OXIDATION OF FATTY ACIDS

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Fatty Acids

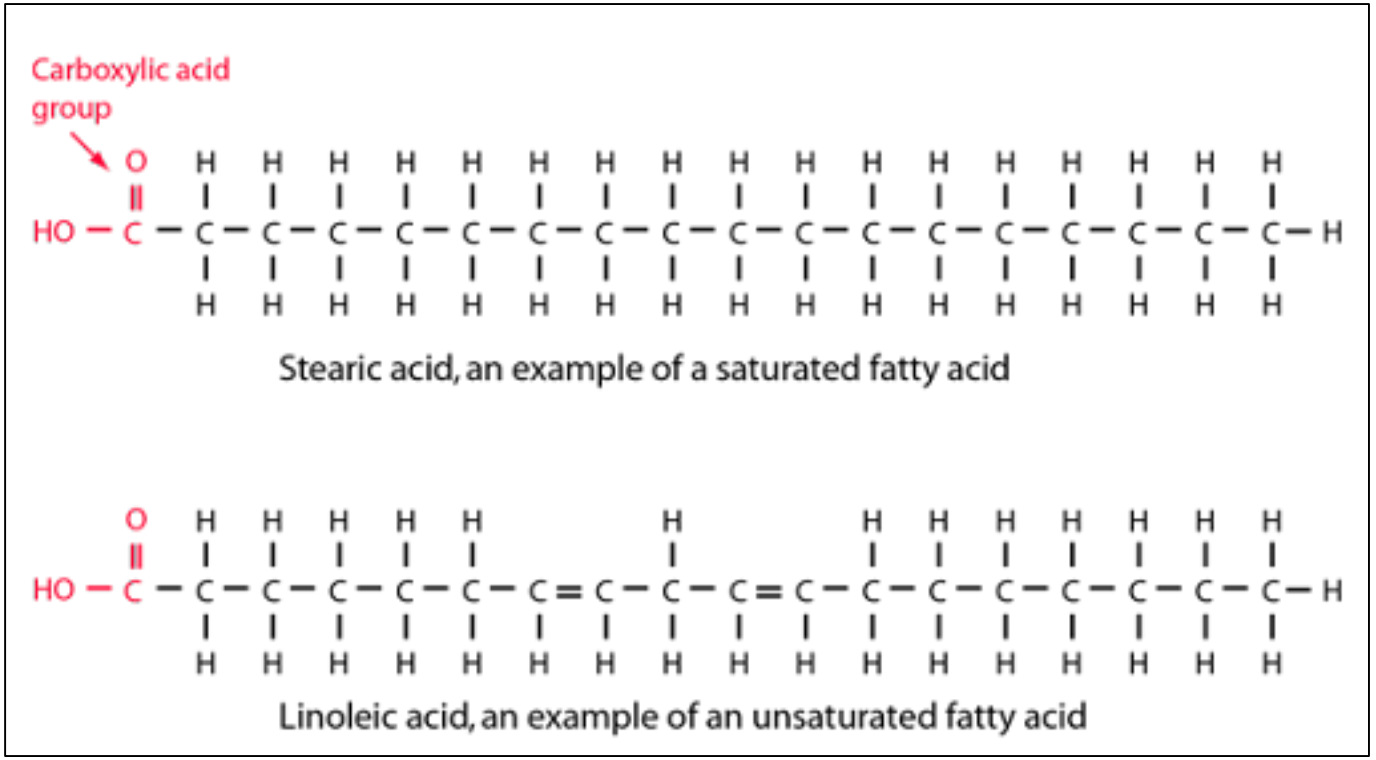
- Fats are important source of energy as (1gm of fat gives 9 kcal energy) mainly as triacylglycerols (triglycerides) in adipose cells.
- Fats Constitute 84% of stored energy

  (Protein - 15%

  Carbohydrate (glucose or glycogen) - <1%)
- Insoluble in water & soluble in non-polar solvents
- A fatty acid contains a long hydrocarbon chain and a terminal carboxylate group.

Fatty Acids

The hydro carbon chain may be saturated (with no double bond) or may be unsaturated (containing double bond).



