Dr. Mustafa Mohammed & Dr. Marowa Hashim

Metabolism of lipids

In both animals and plants, the excessive fat is stored in various parts of the body in large quantities in the form of neutralized and insoluble triglycerides (fat). It decomposes and quickly destroys to provide energy necessary for the cell.

Fat has an important role in nutrition, because it has a high energy value (9.3 kilocalories per gram)

Oxidation (catabolism) of fatty acid

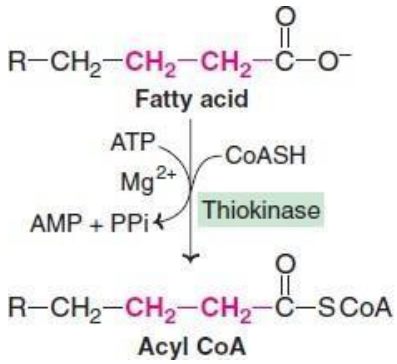
The main path to catabolize fatty acid is β-oxidation. β-Oxidation may be defined as the **oxidation of fatty acids on the β-carbon atom**. This results in the sequential removal of a two carbon fragment from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and $FADH_2$. β-oxidation of fatty acid are performed within mitochondrial matrix which contains all the enzymes and coenzymes necessary for catabolism.

The β-oxidation of fatty acids involves three stages

I. Activation of fatty acids occurring in the cytosol

Fatty acids are found in the cytoplasm in their inactive raw form, so they must be activated in the cytoplasm before they enter the mitochondrial matrix. This is the only step in the complete degradation of a fatty acid that requires energy from ATP. In the presence of ATP and coenzyme A, the enzyme acyl-CoA synthetase (thiokinase) catalyzes the conversion of a fatty acid (or FFA) to an "active fatty acid" or acyl-CoA, using ATP and forming AMP and PPi.

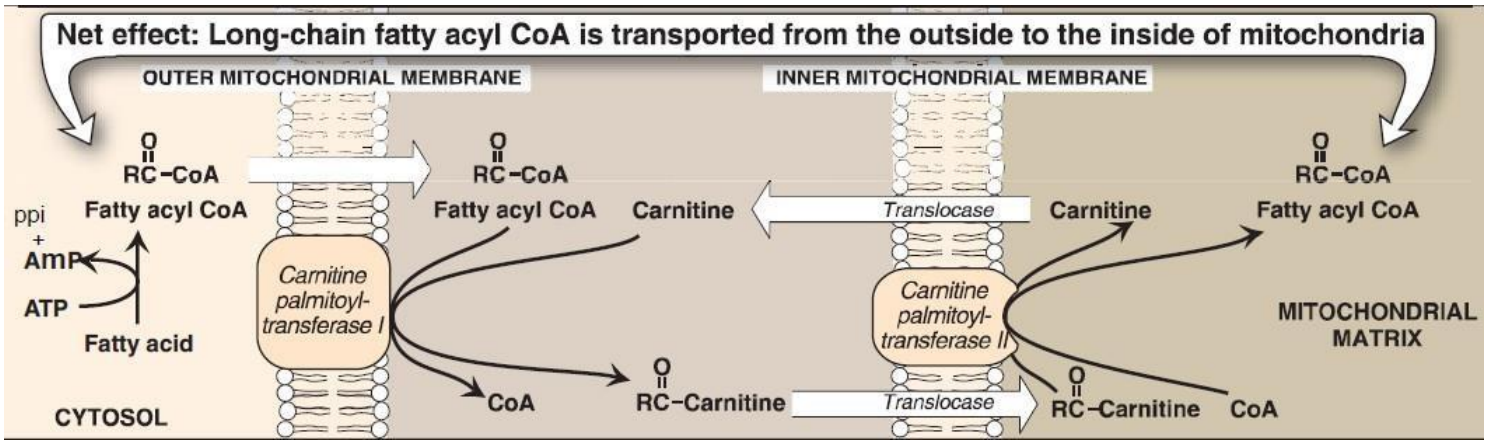
$$\text{Fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{fatty acyl CoA} + \text{AMP} + \text{PP}_i$$



II. Transport of long-chain fatty acids into mitochondria

The inner mitochondrial membrane is impermeable to fatty acids. A specialized carnitine carrier system (**carnitine shuttle**) operates to transport activated fatty acids from cytosol to the mitochondria. This occurs in **four** steps (figure 1)

1. Acyl group of acyl CoA is transferred to **carnitine** (β-hydroxy γ-trimethyl aminobutyrate), catalyzed by carnitine acyltransferase I (present on the outer surface of inner mitochondrial membrane).
2. The acyl-carnitine is transported across the membrane to mitochondrial matrix by a specific carrier protein.
3. Carnitine acyl transferase II (found on the inner surface of inner mitochondrial membrane) converts acyl-carnitine to acyl CoA.
4. The carnitine released returns to cytosol for reuse.



