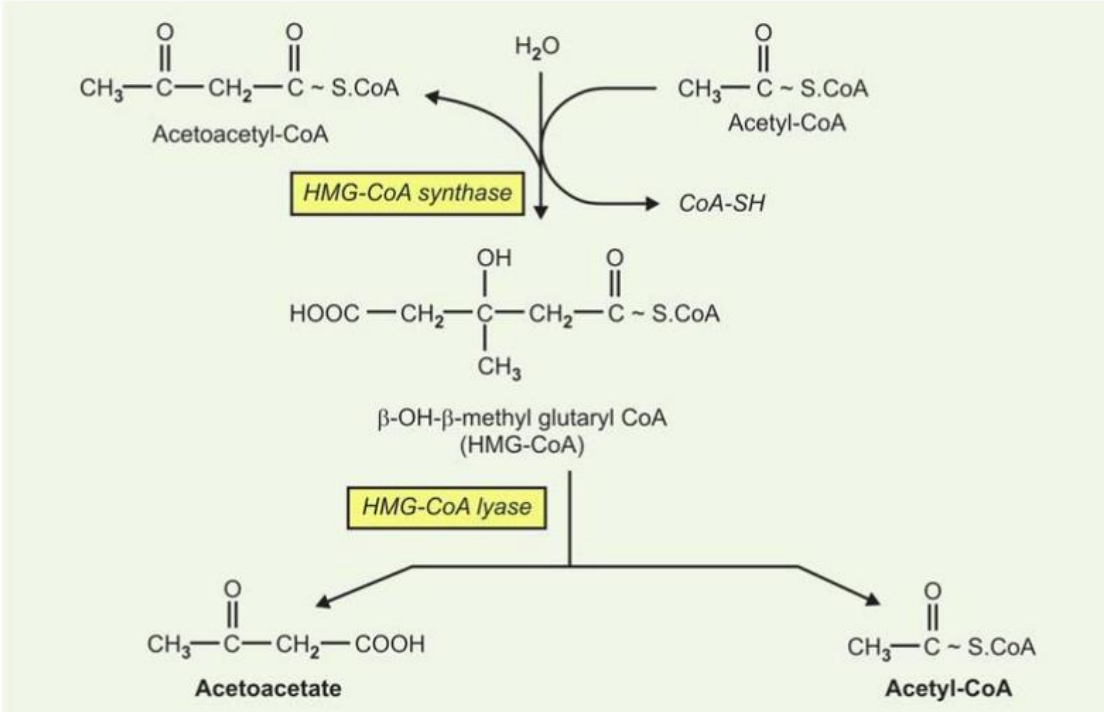
Steps Involves two steps:

a. Condensation of aceto-acetyl-CoA with another molecule of acetyl-CoA to form β-OH-β methyl glutaryl-CoA (HMG-CoA) catalysed by the enzyme HMG-CoA synthase (mitochondrial enzyme).

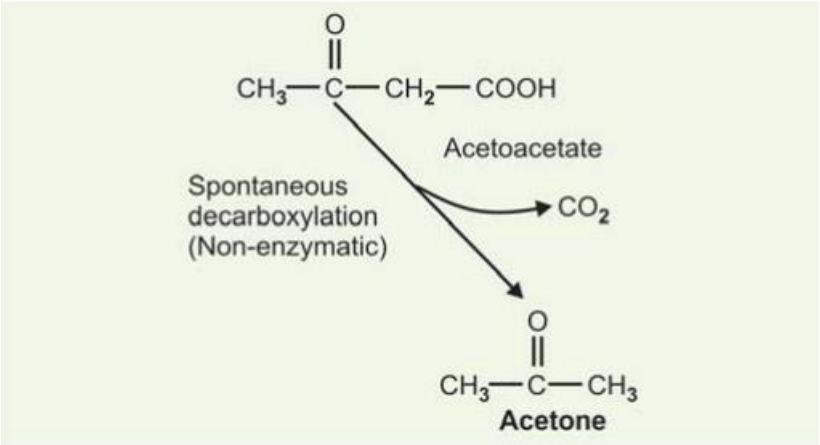
b. HMG-CoA is then acted upon by an another enzyme, HMG-CoA Lyase, which is also mitochondrial enzyme, to produce one molecule "acetoacetate" and one molecule of acetyl-CoA.

Note

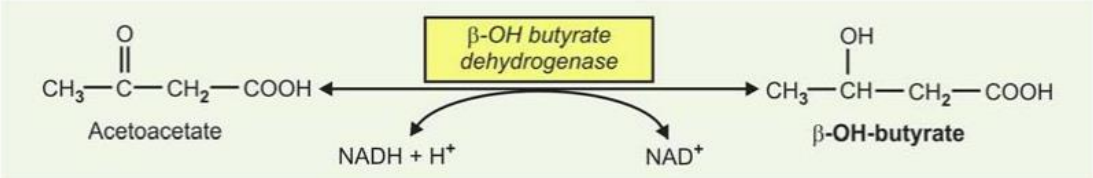
• Both the enzymes HMG-CoA synthase and HMG-CoA Lyase are mitochondrial and must be available in mitocondrion for ketogenesis to occur.

