

OXIDATION OF FATTY ACIDS

1. **Beta- Oxidation**
2. **Minor fatty acid oxidation**
 - ✓ **Alpha oxidation**
 - ✓ **Omega oxidation**
 - ✓ **Peroxisomal beta oxidation**

Major and minor fatty acid oxidation

- ***Major oxidation:***

Mitochondrial beta oxidation

- ***Minor Oxidation:***

Alpha oxidation

Omega oxidation

Peroxisomal Beta oxidation

Beta- Oxidation

- **Beta –oxidation** is defined as the oxidation and splitting of two carbon units at beta carbon atom.
- This results in sequential removal of 2 carbon fragments as **acetyl CoA** until the complete oxidation of fatty acids.
- Beta oxidation occurs almost in all tissues except, erythrocytes and adrenal medulla.

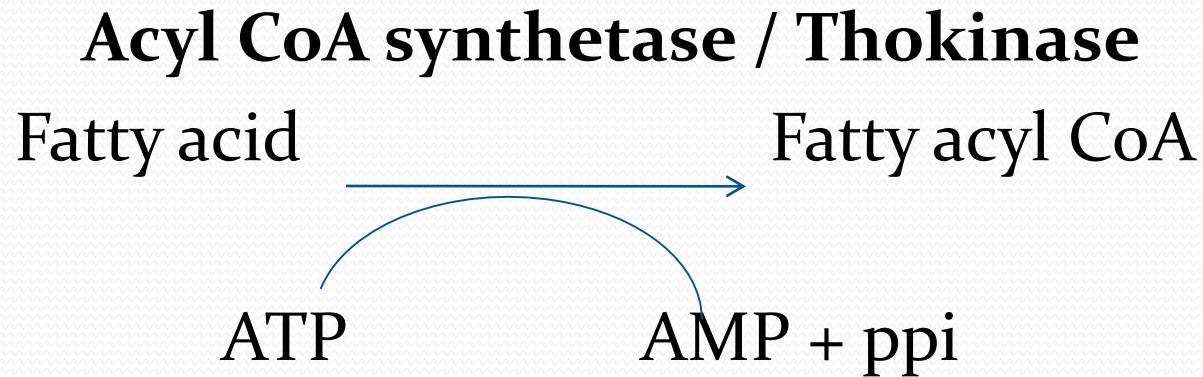
Stages of beta-oxidation

Three major steps involved :

1. *Preparative stage (Activation of fatty acid) occurs in **cytosol**.*
2. *Transport of fatty acyl CoA through carnitine shuttle, present in **mitochondrial membrane***
3. *Beta - oxidation proper in **mitochondrial matrix**.*

