Fatty acids are formed by long hydrocarbon chain with terminal carboxyl group and highly insoluble in water. The oxidation of long-chain fatty acid to acetyl-CoA is a main energy forming pathway in animals, many protists and some bacteria. Fatty acid may be oxidized by i) α oxidation, ii) β-oxidation and ω (omega) oxidation of which the β oxidation is most common.

In 1904, Franz knoop first described the β-oxidation. β-oxidation is so named as the β carbon (third from the COOH group) of fatty acid is oxidized. This carbon is converted into -COOH group and the outer two carbon atoms are split-off. Thus a fatty acid with 2-carbon atom less is is formed that again undergo successive β-oxidation until a four carbon atom butyric acid is formed. The butyric acid is oxidized at β-position to form aceto acetic acid. For example, the 16 carbon Palmitic acid undergoes seven passes through the oxidative sequence, in each pass losing two carbons as acetyl CoA. At the end ~~two~~ of seven cycles the last two carbons remain as acetyl CoA. The overall result is the conversion of the 16 carbon chain of palmitate to eight two carbon acetyl groups of acetyl CoA molecules.

Fatty acids are oxidized in mitochondria. Several enzymes required for oxidation are present in the mitochondrial matrix. Primary step of β oxidation occurs in the cytoplasm while the final reactions are confined to the mitochondria. Thus, the β oxidation occurs in all cells having mitochondria (except mature R.B.C). However, this reaction predominent in liver and muscle cells.

β-oxidation of fatty acids can be described by the following steps -

a) Fatty acid activation:- Before β oxidation begins, each fatty acid is activated by fatty acid thiokinase or acyl CoA synthetase present on the outer mitochondrial membrane in presence of Coenzyme A and ATP. This reaction occurs in two steps. First, fatty acid reacts with ATP to form an acyl adenylate in which the COOH group of fatty acid is bounded to phosphoryl group of AMP. Secondly the -SH (sulfadryl) group of CoA attacks the enzyme bounded acyl adenylate to form acyl CoA + AMP.

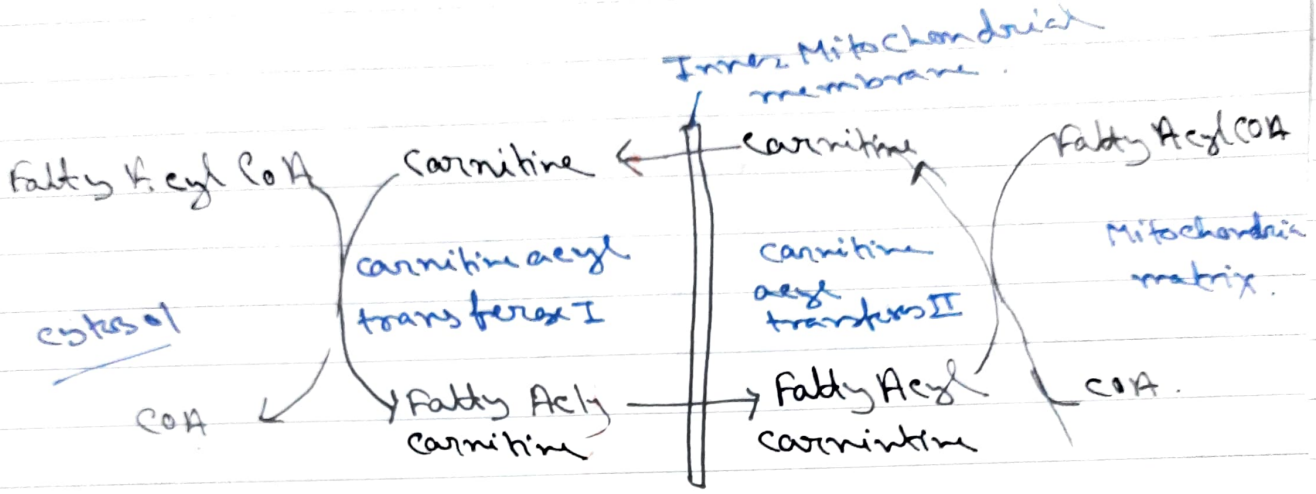
~~$R-C(=O)-OH + CoA + ATP + H_2O \rightarrow$ acyl CoA + AMP + 2Pi + 2H+.~~