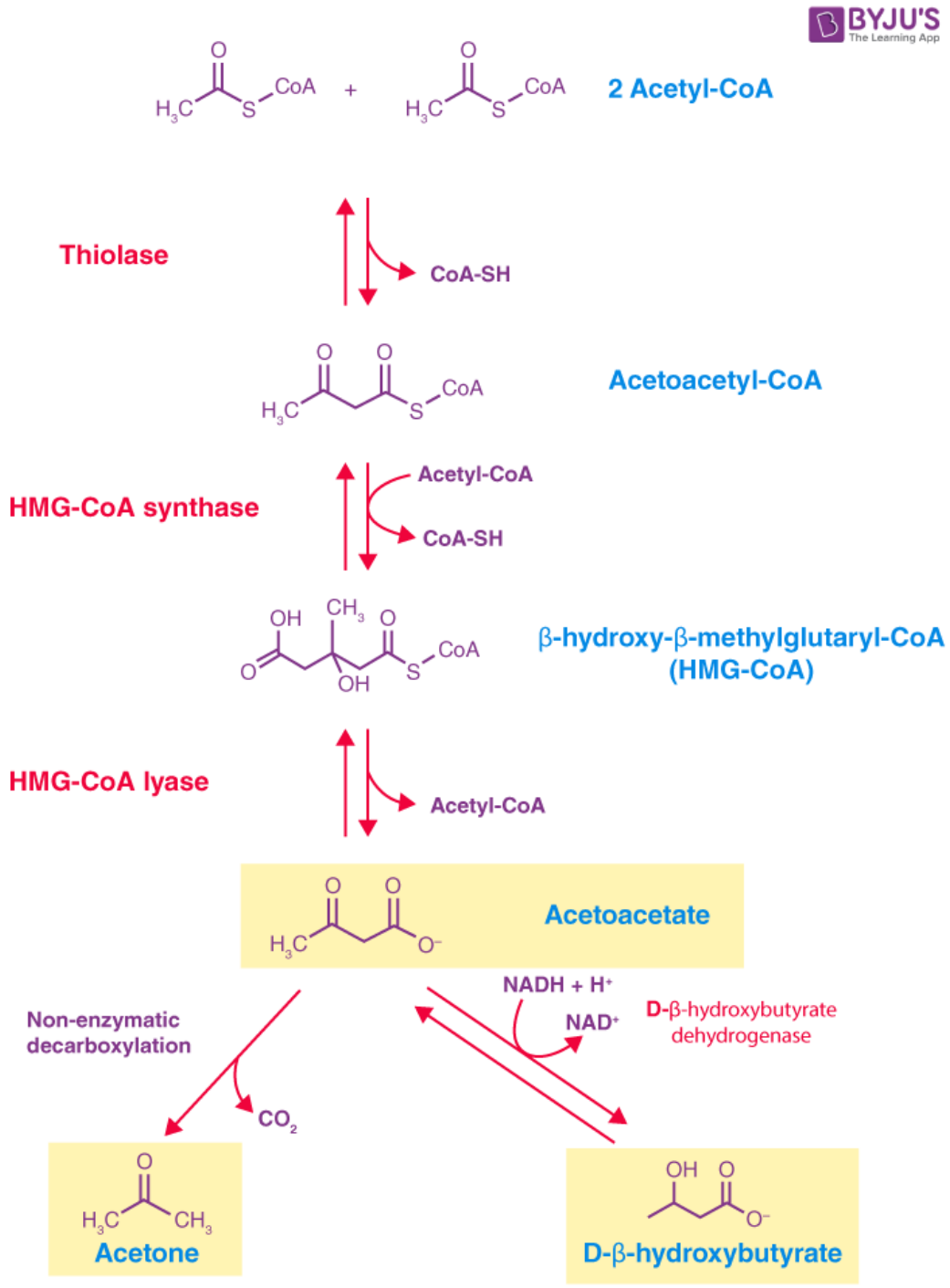


3. Formation of Acetone: As stated earlier, acetone is formed from acetoacetate by spontaneous decarboxylation (Non-enzymatic).



4. Formation of β-OH Butyrate: Acetoacetate once formed is converted to β-OH-butyric acid; the reaction is catalysed by the enzyme β-OH-butyrate dehydrogenase, which is present in liver and also found in many other tissues.




