Ketone Bodies

Under metabolic conditions associated with a high rate of fatty acid oxidation (excess production of acetyl-CoA to enter citric acid cycle), the liver produces considerable quantities of acetoacetate, 3-hydroxybutyrate (β-hydroxybutyrate) & acetone, these 3 substances are collectively known as **ketone bodies** (also called acetone bodies). Therefore, ketogenesis is considered as another way of fatty acids oxidation.

Biosynthesis of Ketone Bodies (Ketogenesis)

Enzymes responsible for ketone bodies formation (**3-hydroxy-3-methylglutaryl-CoA synthase & 3-Hydroxy-3-methylglutaryl-CoA lyase**) are associated mainly within the liver mitochondria; therefore, ketogenesis occurs only in the liver mitochondria through the following steps:

I- Acetoacetyl-CoA, which is the starting material for Ketogenesis is arises from:

a-Two acetyl-CoA molecules formed in β-oxidation condense together to form acetoacetyl-CoA with a loss of one molecule of CoA-SH .

b-Directly from the terminal four carbons of a acyl-CoA during β –oxidation.

II- Condensation of acetoacetyl-CoA with another molecule of acetyl-CoA in the presence of **3-hydroxy-3-methylglutaryl-CoA synthase** enzyme forming 3-hydroxy-3-methylglutaryl-CoA **(HMG-CoA)** with a loss of one molecule of CoA-SH.

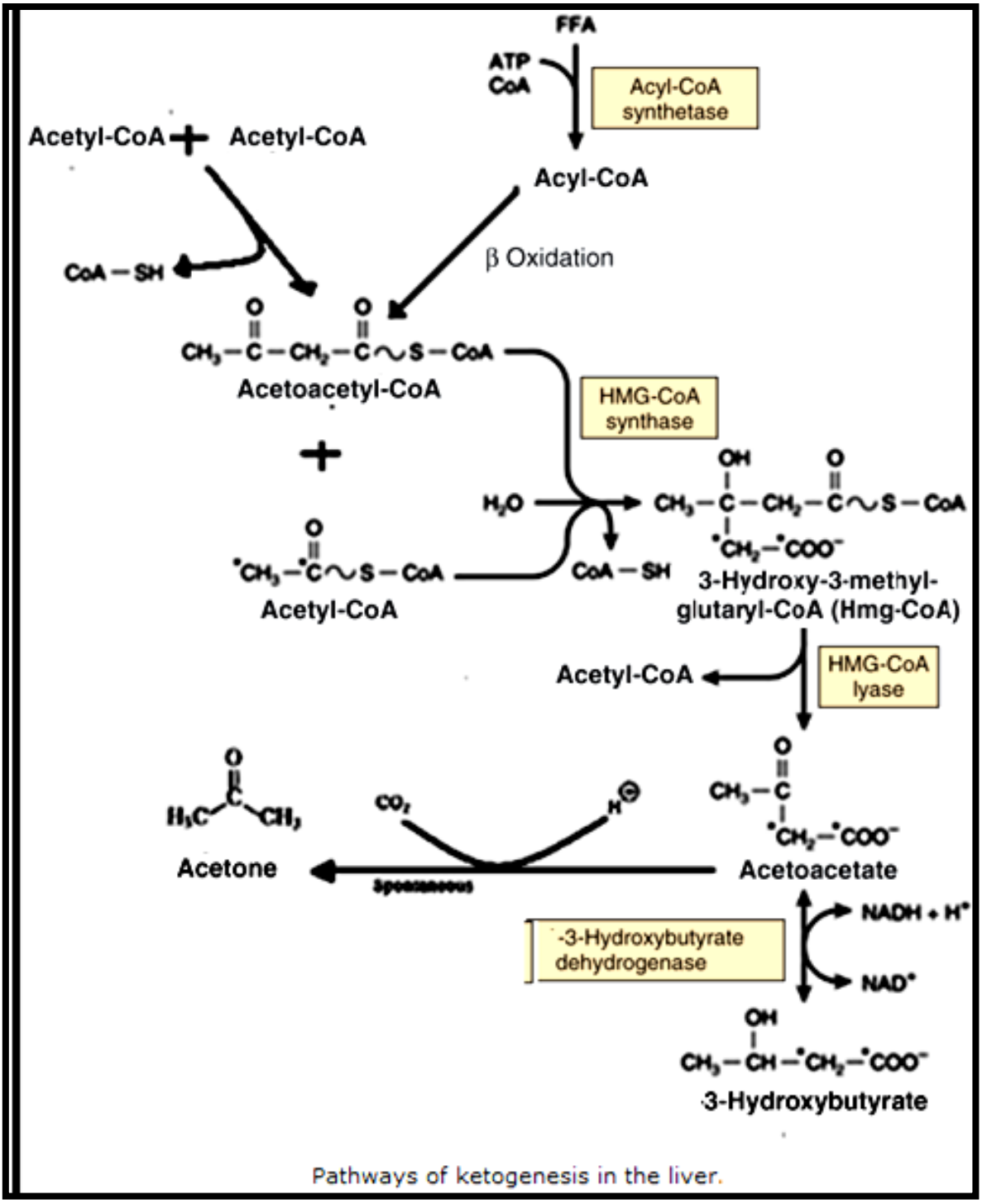
III- 3-Hydroxy-3-methylglutaryl-CoA lyase enzyme split acetyl-CoA from HMG-CoA, leaving free acetoacetate.