Activation of fatty acid

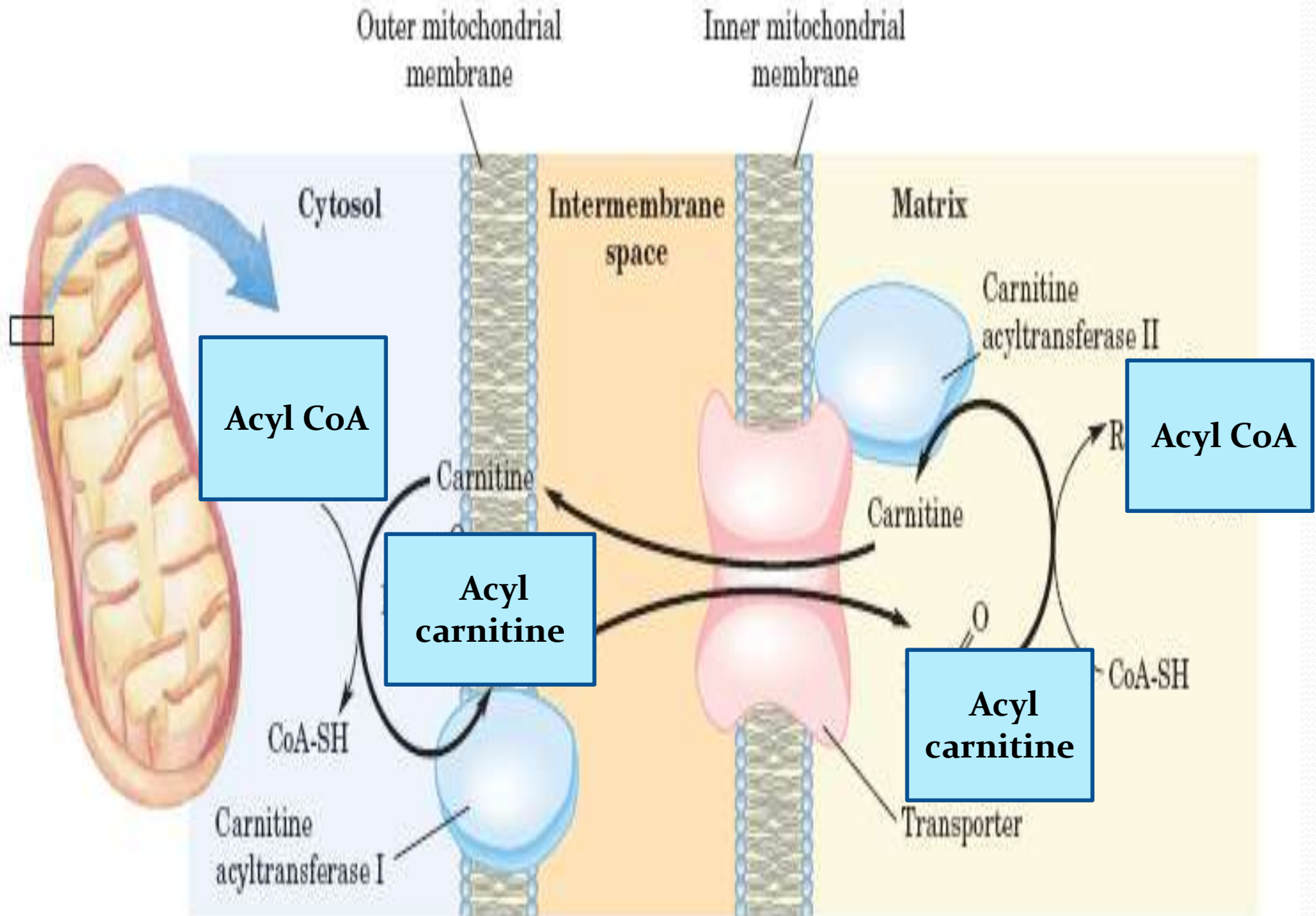
- Activation occurs in Cytosol



LCFA requires *carnitine shuttle* for transport into mitochondrial membrane

SCFA/MCFA do not require *carnitine shuttle*