BYJU'S
The Learning App
2 Acetyl-CoA
Thiolase
CoA-SH
Acetoacetyl-CoA
HMG-CoA synthase
Acetyl-CoA
CoA-SH
β-hydroxy-β-methylglutaryl-CoA
(HMG-CoA)
HMG-CoA lyase
Acetyl-CoA
Acetoacetate
NADH + H+
NAD+
D-β-hydroxybutyrate
dehydrogenase
Non-enzymatic
decarboxylation
CO2
Acetone
D-β-hydroxybutyrate

UTILISATION OF KETONE BODIES

Ketolysis

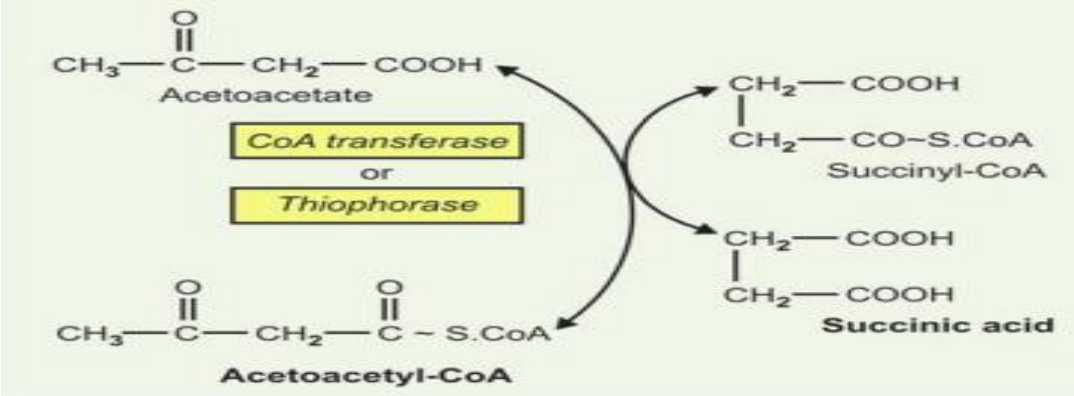
1- Ketone bodies are utilized by extrahepatic tissues as "fuel".

Steps of ketolysis

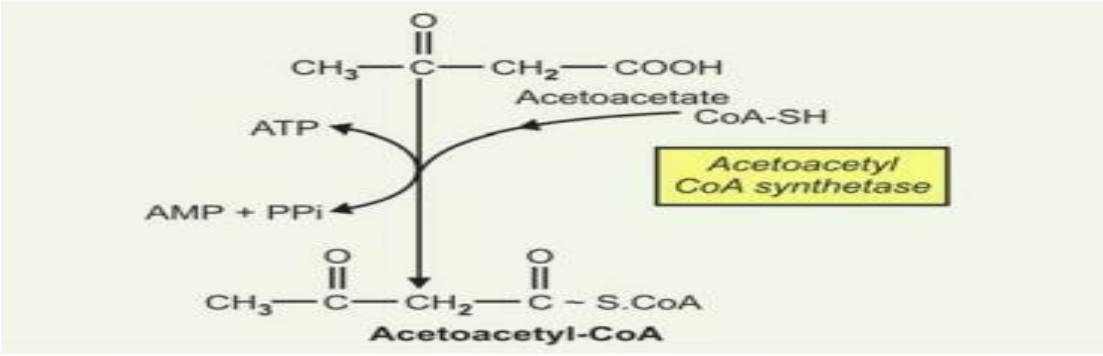
1. Activation of Acetoacetate

Two reactions take place in extrahepatic tissues which activate acetoacetate to form aceto-acetyl-CoA,

(a) Action of acetoacetate with succinyl-CoA: Major Pathway by which acetoacetate is activated in extrahepatic tissues. Acetoacetate reacts with one molecule of succinyl-CoA (intermediate of TCA cycle), catalysed by the enzyme CoA transferase (thiophorase) to forming acetoacetyl-CoA and succinate



(b) Second mechanism: Activation of acetoacetate with ATP and CoA-SH, catalysed by the enzyme Acetoacetyl-CoA synthetase. This is probably not a major pathway.



