Beta oxidation of fatty acids

The best source of energy for eukaryotic organisms are fats.
Glucose produces 6.3 molecules of ATP per carbon while saturated fatty acids produce 8.1 ATP per carbon.
The complete oxidation of fats also yields enormous amounts of water for those organisms that do not have adequate access to drinkable water. Camels and killer whales are good example of that; they obtain their water requirements from the complete oxidation of fats.
Fatty acid degradation takes place within the mitochondria.
In order to enter the mitochondria the assistance of two carrier proteins is required for fatty acids, Carnitine acyltransferase I and II.
There are four distinct stages in the oxidation of fatty acids.
It is interesting to note the similarities between the four steps of beta-oxidation and the later four steps of TCA cycle.

The Entry into Beta-oxidation

Most fats stored in eukaryotic organisms are stored as triglycerides.
In order to enter into beta-oxidation, bonds with glycerol must be hydrolysed usually with the use of a Lipase. The end result of these broken bonds are a glycerol molecule and three fatty acids in the case of triglycerides. Other lipids can be degraded as well.

Activation

Once the triglycerides are broken down into glycerol and fatty acids, the latter must be activated before they can enter into the mitochondria and proceed on with beta-oxidation. This is done by Acyl-CoA synthetase (FACS) to yield fatty acyl-CoA.
La trasformazione avviene in due tappe, richiede il consumo di una molecola di ATP ed è notevolmente spostata a destra grazie all'idrolisi del pirofosfato prodotto:

1) R-COOH + ATP → R-CO-AMP + PPi
2) R-CO-AMP + CoASH → R-CO-S-CoA + AMP

Come abbiamo visto, il CoA lega anche intermedi di altre vie metaboliche (succinil-CoA, maloil-CoA ecc.) e si può considerare un attivatore generale degli acidi carbossilici. Ricordiamo che il legame che si forma in questi composti è un legame tioestere con una elevata energia.
After the fatty acid has been acylated, it is ready to enter into the mitochondria.
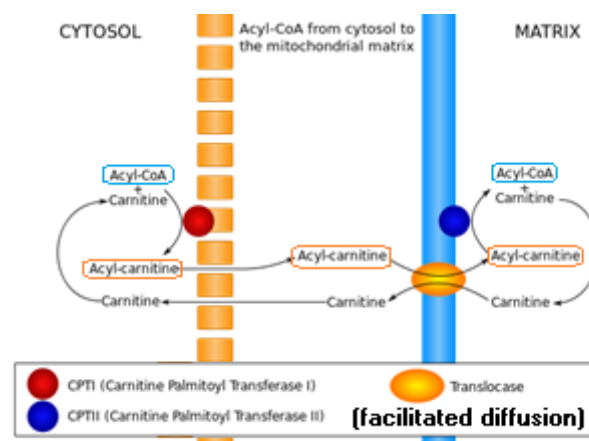
There are two carrier proteins (Carnitine acyltransferase I and II), one located on the outer membrane and one on the inner membrane of the mitochondria. Both are required to entry the Acyl-CoA into the mitochondria.

Carnitine palmitoyltransferase 1 (CPT1) converts the long chain acyl-CoA to long chain acylcarnitine and allows the fatty acid moiety to be transported across the inner mitochondrial membrane via carnitine translocase (CAT)which exchanges long chain acylcarnitine for carnitine. An inner mitochondrial membrane enzyme, CPT2, then converts the long chain acylcarnitine back to long chain acyl-CoA.
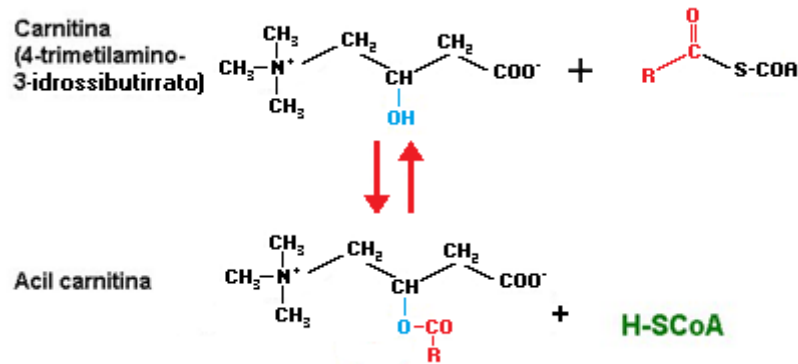
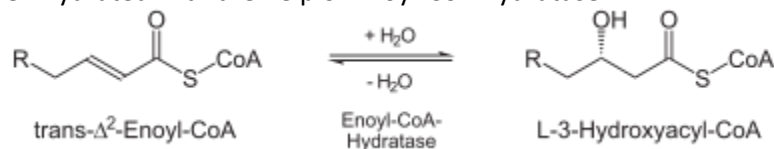Once inside the mitochondria the fatty acyl-CoA can begin the beta-oxidation pathway.