[(figure 1) carnitine shuttle for transport of activated fatty acid (acyl CoA) into mitochondria]

III. β-Oxidation proper in the mitochondrial matrix.

Each cycle of β-oxidation, liberating a two carbon unit-acetyl CoA, occurs in a sequence of four reactions (**Fig.2**).

1. **Oxidation :** Acyl CoA undergoes dehydrogenation by an FAD-dependent flavoenzyme, acyl CoA dehydrogenase. A double bond is formed between β and α carbons (i.e., 2 and 3 carbons).

2. **Hydration :** Enoyl CoA hydratase brings about the hydration of the double bond to form β-hydroxyacyl CoA.

3. **Oxidation :** β-Hydroxyacyl CoA dehydrogenase catalyses the second oxidation and generates NADH. The product formed is β-ketoacyl CoA.

4. **Cleavage :** The final reaction in β-oxidation is the liberation of a 2 carbon fragment, acetyl CoA from acyl CoA. This occurs by a thiolytic cleavage catalysed by β-**ketoacyl CoA thiolase** (or simply thiolase).

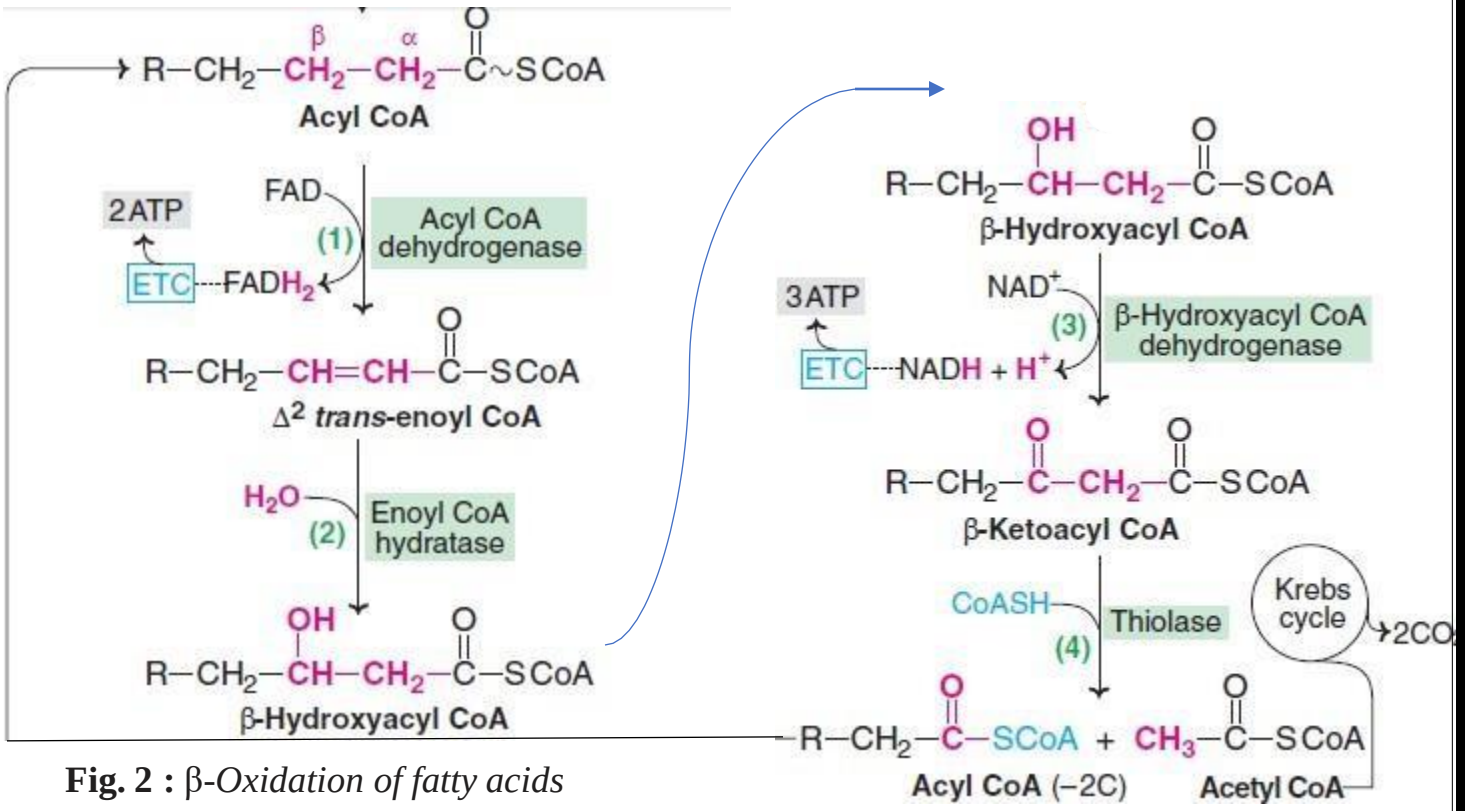
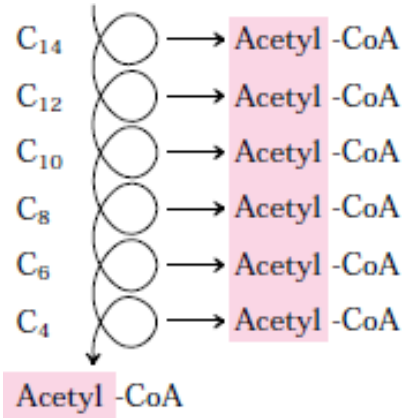


