Oxidation of Fatty acids

by

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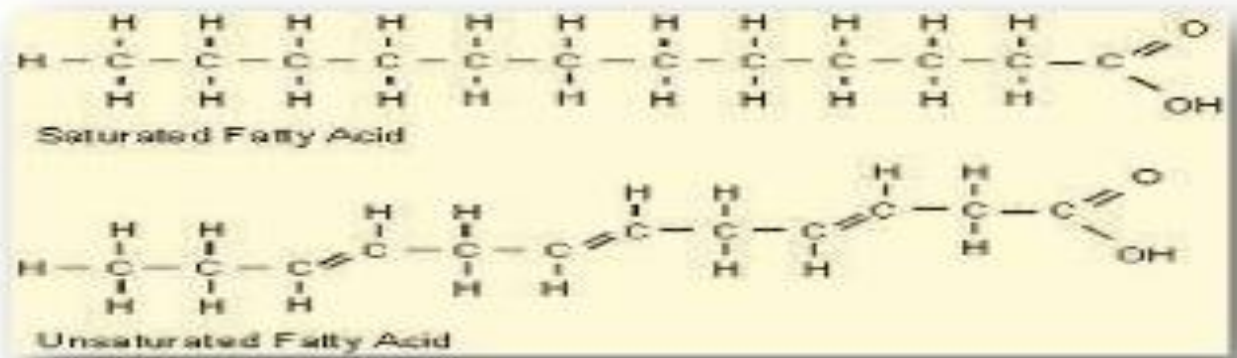
FATTY ACIDS

A fatty acid contains a long hydrocarbon chain and a terminal carboxylate group. The hydrocarbon chain may be saturated (with no double bond) or may be unsaturated (containing double bond).



- Fatty acids can be obtained from-
- Diet
- Adipolysis
- De novo synthesis

FUNCTIONS OF FATTY ACIDS

Fatty acids have four major physiological roles.

1) Fatty acids are **building blocks of phospholipids and glycolipids.**

2) Many proteins are modified by the **covalent attachment of fatty acids, which target them to membrane locations**

3) Fatty acids are **fuel molecules**. They are stored as triacylglycerols. Fatty acids mobilized from triacylglycerols are oxidized to meet the energy needs of a cell or organism.

4) Fatty acid **derivatives serve as hormones and intracellular messengers** e.g. steroids, sex hormones and prostaglandins.

TRIGLYCERIDES

- Triglycerides are **a highly concentrated** stores of energy because they are ***reduced* and *anhydrous*.**
- The yield from the complete oxidation of fatty acids is about 9 kcal g-1 (38 kJ g-1)
- Triacylglycerols are nonpolar, and are stored in a nearly anhydrous form, whereas much more polar proteins and carbohydrates are more highly

TRIGLYCERIDES V/S GLYCOGEN

- ***A gram of nearly anhydrous fat stores more than six times as much energy as a gram of hydrated glycogen,*** which is likely the reason that triacylglycerols rather than glycogen were selected in evolution as the major energy reservoir.
- The glycogen and glucose stores provide enough energy to sustain biological function for about 24 hours, whereas the **Triacylglycerol stores allow survival for several weeks.**

TRANSPORTATION OF FREE FATTY ACIDS

- Free fatty acids—also called unesterified (UFA) or nonesterified (NEFA) fatty acids—are fatty acids that are in the **unesterified state.**
- In plasma, longer-chain FFA are combined with **albumin,** and in the cell they are attached to a **fatty acid-binding protein.**
- **Shorter-chain fatty acids are more water-soluble and exist as the un-ionized acid or as a fatty acid anion.**
- By these means, free fatty acids are made accessible as a fuel in other tissues.

TYPES OF FATTY ACID OXIDATION

Fatty acids can be oxidized by-

1) **Beta oxidation-** Major mechanism, occurs in the mitochondria matrix. 2-C units are released as acetyl CoA per cycle.

2) **Alpha oxidation**- Predominantly takes place in brain and liver, one carbon is lost in the form of CO2 per cycle.

3) **Omega oxidation-** Minor mechanism, but becomes important in conditions of impaired beta oxidation

4) **Peroxisomal oxidation-** Mainly for the trimming of very long chain fatty acids.

