Oxidation of odd chain saturated and unsaturated fatty acids

By

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Beta Oxidation:

- Most common oxidation of fatty acids
- Oxidation of fatty acid on the beta carbon .
- Sequential removal of a two carbon fragment as acetyl CoA

SIGNIFICANCE : ENERGY PRODUCTION

Sites: occurs in most of the tissues

Absent in brain , RBC, and adrenal medulla **cannot utilize fatty acids for energy.**

Sub cellular organelle : enzymes in mitochondrial matrix

- It is one of the important catabolic (oxidative) pathways.
- Beta oxidation is more active in starvation

Beta oxidation of even number saturated fatty acids –palmitic acid (16)

Three steps :

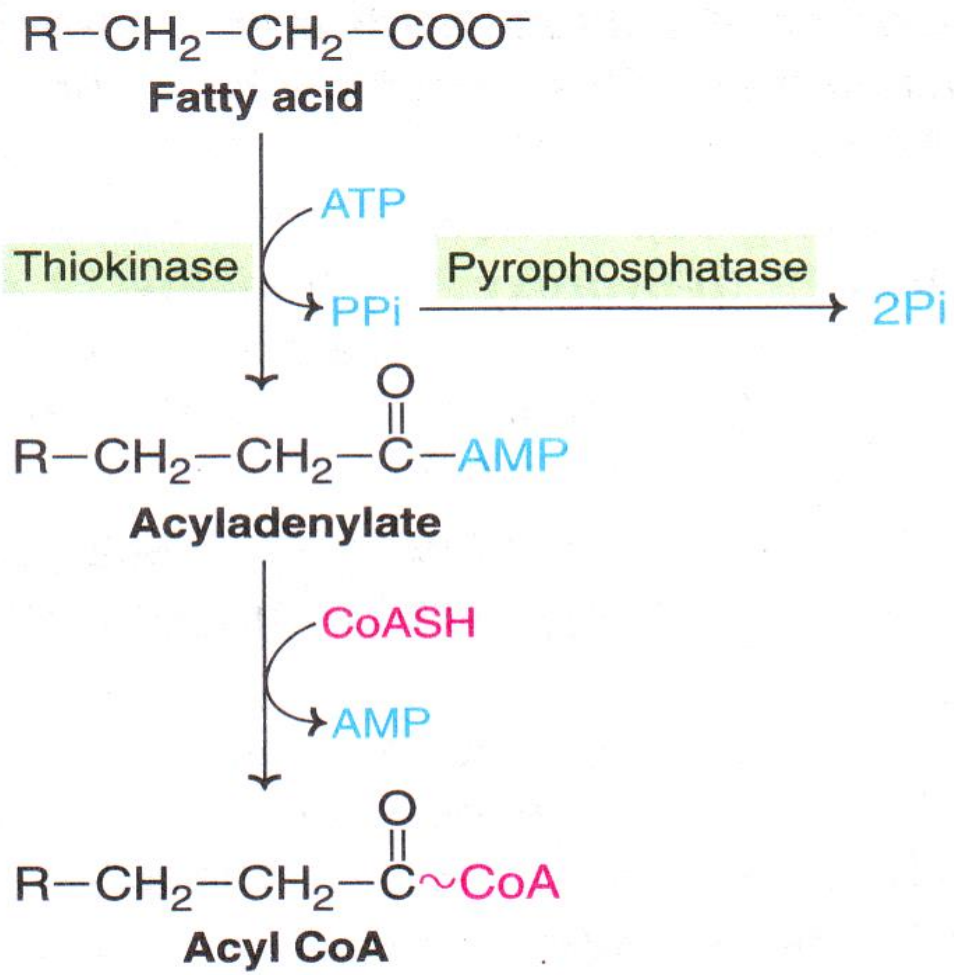
- Activation of fatty acids in cytosol
- Transport of activated fatty acid into mitochondria by carnitine
- Beta oxidation proper

1. Activation of fatty acid in cytosol

Thiokinase / acylCoA synthetase

Fatty acid+ATP+CoA SH ⟶ fattyacyl CoA +AMP+ppi

Activation of FA



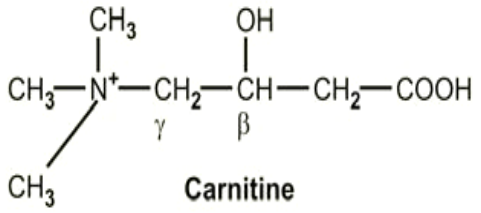
2. Transport of activated fattyacyl CoA into mitochondria via carnitine shuttle.

Carnitine:

- Carnitine is Beta- hydroxy - gamma- trimethyl ammonium butyrate
- Widely distributed in yeast , milk, liver
- Carnitine is synthesized in liver and kidney from **lysine and methionine** and stored in muscle.

Deficiency:

- Seen in premature infants- due to decreased synthesis or renal leakage
- In patients on dialysis