Oxidation

A fatty acyl-CoA is oxidized by Acyl-CoA dehydrogenase to yield a trans alkene. This is done with the aid of a [FAD] prosthetic group.

## *Hydration*

The trans alkene is then hydrated with the help of Enoyl-CoA hydratase

Oxidation

The alcohol of the hydroxyacly-CoA is then <u>oxidized</u> by NAD^+ to a carbonyl with the help of Hydroxyacyl-CoA dehydrogenase. NAD^+ is used to oxidize the alcohol rather than [FAD] because a higher difference of reduction potential is needed to form a double bond C=O than a double bond C=C.
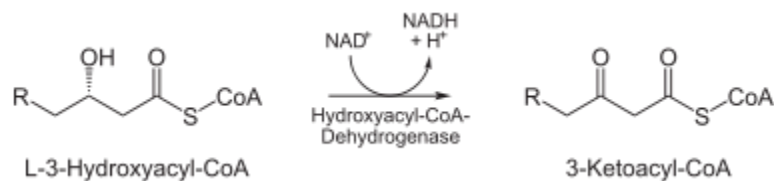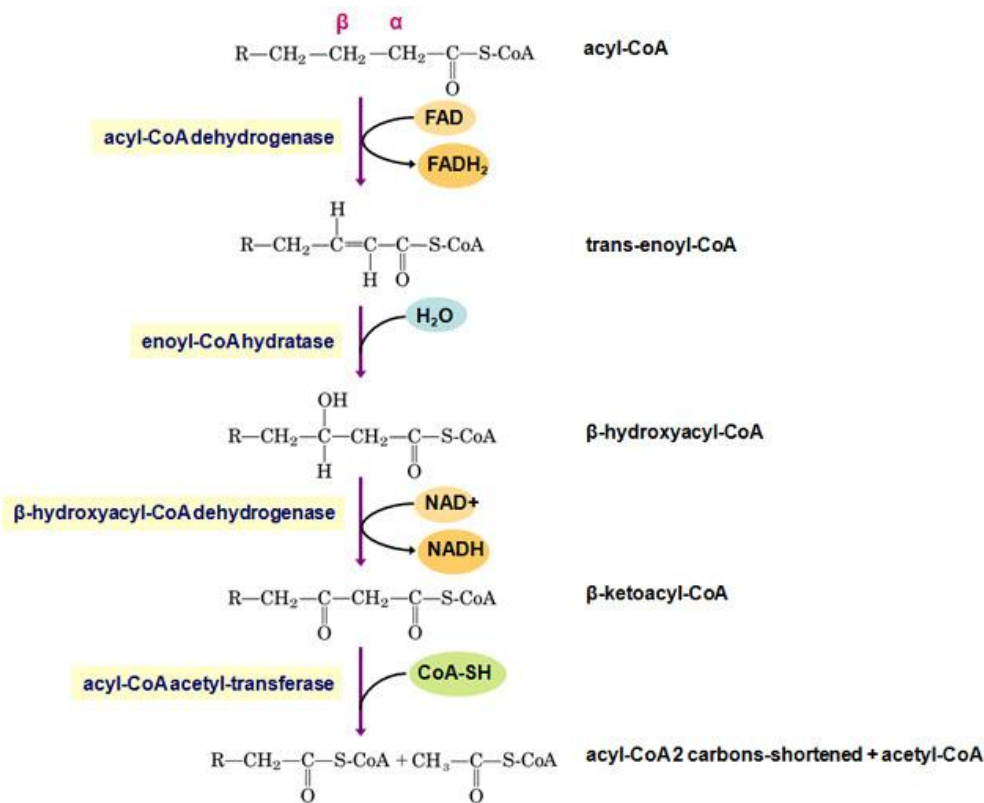