BETA OXIDATION

Overview of beta oxidation

A saturated acyl Co A is degraded by a recurring sequence of four reactions:

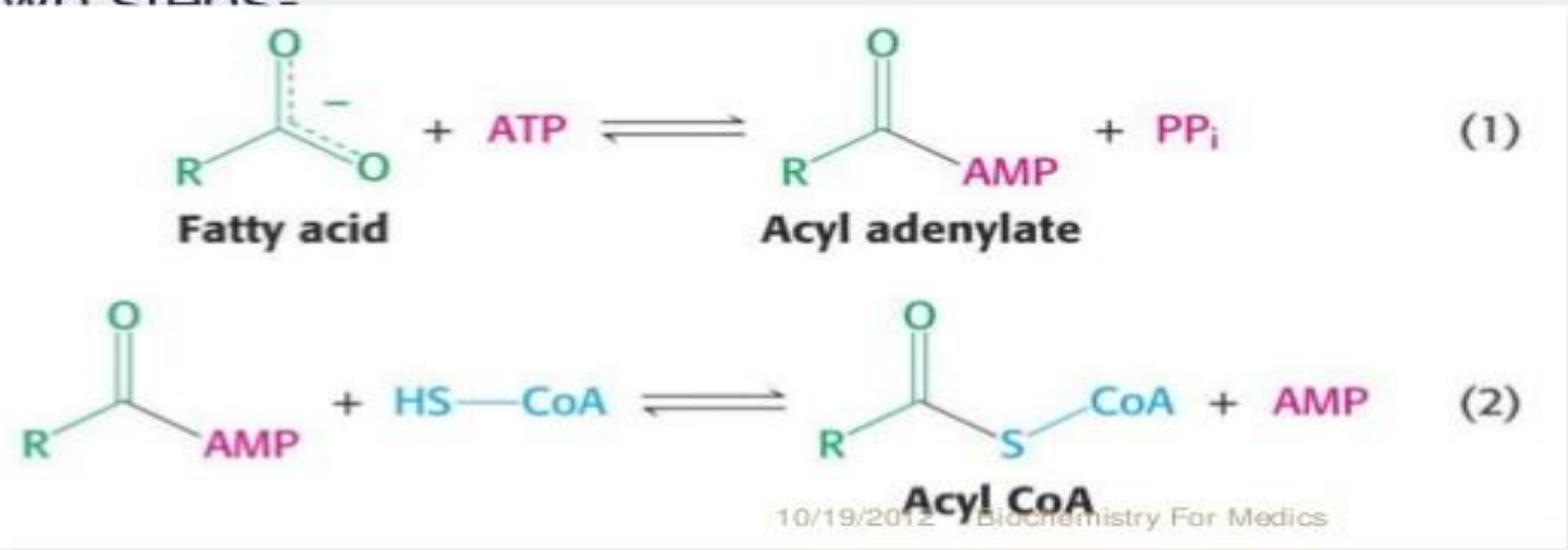
1) **Oxidation** by flavin adenine dinucleotide (FAD)
2) **Hydration,**
3) **Oxidation** by NAD^+, and
4) **Thiolysis** by Co ASH

BETA OXIDATION

- The fatty acyl chain is shortened by two carbon atoms as a result of these reactions,
- FADH2, NADH, and acetyl Co A are generated.
- Because oxidation is on the β carbon and the chain is broken between the α (2)- and β (3)-carbon atoms—hence the name – β oxidation .

