Beta-Oxidation of Fatty acids

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Definition

- Beta-Oxidation may be *defined as the oxidation of fatty acids on the beta-carbon atom.*
- This results in the *sequential removal of a two carbon fragment, acetyl CoA.*

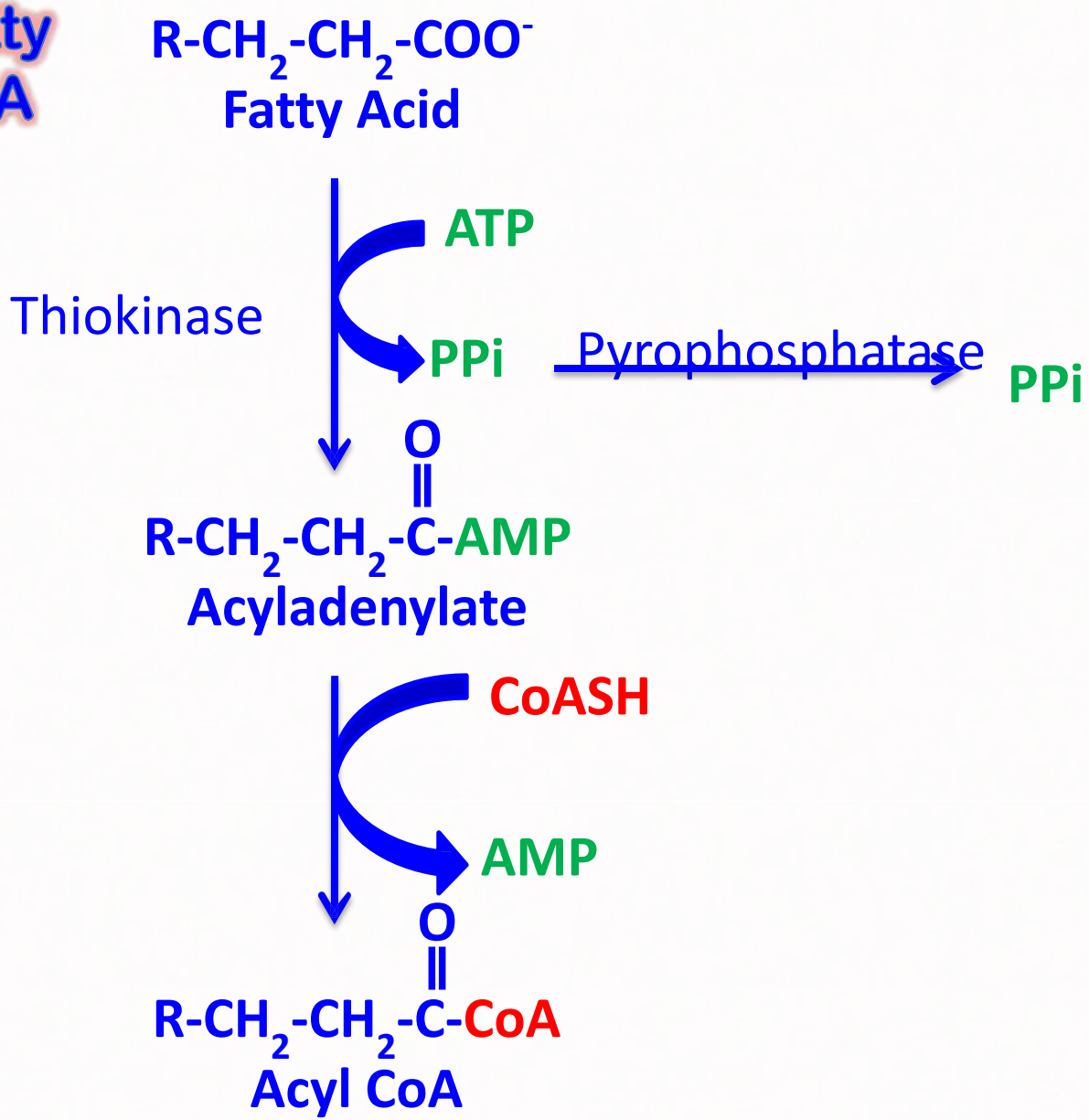
Stages and tissues

- Three stages
- Activation of fatty acids occurring in the cytosol
- Transport of fatty acids into mitochondria
- Beta-Oxidation proper in the mitochondrial matrix
- Fatty acids are oxidized by most of the tissues in the body.
- *Brain, erythrocytes and adrenal medulla cannot utilize fatty acids* for energy requirement.

