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Medical laboratory science
Medical Biochemistry
BCH 204

Describe the three (3) stages of beta oxidation. (Show pathways where necessary)

Beta oxidation is a metabolic process involving multiple steps by which fatty acid molecules are broken down to produce energy. More specifically, beta oxidation consists in breaking down long fatty acids that have been converted to acyl-CoA chains into progressively smaller fatty acyl-CoA chains. Beta oxidation goes on until two acetyl-CoA molecules are produced and the acyl-CoA chain has been completely broken down. It is so called because oxidation and splitting of two-carbon units occur at the beta carbon atom. In eukaryotic cells, beta oxidation takes place in the mitochondrion.

The three stages of beta oxidation are:

1. Activation of fatty acids in the cytosol
2. Transportation of activated fatty acids into the mitochondrion (carnitine shuttle)
3. Oxidation proper or degradation of fatty acid in the mitochondrial matrix. Free fatty acids are formed in the cytoplasm by the action of lipase on stored triglycerides, but the fatty acids themselves are degraded and oxidized only in the mitochondria and peroxisome. The fatty acids have surface activity (they lower the surface tension) and can impair membrane integrity. Therefore, the fatty acids are carried in solution by fatty acid binding proteins.

ACTIVATION OF FATTY ACIDS

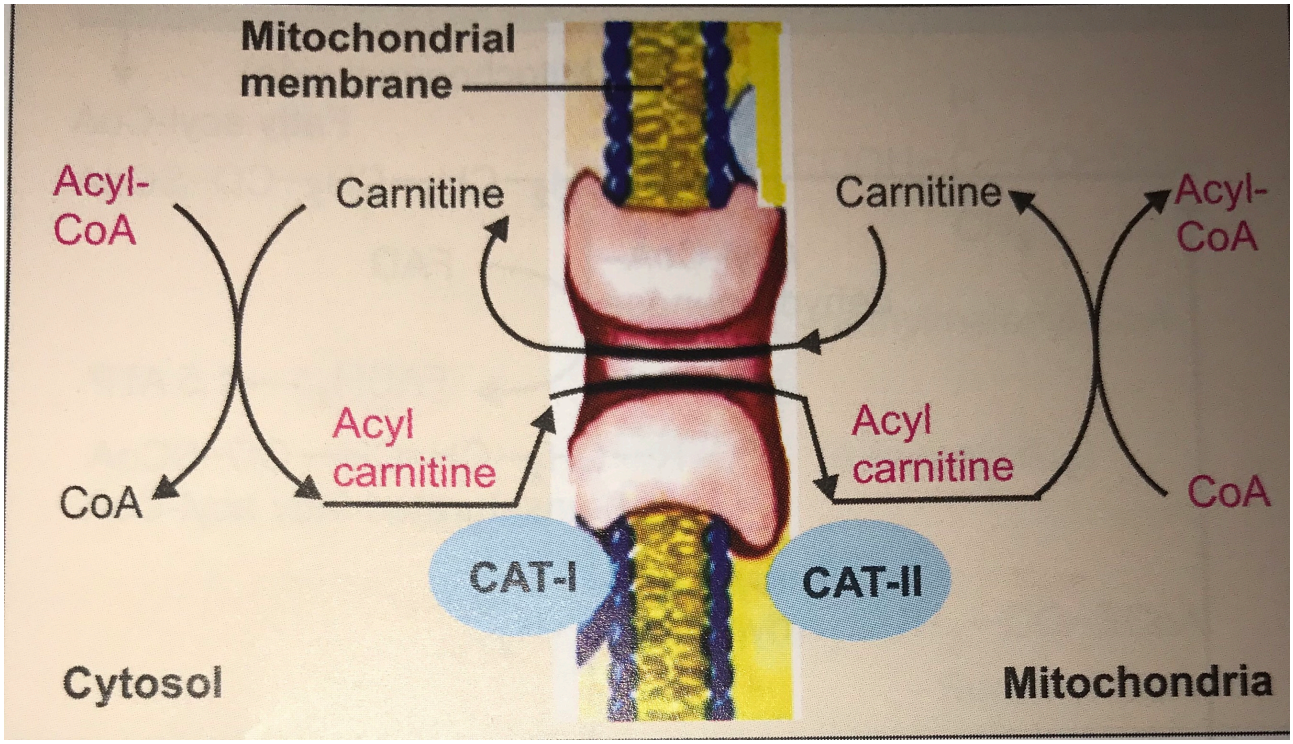
Once the fatty acids make their way into the cytoplasm of target cells, the fatty acids are activated through a two-step process into acyl CoA molecules. The first step of this process transfers an adenine monophosphate component from ATP onto the fatty acid, thereby releasing a pyrophosphate and forming acyl-AMP. The pyrophosphate is then hydrolyzed by pyrophosphatase into two orthophosphates; this drives the activation reaction forward. In the second step, the acyl-AMP reacts with a coenzyme A molecule to form acyl-CoA and release the AMP. Once the fatty acid is activated, it must now be transported into the matrix of the mitochondria.
Fatty acids are activated by fatty acyl CoA synthetase or fatty acid thiokinase.
The reaction:
Fatty acid + CoA + ATP = fatty acid-CoA + AMP + 2Pi