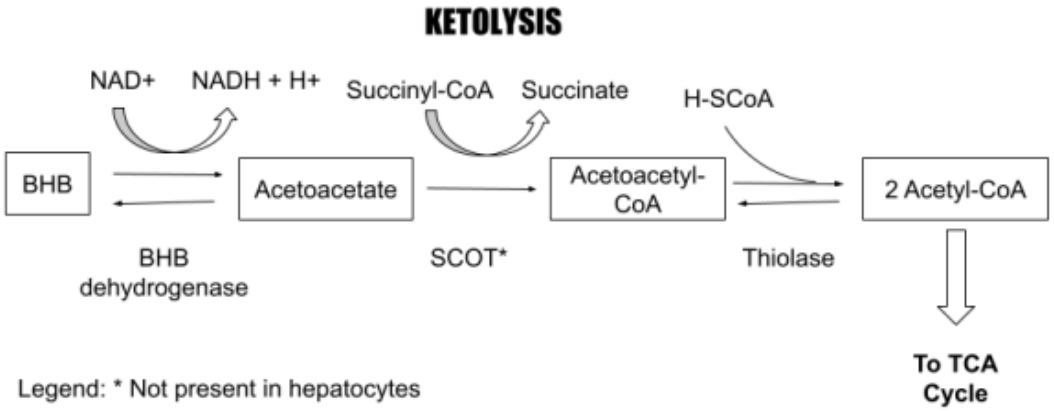
Fate of β-OH-Butyrate

-β-OH-butyrate may be activated directly in extrahepatic tissues by a synthetase.

- β-OH-butyrate can be converted back to "acetoacetate" by the enzyme β-OH-butyrate dehydrogenase and NAD+, as the reaction is reversible.

Fate of acetone:

Acetone is difficult to be oxidised in vivo. Experimental evidences show very slow rate of utilization. Excess of acetone can be breathed out and also excreted in urine.



Regulation of ketogenesis:

Ketogenesis speeds up or slows down depending on three important factors:

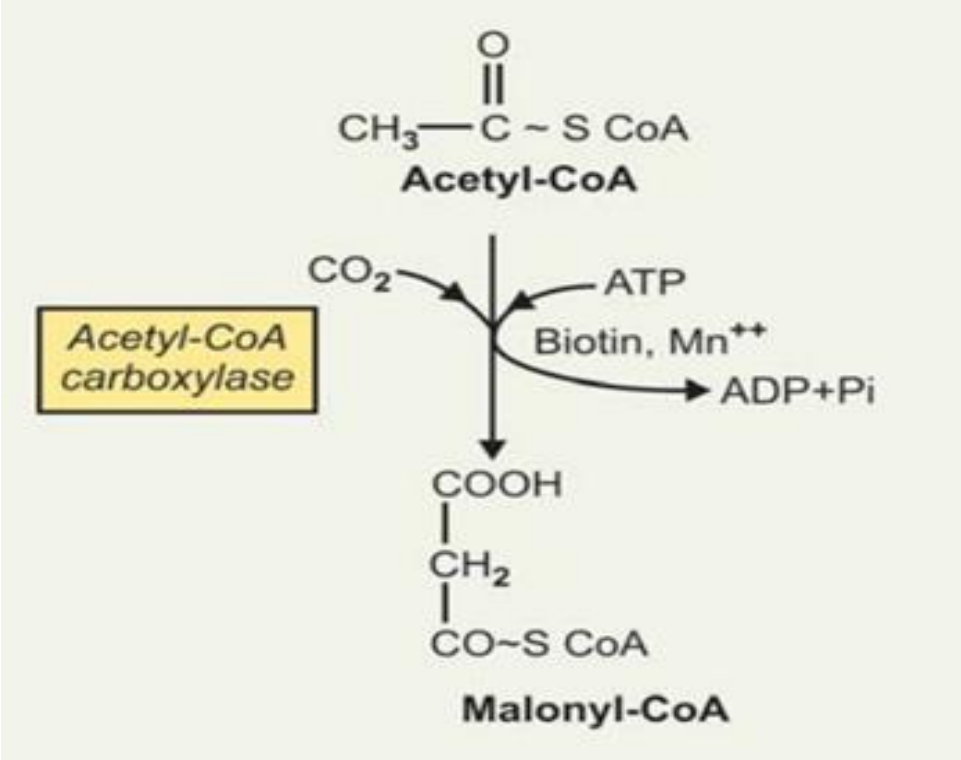
1. The level of circulating F.F.As: Ketosis does not occur in vivo unless there is a rise in the level of circulating F.F.As that arises from lipolysis of TGs in adipose tissues.

Therefore, conditions that affect mobilization of F.F.As from adipose tissues are important in controlling ketogenesis. For example, in starvation the insulin / glucagon ratio decreases, causing increased lipolysis in adipose tissues.

2. Rate of entry of F.F.As into the liver: If F.F.As are entering the liver cells in low concentrations, they will nearly all esterified into TGs and transported out of the liver in very low density lipoproteins (VLDL). However, when high concentrations of F.F.As enter the liver such as in starvation, the acetyl CoA

carboxylase (gate-keeper enzyme) is inhibited and malonyl CoA decreases.

Decrease malonyl CoA result in increased beta oxidation of fatty acid activation of carnitine palmitoyl transferase I and allow more fatty acyl CoA to be oxidized.



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REFRANCES

1. Harper's Biochemistry. Lange, USA.

2. Lippincott Illustrated Reviews: Biochemistry, 7e. Denise R. Ferrier

3. Text book of medical biochemistry. Chtterjea MN. India. Latest edition.