UBA AMALACHUKWU

18/MHS07/051

PHARMACOLOGY

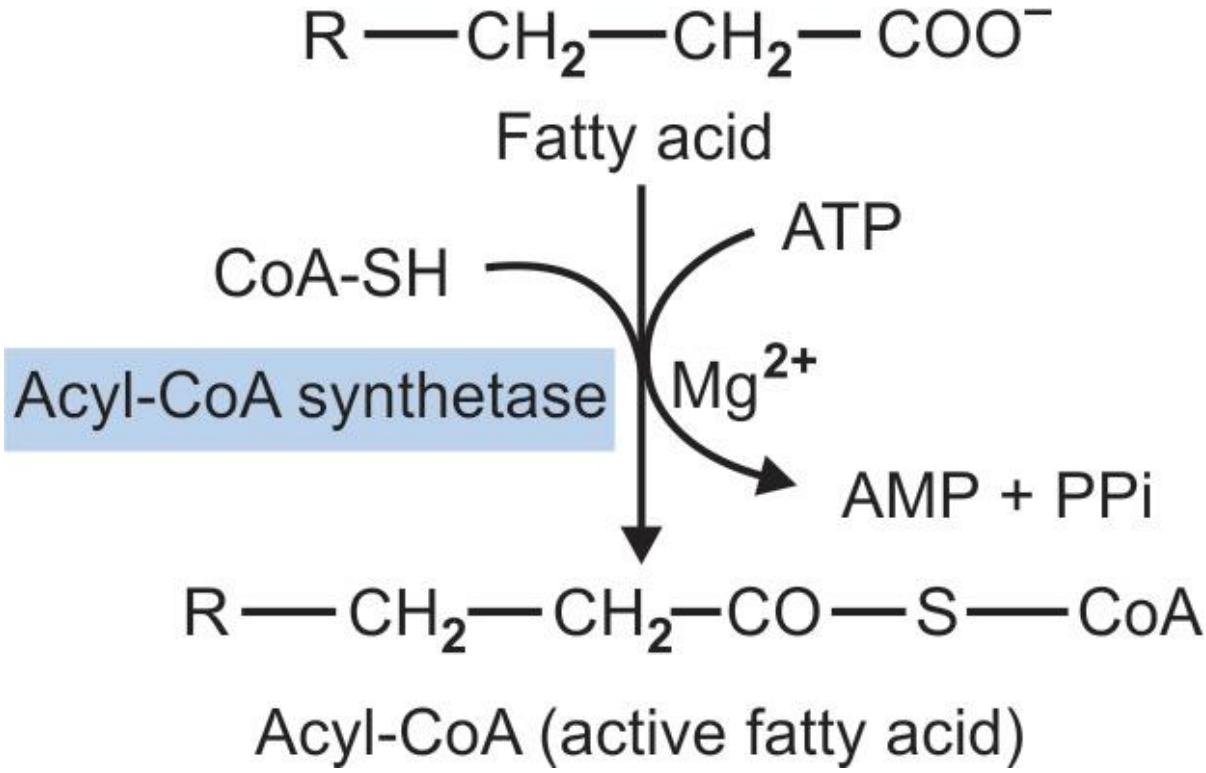
BCH 204 ASSIGNMENT

QUESTION: Describe the three stages of beta oxidation. (Show pathways where necessary)

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 pyro phosphatase 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.