Importance Of FA

- They are important dietary constituents: high energy value and essential fatty acids, fat-soluble vitamins (A,D,E,K) and other lipophilic micronutrients.
- Lipids are transported in the blood combined with proteins in form of lipoprotein particles (it transports cholesterol in the blood to cells throughout the body).
- Non-polar lipids act as electrical insulators.
- Fats stored in adipose tissue acts as an important source of energy.

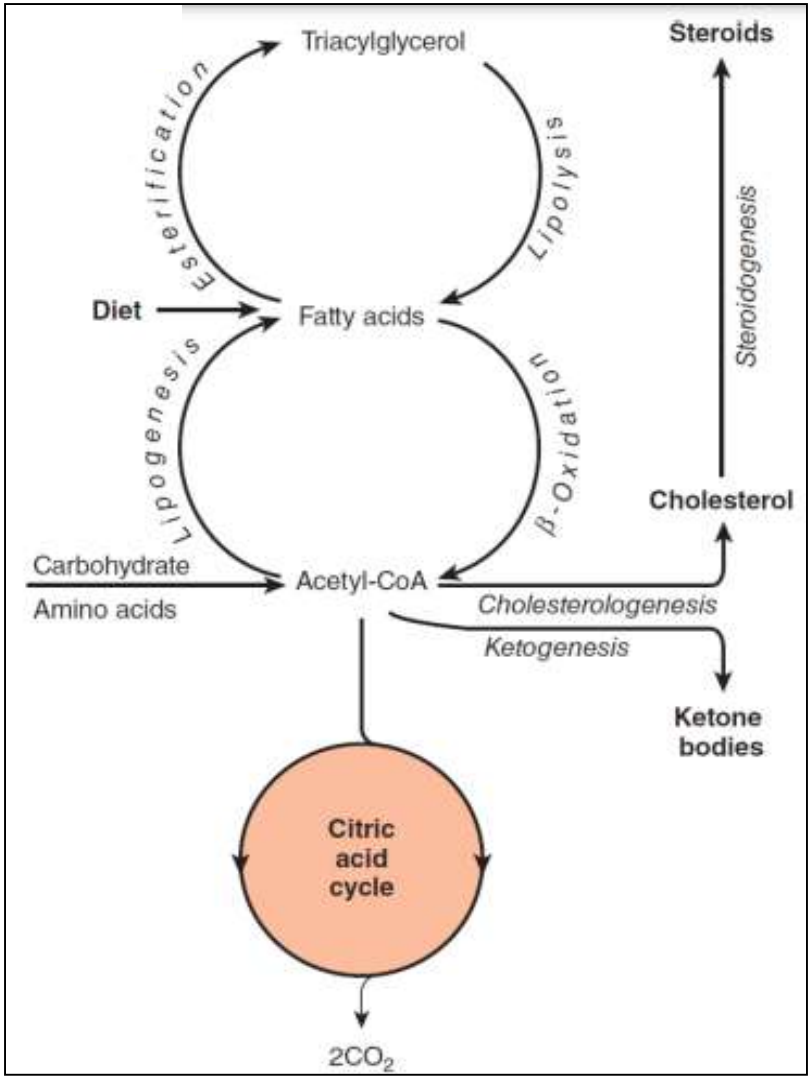
Types Of Fatty Acid oxidation

- 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 CO_2 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.

Overview of fatty acid metabolism

Showing the major pathways and end products



Beta Oxidation Of Fatty Acids

- β-oxidation of fatty acid- The break down of a fatty acid to acetyl-CoA.
- Occurs in the mitochondria
- Process is strictly aerobic
- After production Acetyl-CoA it is fed directly into the Krebs cycle.
- It occurs in many tissues including liver, kidney and heart.