Transport of Fatty acyl CoA



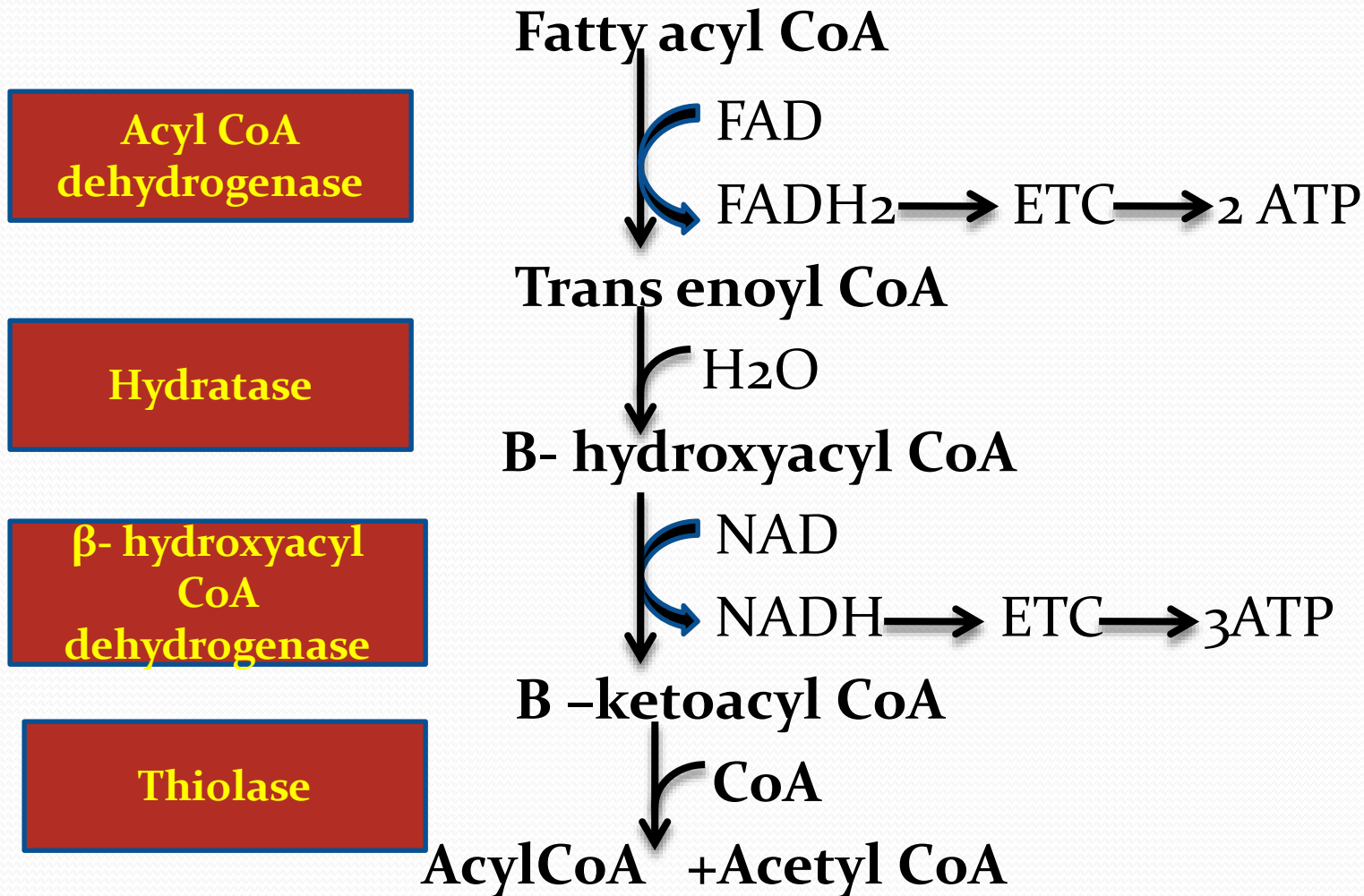
Beta oxidation proper

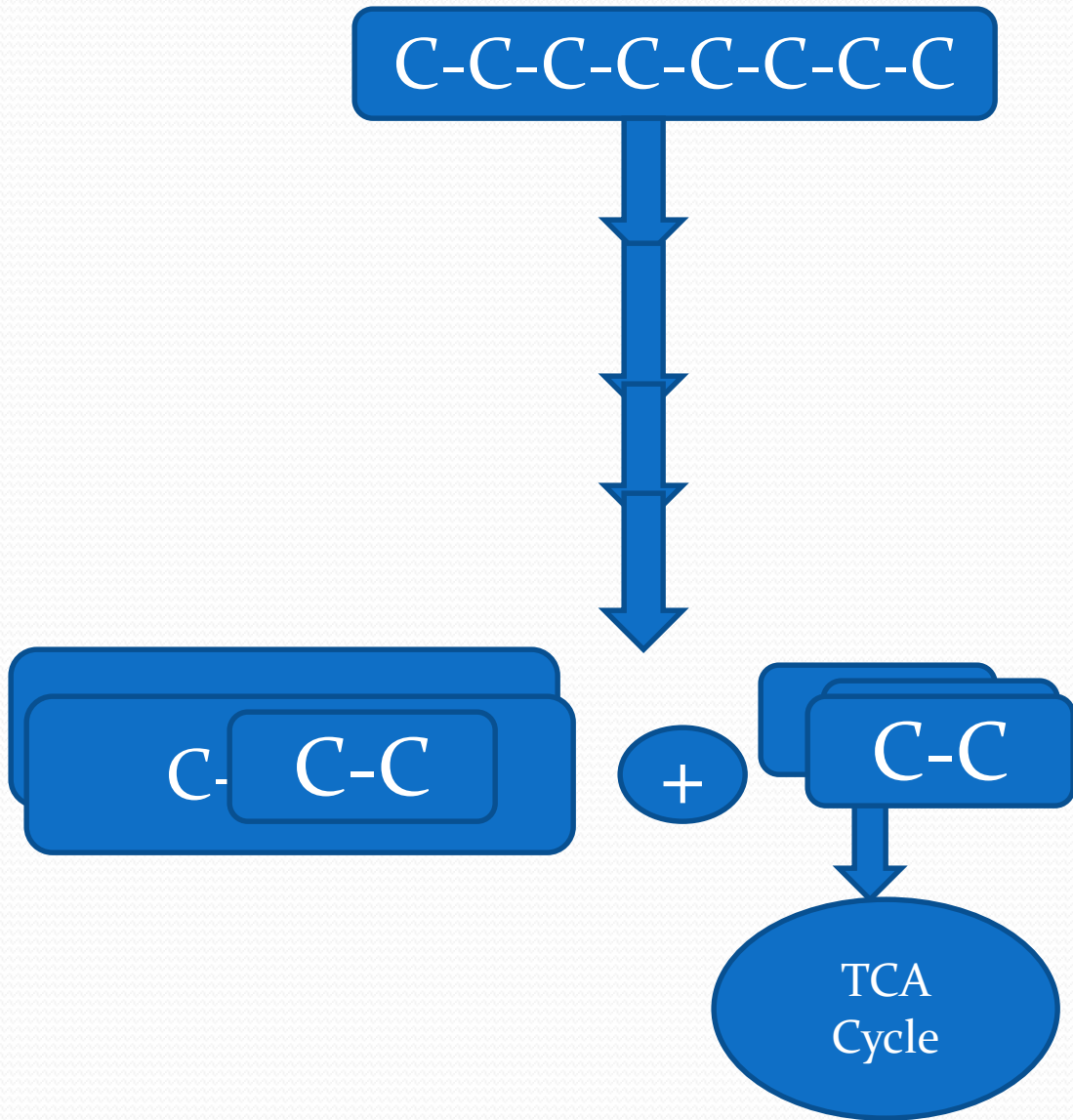
Beta oxidation proper occurs in **mitochondrial matrix** and involves **4 steps**:

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

Steps of Beta-oxidation proper

Inner Mitochondrial Membrane





FORMULA FOR CALCULATING ENERGETICS FOR EVEN CHAIN FATTY ACID

n= Number of carbon atoms present in fatty acid

Number of acetyl CoA produced = $n/2$

Number of cycles for fatty acids = $(n/2 - 1)$

Number of reduced coenzyme = $(n/2 - 1)$ (FADH₂ + NADH)

For example if 16C (palmitic acid) undergoes beta oxidation

- No. of acetyl CoA produced = 8 {1 Acetyl CoA = 12 ATP in TCA}
 $8 \times 12 = 96$ ATPs
- No. of cycles for palmitic acid = 7
- No. of reduced coenzymes produced = 7 (FADH₂ + NADH)
 $7(2+3) = 35$ ATPs
- Total no. of ATPs produced = $96 + 35 = 131$ ATPs
- No. of ATPs utilized during activation = 2 ATPs
- Net gain = $131 - 2 = 129$ (ATPs According to old energetics concept)

FORMULA FOR CALCULATING ENERGETICS FOR

ODD CHAIN FATTY ACID

- No. of acetyl coA produced = $(n-3)/2$
- No. of Cycles = $(n-3)/2$
- No. of reduced coenzymes = $(n-3)/2$ [FADH₂+NADH]
- Remaining 3C is **propionyl CoA**

For example if 17c fatty acid undergoes beta oxidation

No. of acetyl CoA = 7 { 1 acetylCoA = 12 ATP in TCA }

$$7 \times 12 = 84 \text{ ATPs}$$

No. of Cycles = 7

No. of reduced coenzymes = 7 (FADH₂ + NADH)

$$7(2+3) = 35 \text{ ATPs}$$

Total no. of ATPs produced = $84 + 35 = 119 \text{ ATPs}$

No. of ATPs utilized for activation = 2 ATPs

Net gain = $119 - 2 = 117 \text{ ATPs}$

Remaining 3C compound is propionyl CoA which converts to succinyl CoA and enters TCA cycle

β - Oxidation for odd chain fatty acid

- Beta oxidation for odd chain fatty acid occurs in the same way as for even chain fatty acid except the cleavage step yields *propionyl CoA* and *Acetyl CoA*