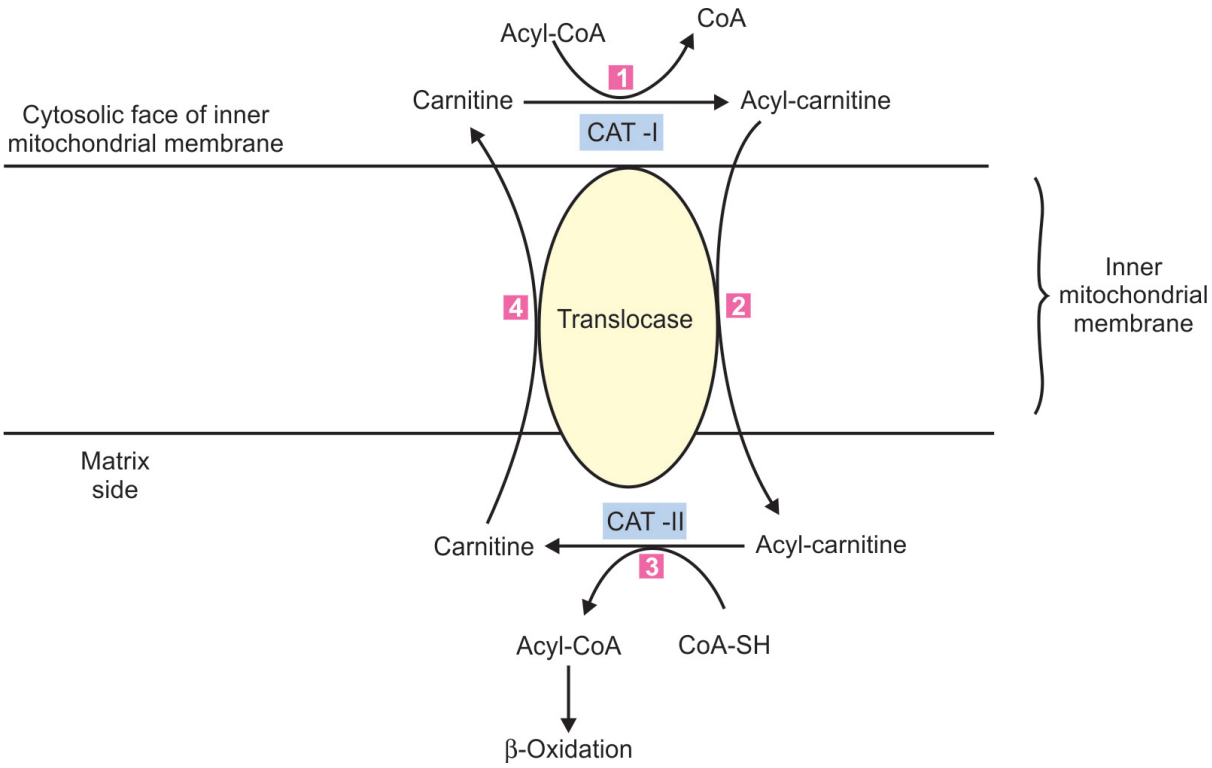


B. Transport of fatty acyl-CoA from the cytosol into mitochondria by Carnitine Transport System

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 catalyses 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

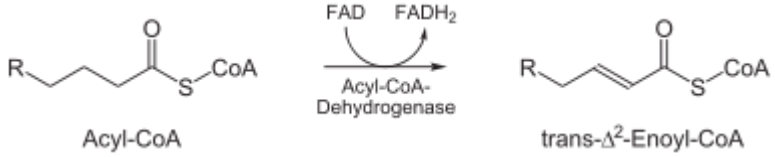
being synthesized in the cytosol, malonyl-CoA inhibits their transport into mitochondria and, thus, prevents a futile cycle (synthesis followed by immediate degradation). Inside the mitochondrion, the fatty acyl-CoA undergoes beta-oxidation.



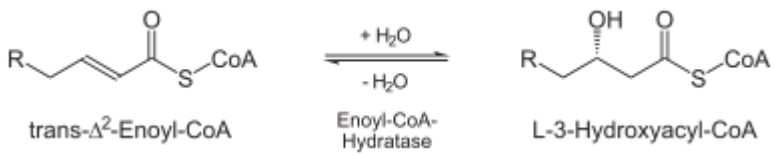
C. β-Oxidation of even-chain fatty acids

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

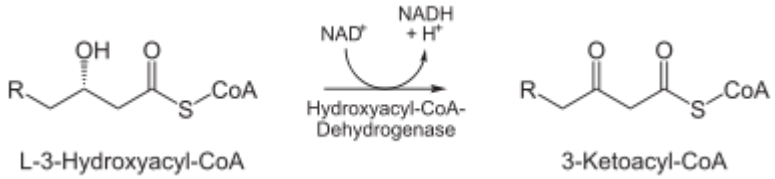
Dehydrogenation by FAD: The first step is the oxidation of the fatty acid by Acyl-CoA Dehydrogenase. The enzyme catalyzes the formation of a double bond between the C-2 and C-3.



Hydration: The next step is the hydration of the bond between C-2 and C-3. The reaction is stereospecific, forming only the L isomer.

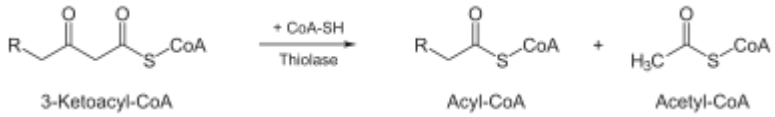


Oxidation by NAD+: The third step is the oxidation of L-β-hydroxyacyl CoA by NAD+. This converts the hydroxyl group into a keto group.



L-3-Hydroxyacyl-CoA 3-Ketoacyl-CoA

Thiolysis: The final step is the cleavage of β-ketoacyl CoA by the thiol group of another molecule of Coenzyme A. The thiol is inserted between C-2 and C-3.



3-Ketoacyl-CoA Acyl-CoA Acetyl-CoA

This process continues until the entire chain is cleaved into acetyl CoA units. The final cycle produces two separate acetyl CoAs, instead of one acyl CoA and one acetyl CoA. For every cycle, the Acyl CoA unit is shortened by two carbon atoms.

The new acyl-CoA containing two carbons less than the original re-enters the beta oxidation pathway at reaction catalysed by acyl-CoA dehydrogenase. The process continues till the fatty acid degraded completely to acetyl-CoA. Acetyl-CoA can be oxidized to CO2 and H2O via citric acid cycle in mitochondria and thus oxidation of fatty acids is completed.