Stages of β- oxidation of fatty acid

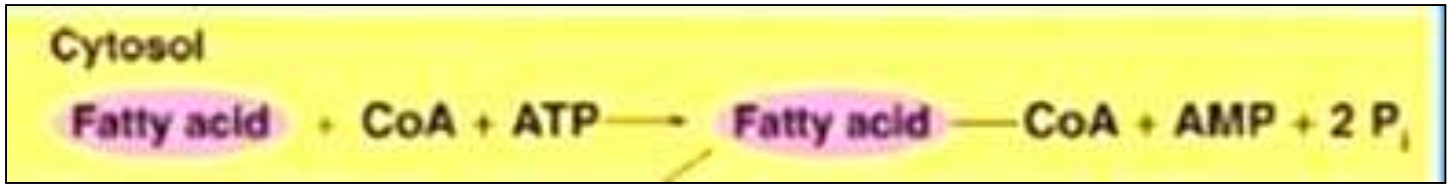
- The beta oxidation of fatty acids involve three stages:

1) Activation of fatty acids in the cytosol
2) Transport of activated fatty acids into mitochondria
3) Beta oxidation proper in the mitochondrial matrix

Stage 1

Activation of FA:

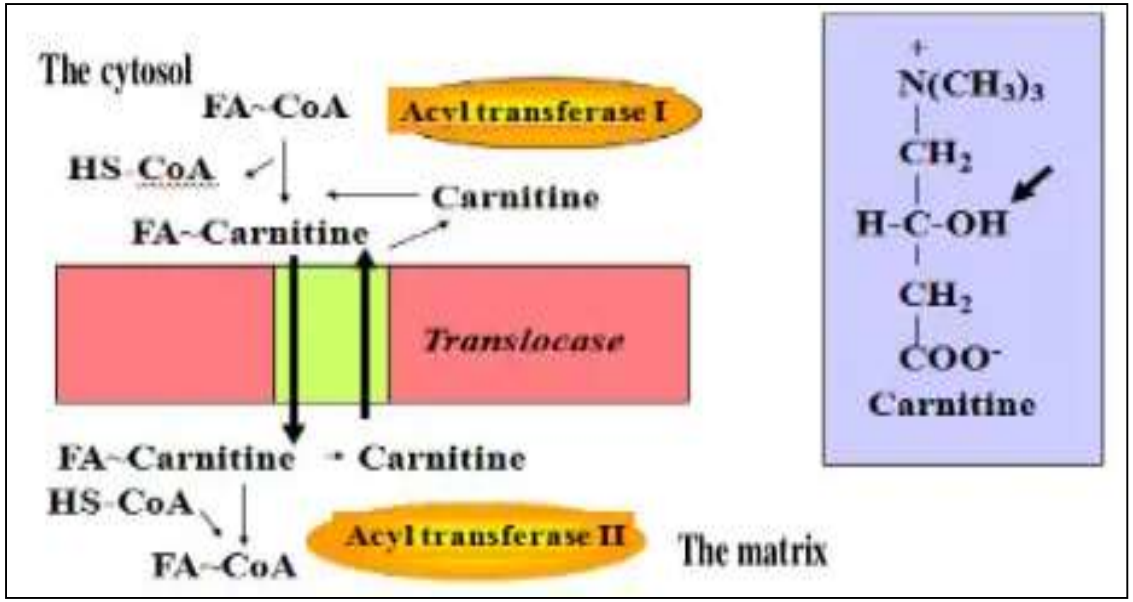
- This proceeds by FA thiokinase (acyl COA synthetase) present in cytosol
- Thiokinase requires ATP, CoASH, Mg++.
- The product of this reaction is FA acyl COA and water.



Stage 2

Part 1 : Transport of fatty acyl CoA from cytosol into mitochondria

Long chain acyl CoA trafers the inner mitochondria membrane with a special transport mechanism called Carnitine shuttle.