Fatty acid activation

- Fatty acids are activated to acyl CoA by thiokinases or acyl CoA synthetases
- The reaction occurs in two steps and requires ATP, coenzyme A and Mg^{2+}
- Fatty acid reacts with ATP to form acyladenylate which then combines with coenzyme A to produce acyl CoA.
- Two high energy phosphates are utilized, since ATP is converted to pyrophosphate (PPi).
- The enzyme inorganic pyrophosphafase hydrolyses PPi to phosphate.
- The immediate elimination of PPi makes this reaction totally irreversible.

Activation of fatty acid to Acyl CoA



Transport of Acyl CoA into Mitochondrda

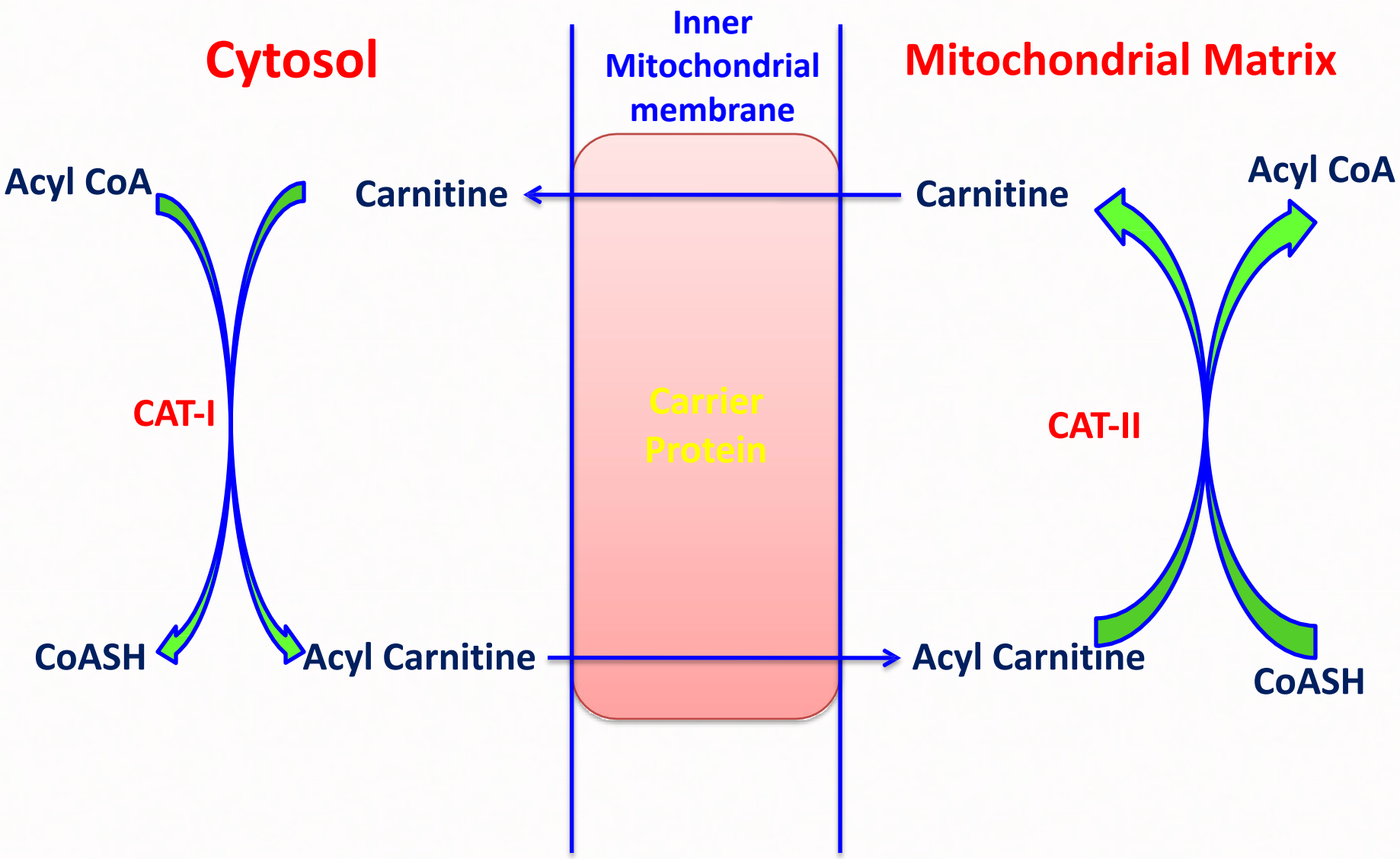
- The inner mitochondrial membrane is impermeable to fatty acids.
- A specialized carnitine carrier system (carnitine shuttle) operates to transport activated fatty acids from cytosol to the mitochondria.
- This occurs in four steps