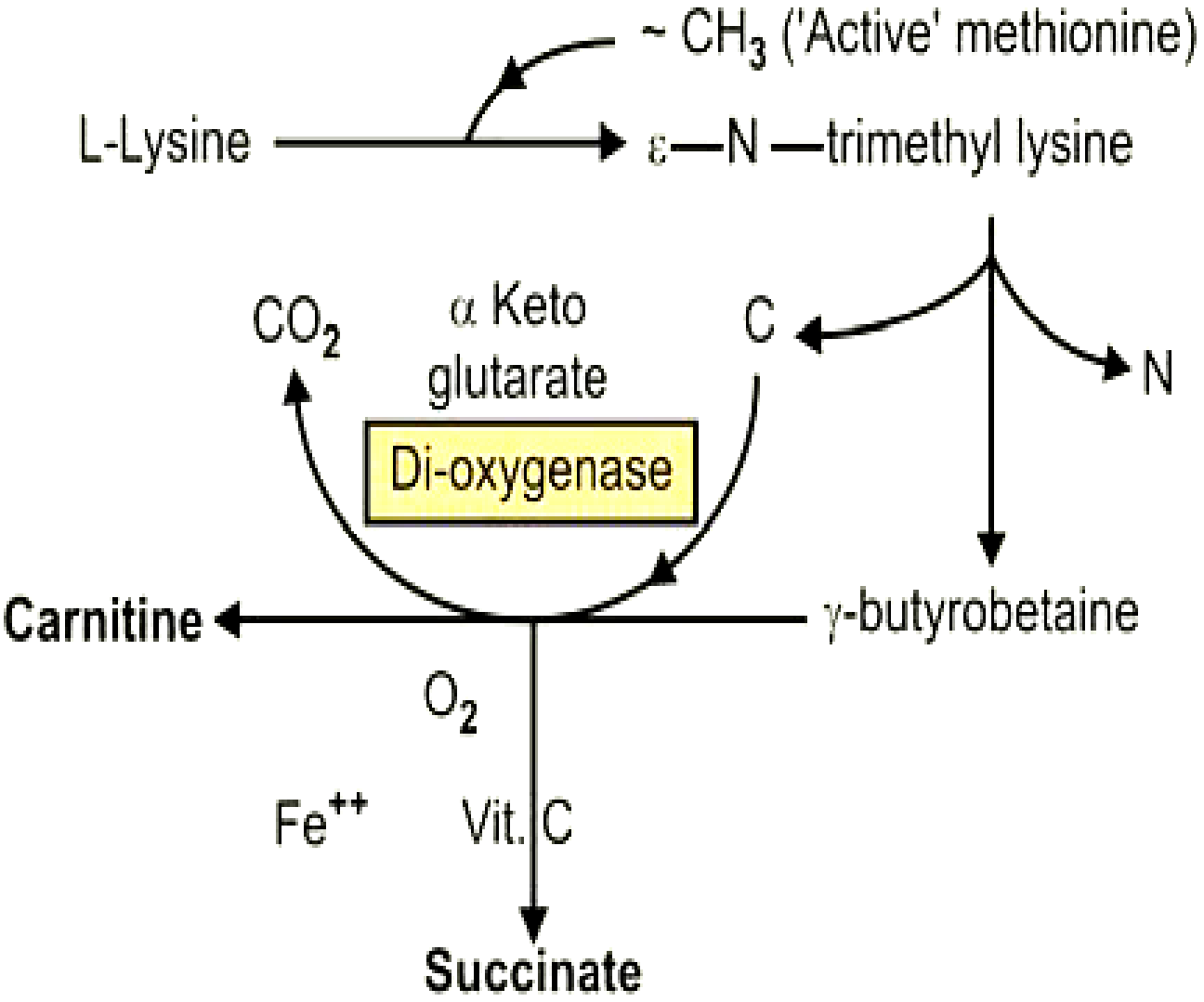


Carnitine

Symptoms: hypoglycemia

Treatment : oral supplementation of carnitine

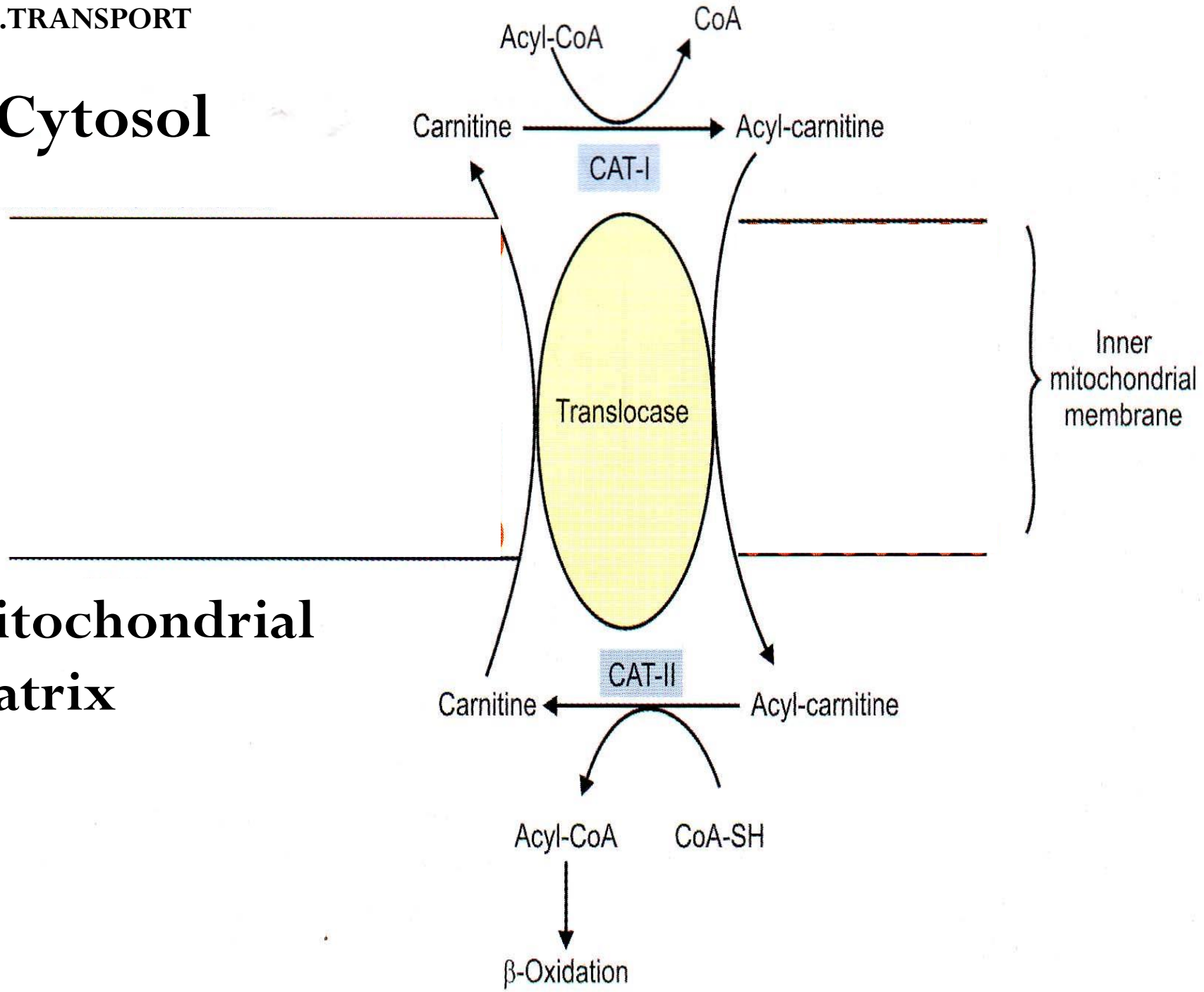
Biosynthesis of Carnitine



Transport Of Acyl CoA Into Mitochondria

- The inner mitochondrial membrane is impermeable to fatty acids.
- Carnitine carrier system (carnitine shuttle) transport active fatty acids from cytosol to mitochondria.
- Occurs in 4 steps