IV- Acetoacetate can be converted to other ketone bodies through the following:

a- Hydrogenation of acetoacetate in reaction catalyzed by **3-hydroxybutyrate dehydrogenase** enzyme forming 3-hydroxybutyrate.

b- spontaneous decarboxylation of acetoacetate forming acetone.

Note: 3-hydroxybutyrate is quantitatively the predominant ketone body present in the blood & urine in ketosis.



Pathways of ketogenesis in the liver.

Fate of Ketone Bodies

Normally; in human the liver produces trace amount of ketone bodies that their blood concentration of well-fed human does not exceed 0.2 mmol/L.

The fate of ketone bodies are:

A- Fate inside the liver.

B- Fate outside the liver.

A- Fate inside the liver.

Acetoacetate once formed in the liver it is used as a precursor in cholesterol synthesis, this accounts for the net production of ketone bodies by the liver.

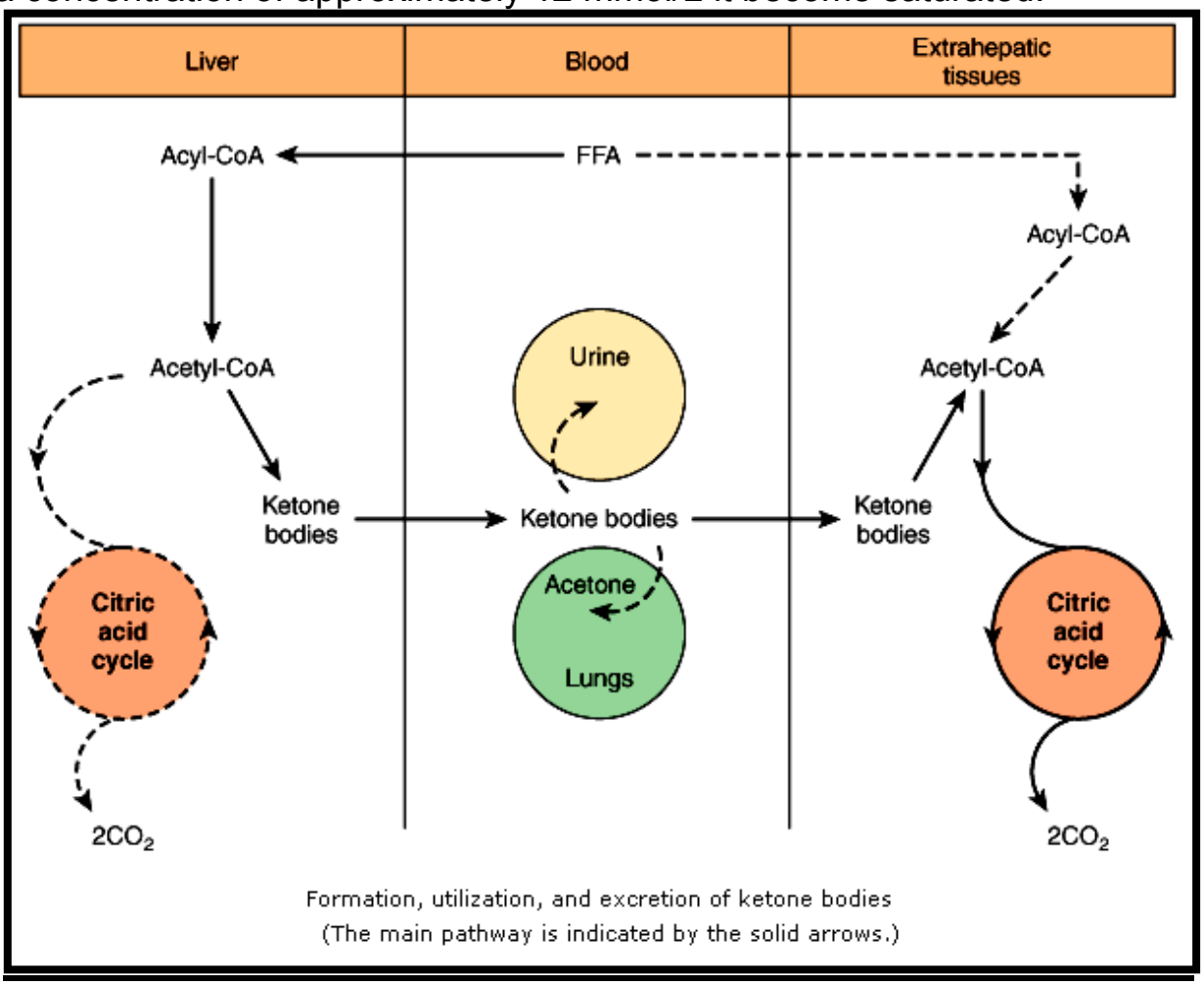
B- Fate outside the liver.

Outside the liver, ketone bodies are either:

A- Excreted through the lung (mainly acetone) & kidney.

B-Reform acetyl-CoA in the extrahepatic tissues (not by the reverse pathway of ketone bodies formation) to enter the citric acid cycle, therefore, ketone bodies serve as a fuel for extrahepatic tissues.

If the blood level of ketone bodies raised, this pathway is also increases until at a concentration of approximately 12 mmol/L it become saturated.



Formation, utilization, and excretion of ketone bodies
(The main pathway is indicated by the solid arrows.)

Ketonemia (Hyperketonemia)

Ketonemia is the presence of excess ketone bodies in the blood, in most cases it is due to increased production of ketone bodies by the liver rather than to a deficiency in their utilization by extrahepatic tissues. Acetoacetate & 3-hydroxybutyrate are readily reform acetyl-CoA while acetone is difficult to do so & to a large extent is volatilized in the lungs.

Regulation of Ketogenesis

Ketogenesis is regulated mainly by nutritional status as follow:

After uptake of free fatty acids by liver, they are either:

A- β-oxidized to form acetyl-Co A that enter citric acid cycle & the excess of acetyl-Co A forms the ketone bodies.

B- Esterified to form triacylglycerol & phospholipid.