Fatty acid + CoA + ATP ⟶ Fatty acyl-CoA + AMP + 2 Pi

b. Entry of activated fatty acid into Mitochondrion

Although fatty acid are activated for oxidation in the cytosol, they are oxidized in the mitochondrion. A long chain fatty ~~acyl~~ acyl-CoA cannot directly cross the inner mitochondrial membrane. They are transported by conjugating with Carnitin, a compound (β-hydroxy γ-trimethyl ammonium butyrate) formed from lysine. The acyl group is conjugated with the -OH group of carnitin to form acyl carnitine by Carnitin acyl transferase I. Acyl carnitine is moved across inner mitochondrial membrane by a translocase. The acyl group is transferred to CoA on matrix side by Carnitin acyl transferase II.

Carnitine is returned to outer membrane (to the cytosol side) by translocase in exchange for an incoming acyl Carnitine.

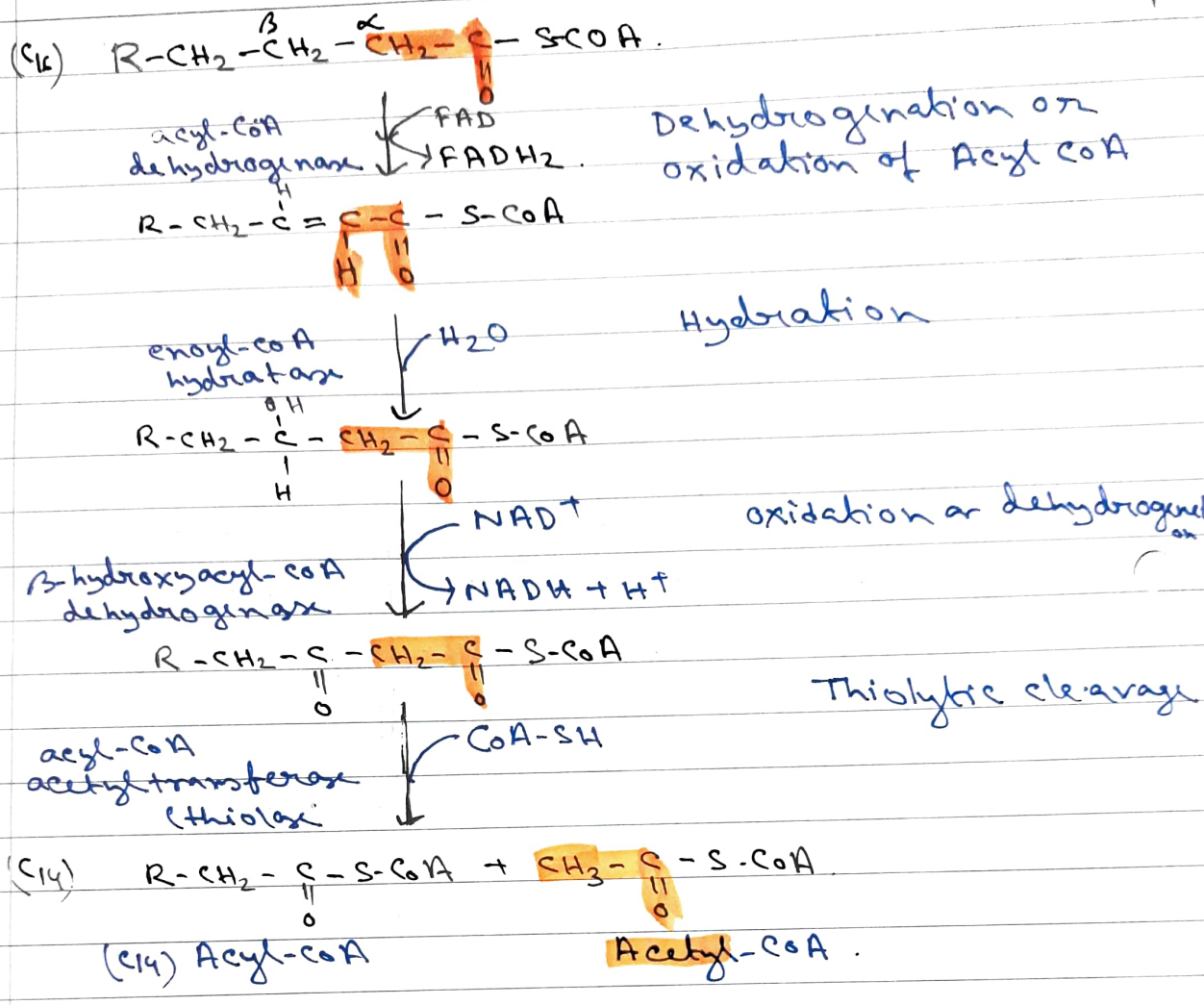


Transport of Fatty acids into mitochondria.

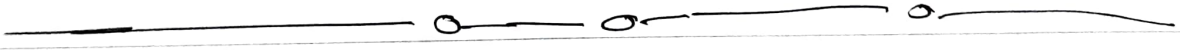