1. Acyl group of acyl CoA is transferred to carnitine (β-hydroxy γ-trimethyl aminobutyrate)

catalyzed by *carnitine acyltransferasle (CAT)* (present on the outer surface of inner mitochondrial membrane).

2. The acyl-carnitine is transported across the membrane to mitochondrial matrix by a specific carrier protein.
3. Carnitine acyl transferase II (found on the inner surface of inner mitochondrial membrane) converts acyl-carnitine to acyl CoA.
4. The carnitine released returns to cytosol for reuse.

Carnitine transport system



β-Oxidation Proper

- Each cycle of β -oxidation, liberating a two carbon unit-acetyl CoA, occurs in a sequence of four reactions

1. Oxidation
2. Hydration
3. Oxidation
4. Cleavage

1.Oxidation

- Acyl CoA undergoes dehydrogenation by an FAD-dependent flavoenzyme, acyl CoA dehydrogenase.
- A double bond is formed between α and β carbons (i.e., 2 and 3 carbons)

2.Hydration:

- Enoyl CoA hydratase brings
- about the hydration of the double bond to form β -hydroxyacyl CoA.

3.Oxidation

- β-Hydroxyacyl CoA dehydrogenase catalyses the second oxidation and generates NADH.
- The product formed is β-ketoacyl CoA.