There is regulation of entry of fatty acids into the oxidative pathway by **carnitine palmitoyltransferase-I** (CPT-I). CPT-I activity is affected by nutritional status as follow:

A- CPT-I activity is low in well fed state, leading to depression of β-oxidation & so ketogenesis. Therefore, most of fatty acids are esterified to form triacylglycerol & phospholipid.

B- CPT-I activity is high in starvation, allowing β-oxidation to increase & as the level of serum free fatty acids is also raised in starvation, therefore, more acetyl-Co A is converted to ketone bodies.

Clinical Aspects of Ketogenesis

Ketoacidosis

Ketoacidosis results from prolonged ketosis.

Higher than normal quantities of ketone bodies present in the blood and/or urine constitute **ketonemia** (hyperketonemia) and/or **ketonuria** respectively. The overall condition is called **ketosis.** Ketosis occurs in the following conditions:

1- Starvation.

2- Pathologic states as found in:

A- Diabetes mellitus due to:

i- Reduction of glucose utilization for energy production.

ii- Excess lipolysis due to absence or defect of insulin.

B- Hypoglycemia due to:

i- Reduction of glucose concentration available for energy production.

ii- Excess lipolysis due to reduction of insulin.

3- Nonpathologic forms of ketosis are found under conditions of high-fat feeding & after severe exercise.

Acetoacetate & 3-hydroxybutyrate are both moderately strong acids & their continual excretion in excess quantity (ketosis) cause **ketoacidosis,** this may be fatal especially in uncontrolled diabetes mellitus.

De Novo Synthesis of Fatty Acids

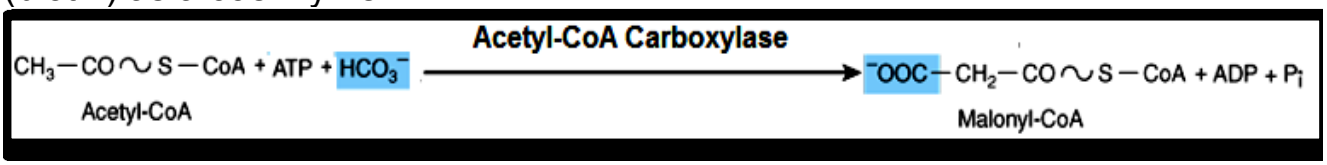
Fatty acids are synthesized by an extramitochondrial system which is responsible for the complete synthesis of palmitate from acetyl-CoA in the cytosol. In human excess glucose is the primary substrate for de novo synthesis.

Lipogenesis occurs in liver, kidney, brain, lung, mammary gland & adipose tissue. Its cofactor requirements include NADPH, ATP, Mn^{2+}, biotin & HCO_3^-.

Lipogenesis occur through the following steps:

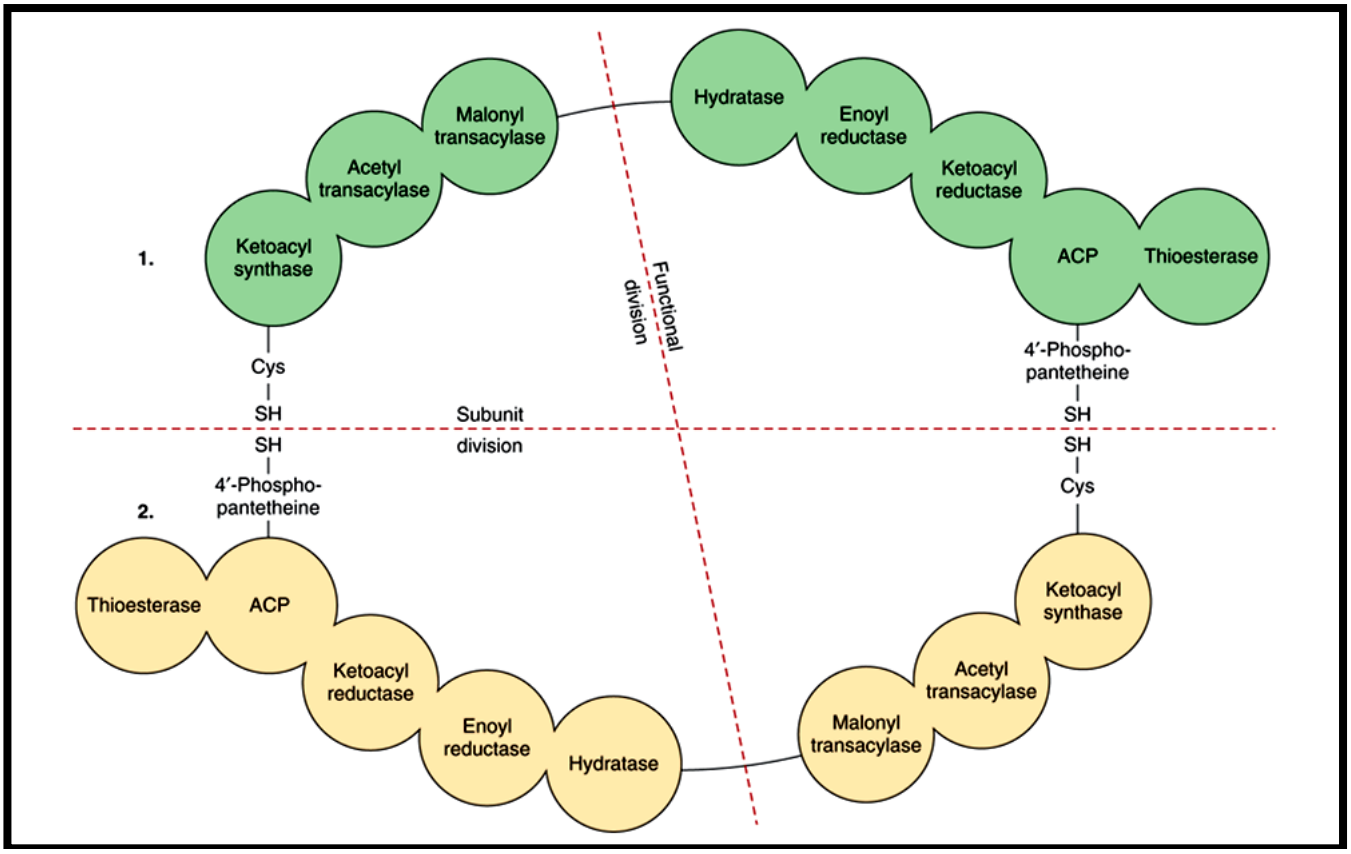
Step I (Production of Malonyl-CoA):

Production of Malonyl-CoA is the initial & controlling (rate limiting) step in fatty acid synthesis. Bicarbonate as a source of CO_2 is required for the carboxylation of acetyl-CoA to form malonyl-CoA in the presence of ATP, this reaction is catalyzed by **acetyl-CoA carboxylase** enzyme which requires vitamin B_7 (biotin) as a coenzyme.



Step II (Fatty Acid Synthase Complex):