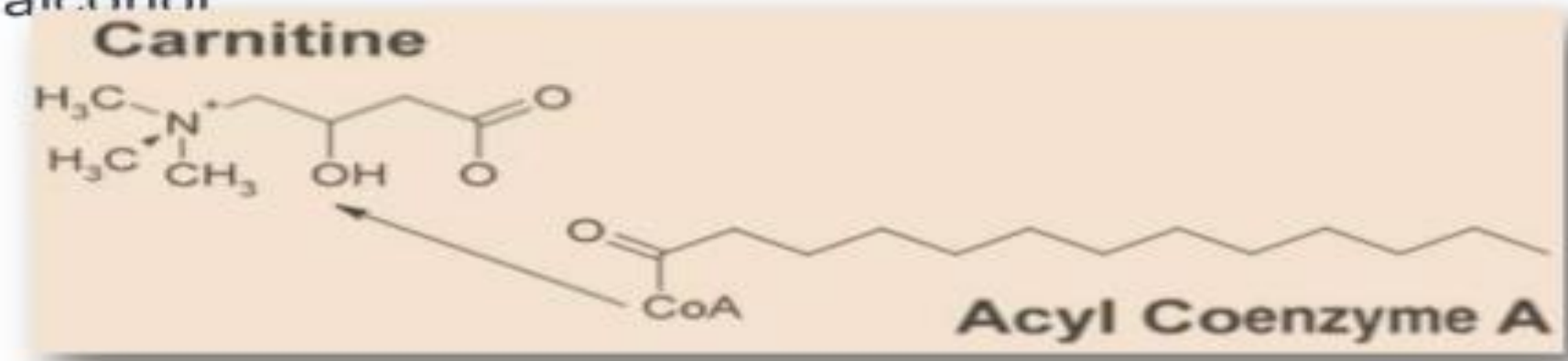
ACTIVATION OF FATTY ACIDS

Fatty acids must first be converted to an active intermediate before they can be catabolized. This is the only step in the complete degradation of a fatty acid that requires energy from ATP. The activation of a fatty acid is accomplished in two steps-



TRANSPORT OF FATTY ACID IN TO MITOCHONDRIAL MATRIX

- Fatty acids are activated on the outer mitochondrial membrane, whereas they are oxidized in the mitochondrial matrix.
- Activated long-chain fatty acids are transported across the membrane by conjugating them to *carnitine*, a zwitterionic alcohol



Carnitine (ß-hydroxy-Y-trimethyl ammonium butyrate), $(CH_3)_3N^+—CH_2—CH(OH)—CH_2—COO^-$, is widely distributed and is particularly abundant in muscle. Carnitine is obtained from foods, particularly animal-based foods, and via endogenous synthesis.

ROLE OF CARNITINE

1) The acyl group is to the hydroxyl group of carnitine to form *acyl carnitine*. This reaction is catalyzed by ***carnitine acyl transferase I***

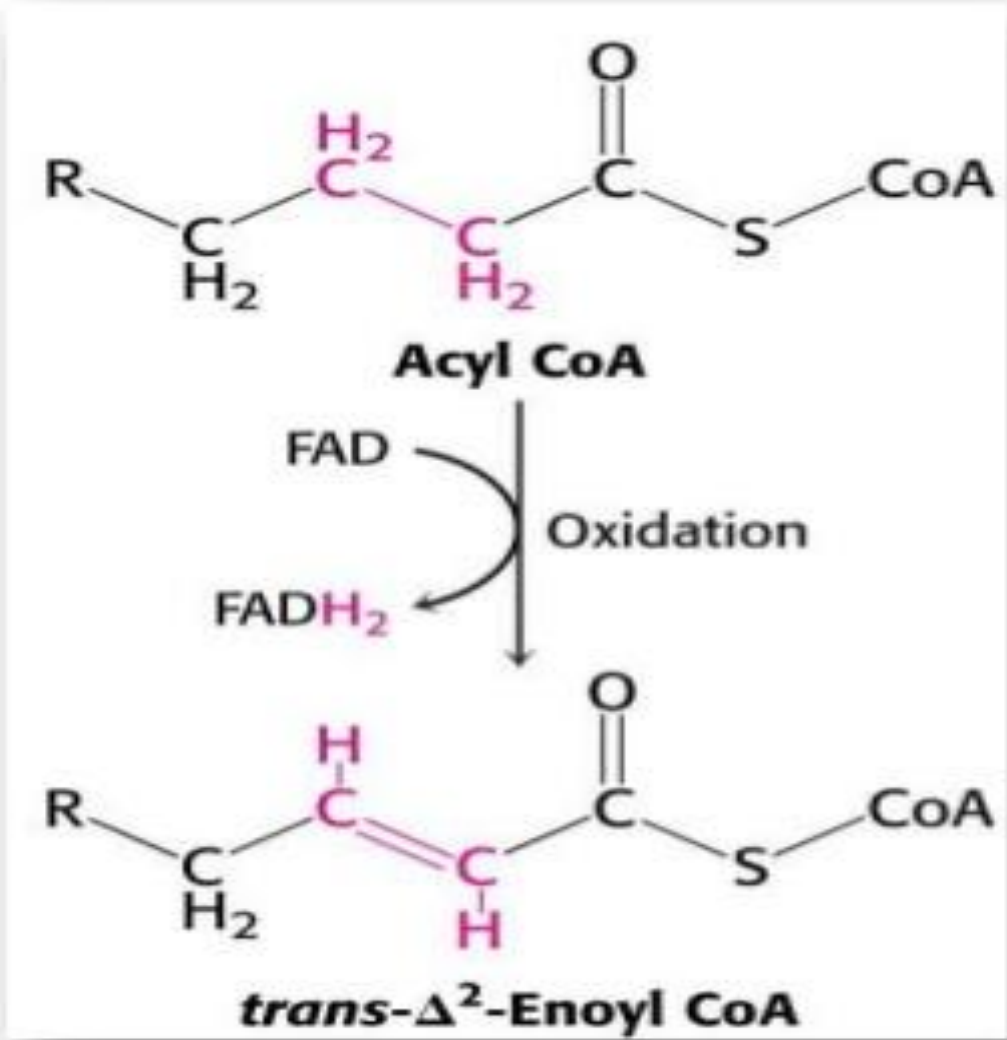
2) Acyl carnitine is then shuttled across the inner mitochondrial membrane by a **translocase.**

