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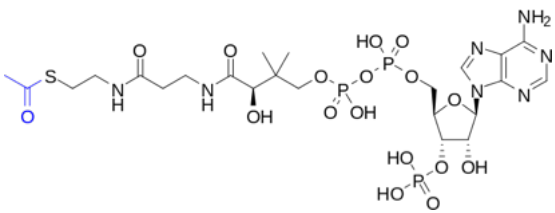
Stage one
Activation of fatty acid to acyl-CoA
Acetyl-CoA (**acetyl coenzyme A**) is a molecule that participates in many biochemical reactions in protein, carbohydrate and lipid metabolism. Its main function is to deliver the acetyl group to the citric acid cycle (Krebs cycle) to be oxidized for energy production. Coenzyme A (CoASH or CoA) consists of a β-mercaptoethylamine group linked to the vitamin

pantothenic acid through an amide linkage and 3'-phosphorylated ADP. The acetyl group (indicated in blue in the structural diagram on the right) of acetyl-CoA is linked to the sulfhydryl substituent of the β-mercaptoethylamine group. This thioester linkage is a "high energy" bond, which is particularly reactive. Hydrolysis of the thioester bond is exergonic (−31.5 kJ/mol).

Acetyl-CoA



Stage two.

Transfer of acyl-CoA into mitochondria by carnitive

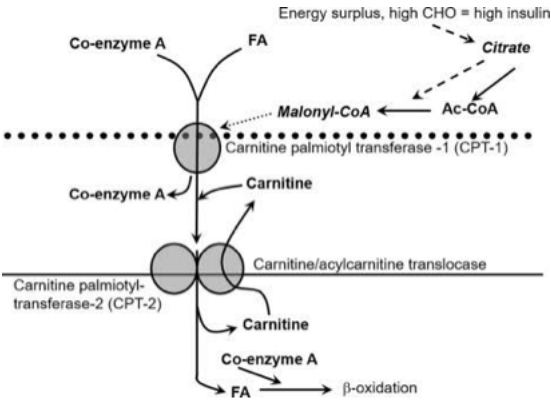
transport system.

In the β-oxidation pathway, two carbons are cleaved from the carboxyl end of acylCoA by breakage of the bond between the α-carbon and the β-carbon. This location of the break informs the reaction as β-oxidation. The products of β-oxidation are acetyl-CoA, NADH, and FADH2. The acetyl-CoA product(s) can enter the TCA cycle for complete oxidation. The reduced coenzymes take part in the electron transport chain for the production of ATP. The resulting acylCoA, now reduced by a two-carbon

fragment, enters the cycle again for further reaction until all pairs of carbons in the fatty acid chain have been converted to acetyl-CoA. If the original fatty acid has an odd number of carbons, propionylCoA is the final product instead of acetyl-CoA and becomes converted to succinylCoA in order to enter the TCA cycle. Through this path, propionylCoA can give rise to glucose. There is a concensus that glucose cannot be formed from even-numbered fatty acids in the human or other animals because they lack the glyoxylate cycle (that some plants

and bacteria have) that makes such a conversion possible. The way this works is that even-numbered fatty acids are reduced to acetyl-CoAs that enter the (incomplete) TCA cycle. At the level of isocitrate, isocitritase converts isocitrate to glyoxalate and, with CoA, malate synthetase converts glyoxalate to malate (α-ketoglutarate is not formed in many lower organisms or α-ketoglutarate dehydrogenase may be absent). Then, malate can be converted to oxaloacetate that can enter gluconeogenesis

and form glucose. So, odd-numbered fatty acids yielding a final propionylCoA are the only candidates for a precursor for glucose derived from fatty acids in the human. The β-oxidation pathway, starting with a 16-carbon fatty acid, palmitic acid as palmitoylCoA.



Stage three
Reactions of beta oxidation in mitochondria

Mitochondrial β-oxidation of fatty acids generates acetyl-coA, NADH and FADH2. Acyl-coA synthetases catalyze the binding of fatty acids to coenzyme A to form fatty acyl-coA thioesters, the first step in the intracellular metabolism of fatty acids. l-carnitine system facilitates the transport of fatty acyl-coA esters across the mitochondrial membrane. Carnitine palmitoyltransferase-1 transfers acyl groups from coenzyme A to l-carnitine, forming acyl-carnitine esters at the outer mitochondrial membrane.