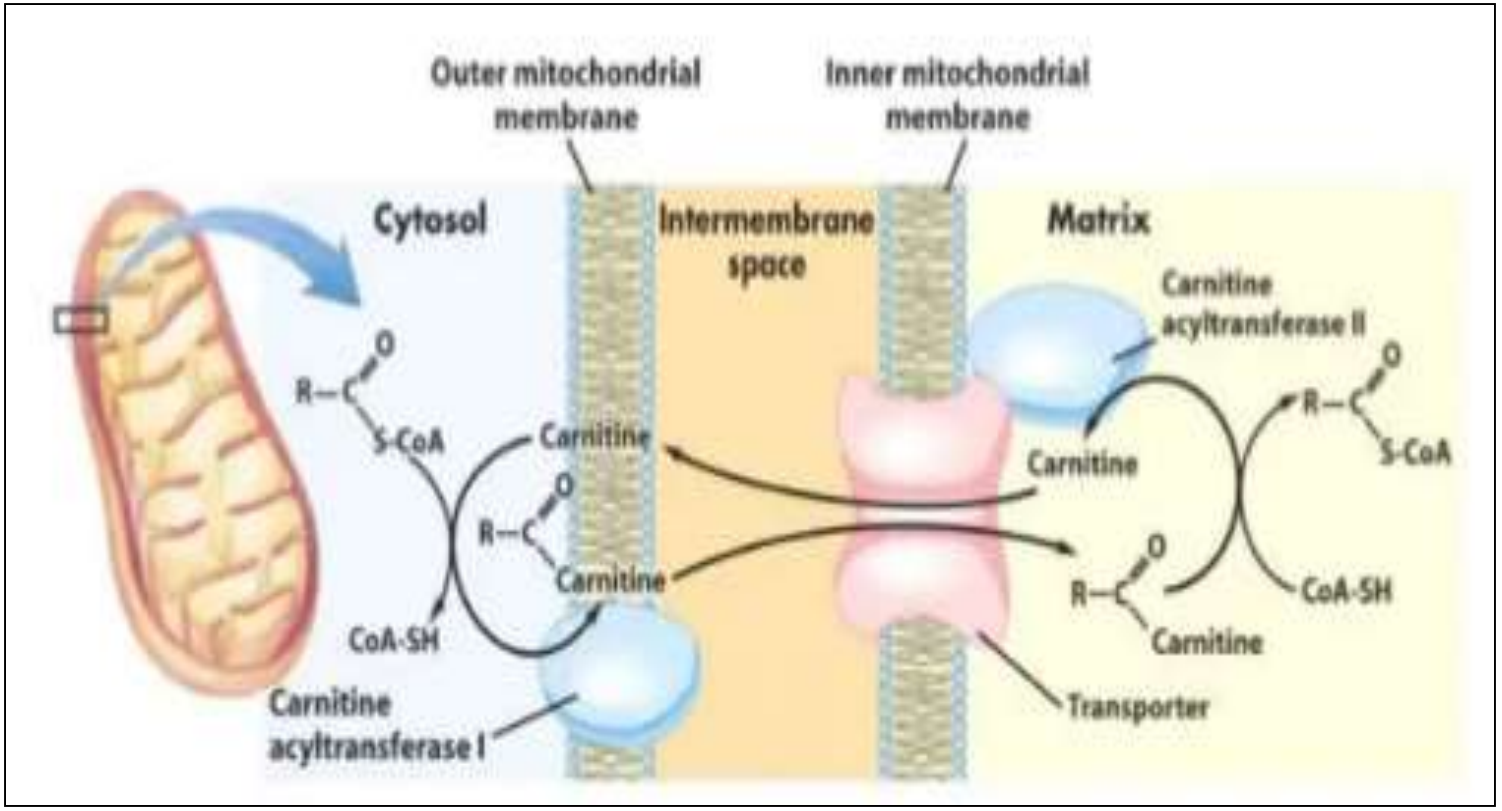


Stage 2

Part 2 : Transport of acyl CoA into the mitochondria (rate-limiting step)

1) Acyl groups from acyl COA is transferred to carnitine to form acyl carnitine catalyzed by carnitine acyltransferase I, in the outer mitochondrial membrane.
2) Acylcarnitine is then shuttled across the inner mitochondrial membrane by a translocase enzyme.
3) The acyl group is transferred back to CoA in matrix by carnitine acyl transferase II.
4) Finally, carnitine is returned to the cytosolic side by translocase, in exchange for an incoming acyl carnitine.

