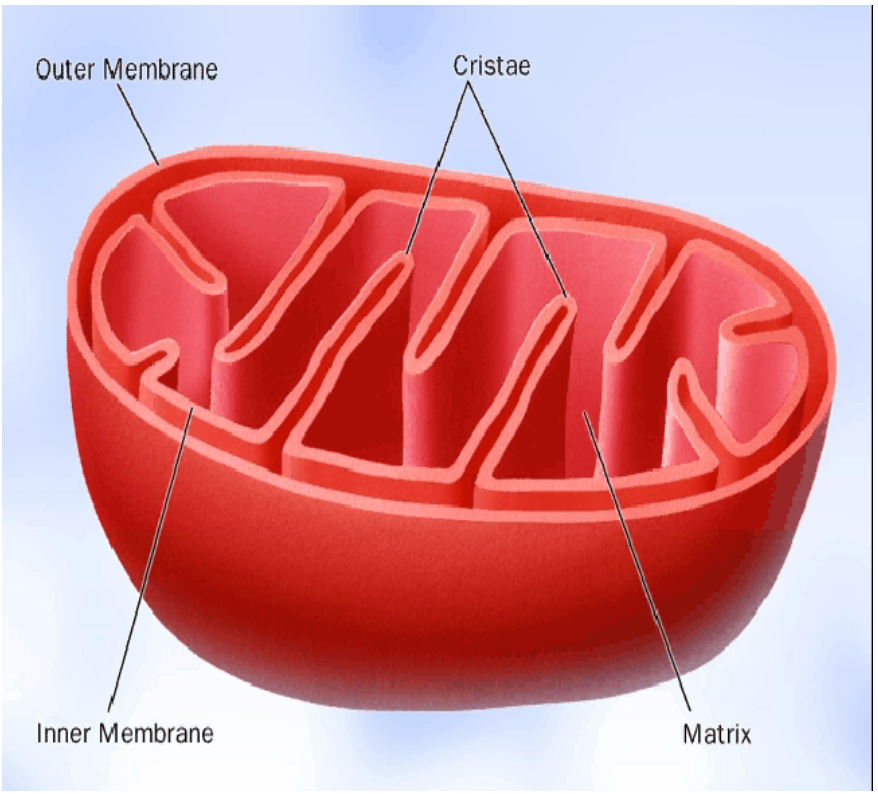
LIPID METABOLISM

β oxidation

- Def: Oxidation & splitting of fatty acid takes place at the β (3rd) carbon atom so there is a sequential removal of 2 carbon unit as acetyl CoA, starting at the carboxyl end