2.TRANSPORT


Cytosol
Acyl-CoA
CoA
Carnitine
Acyl-carnitine
CAT-I
Translocase
Inner mitochondrial membrane
Mitochondrial Matrix
CAT-II
Carnitine
Acyl-carnitine
Acyl-CoA
CoA-SH
β-Oxidation

- The cell has 2 separate pools (cytosolic and mitochondrial) of coenzyme A.

- CAT- I is inhibited by malonyl CoA, a key metabolite involved in fatty acid synthesis.

3. **Betaoxidation proper steps**

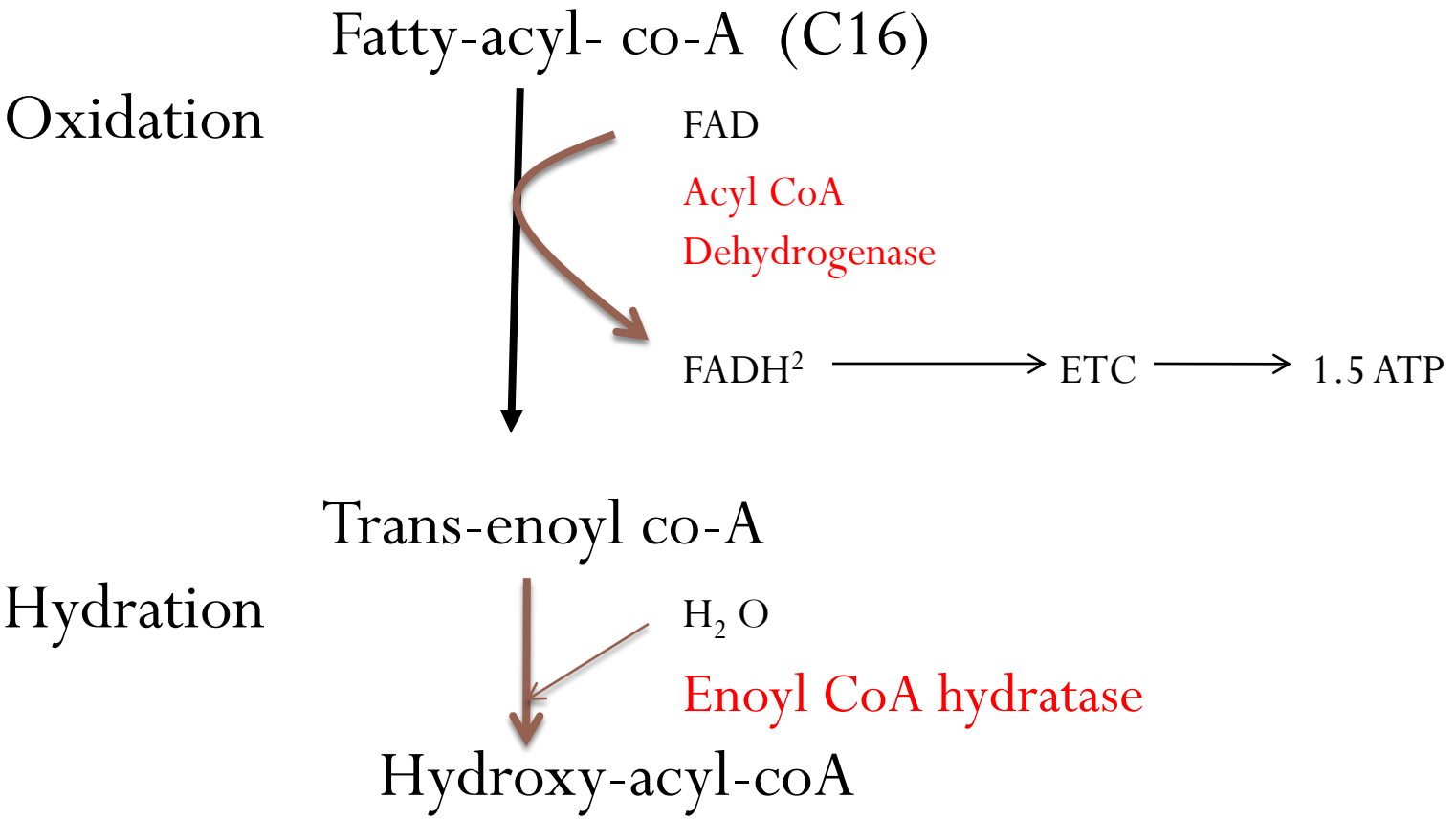
a. Oxidation by FAD

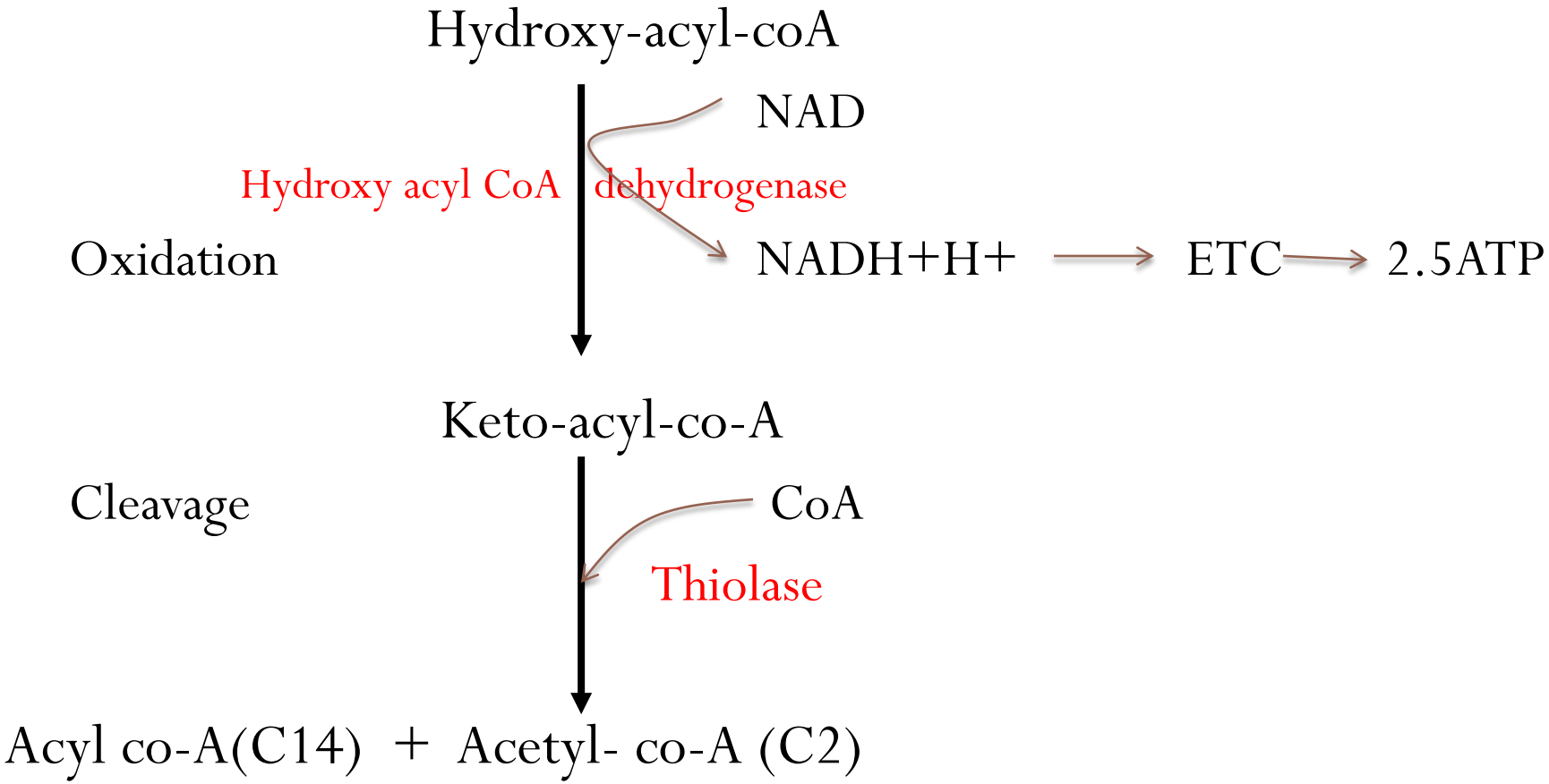
b. Hydration

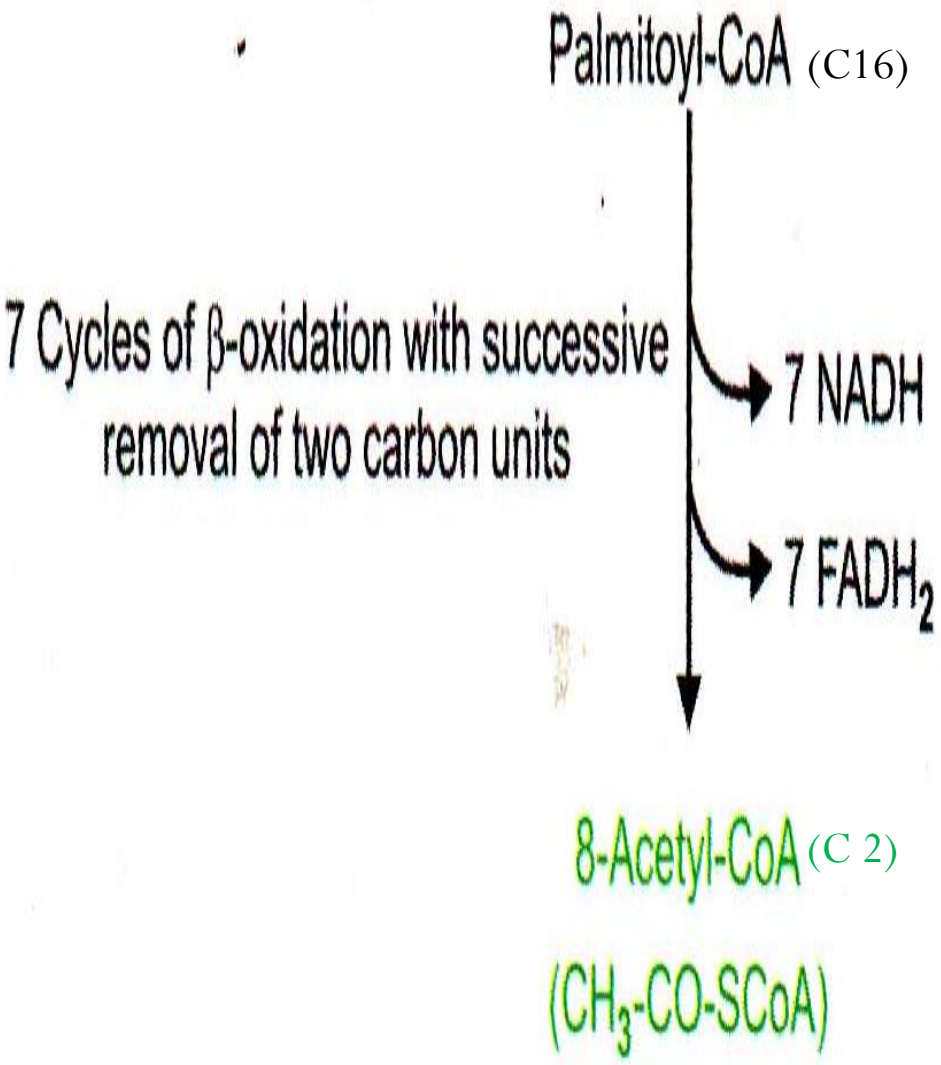
c. Oxidation by NAD

d. Thiolysis

BETA OXIDATION




Hydroxy-acyl-coA
NAD
Hydroxy acyl CoA dehydrogenase
Oxidation
NADH+H+
ETC
2.5ATP
Keto-acyl-co-A
Cleavage
CoA
Thiolase
Acyl co-A(C14) + Acetyl- co-A (C2)



- Palmitic acid is a 16 carbon(even) saturated fatty acid.