R-COOH + CoASH + ATP <--> R-CO-SCoA + AMP + PPi
The subsequent hydrolysis of PPi draws the reaction in the forward direction, maintaining a low cytosolic free fatty acid concentration:
PPi + H2O --> 2 Pi
The product of this reaction is fatty acyl CoA and water.

TRANSPORTATION OF ACTIVATED FATTY ACID INTO THE MITOCHONDRION

Fatty acids are activated in the cytoplasm, but beta oxidation is in the mitochondrion. Therefore activated fatty acid must be transported into the mitochondrion. The long chain fatty acyl-CoA cannot pass through the inner mitochondrial membrane, it must be combined with a carrier substance, carnitine. Carnitine acyl tranferase-I will transfer the fatty acyl group to the hydroxyl group of carnitine to form acyl carnitine. A protein translocase will carry the acyl carnitine across the membrane to the matrix of mitochondria. On the matrix side of the membrane another enzyme, carnitine acyl transferase II will transfer the acyl group back to coenzyme A (CoA) molecule. In this form (fatty acyl

CoA) and in this place, the fatty acid can be oxidized in a systematic way to produce energy.
Carnitine is returned to the cytosolic side by the translocase.



Role of carnitine in the transport of acyl groups.

PROPER BETA-OXIDATION OF FATTY ACID

Fatty acid oxidation is the mitochondrial aerobic process of breaking down a fatty acid into acetyl-CoA units. Fatty acids move in this pathway as CoA derivatives utilizing NAD and FAD. It involves 4 stages:
Oxidation by FAD linked dehydrogenase
Hydration by hydratase
Oxidation by NAD linked dehydrogenase
Thiolytic cleavage by thiolase