Inside the Mitochondrial Matrix (example (C16) Palmitic acid)

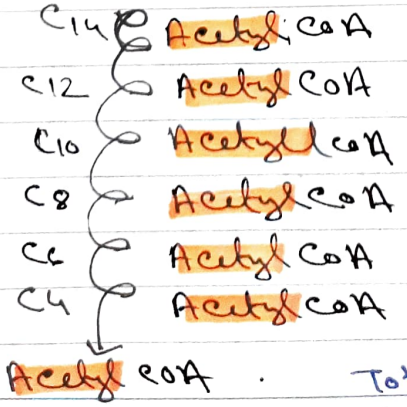
a) Dehydrogenation or oxidation of Acyl CoA – In this step, 2 hydrogen atom from the α and β carbon are removed from acyl CoA by the enzyme acyl CoA dehydrogenase and form α,β-unsaturated or Δ^2 unsaturated acyl CoA. The co enzyme for this reaction is FAD.

Like the kinases, at least three dehydrogenases are present, specific for different fatty acid chain. G1 is specific for oxidize C4–C8 fatty acid chain, Y1 & Y4 for C8–C12 and more numbered fatty acids.



→ Through this four-step sequence, one acetyl residue is removed in the form of acetyl CoA from the carboxyl end of fatty acid chain, this is example of Palmitate (C16)





Six more steps produce seven more molecules of acetyl-CoA. the seventh arising from the last two carbon atoms of 16 carbon chain.

Total- Eight molecules of acetyl CoA are formed.

Ref - Lehninger - Principles of Biochemistry.