- It undergoes 7 cycles of betaoxidation producing 8 acetyl CoA which enters TCA cycle

ENERGITICS of complete oxidation of Palmitate

				Old concept	New concept
7 $FADH_2$ ----------	7	X	2	= 14 ATP	(10.5 ATP)
7 NADH ----------	7	X	3	= 21 ATP	(17.5 ATP)
8 Acetyl- coA --------	8	X	12	= 96 ATP	(80 ATP)
				131	(108 ATP)
Activation of fatty acid				- 2	
NET ATP formed				= 129	(106 ATP)

Disorders of oxidation of fattyacids :

Sudden infant death syndrome(SIDS):

- Sudden, Unexpected death of a healthy infants usually overnight.

Cause : deficiency of medium chain acyl CoA dehydrogenase leads to block in betaoxidation of fatty acids.

- When the baby does not get feeding for 12 hrs or more, the glucose levels in blood are depleted leading to hypoglycemia.
- Due to the blockage in betaoxidation, fatty acids do not meet the energy requirements.
- This cause sudden death overnight.

Jamaican vomiting sickness :

- Caused by intake of unripe ackee fruit , that contains hypoglycin A
- This inhibits acyl CoA dehydrogenase

Oxidation of odd chain saturated fatty acids:

- Cow's milk contains significant quantity of odd chain fatty acids.
- Steps are similar to that of oxidation of even number saturated fatty acids , except that in the final betaoxidation cycle.
- The end products of final cycle are a three carbon fragment **PROPIONYL CoA** and a two carbon molecule ACETYL COA (3+2) rather than 2 molecules of acetyl CoA (2+2).
- Propionyl CoA is not a substrate for enzymes of betaoxidation.
- Hence the pathway terminate here and takes different pathway.

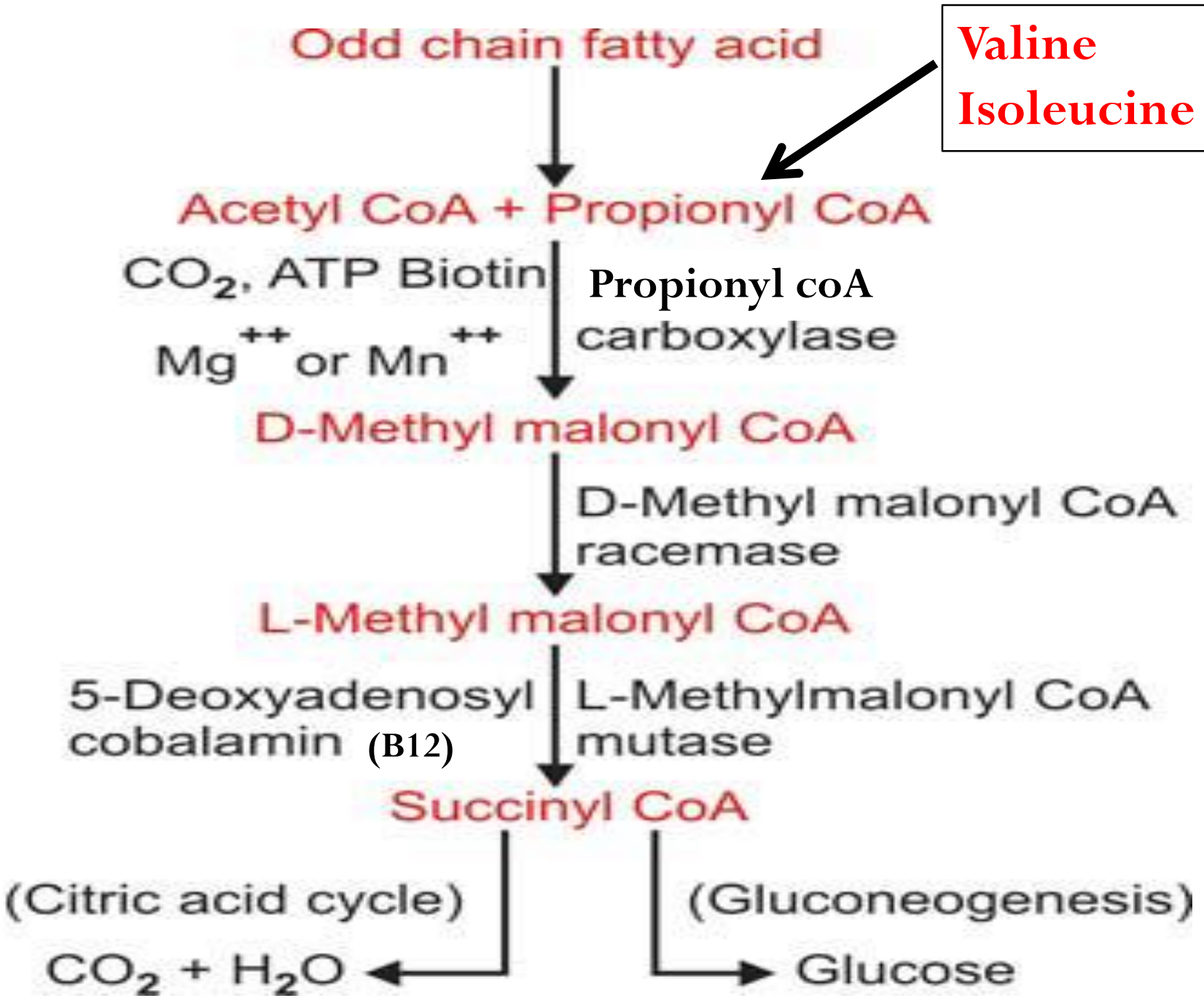
- Propionyl-CoA formed from an odd-chain FA is the only part of the FA which is glucogenic.
- Propionyl CoA is also derived from the metabolism of **valine and isoleucine**

Fate of Propionyl CoA

- Propionyl CoA is converted to SUCCINYL CoA through the formation of intermediates D-methyl malonyl CoA and L-methyl malonyl CoA.