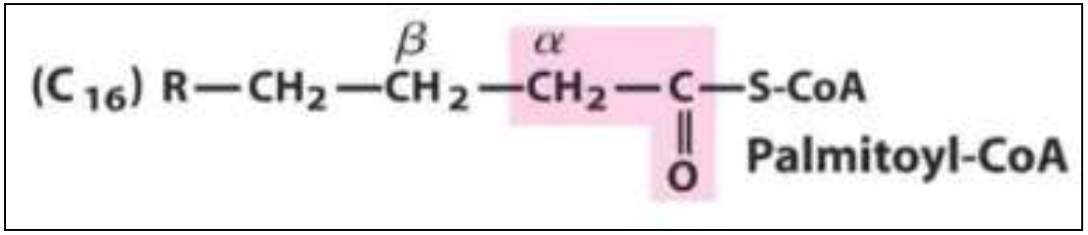
Stage 2


Outer mitochondrial membrane
Inner mitochondrial membrane
Cytosol
Intermembrane space
Matrix
Carnitine acyltransferase II
R—C(=O)—S-CoA
Carnitine
R—C(=O)
Carnitine
CoA-SH
Carnitine acyltransferase I
Carnitine
R—C(=O)—S-CoA
CoA-SH
R—C(=O)
Carnitine
Transporter

Stage 3

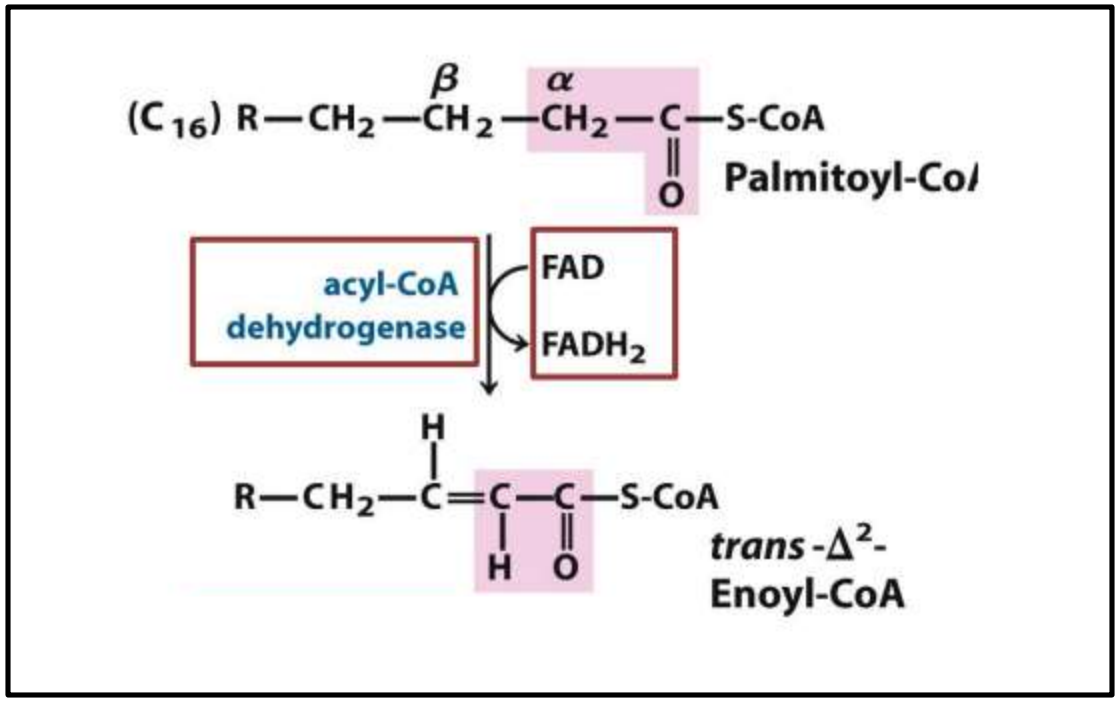
Proper of β – oxidation in the mitochondrial matrix

- <u>There are 4 steps in β – oxidation</u>
  - ✓Step I – Oxidation by FAD linked dehydrogenase
  - ✓Step II – Hydration by Hydratase
  - ✓Step III – Oxidation by NAD linked dehydrogenase
  - ✓Step IV – Thiolytic clevage Thiolase