3) The acyl group is transferred back to CoA on the matrix side of the membrane. This reaction, which is catalyzed by ***carnitine acyl transferase II.***

Finally, the translocase returns carnitine to the cytosolic side in exchange for an incoming acyl carnitine

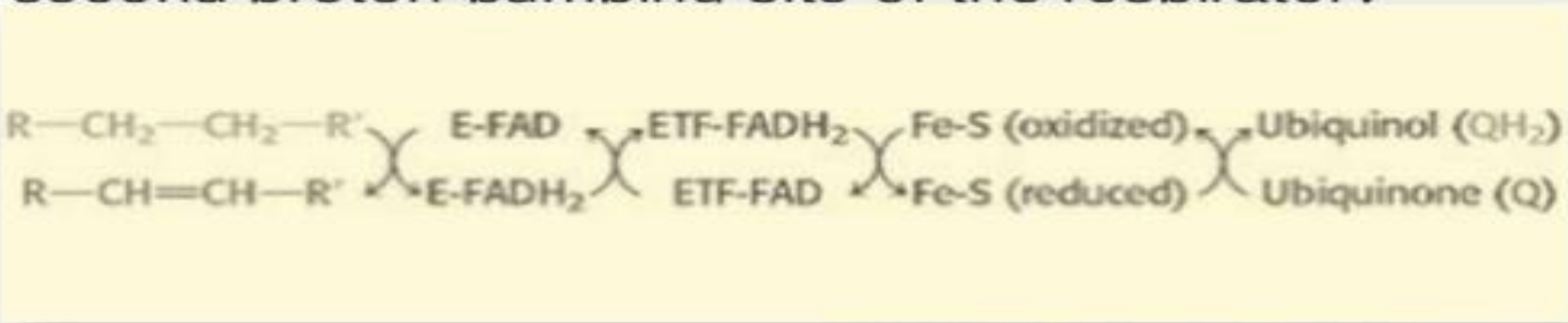
STEPS OF BETA OXIDATION

Step-1
Dehydrogenation-
The first step is the removal of two hydrogen atoms from the 2(α)- and 3(β)-carbon atoms, catalyzed by **acyl-CoA dehydrogenase** and requiring FAD. This results in the formation of Δ^2-*trans*-enoyl-CoA and $FADH_2$.