Fig. 2 : β-*Oxidation of fatty acids*

The new acyl CoA, containing two carbons less than the original, reenters the β-oxidation cycle. The process continues till the fatty acid is completely oxidized.



The overall reaction for each cycle of β-oxidation

C_n Acyl CoA + FAD + NAD^+ + H_2O + CoASH ⟶ $C_{(n-2)}$ Acyl CoA + Acetyl CoA + $FADH_2$ + NADH + H^+.

Energy yield from fatty acid oxidation

The energy yield from the β-oxidation pathway is high. For example, the oxidation of a molecule of palmitoyl CoA to CO2 and H2O produces 8 acetyl CoA, 7 NADH, and 7 FADH2, from which 131 ATP can be generated; however, activation of the fatty acid requires 2 ATP. Thus, the net yield from palmitate is 129 ATP (Figure 3)

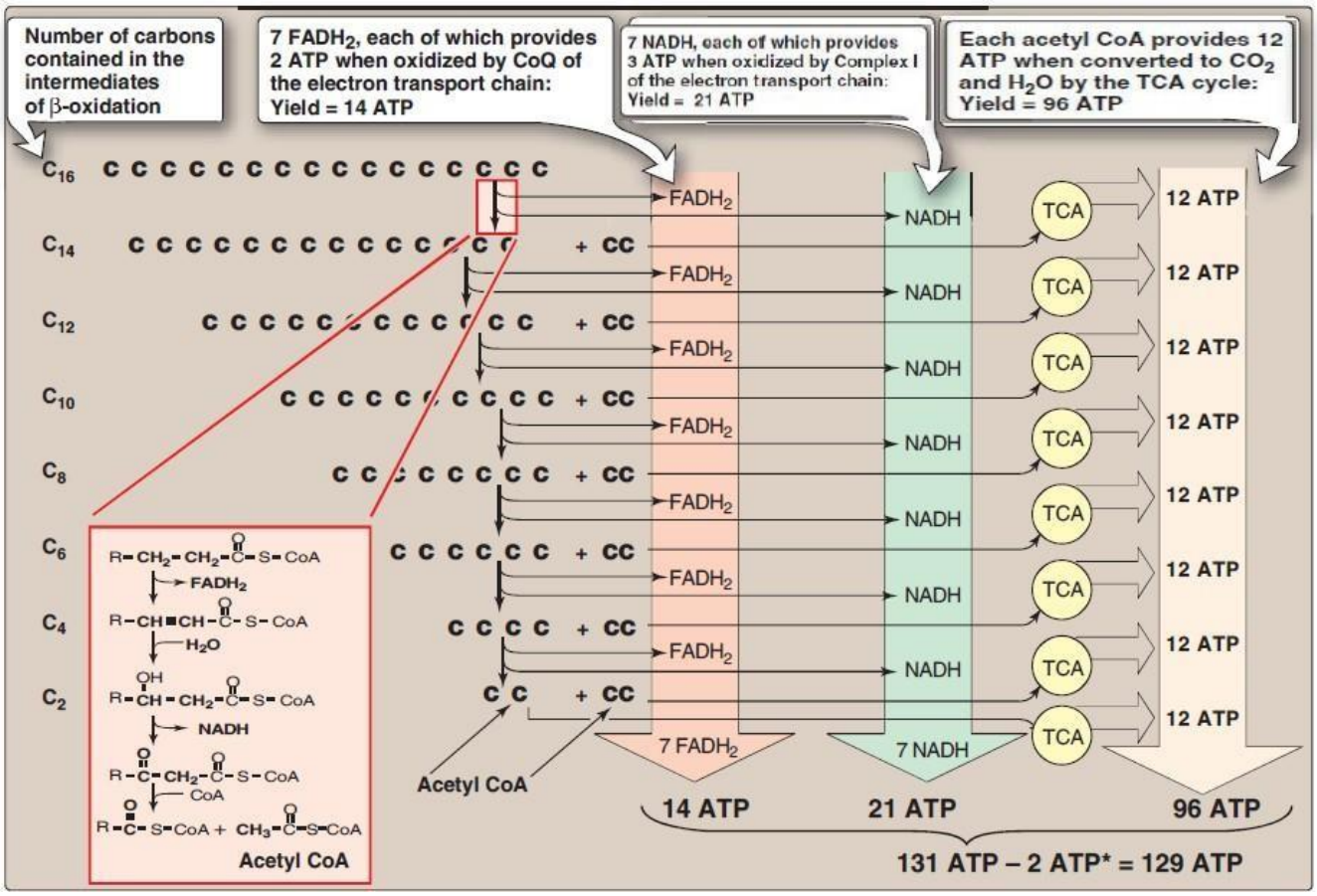


Figure (3) Summary of the energy yield from the oxidation of palmitoyl CoA (16 carbons). CC = acetyl CoA. *Activation of palmitate to palmitoyl CoA requires the equivalent of 2 ATP.

Energy calculation:

Number of round = number of carbon atom of fatty acid / 2 = 16/2= 8 round

8 rounds give 7 $FADH_2$ = 7 *2 = 14 ATP

8 rounds give 7 NADH = 7 *3 = 21 ATP

8 rounds give 8 acetyl CoA (8 TCA cycle)= 8 * 12= 96 ATP

Activation step of fatty acid consumed two ATP = - 2 ATP

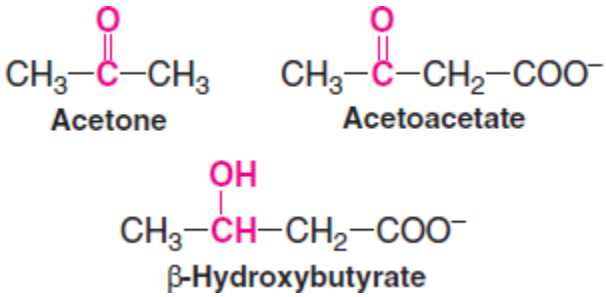
Overall net energy = 14 + 21+ 96 – 2 = 129 ATP

Ketone bodies (an alternate fuel for cells)

In humans and most other mammals, acetyl-CoA formed in the liver during **oxidation of fatty acids** can either enter the citric acid cycle or undergo conversion to the "ketone bodies,".

The compounds namely **acetone, acetoacetate** and β-**hydroxybutyrate** (or 3-hydroxybutyrate) are known as **ketone bodies** Only the first two are true ketones while β- hydroxybutyrate does not possess a keto (C=O) group.