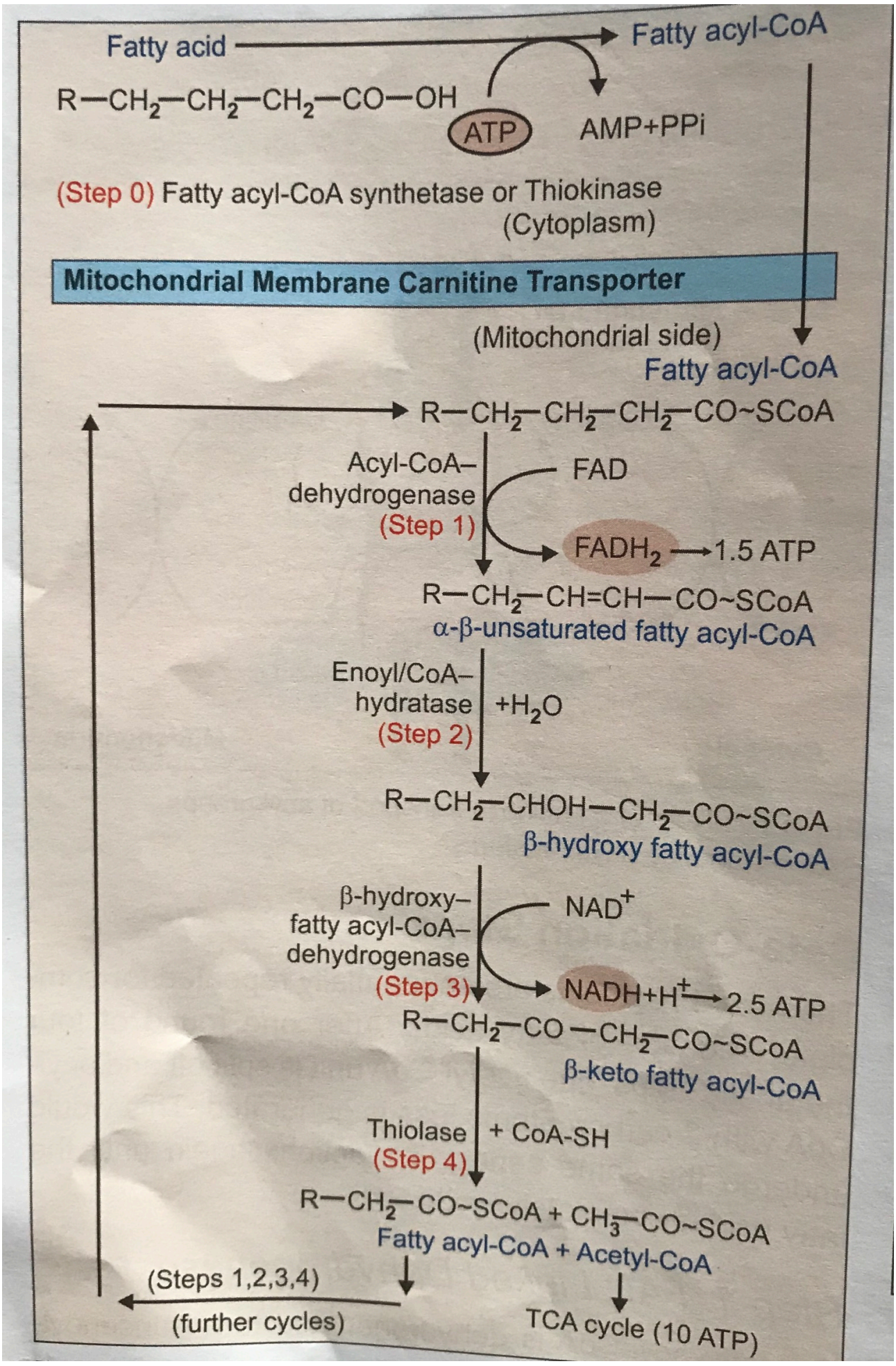
FAD linked dehydrogenase

The fatty acyl CoA is dehydrogenated to a transenoyl CoA with FAD accepting the hydrogen atoms. FADH2 when oxidised in electron transport chain will produce 1.5 ATP molecules.

HYDRATION
This is catalysed by an enoyl CoA hydratase. This step forms a beta-hydroxy fatty acyl CoA. The L isomer alone is formed during the hydration of the trans double bond.

NAD dependent dehydrogenase
The beta- hydroxy fatty acyl CoA is again oxidised to form beta- keto fatty acyl CoA. This dehydrogenase acts inly on L isomer. The NADH when oxidised in electron transport chain will generate 2.5 ATPs.

THIOLYTIC CLEAVAGE
The beta-keto fatty acyl CoA now undergoes thiolytic cleavage, splitting off a molecule of acetyl CoA and leaving behind a fatty acid with 2 carbon atoms less.


Fatty acid
Fatty acyl-CoA
R—CH2—CH2—CH2—CO—OH
ATP
AMP+PPi
(Step 0) Fatty acyl-CoA synthetase or Thiokinase
(Cytoplasm)
Mitochondrial Membrane Carnitine Transporter
(Mitochondrial side)
Fatty acyl-CoA
R—CH2—CH2—CH2—CO~SCoA
Acyl-CoA–
dehydrogenase
(Step 1)
FAD
FADH2 → 1.5 ATP
R—CH2—CH=CH—CO~SCoA
α-β-unsaturated fatty acyl-CoA
Enoyl/CoA–
hydratase
(Step 2)
+H2O
R—CH2—CHOH—CH2—CO~SCoA
β-hydroxy fatty acyl-CoA
β-hydroxy–
fatty acyl-CoA–
dehydrogenase
(Step 3)
NAD+
NADH+H+ → 2.5 ATP
R—CH2—CO—CH2—CO~SCoA
β-keto fatty acyl-CoA
Thiolase
(Step 4)
+ CoA-SH
R—CH2—CO~SCoA + CH3—CO~SCoA
Fatty acyl-CoA + Acetyl-CoA
(Steps 1,2,3,4)
(further cycles)
TCA cycle (10 ATP)