

Lecture: 26

OXIDATION OF FATTY ACIDS

Fatty acids obtained by hydrolysis of fats undergo different oxidative pathways designated as alpha (α), beta (β) and omega (ω) pathways.

α -oxidation

- ❖ α -Oxidation of fatty acids has been found in certain tissues especially in **brain tissue of mammals and plant systems**.
- ❖ It does not require CoA intermediates and no high-energy phosphates are generated.
- ❖ This type of oxidation results in the **removal of one carbon** at a time from the **carboxyl end of the fatty acid**.
- ❖ The physiological role of α -oxidation in plants is not yet fully established but it has been suggested that it may be **involved in the degradation of long chain fatty acids** as observed in many animal tissues.
- ❖ α -Oxidation is clearly the **main source of the odd-carbon fatty acids** and their derivatives that occur in some plant lipids.
- ❖ In this process, sequential removal of one carbon at a time from free fatty acids of chain length ranging from C₁₃ to C₁₈ occur.

ω -Oxidation

- ❖ ω -Oxidation is normally a very minor pathway brought about by **hydroxylase enzymes** involving **cytochrome P-450** in the **endoplasmic reticulum**.
- ❖ Fatty acids with oxygen function (alcoholic or carboxyl) at the methyl terminal end (ω -end) are formed by ω -oxidation and frequently occur as constituents of **cutin and suberin**.
- ❖ The requirements for the oxygenase-mediated conversion of a ω -methyl fatty acyl CoA into a ω -hydroxymethyl fatty acyl CoA are **molecular oxygen**, reduced pyridine nucleotide and **a non-heme iron protein** in higher plants.

β -Oxidation of fatty acids

In 1904, Franz Knoop made a critical contribution to the elucidation of the mechanism of fatty acid oxidation and demonstrated that most of the fatty acids are degraded by oxidation at the **β -carbon**.

- ❖ β -Oxidation of fatty acids takes place in **mitochondria**.

- ❖ Fatty acids are activated before they enter into mitochondria for oxidation.

Activation of fatty acids

- ❖ Fatty acids are converted into active intermediate in a reaction with **ATP and coenzyme A**.
- ❖ A **thioester linkage** between the carboxyl group of a fatty acid and the sulfhydryl group of coenzyme A is formed with the hydrolysis of ATP.
- ❖ This activation reaction takes place on the **outer mitochondrial membrane** catalysed by **acyl CoA synthetase**.
- ❖ Several **acyl CoA synthetases** each specific for fatty acids of different chain length are present in the membrane of mitochondria.

Penetration of long chain fatty acids into mitochondria

- ❖ Long chain acyl-CoA molecules do not readily get into the inner mitochondrial membrane and are carried across the inner membrane by conjugating with **carnitine** (β -hydroxy γ -trimethyl ammonium butyrate), a zwitterionic compound formed from lysine.
- ❖ Activation of lower fatty acids and their oxidation within the mitochondria occur independently of carnitine, but long-chain acyl CoA will become oxidised unless they form acylcarnitines.
- ❖ The acyl CoA combines with carnitine in the presence of **carnitine acyltransferase I**, which is bound to the outer mitochondrial membrane.
- ❖ **Acylcarnitine** is transported in, coupled with the transport out of one molecule of carnitine.
- ❖ The acylcarnitine then reacts with coenzyme A catalyzed by **carnitine palmitoyl transferase II**, located on the inside of the inner membrane.
- ❖ Acyl CoA is reformed in the mitochondrial matrix and carnitine is liberated.

Oxidation

A saturated acyl CoA is oxidised by a **recurring sequence of four reactions**

- ❖ Oxidation in presence of FAD, hydration, oxidation in presence of NAD^+ , and thiolysis by CoASH.
- ❖ In β -oxidation, **2 carbons are cleaved** at a time from acyl CoA molecules, starting from the carboxyl end.
- ❖ The chain is **broken** between the α -and β -carbon atoms.
- ❖ The two-carbon units formed are acetyl CoA.

i) The first reaction in β -oxidation of acyl CoA is the formation of *trans* Δ^2 - enoyl CoA or α , β -unsaturated acyl CoA in presence of acyl-CoA dehydrogenase and the coenzyme, FAD.

ii) The next step is the **hydration of the double bond** between C-2 and C-3 by enoyl CoA hydratase with the formation of β -hydroxy acyl CoA.

iii) In the third step, the β -hydroxy acyl CoA is **dehydrogenated** in the presence of **β -hydroxy acyl CoA dehydrogenase** and NAD^+ forming β -ketoacyl CoA.

iv) In the last step of β -oxidation, β -ketoacyl CoA reacts with coenzyme A in the presence of the enzyme, **thiolase**.