Fate of Succinyl CoA

- Succinyl CoA either enters the citric acid cycle for oxidation or utilized for the gluconeogenesis.


Odd chain fatty acid
Valine
Isoleucine
Acetyl CoA + Propionyl CoA
CO_2, ATP Biotin
Mg^{++} or Mn^{++}
Propionyl coA carboxylase
D-Methyl malonyl CoA
D-Methyl malonyl CoA racemase
L-Methyl malonyl CoA
5-Deoxyadenosyl cobalamin (B12)
L-Methylmalonyl CoA mutase
Succinyl CoA
(Citric acid cycle)
$CO_2 + H_2O$
(Gluconeogenesis)
Glucose

Inborn Errors of Propionate Metabolism

Propionyl CoA carboxylase deficiency:

It is characterized by

- **Propionic acidemia**
- **Ketoacidosis**
- **Mental abnormalities**

Methyl malonic aciduria:

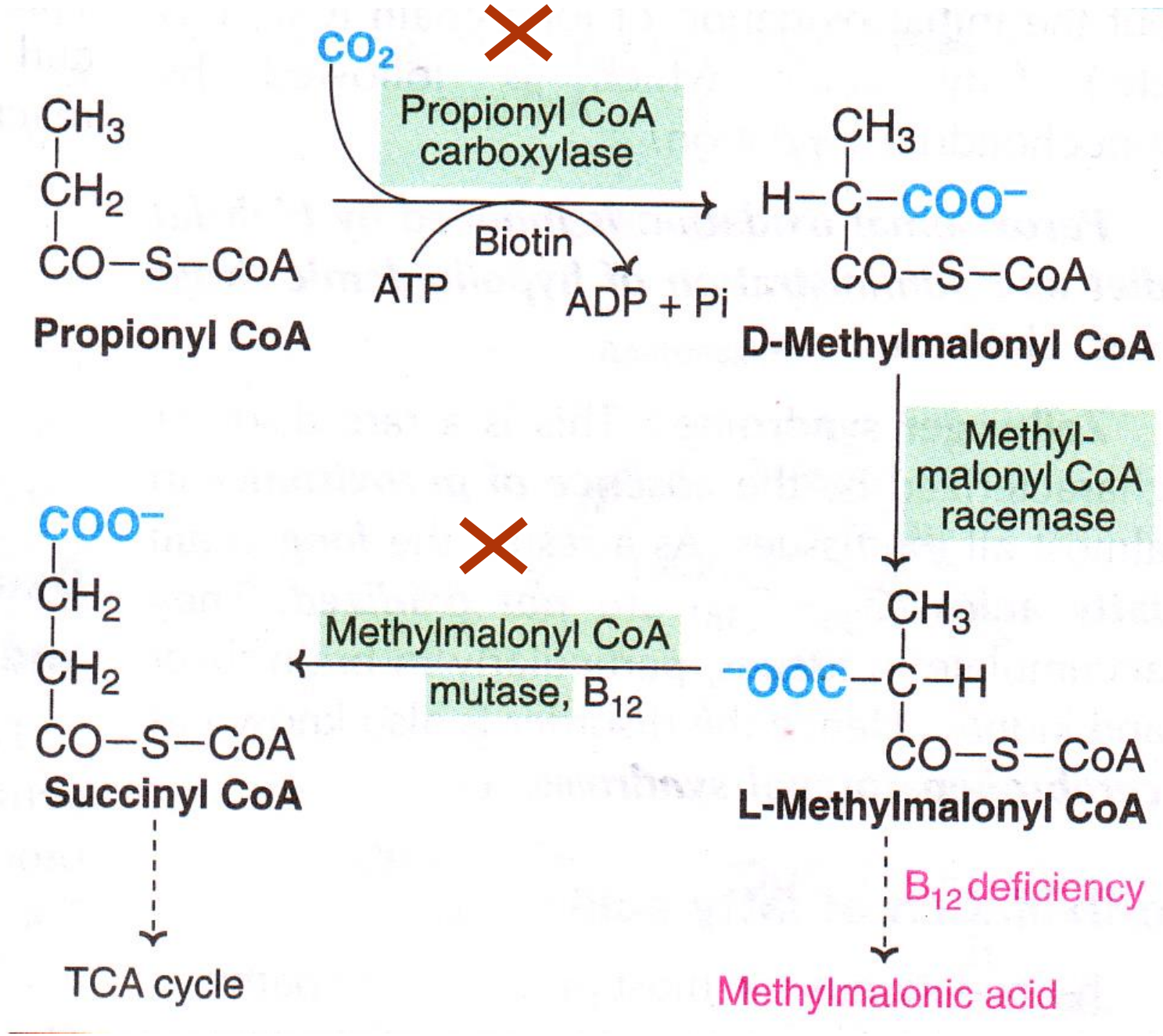
Two types

1. Due to **deficiency of vitamin B12**
2. Due to defect in the enzyme **methylmalonyl CoA mutase**.

- In either case, there is an accumulation of methylmalonic acid in body, followed by its increased excretion in urine.

- This causes - **Severe metabolic acidosis**
  - **Damages the central nervous system and**
  - **Retards the growth.**

- It is often fatal in the early years of life.
- First type patients respond to treatment with B12.
- The second type did not respond to cyanocobalamin.