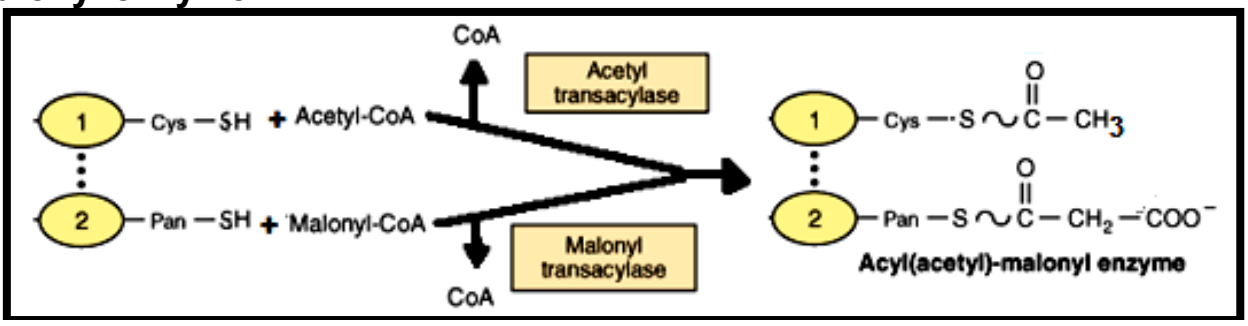
In human; fatty acid synthase system is a multienzyme polypeptide complex that incorporates acyl carrier protein (ACP) which contains vitamin B_5 (pantothenic acid**)** in the form of 4'-phosphopantetheine. The presence of one multienzyme functional unit in fatty acid synthase has the advantages of achieving its effect within the cell without the problem of permeability barriers & synthesis of all enzymes in the complex is coordinated since it is encoded by a single gene. In human; fatty acid synthase complex is a dimer comprising two identical monomers, each containing all seven enzymes of fatty acid synthase on one polypeptide chain. The —SH of 4'-phosphopantetheine of one monomer is in close proximity to the —SH of the cysteine residue of the other monomer.



Reactions catalyzed by fatty acid synthase complex occur through the following sequences:

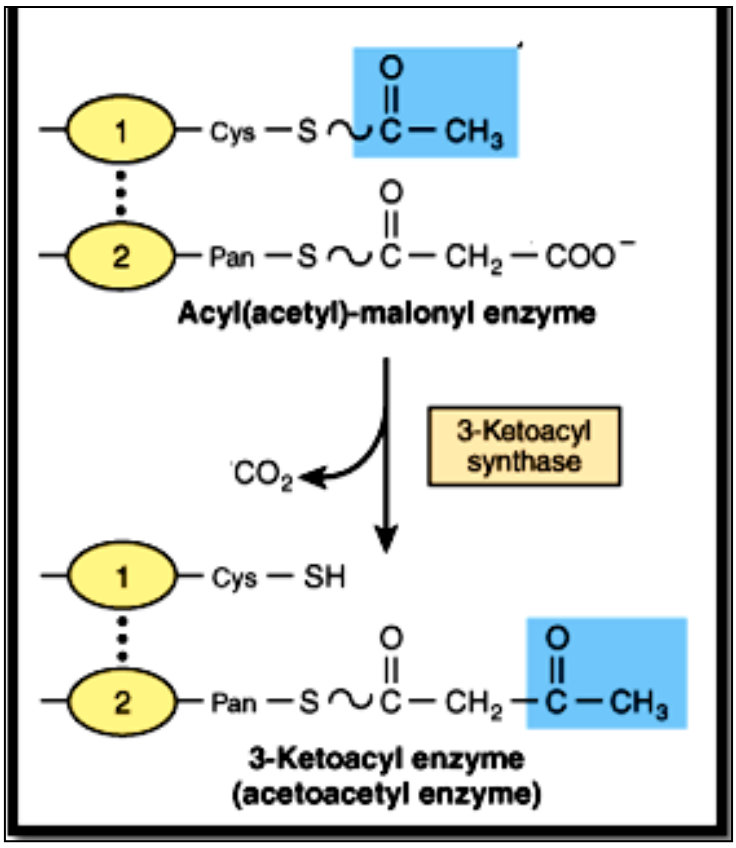
Reaction 1

Acetyl-CoA combines with a cysteine —SH group catalyzed by **acetyl transacylase** enzyme with loss of CoA. Malonyl-CoA combines with the adjacent —SH on the 4'-phosphopantetheine of the other monomer with loss of CoA catalyzed by **malonyl transacylase** enzyme to form **acetyl (acyl)-malonyl enzyme.**