The products of this reaction are acetyl CoA and an acyl CoA containing **two carbons less than the original acyl CoA molecule** that underwent oxidation.

By the above steps of β -oxidation fatty acids are completely degraded to acetyl CoA units. The acetyl CoA formed from fatty acids can be oxidised to carbon dioxide and water via citric acid cycle.

Energetics of β oxidation

The energetics or the energy conserved in terms of ATP by oxidation of a molecule of palmitic acid is given below:

- ❖ Palmitic acid (16 carbons) undergoes β -oxidation forming eight molecules of acetyl CoA by undergoing **seven β -oxidation spirals**.
- ❖ When one cycle of β -oxidation takes place, one molecule of FADH_2 , one molecule of NADH and one molecule of acetyl CoA are produced.
- ❖ Electrons from these reducing equivalents (FADH_2 and NADH) are transported through the **respiratory chain in mitochondria** with simultaneous regeneration of high-energy phosphate bonds.
- ❖ Mitochondrial oxidation of FADH_2 eventually results in the net formation of about 1.5 ATP.
- ❖ Likewise, oxidation of electrons from NADH yields 2.5 molecules of ATP. Hence, a total of **four ATP molecules** are formed per cycle and **ten molecules of ATP** are formed through Krebs's cycle from each molecule of acetyl CoA.

8 Acetyl CoA through TCA cycle yield (8x10)	= 80 ATP
7 β -oxidation spiral reactions yield (7x4)	= 28 ATP

Total	108 ATP

ATP utilized in the initial step	= 2 ATP
Hence, complete oxidation of palmitic acid yields 106 ATP.	

Oxidation of monounsaturated fatty acids

❖ Oxidation of monounsaturated fatty acids follows many of the reactions of saturated fatty acids except the requirement of **two additional enzymes, an isomerase and a novel reductase.**

❖ Reactions of monounsaturated fatty acid are explained by considering the oxidation of a C-16 unsaturated fatty acid, palmitoleic acid, having a single double bond between C-9 and C-10 .

❖ Palmitoleic acid is activated and transported across the inner mitochondrial membrane in the same way as saturated fatty acids.

❖ Palmitoleoyl CoA undergoes three cycles of degradation as in β oxidation. But the *cis* Δ^3 decenoyl CoA formed after the third cycle does not serve as a substrate for acyl CoA dehydrogenase.

❖ The presence of a double bond between C-3 and C-4 prevents the formation of another double bond between C-2 and C-3.

❖ **An isomerase** converts the *cis* double bond into a *trans* double bond and shifts the position of double bond between C-2 and C-3.

❖ The subsequent or follow up reactions are those of the β oxidation pathway in which the *trans* Δ^2 decenoyl CoA is a regular substrate.

Oxidation of polyunsaturated fatty acids

The oxidation of a polyunsaturated fatty acid, linoleic acid, with *cis*- Δ^9 and *cis*- Δ^{12} double bonds, is considered.

❖ The *cis*- Δ^3 double bond formed after three rounds of β -oxidation is converted into a *trans* double bond by the **isomerase**.

❖ This permits one more round of β -oxidation.

- ❖ The acyl CoA produced by four rounds of β -oxidation of linoleic acid contains a *cis*- Δ^4 double bond, which undergoes dehydrogenation by **acyl CoA dehydrogenase** yielding *trans* Δ^2 , *cis*- Δ^4 dienoyl intermediate.
- ❖ This intermediate is not a substrate for the next enzyme in the β -oxidation pathway.
- ❖ This intermediate is converted into a ***trans* Δ^3 enoyl CoA** to the *trans* Δ^2 form, an intermediate generally found in β -oxidation pathway and results in complete oxidation of the fatty acid.