CO2
Propionyl CoA carboxylase
Biotin
ATP
ADP + Pi
CH3
CH2
CO–S–CoA
Propionyl CoA
CH3
H–C–COO–
CO–S–CoA
D-Methylmalonyl CoA
Methyl-malonyl CoA racemase
COO–
CH2
CH2
CO–S–CoA
Succinyl CoA
Methylmalonyl CoA mutase, B12
CH3
–OOC–C–H
CO–S–CoA
L-Methylmalonyl CoA
B12 deficiency
TCA cycle
Methylmalonic acid

Oxidation of unsturated fatty acids:

- Due to presence of double bonds, provides less energy than saturated fattyacids
- Most reactions are same as that for saturated fatty acids but presence of double poses problem.

This is overcome by

- Odd chain fattyacids- double bond by isomerase
- Even chain fattyacids- double bond by reductase and isomerase

Peroxisomal oxidation:

- Peroxisomes facilitate the oxidation of **very long chain fatty acids** like C20, C22.
- VLCFAs undergo a preliminary β-oxidation in peroxisomes, because peroxisomes are the primary site of the synthetase which activates VLCFAs.
- Now it is believed that the peroxisomes carry out the initial oxidation of long chain (C20, C22 etc.) fatty acids which is followed by mitochondrial oxidation.
- The enzymes in peroxisomes do not attack shorter chain fatty acids.

- A modified form of β-oxidation is occured in peroxisomes and leads to the formation of **acetyl- CoA and H2O2—from the Fp linked dehydrogenase** step.
- Initial step of dehydrogenation in peroxisomes is catalyzed by a **FAD-containing acyl CoA oxidase**.
- The produced FADH2 is oxidized by molecular oxygen, reducing equivalents handed over directly to O2 which is reduced to H2O2.

- H2O2 formed in the process is broken down by the enzyme **Catalase.**

$$\text{E-FADH2} + \text{O2} \longrightarrow \text{E-FAD} + \text{H2O2}$$

$$\text{H2O2} \xrightarrow{\text{Catalase}} \text{H2O} + 1/2\,\text{O2}$$

- Here the dehydrogenation is not linked to phosphorylations , therefore there is **no ATP formation.**

- End-products are ***octanoyl-CoA and acetyl-CoA,*** which are removed from peroxisomes to mitochondria with the help of carnitine for further oxidation.

- The enzymes of peroxisomes are **induced by high fat diets and administration of hypolipidemic drugs** (e.g. clofibrate).

- Another role of peroxisomal β-oxidation is to shorten the side chain of cholesterol in bile acid formation.

- Peroxisomes also take part in the synthesis of:
  - ***Glycolipids***
  - ***Cholesterol***
  - ***Dolichol***

Disorders of peroxisomal oxidation

Zellweger's syndrome (Cerebro hepato-renal syndrome) :

- Rare inherited **peroxisomal biogenesis disorder**

- Due absence of peroxisomes in all tissues leading to inability to oxidize **Very long chain fatty acids** and their accumulation in brain , liver and kidney – **cerebrohepatorenal syndrome**.

Brown–Schilder's Disease (Adreno leukodystrophy (ALD):

- Inherited as autosomal recessive.
- Main defect is **insufficient oxidation of very long chain fatty acids** by peroxisomes due to deficiency of **peroxisomal matrix proteins.**
- **VLCFAS are accumulated and myelin sheaths are destroyed.**
- It characterised by progressive degeneration of liver, kidney and brain.

ALPHA OXIDATION

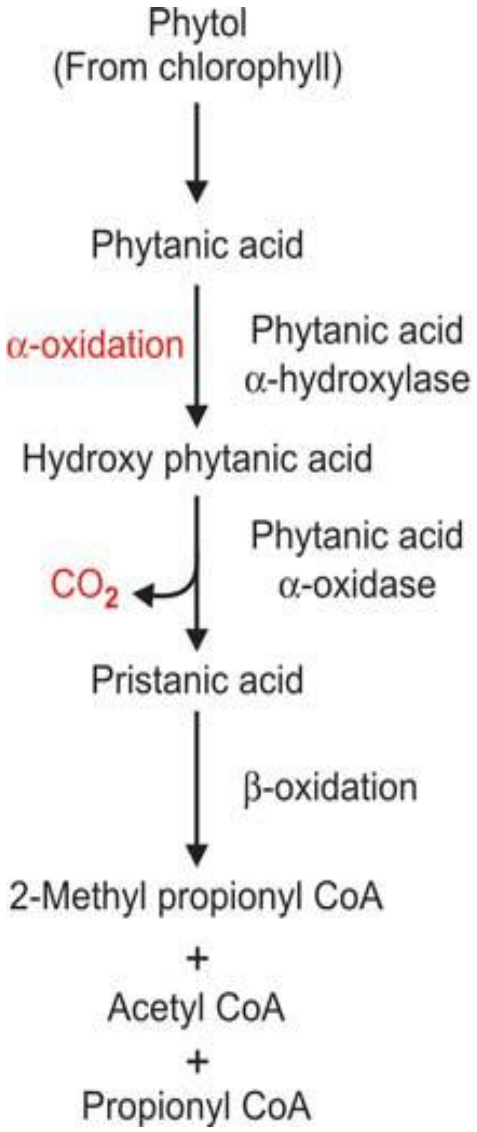
- Usually Beta Oxidation is the most predominant pathway for fatty acid degradation.
- Alpha-oxidation is mainly used for fatty acids that have a methyl group at the beta-carbon, which blocks beta-oxidation.
- **Removal of one carbon unit at a time by the oxidation of** alpha-carbon atom from the carboxyl end of fatty acid is known alpha oxidation.
- α-Oxidation does not involve the binding of fatty acid to coenzyme A (***No initial activation of FA)*** and no energy is produced.
- The process is **important in brain.**