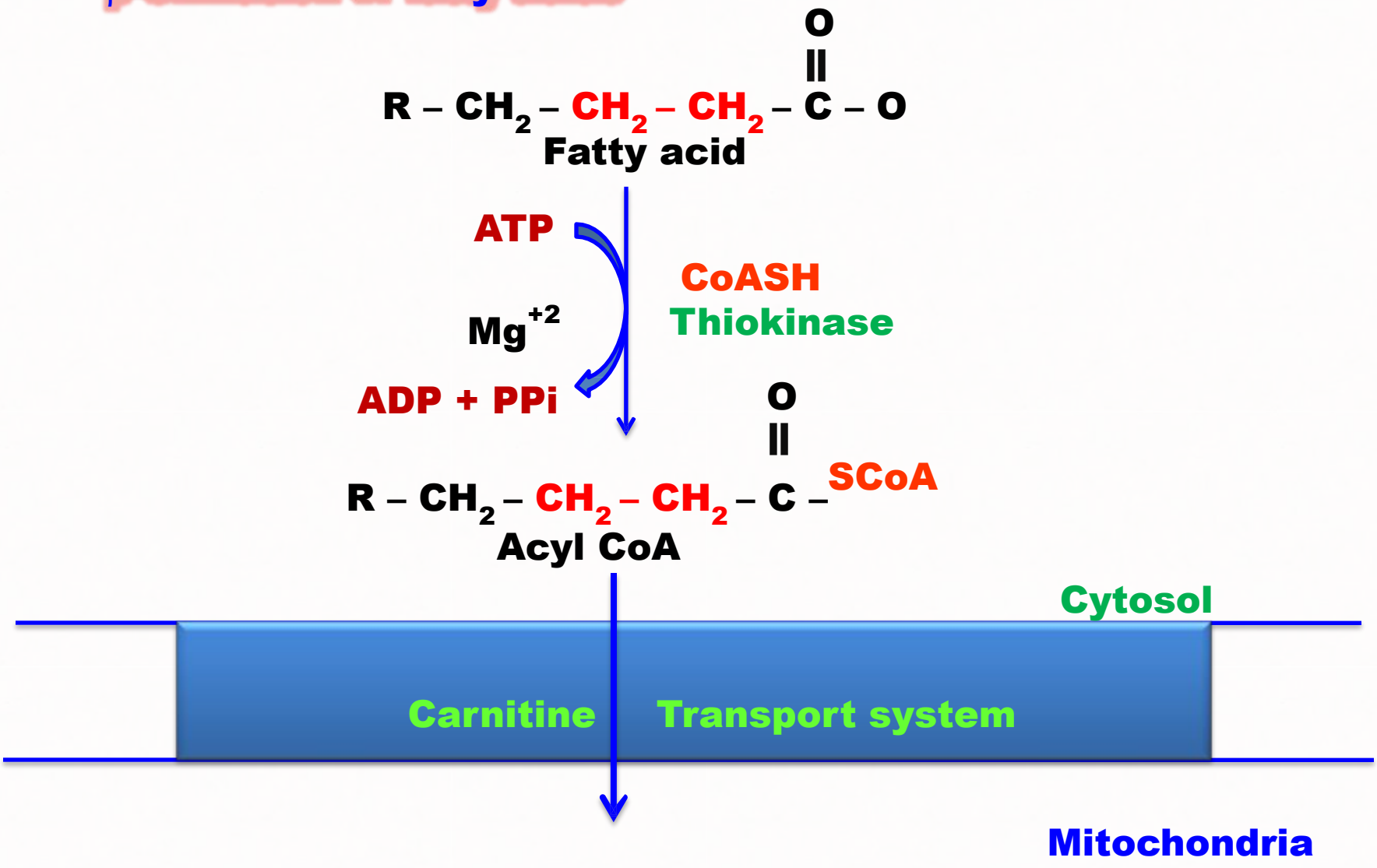
4.Cleavage

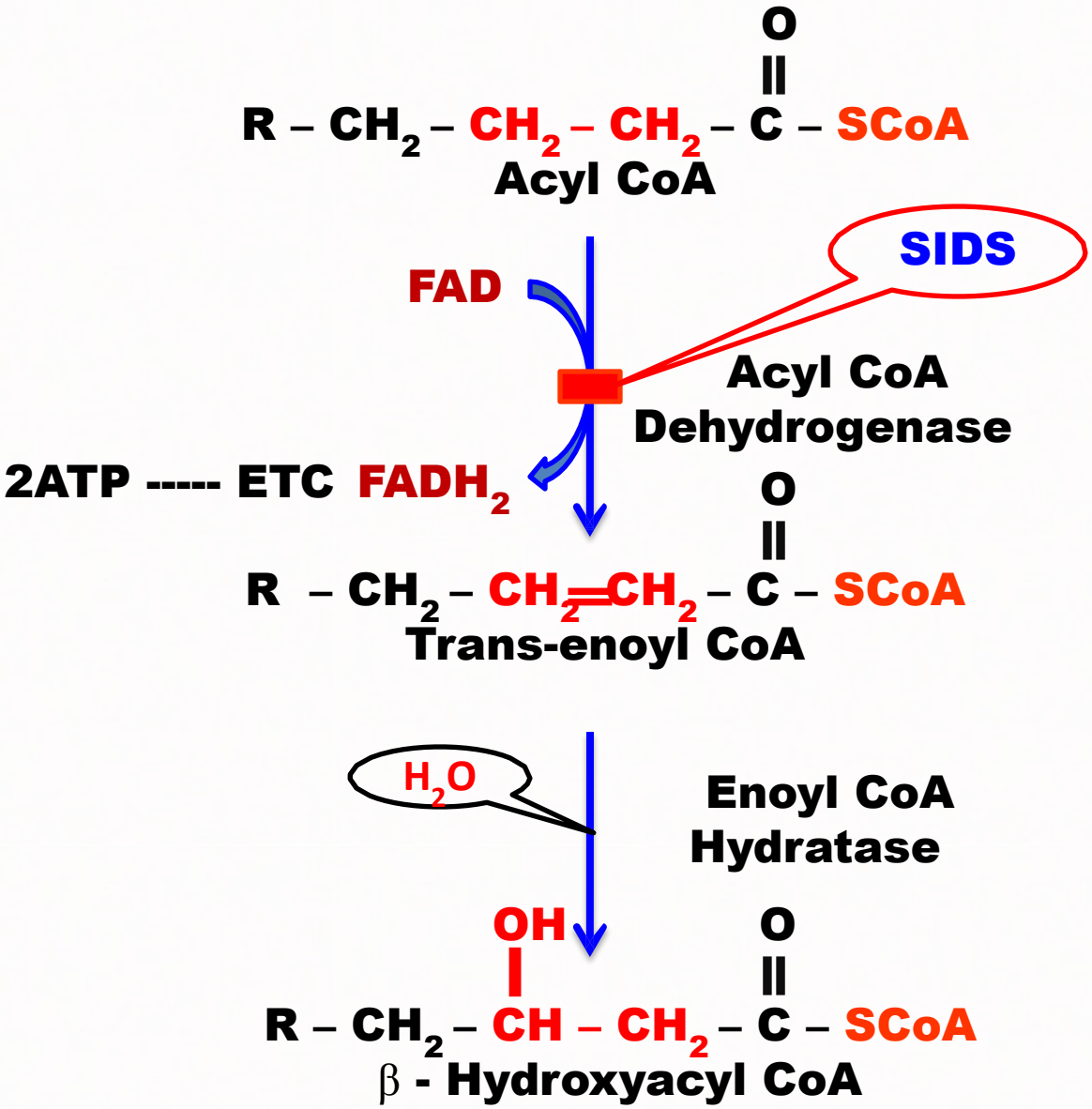
- The final reaction in β -oxidation is the liberation of a 2 carbon fragment, acetyl CoA from acyl CoA.
- This occurs by a thiolytic cleavage catalysed by β-ketoacyl CoA thiolase (or thiolase).