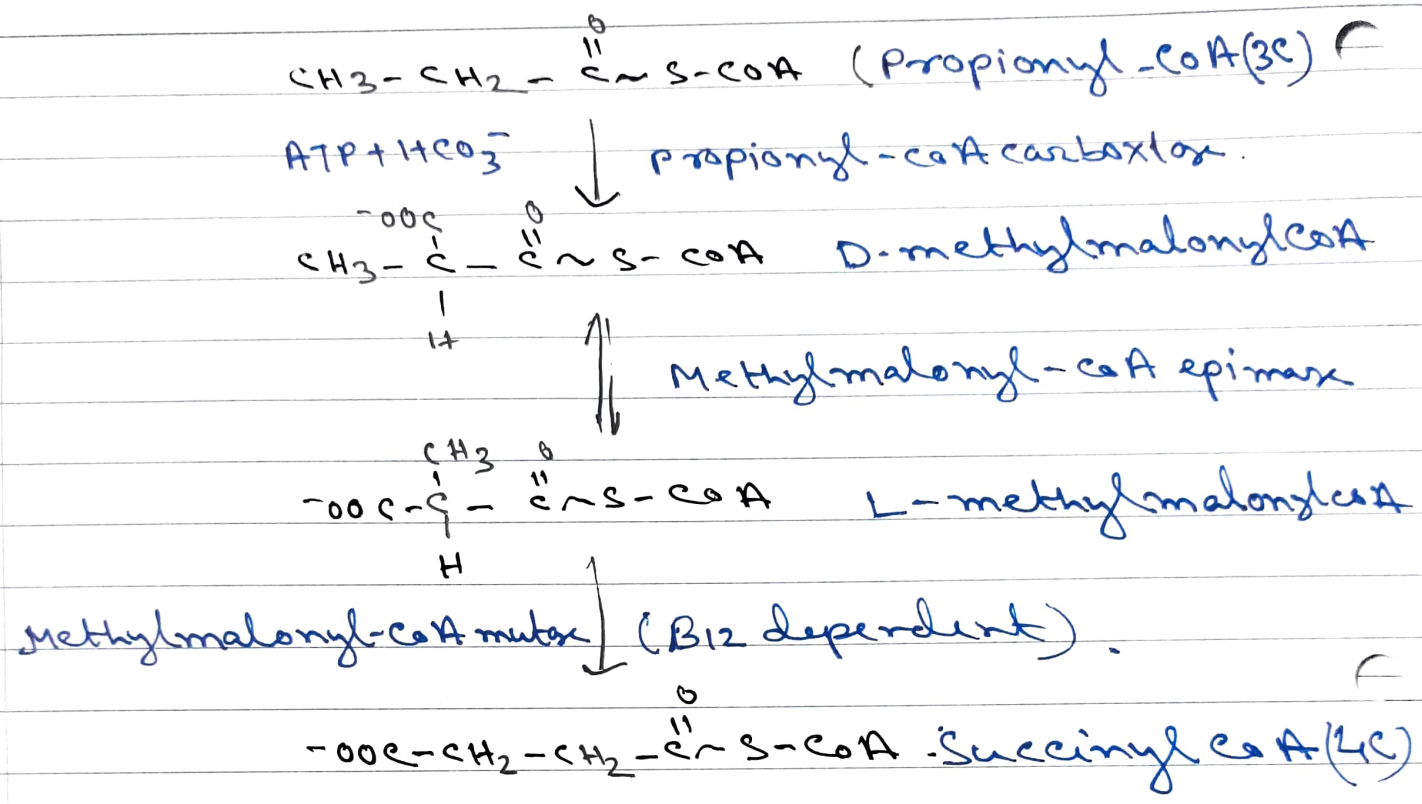
b. Hydration – Addition of H_2O is occured by the enzyme enoly enoyl hydrase or crotanase and β-hydroxy activated fatty acid is produced.

c. oxidation or dehydrogenation – Now Hydroxyacyl-CoA undergo second oxidation that converts the OH group at C-3 into a keto group by the enzyme L-3 hydroxyacyl CoA dehydrogenase. The NAD+ acts as an coenzyme and this reaction is very specific for L-isomer only.

d. Thiolytic cleavage – Now, β-ketoacyl CoA is cleaved at β carbon atom by thiolase or β-ketothiolase or acetyl CoA acyl transferase. in presence of CoA and thus acetyl CoA is produced leaving the original activated fatty acid by 2C.
The newly formed acyl CoA re enters into β-oxidation in the mitochondrial matrix again again until it is degraded completely to acetyl CoA.
Acetyl CoA is finally oxidized to CO_2 and water by citric acid cycle.

Fatty acid with odd-number of carbon atom are oxidized until a 3-carbon propionyl CoA is produced that is converted to ~~succi~~ Succinyl CoA, a component of citric acid cycle.
Branched chain fatty acids is splitted into acetyl CoA and propionyl CoA by oxidation.