Cleavage

Acetyl-CoA is finally cleaved off with the help of Thiolase to yield an Acyl-CoA that is two carbons shorter than before. The cleaved acetyl-CoA can easily enter the TCA and ETC because it is already within the mitochondria.

3-Ketoacyl-CoA → Acyl-CoA + Acetyl-CoA
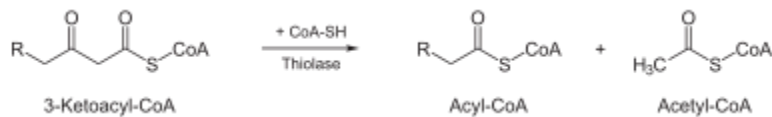
Summarizing

Odd carbon atoms fatty acids

Fatty acids with an odd number of carbon atoms are common in vegetal.
They follow the beta oxidation pathway too. All the steps are the same until the last one in which, instead of two molecules of acetyl-CoA, one molecule of acetyl-CoA and one of propionyl-CoA are produced.
The latter is carboxylated to methyl-malonyl-CoA first and after isomerized to succinyl-CoA by an isomerase, which uses vitamin B as coenzyme.

Unsaturated fatty acids

Unsaturated fatty acids have one or more double bonds between carbon atoms. The chain can occur in a *cis* or *trans* configuration. Cis-configuration are more common by far.
A *cis* configuration means that the two hydrogen atoms adjacent to the double bond stick out on the same side of the chain. The rigidity of the double bond freezes its conformation and causes the chain to bend and restricts the conformational freedom of the fatty acid.
The more double bonds the chain has in the *cis* configuration, the less flexibility it has. When a chain has many *cis* bonds, it becomes quite curved. For example, oleic acid, with one double bond, has a "kink" in it, whereas linoleic acid, with two double bonds, has a more pronounced bend. Linolenic acid, with three double bonds, favors a hooked shape. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer, or triglycerides in lipid droplets, cis bonds limit the ability of fatty acids to be closely packed, and therefore can affect the melting temperature of the membrane or of the fat.

In most naturally occurring unsaturated fatty acids (as the ones quoted above), the first double bond is Δ9 and any other extra double bond is three carbon atoms after the first.
In the cells, unsaturated fatty acids are reduced and isomerized to beta unsaturated to enoyl-CoA and join beta-oxidation in the first step.
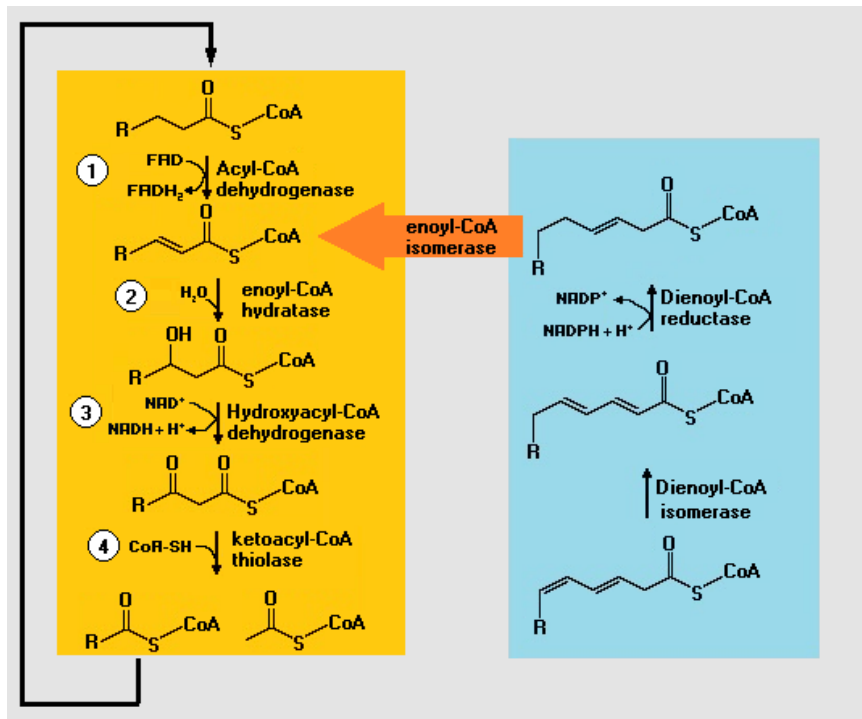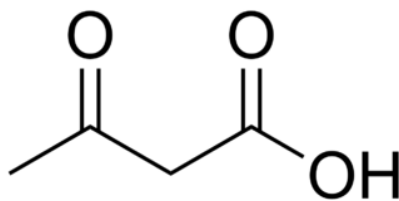