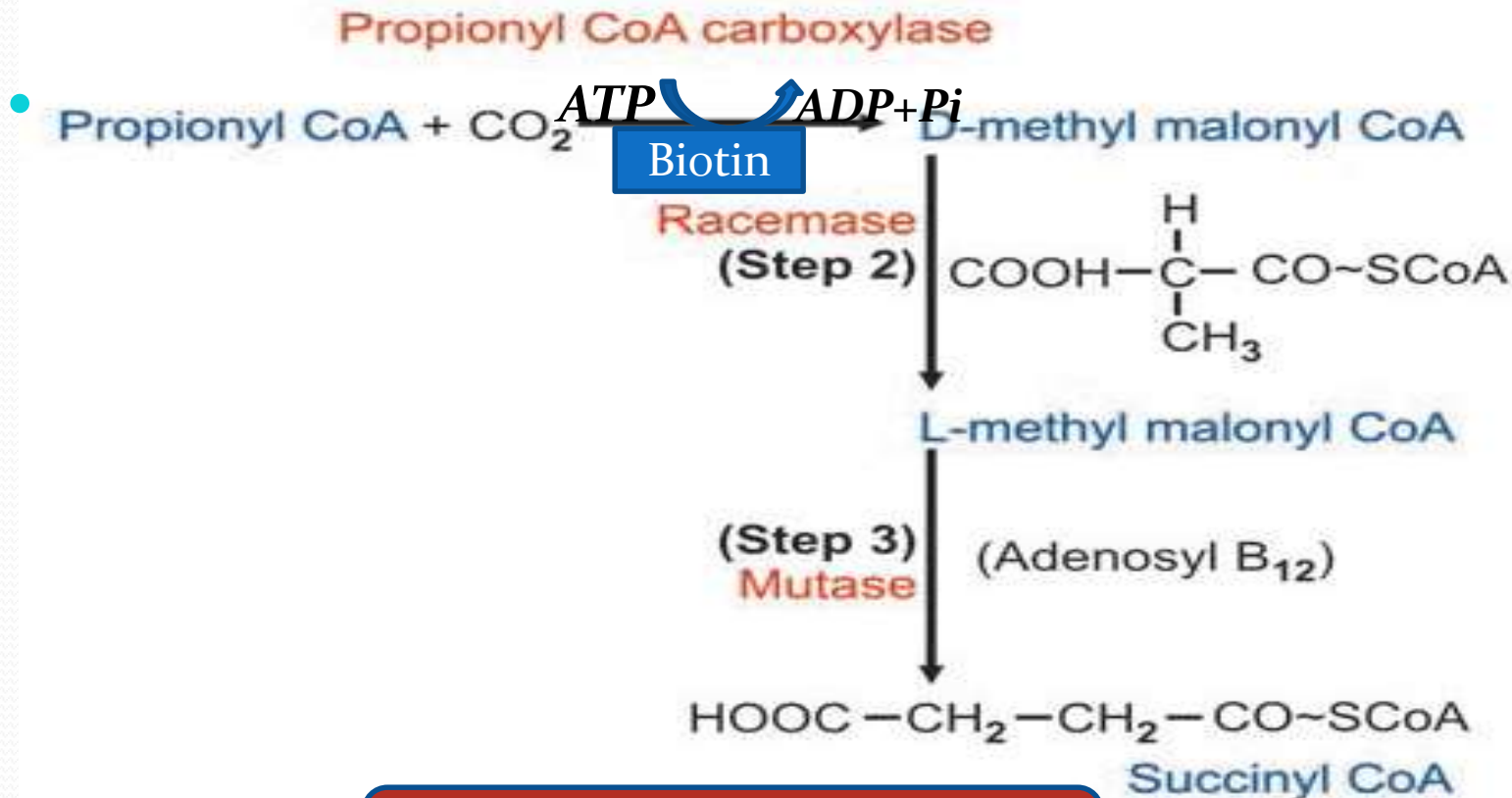


Fig: -Fate of Propionyl CoA

Regulation of beta-oxidation

- Increased availability of FFA increases the rate of beta oxidation
- Glucagon increases FFA and Insulin decreases FFA
- CAT-I is inhibited by Malonyl CoA(substrate for fatty acid synthesis). Thus during denovo synthesis of fatty acid beta oxidation is inhibited