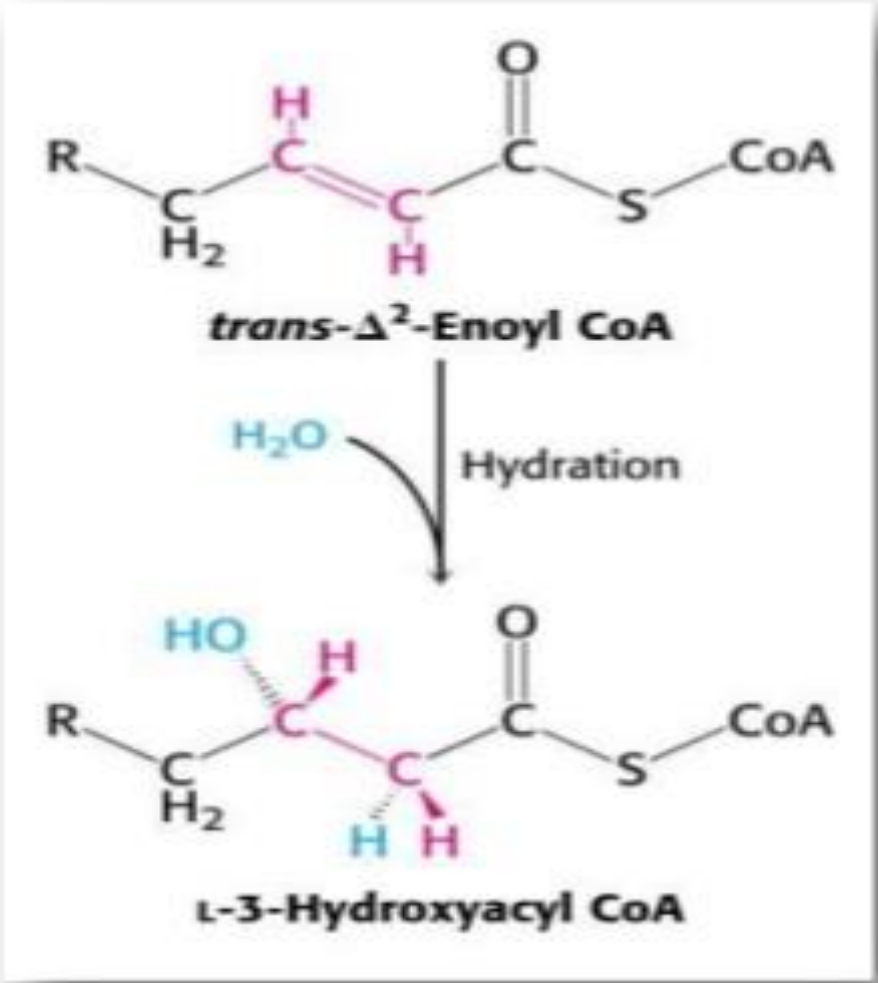


STEPS OF BETA OXIDATION

- Electrons from the FADH2 prosthetic group of the reduced acyl CoA dehydrogenase are transferred to ***electron-transferring flavoprotein*** **(ETF).**
- ETF donates electrons to ***ETF: ubiquinone reductase*****, an iron-sulfur protein.**
- Ubiquinone is thereby reduced to ubiquinol, which delivers its high-potential electrons to the second proton-pumping site of the respiratory



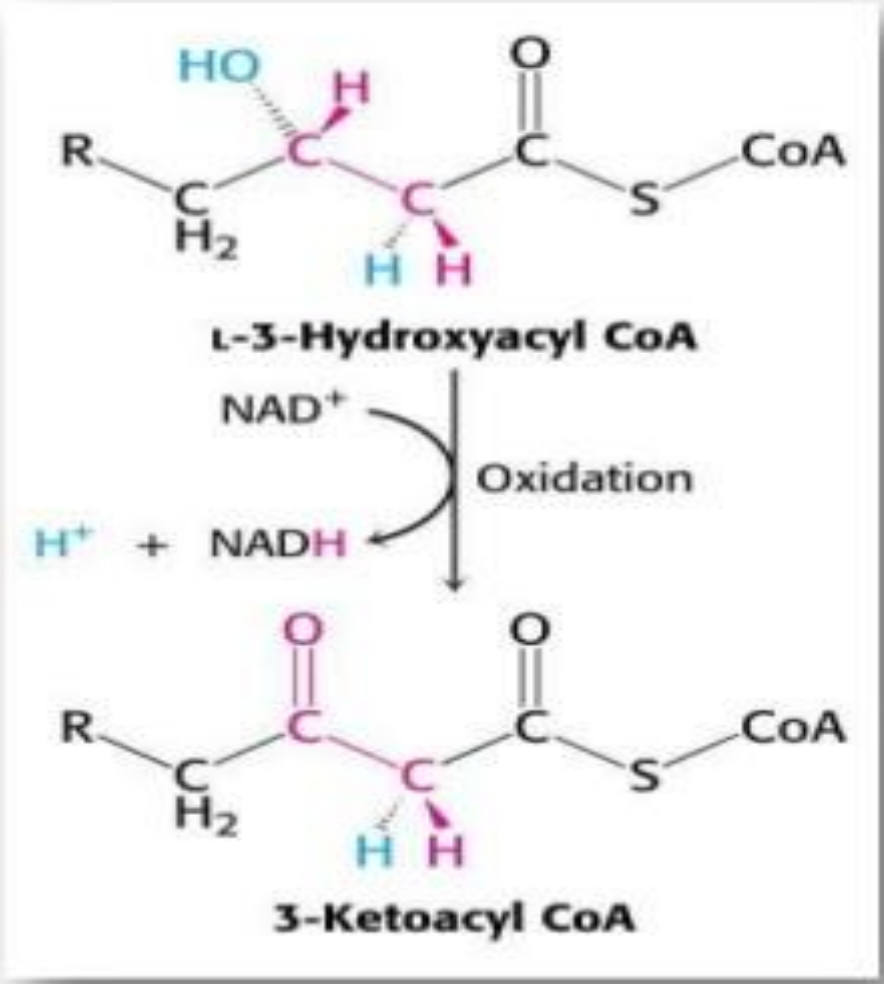
STEPS OF BETA OXIDATION



Step-2- Hydration

Water is added to saturate the double bond and form 3-hydroxyacyl-CoA, catalyzed by **Δ ²-enoyl-CoA hydratase.**