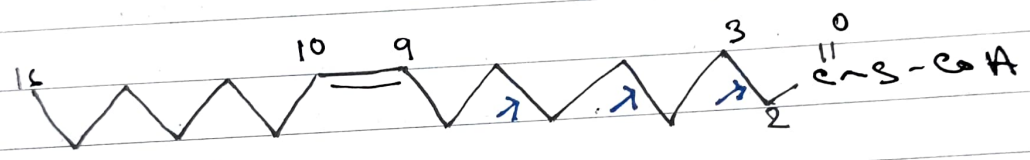
P-L



Odd numbered fatty acid yield propionyl CoA, a three carbon compound after the last cycle of β-oxidation. Propionyl CoA finally gives Succinyl CoA through biotin dependent carboxlation at a co-enzym B12 dependent rearrangment. Succinyl CoA can enter TCA cycle.

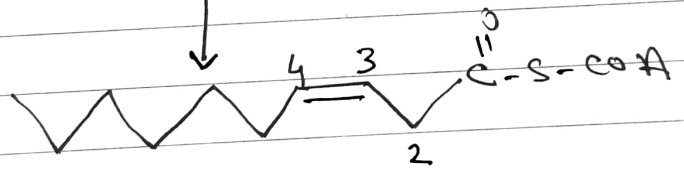
Oxidation of unsaturated fatty acid:-

Two additional enzymes viz reductase and a epimerase enzyme is required. The reductase with the help of $NADH_2$ forms the double bond compound into single bond and the product is the cis-derivative. Now, the cis- compound is not the substrate for next enzyme in β-oxidation pathway, an epimerase converts the cis- compound into trans form, a suitable form in the β-oxidation pathway.

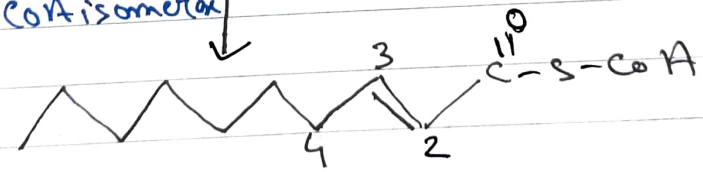


eg. Palmitoleoyl CoA

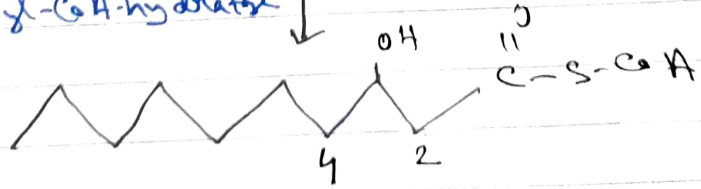
After 3 cycles of β-oxidation



Enoyl-CoA isomerase



Enoyl-CoA-hydratase | H_2O



Continuation of β-oxidation

β-Oxidation in fasting or diabetes:-

During fasting or diabetes mellitus, when the cell does not get a continuous supply of glucose, stored fat is consumed to form ATP for metabolic activity. As a result, more acetyl CoA is produced. At the same time, oxaloacetate is utilized to form glucose by gluconeogenesis. Now, acetyl CoA is not totally condensed with oxaloacetate to form citrate. In this stage, accumulated acetyl CoA is diverted to form acetoacetate, 3 hydroxybutyrate and acetone. All these compounds are known as ketone bodies. When ketone bodies are present in abnormally high concentration in blood, it is called ketonemia and when it is present in urine, it is called ketonuria.

Stoichiometry of β-oxidation — example

β-oxidation of palmitate (16 carbons)

Palmitoyl CoA + 7 CoA + 7 FAD + 7 NAD + 7 H_2O →

8 acetyl CoA + 7 $FADH_2$ + 7 NADH

Acetyl CoA is catabolized via TCA cycle and $FADH_2$ and NADH transfer electrons to ETC chain.

Reaction	ATP yield	ATP consumed
oxidation of 8 acetyl CoA	8 × 10 = 80	−2
oxidation of 7 $FADH_2$	7 × 1.5 = 10.5	
oxidation of 7 NADH	7 × 2.5 = 17.5	
	108	

Net: Palmitate → 16 CO_2 + 130 H_2O + (108 − 2) = 106 ATP

* Assume that 1.5 ATP per $FADH_2$, 2.5 ATP per NADH oxidized.