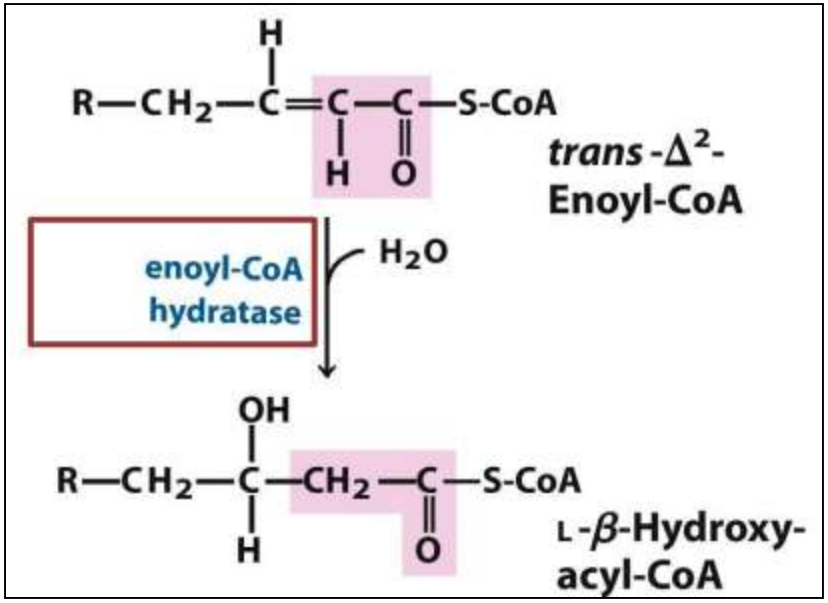
Stage 3

- The **first reaction** is the oxidation of acyl CoA by an acyl CoA dehyrogenase to give α-β unsaturarted acyl CoA (enoyl CoA). FAD is the hydrogen acceptor.



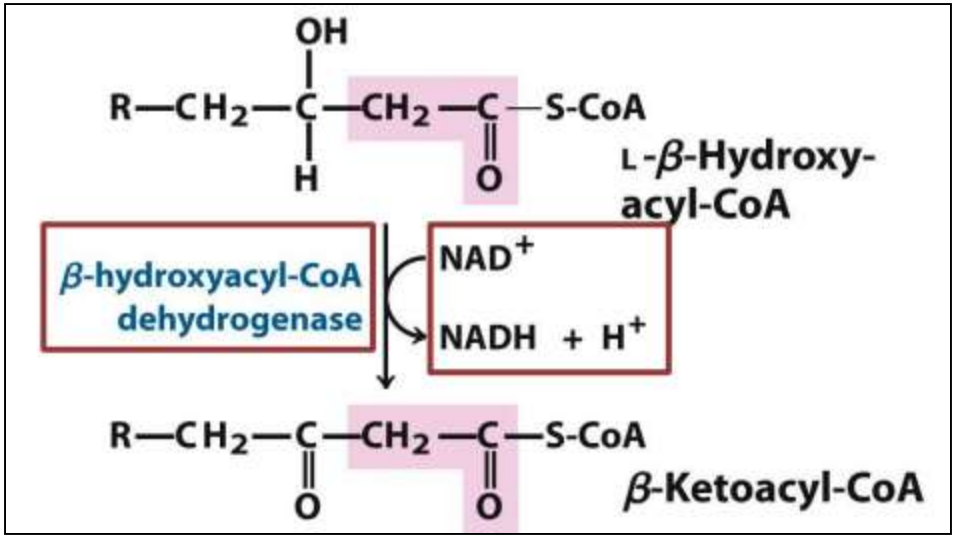
Stage 3

- The **second reaction** is the hydration of the double bond to β-hydroxyacyl CoA (p- hydroxyacyl CoA).