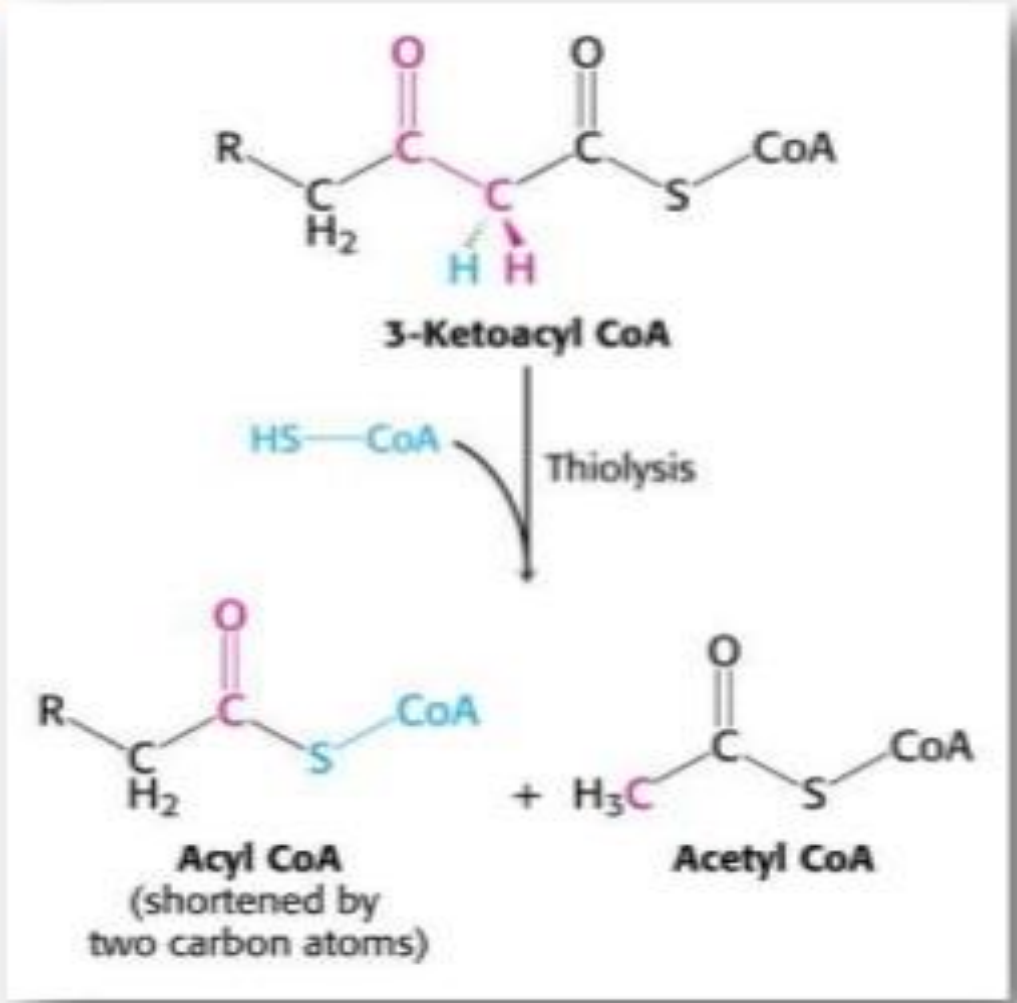
STEPS OF BETA OXIDATION



Step-3-dehydrogenation-

The 3-hydroxy derivative undergoes further dehydrogenation on the 3-carbon catalyzed by **L(+)-3-hydroxyacyl-CoA dehydrogenase** to form the corresponding 3-ketoacyl-CoA compound. In this case, NAD^+ is the coenzyme involved.