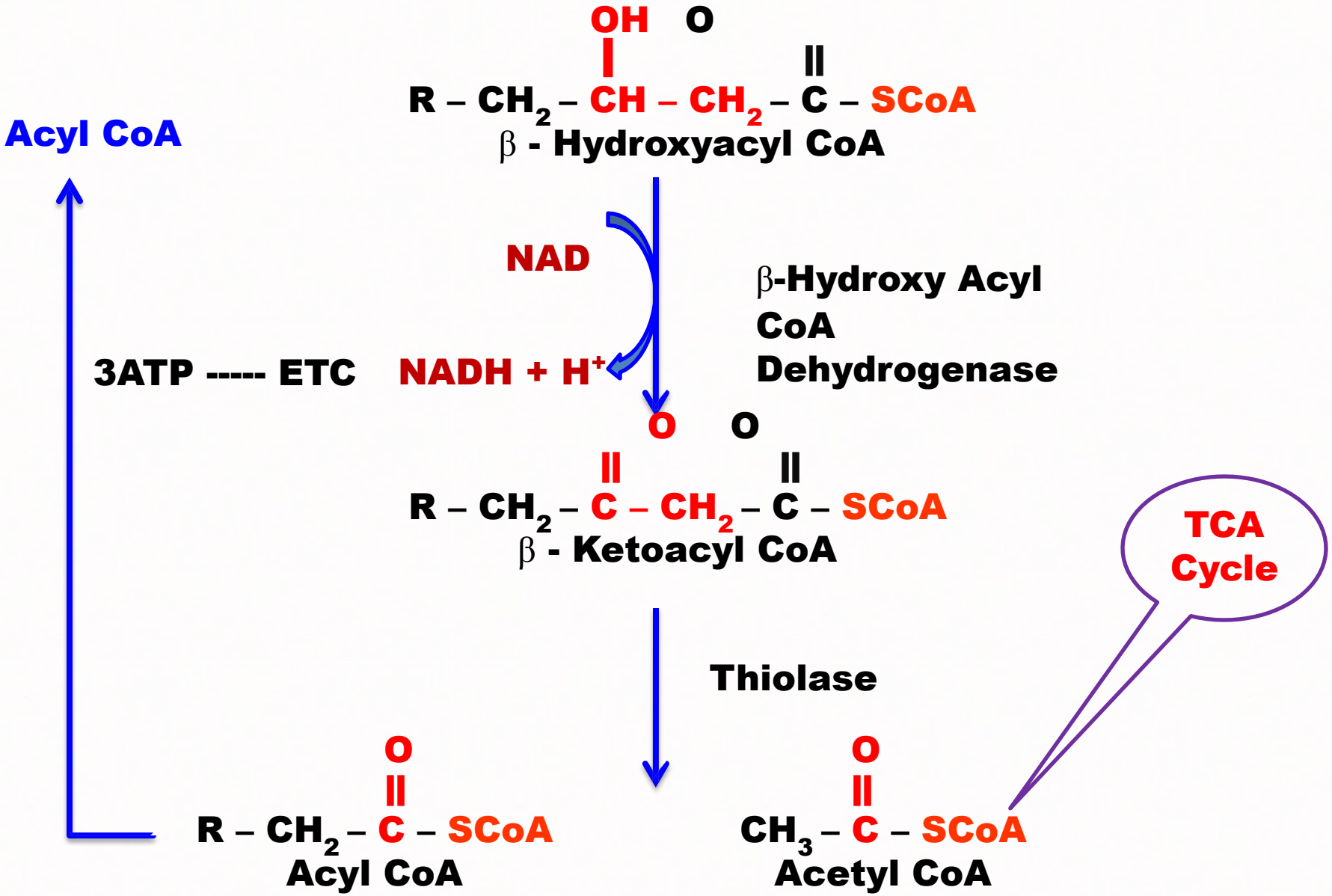
- **The new acyl CoA, containing two carbons less than the original, reenters the β-oxidation cycle.**