Ketone bodies are water-soluble and **energy yielding**. Acetone, however, is an exception, since it cannot be metabolized.



Ketone bodies are formed in the mitochondrial matrix in the liver and are released from the liver to the blood, generating what is called **ketosis**, then they are transported through the blood to the surrounding tissues such as the brain, heart, kidney and muscles, where they are oxidized by TCA. ketone bodies reach the highest levels in the event of extreme hunger or eating large quantities of fat or diabetes.

Ketone bodies are important sources of energy for the peripheral tissues because:

1) they are soluble in aqueous solution and, therefore, do not need to be incorporated into lipoproteins or carried by albumin as do the other lipids.
2) serve as important sources of energy for the **peripheral tissues** such as skeletal muscle, cardiac muscle, renal cortex etc. Also during prolonged **starvation**,

ketone bodies are the major **fuel source for the brain** and other parts of central nervous system.

3) The production of ketone bodies and their utilization become more benefit when glucose is in short supply to the tissues, as observed in **starvation**, and **diabetes mellitus**.

Synthesis of ketone bodies by the liver (Ketogenesis)

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. **Ketogenesis occurs through the following reactions** (**Fig.4**).

1. Two moles of acetyl CoA condense to form acetoacetyl CoA. This reaction is catalysed by thiolase, an enzyme involved in the final step of β-oxidation. Hence, acetoacetate synthesis is appropriately regarded as the reversal of thiolase reaction of fatty acid oxidation.