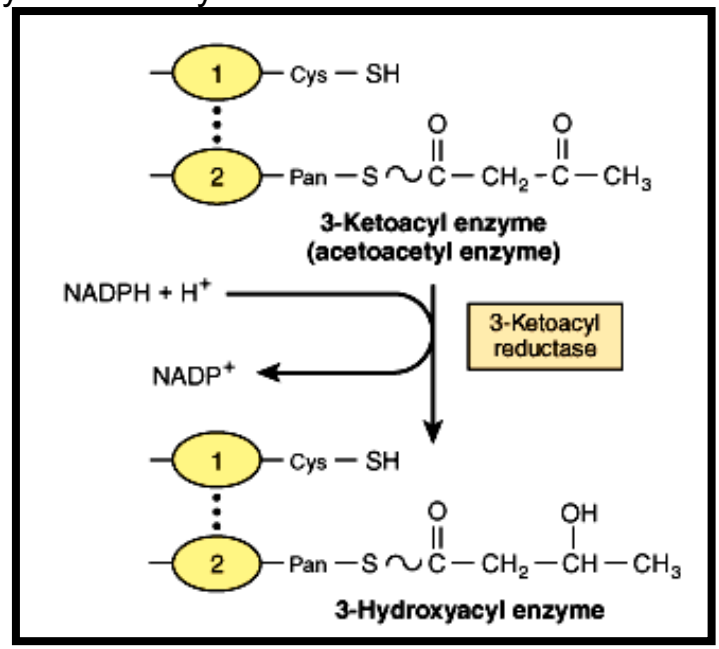
Reaction 2

The acetyl group of acetyl residue of the acetyl(acyl)-malonyl enzyme attacks the methylene group of the malonyl residue, catalyzed by **3-ketoacyl synthase** enzyme with CO_2 liberation, forming **3-ketoacyl enzyme (acetoacetyl enzyme)** freeing the cysteine —SH group.



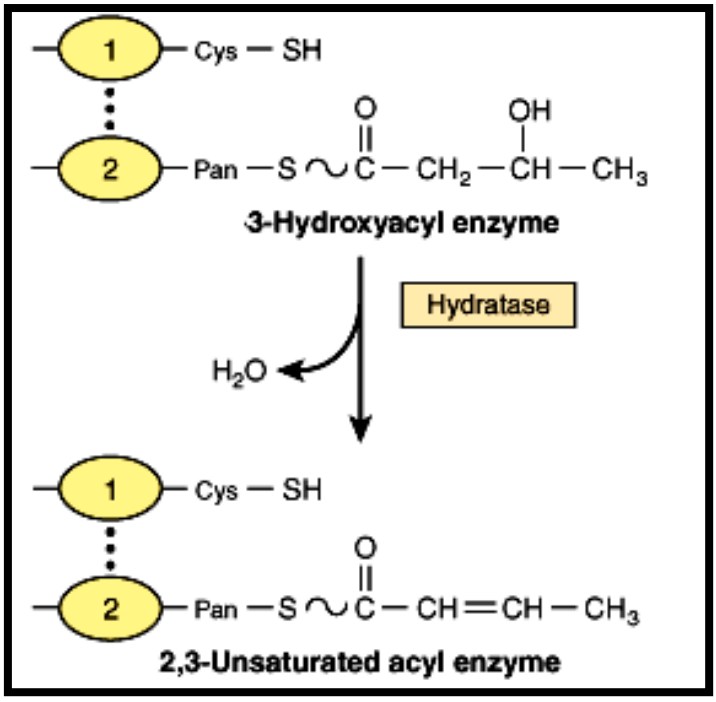
Reaction 3

Reduction of 3-ketoacyl enzyme (acetoacetyl enzyme) is catalyzed by **3-ketoacyl reductase** enzyme in the presence of NADPH + H^+ that converted into NADP forming **3-Hydroxyacyl enzyme**. The main source of NADPH is from pentose phosphate pathway that also occurs in the cytoplasm, therefore, no barrier with fatty acids biosynthesis.