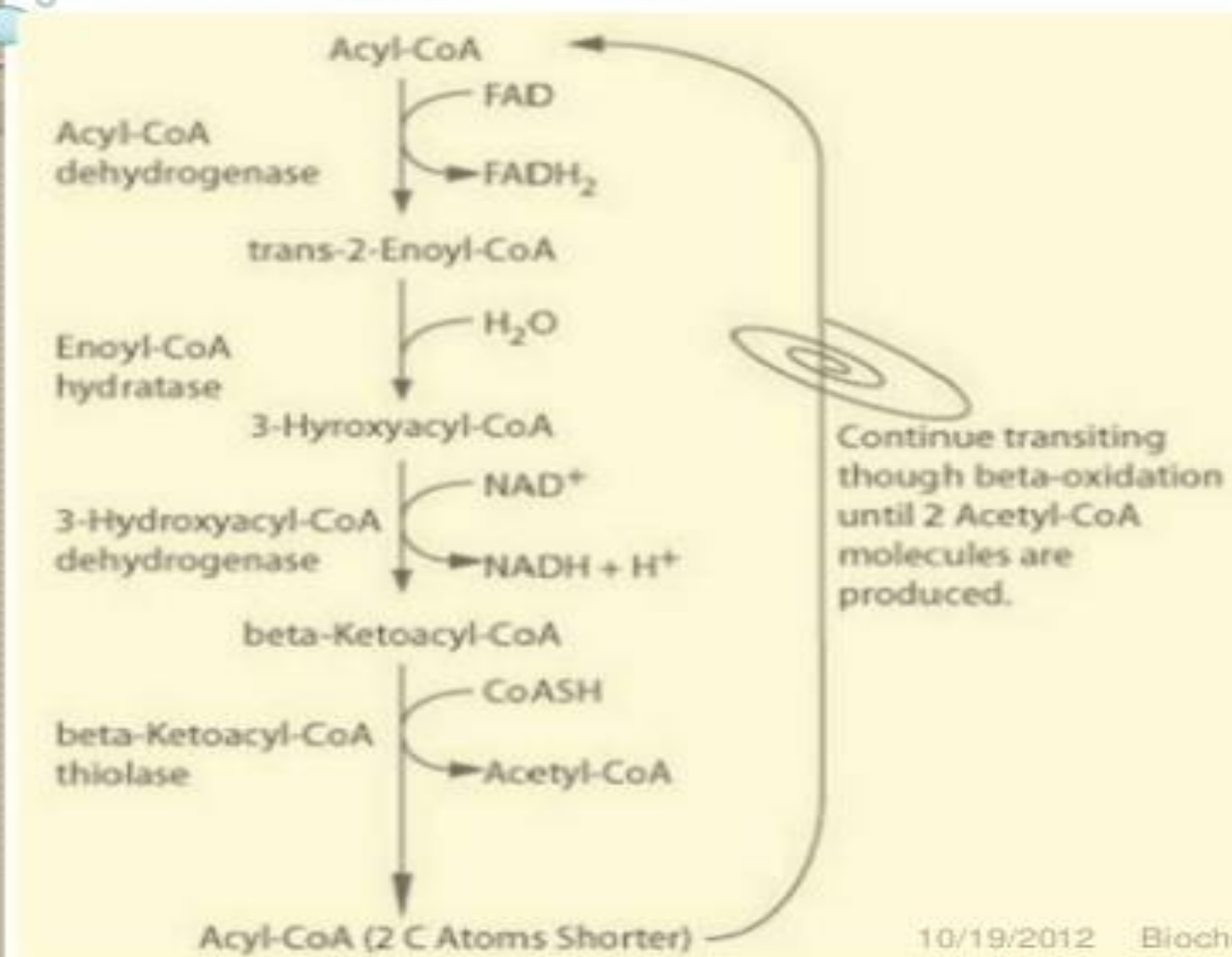
STEPS OF BETA OXIDATION



Step-4-
Thiolysis-

3-ketoacyl-CoA is split at the 2,3-position by **thiolase** (3-ketoacyl-CoA-thiolase), forming acetyl-CoA and a new acyl-CoA two carbons shorter than the original acyl-CoA molecule.

STEPS OF BETA OXIDATION



- The acyl-CoA formed in the cleavage reaction reenters the oxidative pathway at reaction 2.
- Since acetyl-CoA can be oxidized to CO_2 and water via the citric acid cycle the complete oxidation of fatty acids is achieved

BETA OXIDATION

The overall reaction can be represented as follows-

$$C_n\text{-acyl CoA} + FAD + NAD^+ + H_2O + CoA \longrightarrow C_{n-2}\text{-acyl CoA} + FADH_2 + NADH + \text{acetyl CoA} + H^+$$

BETA OXIDATION- ENERGY YIELD

Energy yield by the complete oxidation of one mol of Palmitic acid-

The degradation of palmitoyl CoA (C16-acyl Co A) requires seven reaction cycles. In the seventh cycle, the C4-ketoacyl CoA is thiolyzed to two molecules of acetyl CoA.

$$\text{Palmitoyl CoA} + 7\,\text{FAD} + 7\,\text{NAD}^+ + 7\,\text{CoA} + 7\,\text{H}_2\text{O} \longrightarrow 8\,\text{acetyl CoA} + 7\,\text{FADH}_2 + 7\,\text{NADH} + 7\,\text{H}^+$$

106 (129 As per old concept) ATP are produced by the complete oxidation of one mol of Palmitic acid.