Carnitine acyl-carnitine translocase exchanges acyl-carnitine esters that enter the mitochondria, by free l-carnitine. Carnitine palmitoyltransferase-2 converts acyl-carnitine esters back to acyl-coA esters at the inner mitochondrial membrane. The β-oxidation pathway of fatty acyl-coA esters includes four reactions. Fatty acyl-coA dehydrogenases catalyze the introduction of a double bond at the C2 position, producing 2-enoyl-coA esters and reducing equivalents that are transferred to the respiratory chain via electron transferring

flavoprotein. Enoyl-coA hydratase catalyzes the hydration of the double bond to generate a 3-l-hydroxyacyl-coA derivative. 3-l-hydroxyacyl-coA dehydrogenase catalyzes the formation of a 3-ketoacyl-coA intermediate. Finally, 3-ketoacyl-coA thiolase catalyzes the cleavage of the chain, generating acetyl-coA and a fatty acyl-coA ester two carbons shorter. Mitochondrial trifunctional protein catalyzes the three last steps in the β-oxidation of long-chain and medium-chain fatty acyl-coA esters while

individual enzymes catalyze the β-oxidation of short-chain fatty acyl-coA esters. Clinical phenotype of fatty acid oxidation disorders usually includes hypoketotic hypoglycemia triggered by fasting or infections, skeletal muscle weakness, cardiomyopathy, hepatopathy, and neurological manifestations. Accumulation of non-oxidized fatty acids promotes their conjugation with glycine and l-carnitine and alternate ways of oxidation, such as ω-oxidation.

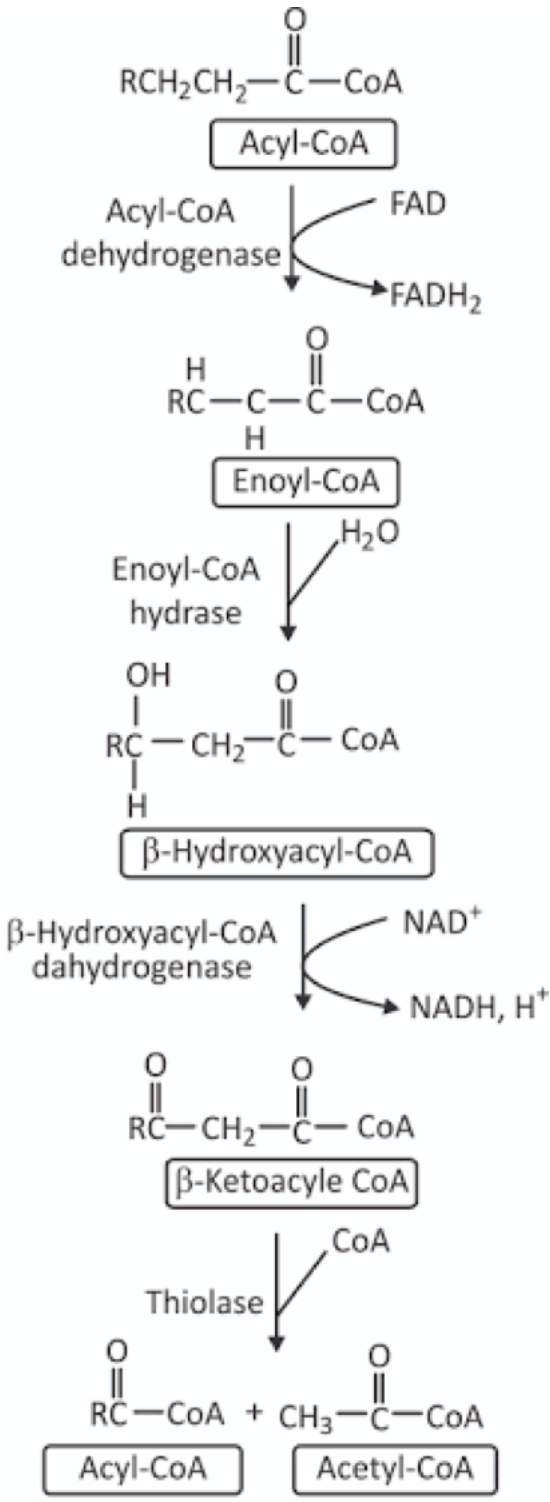

RCH2CH2—C—CoA
Acyl-CoA
Acyl-CoA dehydrogenase
FAD
FADH2
RC—C—C—CoA
H
H
Enoyl-CoA
Enoyl-CoA hydrase
H2O
OH
RC—CH2—C—CoA
H
β-Hydroxyacyl-CoA
β-Hydroxyacyl-CoA dahydrogenase
NAD+
NADH, H+
RC—CH2—C—CoA
β-Ketoacyle CoA
Thiolase
CoA
RC—CoA + CH3—C—CoA
Acyl-CoA
Acetyl-CoA

Fig. : Steps of β-oxidation of fatty acid