Minor Fatty acid Oxidation

- Alpha Oxidation

- Omega Oxidation

- Peroxisomal Beta Oxidation

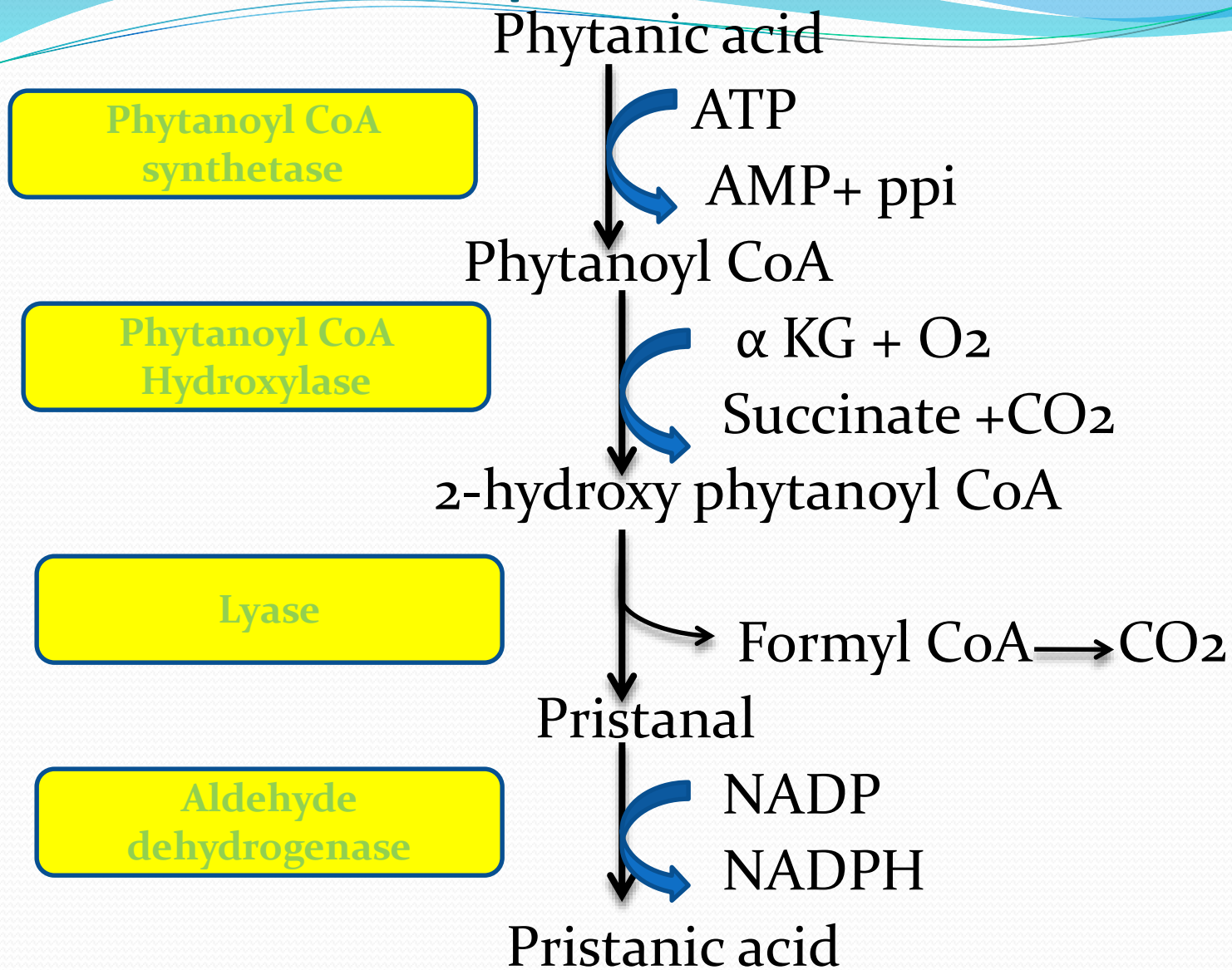
Alpha - oxidation

- *Defined as the oxidation of fatty acid (methyl group at beta carbon) with the removal of one carbon unit adjacent to the α carbon from the carboxylic end in the form of CO_2*
- *Alpha oxidation occurs in those fatty acids that have a **methyl group**(CH_3) at the beta-carbon, which blocks beta oxidation.*
- *Substrate:-**Phytanic acid**, which is present in milk or derived from phytol present in chlorophyll and animal fat*
- ***peroxisomes** is the cellular site.*
- *No production of ATP*

Steps of alpha oxidation

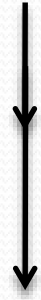
1. *Activation of phytanic acid*
2. *Hydroxylation*
3. *Removal of formyl CoA(CO₂)*
4. *Oxidation of Pristanal*
5. *Beta-oxidation of pristanic acid*

Alpha Oxidation



Pristanic acid undergoes beta oxidation

Pristanic acid



Activation

Beta oxidation proper

2- methyl propionyl CoA+ 3Acetyl CoA+ 3 Propionyl CoA

Significance of alpha oxidation

- Oxidation of methylated fatty acid
- Production of cerebronic acid which synthesizes cerebroside and sulfatides
- Production of odd chain fatty acids

Adult Refsum's Disease

Biochemical defect

- *Defect in enzyme phytanoyl CoA hydroxylase(Phytanic acid oxidase)*
- *Autosomal recessive*
- **Phytanic acid is accumulated in brain and other tissue**

lab Findings

Plasma Level of phytanic acid > 200 μ mol/L

Normal < 30 μ mol/L

Infantile Refsum's Disease

Biochemical defect

It is a disorder observed in Zellweger syndrome.