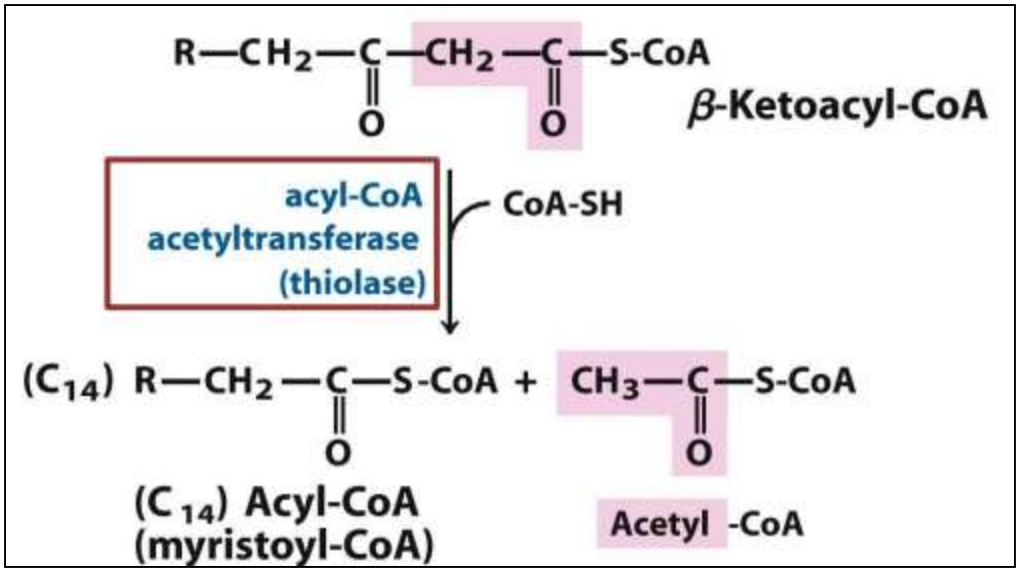
Stage 3

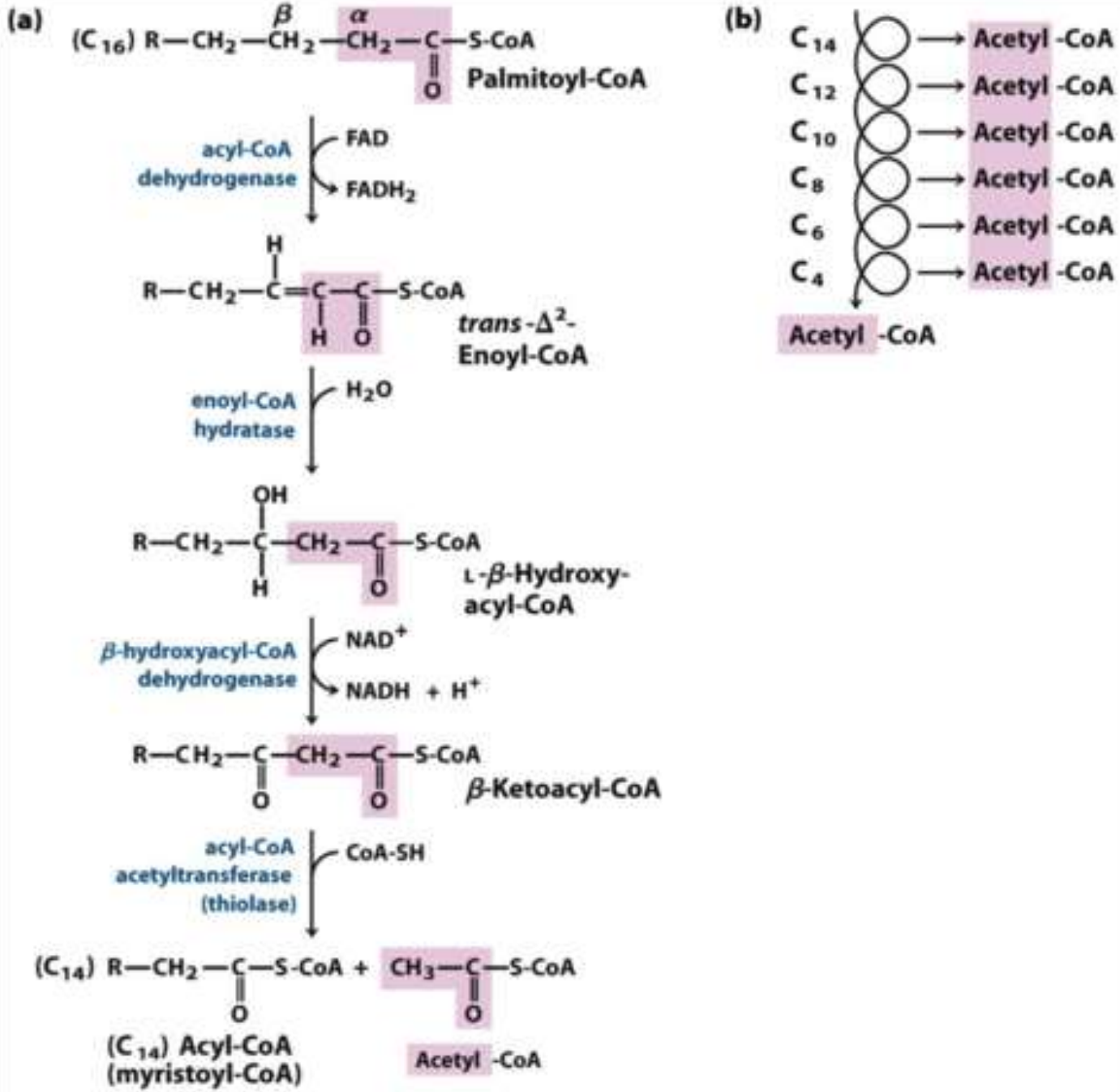
- The **third reaction** is the oxidation of β- hydroxyacyl CoA to produce β-Ketoacyl CoA a NAD-dependent reaction.