BETA OXIDATION- ENERGY YIELD

2.5 ATPs per NADH = 17.5

1.5 ATPs per FADH2 = 10.5

10 ATPs per acetyl-CoA = 80

Total = 108 ATPs

2 ATP equivalents (ATP $\longrightarrow$ AMP + PPi

PPi $\longrightarrow$ 2 Pi)

consumed during activation of palmitate to Palmitoyl CoA

Net Energy output- 108-2 = 106 ATP

DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

1) Deficiencies of carnitine or carnitine transferase or translocase

- Symptoms include muscle cramps during exercise, severe weakness and death.
- Muscle weakness related to importance of fatty acids as long term energy source
- Hypoglycemia and hypo ketosis are common findings
- Diet containing medium chain fatty acids is recommended since they do not require carnitine shuttle to enter mitochondria.

DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

2) Jamaican Sickness- Jamaican vomiting sickness is caused by eating the unripe fruit of akee tree, which contains the toxin hypoglycin, that inactivates medium and short-chain acyl-CoA dehydrogenases, inhibiting β oxidation and thereby causing hypoglycemia.

3) Dicarboxylic aciduria is characterized by-

i) Excretion of C_6–C_{10} -dicarboxylic acids and

ii) **Nonketotic hypoglycemia** which is caused by lack of mitochondrial **medium chain acyl-CoA dehydrogenases.**

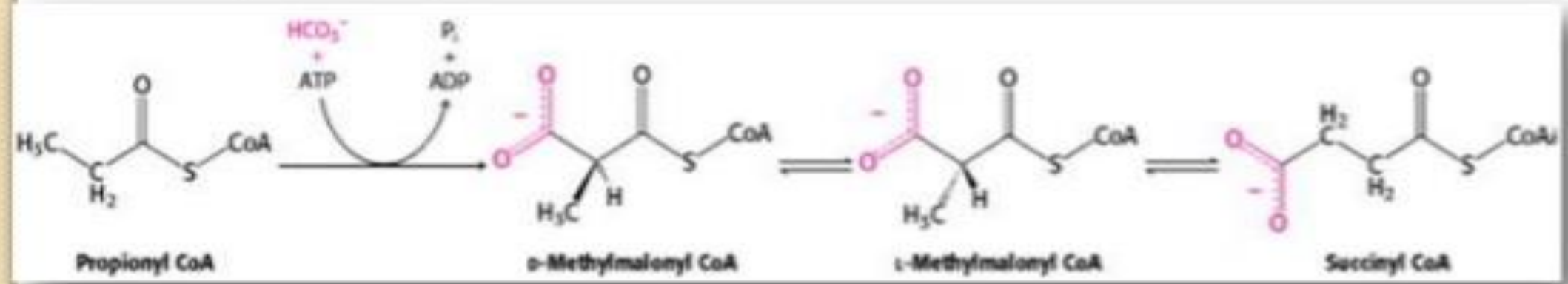
DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

4) Acute fatty liver of pregnancy

- Manifests in the second half of pregnancy, usually close to term, but may also develop in the postpartum period.
- The patient developed symptoms of hepatic dysfunction at 36 weeks of gestation.
- Short history of illness, hypoglycemia, liver failure, renal failure, and coagulopathy are observed.
- Diagnosis is made based on an incidental finding of abnormal liver enzyme levels.
- Affected patients may become jaundiced or develop encephalopathy from liver failure, usually reflected by an elevated ammonia level.
- Profound hypoglycemia is common.

BETA OXIDATION OF ODD CHAIN FATTY ACIDS

Fatty acids with an odd number of carbon atoms are oxidized by the pathway of β-oxidation, producing acetyl-CoA, until a three-carbon (propionyl-CoA) residue remains. This compound is converted to Succinyl-CoA, a constituent of the citric acid cycle



The propionyl residue from an odd-chain fatty acid is the only part of a fatty acid that is glucogenic. Acetyl CoA cannot be converted into pyruvate or Oxaloacetate in animals.