- ***The process continues till the fatty acid is completely oxidized.***

β-Oxidation of fatty acids




O
R – CH2 – CH2 – CH2 – C – SCoA
Acyl CoA
FAD
SIDS
Acyl CoA
Dehydrogenase
2ATP ----- ETC FADH2
O
R – CH2 – CH=CH2 – C – SCoA
Trans-enoyl CoA
H2O
Enoyl CoA
Hydratase
OH
O
R – CH2 – CH – CH2 – C – SCoA
β - Hydroxyacyl CoA


OH O
R – CH2 – CH – CH2 – C – SCoA
β - Hydroxyacyl CoA
Acyl CoA
NAD
β-Hydroxy Acyl CoA Dehydrogenase
3ATP ----- ETC
NADH + H+
O O
R – CH2 – C – CH2 – C – SCoA
β - Ketoacyl CoA
TCA Cycle
Thiolase
O
R – CH2 – C – SCoA
Acyl CoA
O
CH3 – C – SCoA
Acetyl CoA

Oxidation of palmitoyl CoA

- Palmitoyl CoA + 7 CoASH + 7 FAD^+ 7 NAD^+ + 7 H_2O → 8 Acetyl CoA + 7 $FADH_2$ + 7 NADH + 7H^+
- *Palmitoyl CoA undergoes 7 cycles of β - oxidation to yield 8 acetyl CoA.*

- *Acetyl CoA can enter citric acid cycle and get completely oxidized to CO_2 and H_2O.*

Energetics of β -oxidation

Mechanism	ATP yield
I. β- 0xidation 7 cycles 7 FADH2 [Oxidized by electron transport Chain (ETC) each FADH2 gives 2 ATP] 7 NADH (Oxidized by ETC, each NADH Liberate 3A TP)	14 21
II. From 8 Acetyl CoA Oxidized by citric acid cycle, each acetyl CoA provides 12 A TP	96
Total energy from one molecule of palmitoyl CoA Energy utilized for activation (Formation of palmitoyl Co A)	131 -2
Net yield of oxidation of one molecule of palmitate	=129

Sudden infant death syndrome (SIDS)

- **Unexpected death** of healthy infants, usually overnight
- ***Due to deficiency of medium chain acyl CoA dehydrogenase.***
- Glucose is the principal source of energy, soon after eating or feeding babies.
- After a few hours, the glucose level and its utilization decrease and the rate of fatty acid oxidation must simultaneously increase to meet the energy needs.
- The sudden death in infants is *due to a blockade in β -oxidation caused by a deficiency in medium chain acyl CoA dehydrogenase (MCAD)*