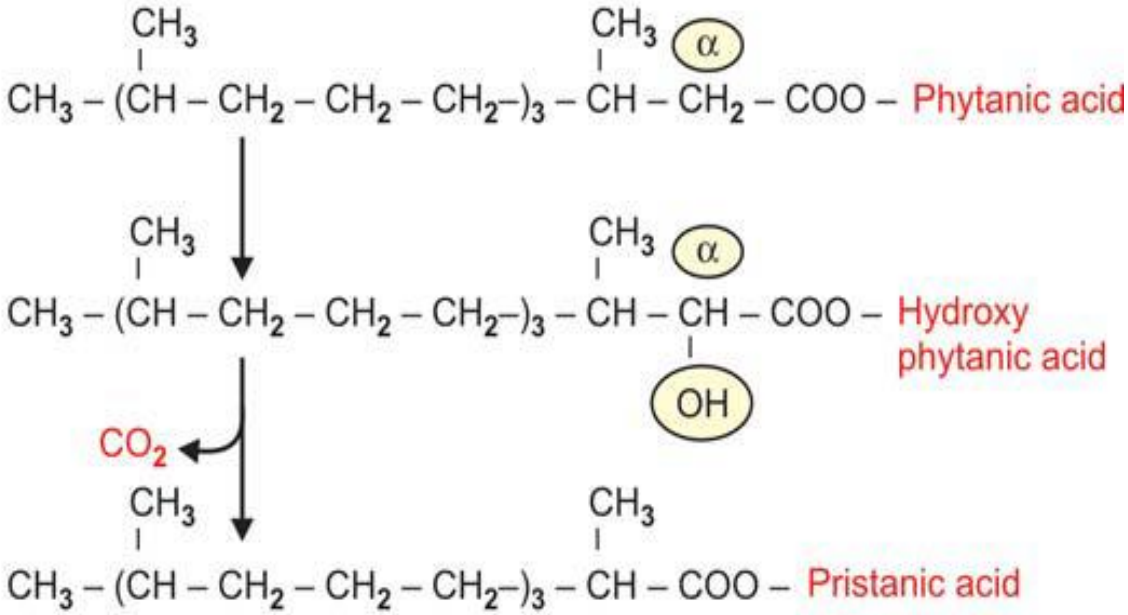
Steps :

- Hydroxylation occurs at the alpha-carbon atom.
- Then it is oxidized to alpha-keto acid.
- The keto acid then undergoes decarboxylation yielding a molecule of CO_2 and a fatty acid with one carbon atom less.
- This process occurs in the **endoplasmic reticulum and Mitochondria.**
- Some fatty acids undergo alpha hydroxylation in peroxisomes also.

- A major dietary methylated fatty acid is **phytanic acid.**
- It is derived from phytol present in **chlorophyll of green vegetabls as well as ruminant milk and meat.**
- The phytanic acid is initially oxdized by α oxidation.
- This is followed by a round of β-oxidation and β-oxidation yields propionyl CoA.

α oxidation of phytanic acid





Purpose:

- Synthesize alpha hydroxy fatty acids like cerbronic acid of brain cerebrosides

- Form odd carbon long chain fattyacids required for brain sphingolipids.

Disorders of alpha oxidation

Refsum's disease:

Defect: alpha hydroxylase /phytanic acid oxidase

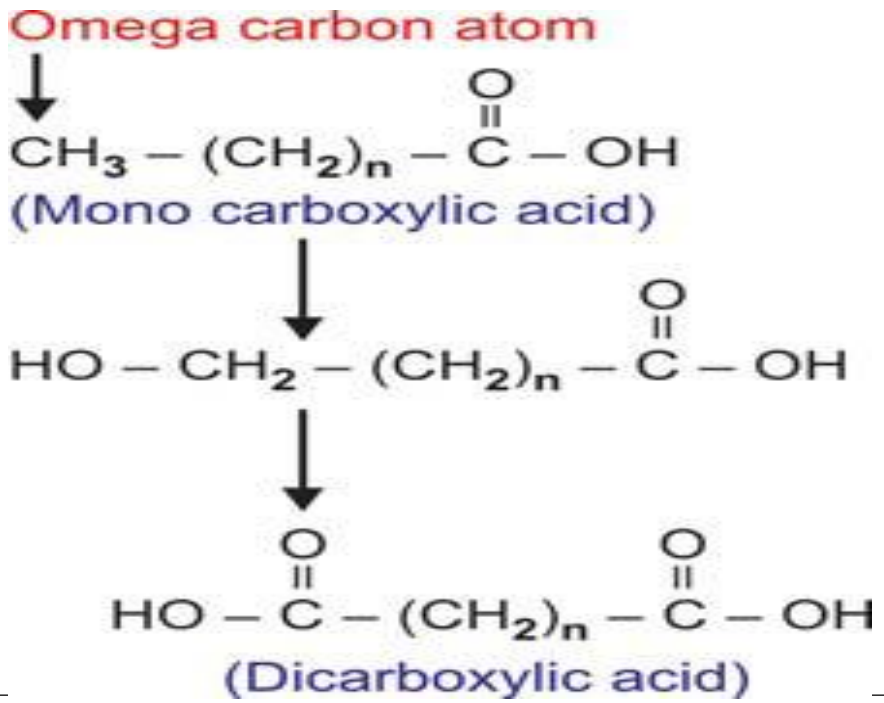
- Phytanic acid accumulates
- Neurological manifestations such as cerebellar ataxia, peripheral neuropathy, motor weakness, nerve deafness and retinitis pigmentosa
- But mental development is normal
- **Treatment :** Avoid dietary phytols, that is precursor of phytanic acids (green vegetables, ruminant milk and meat)

Infantile Refsum's Disease:

- It is a peroxisomal disorder.
- Similar to Zellweger syndrome and adrenoleukodystrophy.
- In this, phytanic acid accumulates along with VLCFA.
- The child do not survive long.

Omega oxidation:

- Minor pathway taking place in **microsomes**
- ω oxidation is more common with **medium chain fatty acids**.
- Involves hydroxylation followed by oxidation of omega carbon(-CH3) at the other end (at one end carboxyl group is present) of fatty acid, that forms dicarboxylic acids that later undergo betaoxidaiton
- Requires
  - NADPH
  - Cyt p450
  - O2



- ω-oxidation becomes important when β-oxidation is defective and dicarboxylic acids (6C and 8C acids) are excreted in urine causing **dicarboxylic aciduria.**

THANK YOU