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18/MHS07 /005

PHARMACOLOGY

BCH 204 assignment

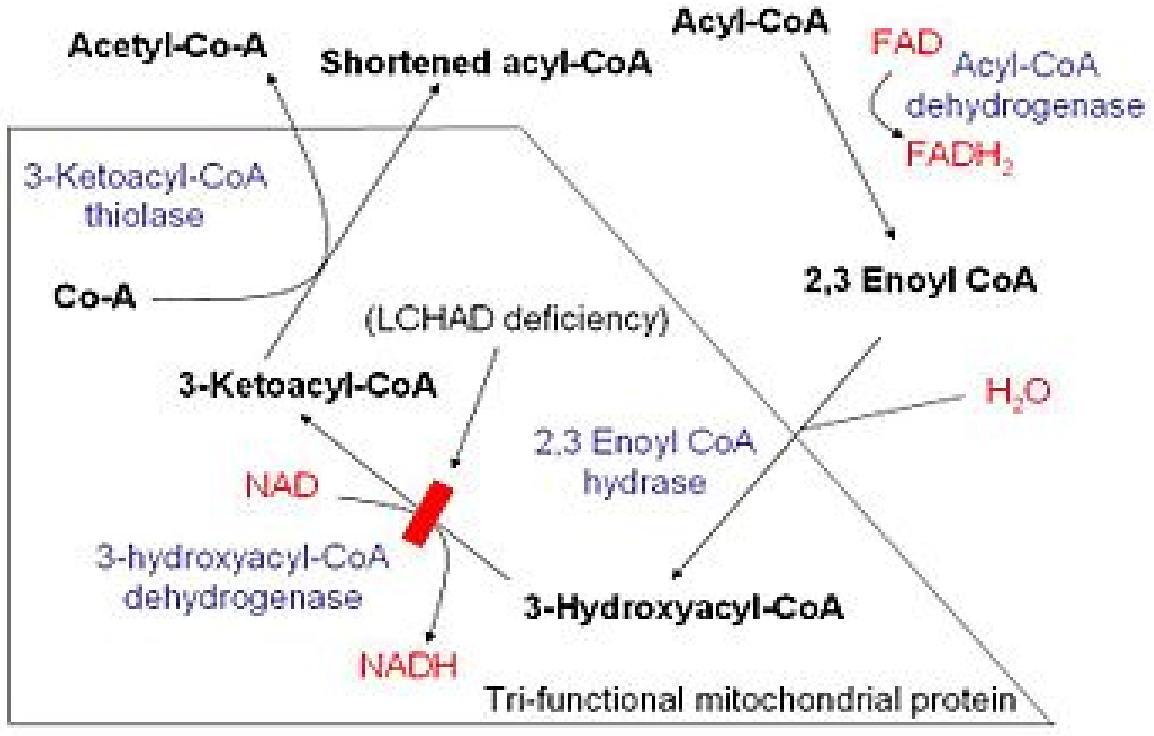
Question :Describe the three stages of beta oxidation

Beta-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA, which enters the citric acid cycle, and NADH and FADH2, which are co-enzymes used in the electron transport chain. It is named as such because the beta carbon of the fatty acid undergoes oxidation to a carbonyl group. Beta-oxidation is primarily facilitated by the mitochondrial trifunctional protein, an enzyme complex associated with the inner mitochondrial membrane, although very long chain fatty acids are oxidized in peroxisomes.

Substrates: Free fatty acids; H2O.

Products: One acetyl CoA, one NADH, and one FADH2 for every removal of a two-carbon group from the fatty acid chain.

The overall reaction for one cycle of beta oxidation is:



Cn-acyl-CoA + FAD + NAD+

+ H

2O + CoA → Cn-2-acyl-CoA + FADH

Beta aoxidation has 3 stages

A. Activation of fatty acids

In the cytosol of the cell, long-chain fatty acids are activated by ATP and coenzyme A, and fatty acyl-CoA is formed. Short-chain fatty acids are activated in mitochondria.