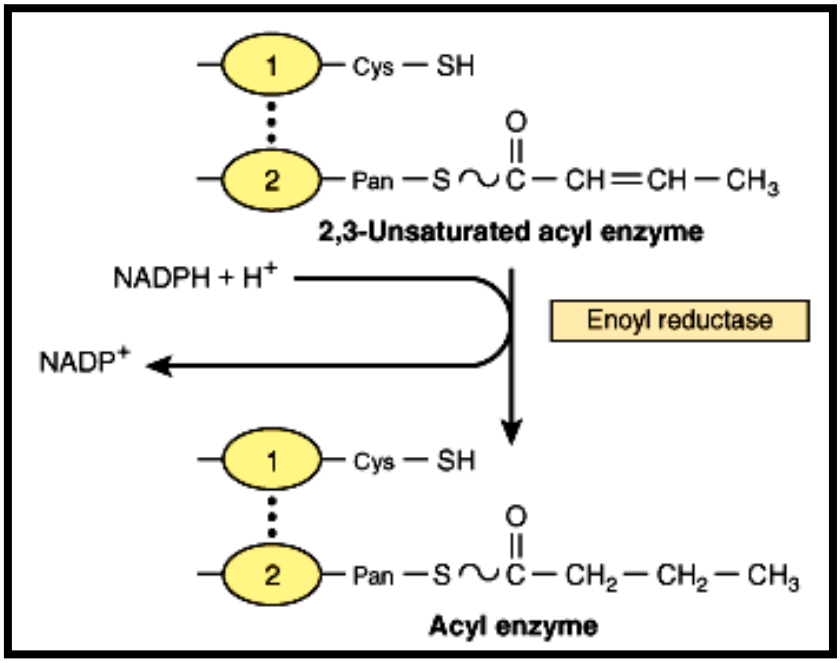
Reaction 4

Dehydration of 3-Hydroxyacyl enzyme catalyzed by **hydratase** enzyme forming **2,3-unsaturated acyl enzyme**.



Reaction 5

Reduction of 2,3-unsaturated acyl enzyme is catalyzed by **enoyl reductase** enzyme forming **acyl enzyme** in the presence of NADPH + H^+ that converted into NADP. The main source of NADPH is from pentose phosphate pathway.



The sequence of reactions 2-5 is repeated 6 more times as mentioned before except that in the reaction 2, the acetyl group of the malonyl residue (not the acetyl group of acetyl residue) attacks the acyl enzyme residue, therefore, with each turn of reactions 2-5 there are 2 more carbon atoms are added to acyl enzyme so that to form a saturated 16-carbon acyl radical (palmityl) the reactions 2-5 should be repeated 6 more times.

Reaction 6

Palmitate is liberated from the enzyme complex by the activity of a seventh enzyme in the fatty acid synthase complex called **thioesterase (deacylase).**
The equation for the overall synthesis of palmitate from acetyl-CoA & malonyl-CoA is the following:

$$CH_3CO\ S\ CoA + 7HOOC\ CH\ CO\ S\ CoA + 14NADPH + 14H^+ \longrightarrow CH^3(CH_2)^{14}\ COOH + 7CO_2 + 8CoA\ SH + 14NADP^+$$

Note: Acetyl-CoA is formed from glucose via the oxidation of pyruvate within the mitochondria. However, it does not diffuse readily into the extramitochondrial cytosol where de-novo synthesis occurs. Citrate is formed after condensation of acetyl-CoA with oxaloacetate in the citric acid cycle within mitochondria which is translocated into the extramitochondrial compartment where in the presence of CoA & ATP; it undergoes cleavage to acetyl-CoA & oxaloacetate catalyzed by **ATP-citrate lyase** enzyme which increases in its activity in the well-fed state. The acetyl-CoA is then available for malonyl-CoA formation & synthesis to palmitate.