2. Acetoacetyl CoA combines with another molecule of acetyl CoA to produce β-hydroxy β-methyl glutaryl CoA (HMG CoA). **HMG CoA synthase**, catalysing this reaction, **regulates the synthesis of ketone bodies**.

3. HMG CoA lyase cleaves HMG CoA to produce acetoacetate and acetyl CoA.

4. Acetoacetate can undergo spontaneous decarboxylation to form acetone.

5. Acetoacetate can be reduced by a dehydrogenease to β-hydroxybutyrate.

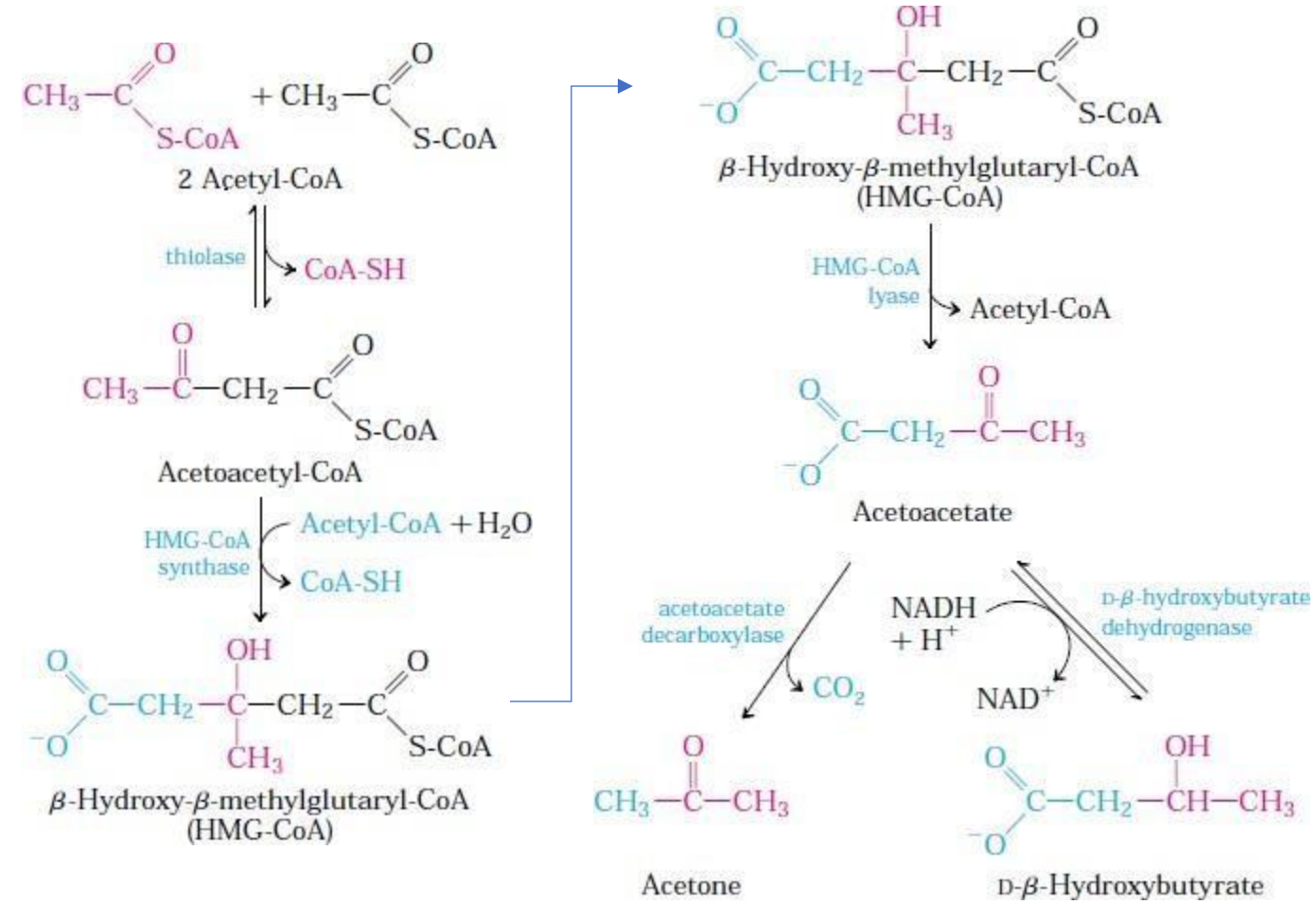


Fig (4): Synthesis of ketone bodies