The ATP is converted to AMP and pyrophosphate (PPi), which is cleaved by pyrophosphatase to two inorganic phosphates (2 Pi). Because two high-energy phosphate bonds are cleaved, the equivalent of two molecules of ATP is used for fatty acid activation.

B. Transport of fatty acyl-CoA from the cytosol into mitochondria

Fatty acyl-CoA from the cytosol reacts with carnitine in the outer mitochondrial membrane, forming fatty acylcarnitine. The enzyme is carnitine acyltransferase I (CAT I), which is also called carnitine palmitoyltransferase I (CPT I). Fatty acylcarnitine passes to the inner membrane, where it re-forms to fatty acyl-CoA, which enters the matrix. The second enzyme is carnitine acyltransferase II (CAT II).

Carnitine acyltransferase I, which catalyzes the transfer of acyl groups from coenzyme A to carnitine, is inhibited by malonyl-CoA, an intermediate in fatty acid synthesis. Therefore, when fatty acids are being synthesized in the cytosol, malonyl-CoA inhibits their transport into mitochondria and, thus, prevents a futile cycle (synthesis followed by immediate degradation).

Inside the mitochondrion, the fatty acyl-CoA undergoes beta-oxidation

C. β-Oxidation of even-chain fatty acids

β-Oxidation (in which all reactions involve the β-carbon of a fatty acyl-CoA) is a spiral consisting of four sequential steps, the first three of which are similar to those in the TCA cycle between succinate and oxaloacetate. These steps are repeated until all the carbons of an even-chain fatty acyl-CoA are converted to acetyl-CoA.

FAD accepts hydrogens from a fatty acyl-CoA in the first step. A double bond is produced between the α- and β-carbons, and an enoyl-CoA is formed. The FADH2 that is produced interacts with the electron transport chain, generating ATP.

Enzyme: Acyl-CoA dehydrogenase (Multiple variants of this enzyme)

H2O adds across the double bond, and a β-hydroxyacyl-CoA is formed.

Enzyme: Enoyl-CoA hydratase

β -Hydroxyacyl-CoA is oxidized by NAD+ to a β-ketoacyl-CoA. The NADH that is produced interacts with the electron transport chain, generating ATP.

Enzyme: L-3-hydroxyacyl-CoA dehydrogenase (which is specific for the L-isomer of the β-hydroxyacyl-CoA).

The bond between the alpha and beta carbons of the β-ketoacyl-CoA is cleaved by a thiolase that requires coenzyme A. Acetyl-CoA is produced from the two carbons at the carboxyl end of the original fatty acyl-CoA, and the remaining carbons form a fatty acyl-CoA that is two carbons shorter than the original.

Enzyme: β -ketothiolase

The shortened fatty acyl-CoA repeats these four steps. Repetitions continue until all the carbons of the original fatty acyl-CoA are converted to acetyl-CoA.

<u>Energy Yield for Even-chain Fatty Acids</u>

- ★ Energy is generated from the products of β-oxidation.
- ★ The 16-carbon palmitoyl-CoA undergoes seven repetitions.
- ★ In the last repetition, a 4-carbon fatty acyl-CoA (butyryl-CoA) is cleaved to two acetyl-CoAs.

1. When one palmitoyl-CoA is oxidized, seven FADH2, seven NADH, and eight acetyl-CoA are formed.The seven FADH2 each generate approximately 1.5 ATP, for a total of about 10.5 ATP.

The seven NADH each generate about 2.5 ATP, for a total of about 17.5 ATP.

The eight acetyl-CoA can enter the TCA cycle, each producing about 10 ATP, for a total of about 80 ATP.

From the oxidation of palmitoyl-CoA to CO2 and H2O, a total of about 108 ATP are produced.

2. The net ATP produced from palmitate that enters the cell from the blood is about 106 because palmitate must undergo activation (a process that requires the equivalent of 2 ATP) before it can be oxidized (108 ATP − 2 ATP = 106 ATP).

3. The oxidation of other fatty acids will yield different amounts of ATP.