Jamaican vomiting sickness

- This disease is characterized by severe hypoglycemia, vomiting, convulsions, coma and death.
- It is caused by eating unriped ackee fruit which contains an unusual toxic amino acid, hypoglycin A.
- This inhibits the enzyme acyl CoA dehydrogenase and thus β -oxidation of fatty acids is blocked, leading to various complications

- **Abnormalities in transport of fatty acids** into mitochondria & defects in oxidation leads to deficient energy production by oxidation of long chain fatty acids.
- **Features:**
- Hypoketotic hypoglycemia, hyperammonemia, skeletal muscle weakness & liver diseases.
- **Acyl carnitine** accumulates when the transferases or translocase is deficient.
- Dietary supplementation of carnitine improve the condition.

Oxidation of odd chain fatty acids

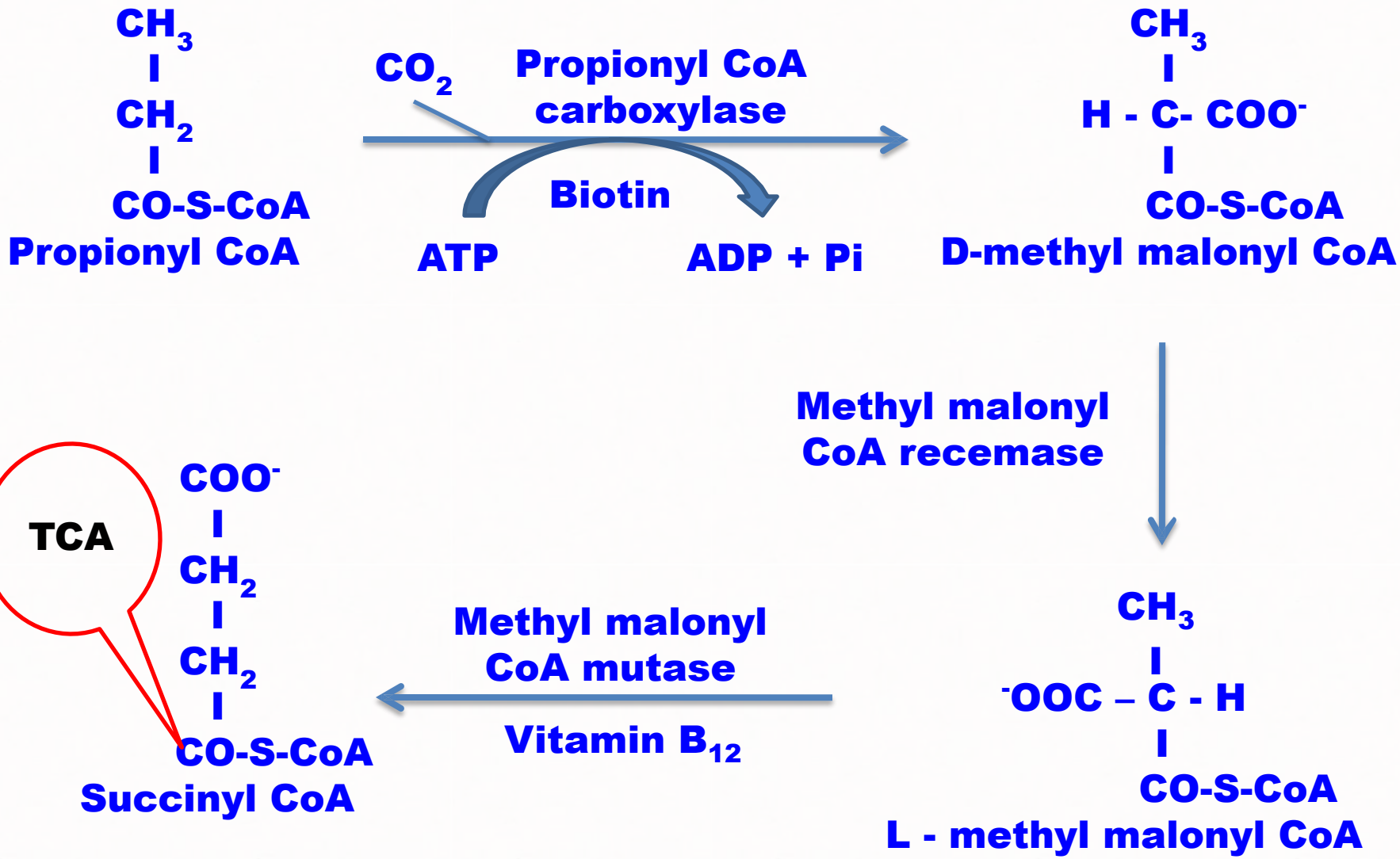
- Oxidation of odd chain fatty acids is similar to that of even chain fatty acids.
- *At the end 3 carbon unit, propionyl CoA is produced.*
- Propionyl CoA is converted into succinyl CoA.
- *Succinyl CoA is an intermediate in TCA cycle*
- *So, propionyl CoA is gluconeogenic.*