Ketone bodies

Ketone bodies are three water-soluble molecules that are produced by the liver from fatty acids during periods of low food intake (fasting) or carbohydrate restriction for cells of the body to use as energy instead of glucose.
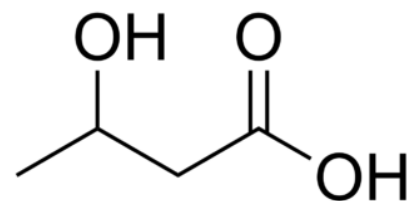Although termed "bodies", they are molecules, not particles.
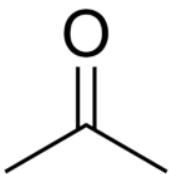
| Acetone | Acetoacetic acid | Beta hydroxy butirric acid |

Two of the three are used as a source of energy in the heart and brain while the third (acetone) is a degradation breakdown product of acetoacetic acid.
Ketone bodies are picked up by cells and converted back into acetyl-CoA, which then enters the citric acid cycle and is oxidized in the mitochondria for energy.
In the brain, ketone bodies are also used to make acetyl-CoA into long chain fatty acids, which cannot pass through the blood-brain barrier.
The liver additionally produces glucose from non-carbohydrate sources other than fatty acids by gluconeogenesis during starvation. In the brain, ketone bodies are a vital source of energy during fasting or strenuous exercise.

Regulation of fatty acids metabolism

Ketone bodies are produced from acetyl-CoA (during the so-called ketogenesis) mainly in the mitochondrial matrix of hepatocytes (liver tissue) when carbohydrates are so scarce that energy must be obtained from breaking down fatty acids.
Because of the high level of acetyl CoA present in the cell:
- The pyruvate dehydrogenase complex is inhibited,
- Whereas pyruvate carboxylase becomes activated.

High levels of ATP and NADH inhibit the enzyme isocitrate dehydrogenase in the TCA cycle and, as a result, cause an increase in the concentration of malate (due to the equilibrium between itself and oxaloacetate). The malate then leaves the mitochondrion and undergoes gluconeogenesis.
The elevated level of NADH and ATP result from β-oxidation of fatty acids. Unable to be used in the citric acid cycle, the excess acetyl-CoA is therefore rerouted to ketogenesis. Such a state in humans is referred to as the fasted state.

Acetone is produced by spontaneous decarboxylation of acetoacetate, meaning this ketone body will break down if it is not used for energy and be removed as waste or converted to pyruvate.
This "use it or lose it" factor may contribute to the weight loss found in ketogenic diets.
Acetone cannot be converted back to acetyl-CoA, so it is excreted in the urine, or (as a consequence of its high vapor pressure) exhaled unless first converted to Pyruvate.
Acetone is responsible for the characteristic "Sweet & fruity" odor of the breath of persons in ketoacidosis.

Metabolism Summary