Stage 3

- The **fourth reaction** is cleavage of the two carbon fragment by splitting the bond between α and β carbons by thiolase enzyme.




(a)
β
α
(C16) R—CH2—CH2—CH2—C—S-CoA
O
Palmitoyl-CoA
acyl-CoA dehydrogenase
FAD
FADH2
H
R—CH2—C=C—C—S-CoA
H O
trans-Δ2-Enoyl-CoA
enoyl-CoA hydratase
H2O
OH
R—CH2—C—CH2—C—S-CoA
H O
L-β-Hydroxy-acyl-CoA
β-hydroxyacyl-CoA dehydrogenase
NAD+
NADH + H+
R—CH2—C—CH2—C—S-CoA
O O
β-Ketoacyl-CoA
acyl-CoA acetyltransferase (thiolase)
CoA-SH
(C14) R—CH2—C—S-CoA + CH3—C—S-CoA
O O
(C14) Acyl-CoA (myristoyl-CoA)
Acetyl -CoA
(b)
C14 → Acetyl -CoA
C12 → Acetyl -CoA
C10 → Acetyl -CoA
C8 → Acetyl -CoA
C6 → Acetyl -CoA
C4 → Acetyl -CoA
Acetyl -CoA

Beta Oxidation process

- The release of acetyl CoA leaves an acyl CoA molecule shortened by 2 carbons.
- This acyl CoA molecule is the substrate for the next round of oxidation starting with acyl CoA dehydrogenase.
- Repetition continues until all the carbons of the original fatty acyl CoA are converted to acetyl CoA.
- In the last round a four carbon acyl CoA (butyryl CoA) is cleaved to 2 acetyl CoA.

Energetics

- Energetics of FA oxidation e.g. Palmitic acid (16C):
- β-oxidation of palmitic acid will be repeated 7 cycles producing 8 molecules of acetyl COA.
- In each cycle FADH2 and NADH+H+ is produced and will be transported to the respiratory chain.

$FADH_2$ ⟶ 2 ATP
$NADH + H^+$ ⟶ 3 ATP
So 7 cycles 5x7 = 35 ATP

- Each acetyl COA which is oxidized in citric cycle gives 12 ATP (8 x 12 = 96 ATP)
- 2 ATP are utilized in the activation of fatty acid (used once).
- Energy gain = Energy produced - Energy utilized
- Energy gain = 35 ATP + 96 ATP - 2 ATP = 129 ATP

THANK YOU