Conversion of propionyl CoA to succinyl CoA

- Propionyl CoA is carboxylated to D-methyl malonyl CoA by a ***biotin dependent carboxylase.***
- Biotin is B7 vitamin & ATP is utilized in this step.
- **Recemase:**
- Recemase acts upon D-methyl malonyl CoA to give L-methyl malonyl CoA.
- This reaction is essential for the entry of this compound into metabolic reactions of body.

- **Mutase:**
- **Mutase catalyzes the *conversion of L-methyl malonyl CoA (a branched chain compound) to succinyl CoA (a straight chain compound).***
- **Mutase is an vitamin B_{12} dependent enzyme.**
- ***Succinyl CoA enters the TCA cycle, & converted into oxaloacetate, it is used for gluconeogenesis.***
- **Propionyl CoA is also derived from metabolism of valine & isoleucine.**

Conversion of succinyl CoA to propionyl CoA



Inborn errors of propionate metabolism

- **Propionyl CoA carboxylase deficiency:**
- Characterized by propionic acidemia, ketoacidosis & developmental abnormalities.
- ***Methyl malonic aciduria:***
- Two types of methyl malonic acidemias
- Due to deficiency of vitamin B_{12}
- Due to defect in the enzyme methyl malonyl CoA mutase or recemase.
- Accumulation of methyl malonic acid in the body.

- Methyl malonic acid is excreted into urine.
- Symptoms:
- Severe metabolic acidosis, damages the central nervous system & growth retardation.
- Fetal in early life.
- Treatment:
- Some patients respond to treatment with pharmacological doses of B_{12}.

α-oxidation

- Oxidation of fatty acids on α-carbon atom is known as α-oxidation.
- In this, removal of one carbon unit from the carboxyl end.
- Energy is not produced.
- No need of fatty acid activation & coenzyme A
- Hydroxylation occurs at α-carbon atom.
- It is then oxidized to α-keto acid.
- This, keto acid undergoes decarboxylation, yielding a molecule of CO_2 & FA with one carbon atom less.

- Occurs in endoplasmic reticulum.
- Some FA undergo α - oxidation in peroxisomes.
- α- oxidation is mainly used for fatty acids that have a methyl group at the beta-carbon, which blocks beta- oxidation.
- Major dietary methylated fatty acid is phytanic acid.
- It is derived from phytol present in chlorophyll, milk & animal fats.

Refsum's disease

- Due to *deficiency of the enzyme α-hydroxylase (phytanic acid oxidase)*
- α – oxidation does not occur.
- Phytanic acid does not converted into compound that can be degraded by beta –oxidation.
- Phytanic acid accumulates in tissues.
- Symptoms:
- Severe neurological symptoms, polyneuropathy, retinitis pigmentosa, nerve deafness & cerebellar ataxia.
- Restricted dietary intake of phytanic acid (including milk-is a good source of phytanic acid)

Omega-oxidation

- Minor pathway, takes place in microsomes.
- *Catalyzed by hydroxylase enzymes involving NADPH & cytochrome P-450.*
- Methyl (CH_3) group is hydroxylated to CH_2OH & subsequently oxidized with the help of NAD^+ to COOH group to produce dicarboxylic acids.
- *When β-oxidation is defective & dicarboxylic acids are excreted in urine causing dicarboxylic aciduria.*

THANK YOU