Congenital peroxisomal biogenesis disorder

Lab findings

- 1. Phytanic acid in the serum is More than $30\mu\text{mol/L}$ and less than $200\mu\text{mol/L}$***
- 2. VLCFA and LCFA in serum is increased***

Molecular Toxicology of Refsum's Disease

- *PA is directly toxic to ciliary ganglion cells and induces calcium -driven apoptosis in purkinji cells*
- *Recent studies has found that PA has a Rotenone like action in inhibiting complex -I and producing reactive oxygen species*
- *This is the reason why neuronal cells and retina rich in mitochondria are prime tissue affected in Refsum's disease*

Refsum's Disease

- ***Clinical manifestations***

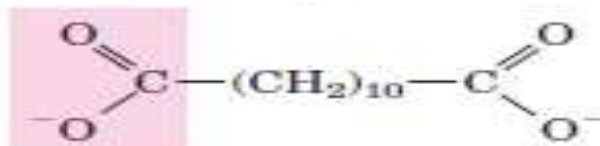
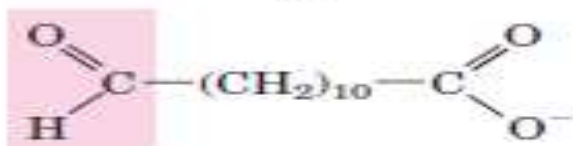
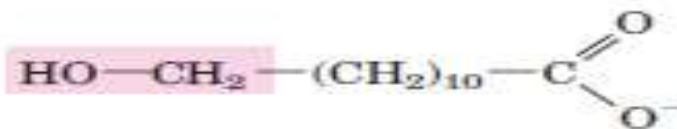
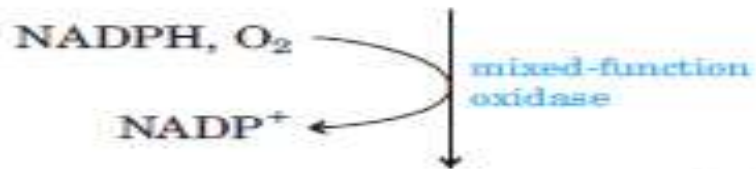
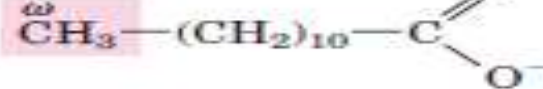
Severe neurological symptoms such as

- ✓ Polyneuropathy,
- ✓ retinitis pigmentosa,
- ✓ Nerve deafness
- ✓ Cerebellar ataxia

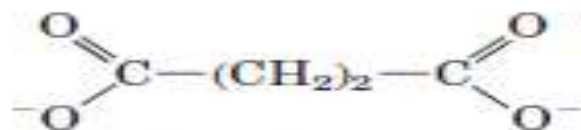
Patients should avoid intake of diet such as green vegetables and milk.

Omega(ω) Oxidation

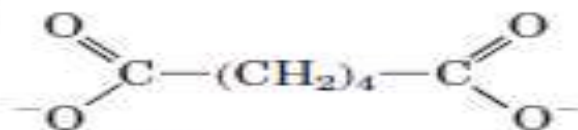
- Cellular site: Endoplasmic reticulum
- **oxidation occurs at (ω -omega) carbon**—the carbon most distant from the carboxyl group.
- Substrates : Medium and long chain fatty acid
- **Importance:** It is a minor pathway but becomes active when **beta oxidation is defective**.
- The product formed are di-carboxylic acid



β oxidation



Succinate

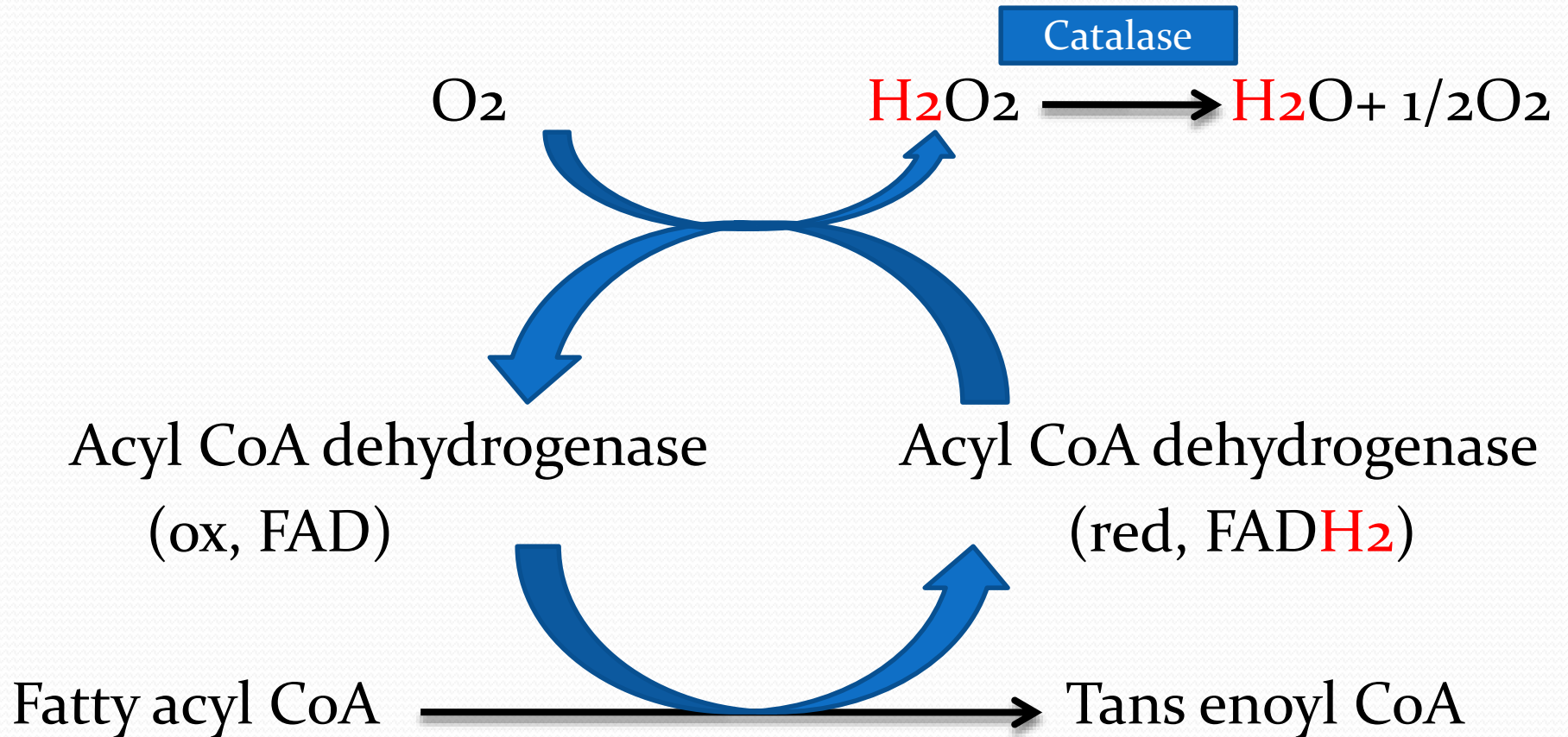


Adipate (adipic acid)

Peroxisomal Beta Oxidation

- Beta oxidation occurs in modified form in peroxisomes.
- Very Long chain fatty acids ($>C_{22}$) are often oxidized in peroxisomes.
- $FADH_2$ produced by the action of **Acyl CoA dehydrogenases** pass electrons **directly to oxygen**.
- This results in formation of **H_2O_2** .
- H_2O_2 is again cleaved by peroxisomal catalase.
- Subsequent steps are identical with their mitochondrial counterparts.
- They are carried out by different isoform of the enzymes.

Initial step of Peroxisomal beta oxidation



Zellweger syndrome

- **Biochemical defect**
- ✓ **Defect in the gene for peroxisome biogenesis**
- ✓ **reduction or absence of Peroxisomes in the cells of the liver, kidneys, and brain.**
- ✓ **VLCFA and LCFA are not oxidized and accumulates in tissue , particularly in brain ,liver and kidney.**

Lab findings:

Increased level of VLCFA in serum

Increased level of phytanic acid in serum

Medium chain acylCoA dehydrogenase deficiency (MCAD deficiency)

- Most common inborn error of **fatty acid oxidation**.
- Being found in 1:14,000 births worldwide.
- Decreased ability to oxidize fatty acids with six to ten carbons.
- MCFA accumulates in tissue and also excreted in urine.

Symptoms:

Hypoglycemia

Sleepiness

Vomiting

Fat accumulation in liver

Deficiencies of Carnitine or carnitine transferase or carnitine translocase

Causes:

- **Deficiency of carnitine**
- **Inherited CPT-I deficiency affects only the liver.**
- **CPT-II deficiency affects primarily skeletal muscle and, when severe, the liver.**

Symptoms:

- muscle cramps are precipitated by fasting, exercise and high fat diet.
- Hypoglycemia

Jamaican vomiting sickness

- Caused by eating **unripe ackee** fruit which contains unusual toxic amino acids **hypoglycin A and B**
- It inhibits enzyme **acyl CoA dehydrogenase** .
- Beta-oxidation is blocked leading to serious complications.
- Symptoms :
Severe hypoglycemia
vomiting
Convulsions
Coma



Ackee fruit