- **Site:**

Mitochondrial matrix



Stages

1

Activation of Fatty acid Reactions

oxidation

site: cytosol

2

transport of fatty acyl CoA across IMM

3

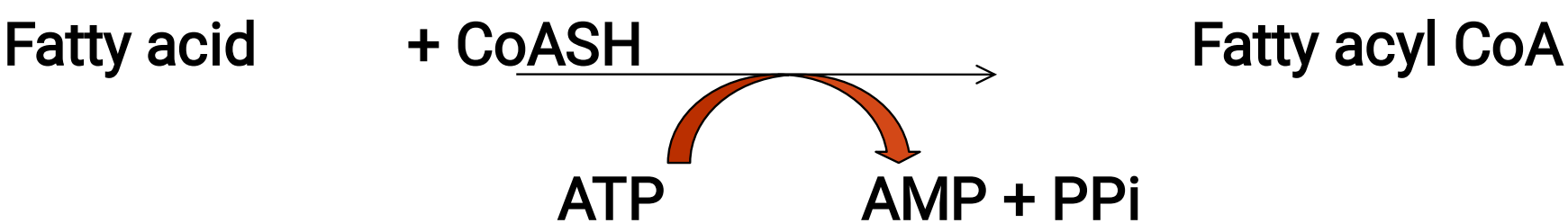
of β

mitochondrial matrix

1. Activation of Fatty Acids

- Fatty acids are activated to CoA derivatives
- This occurs in cytosol

- **Acyl CoA synthetase / Thiokinase**



2. Transport of FattyAcyl CoA to mitochondria

- Long chain fatty acyl CoA cannot pass through inner mitochondrial membrane

- A transporter, *Carnitine* is involved

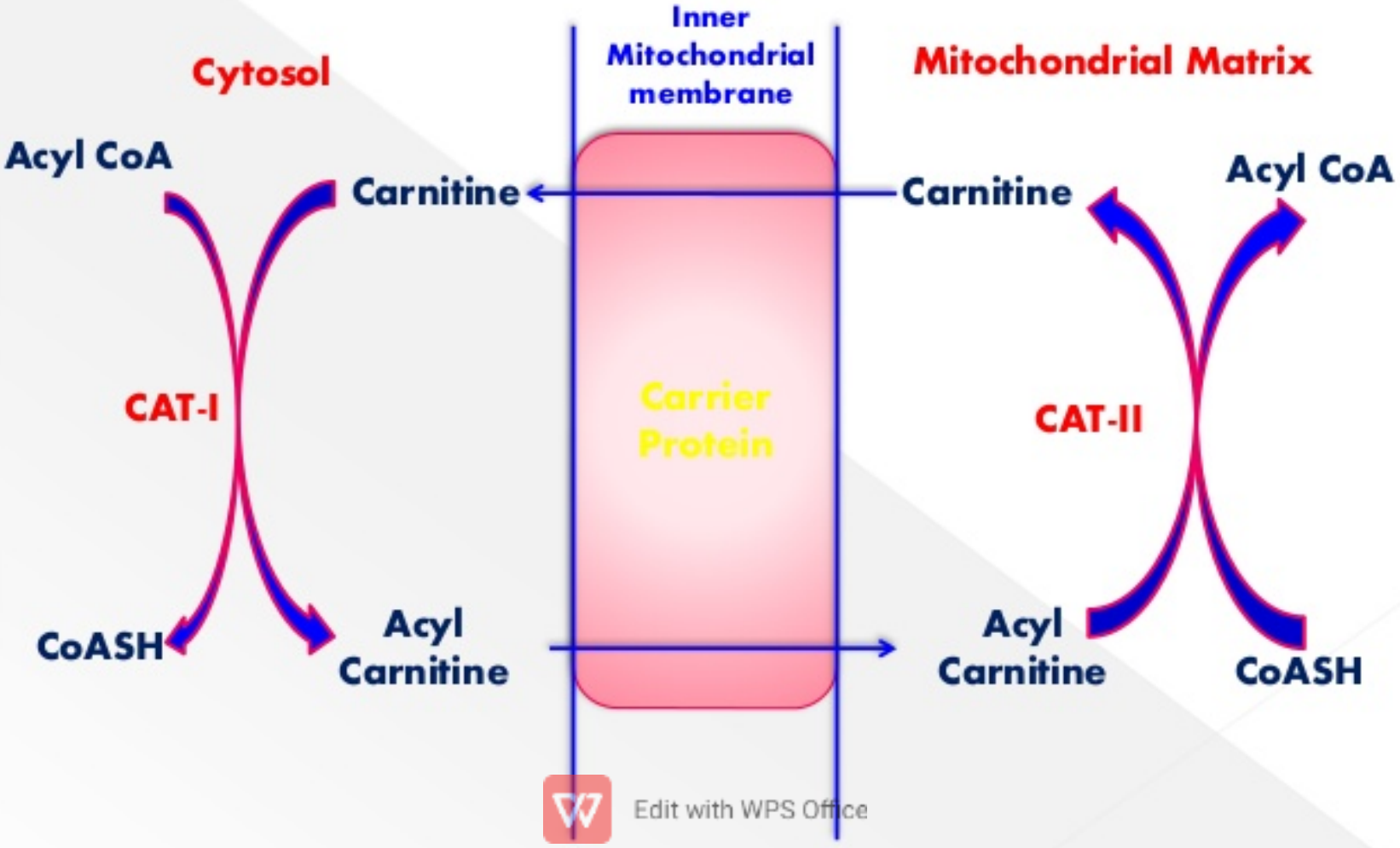
Carnitine

- Def: Carrier molecule involved in the transport of long chain fatty acyl CoA across the inner mitochondrial membrane for β oxidation

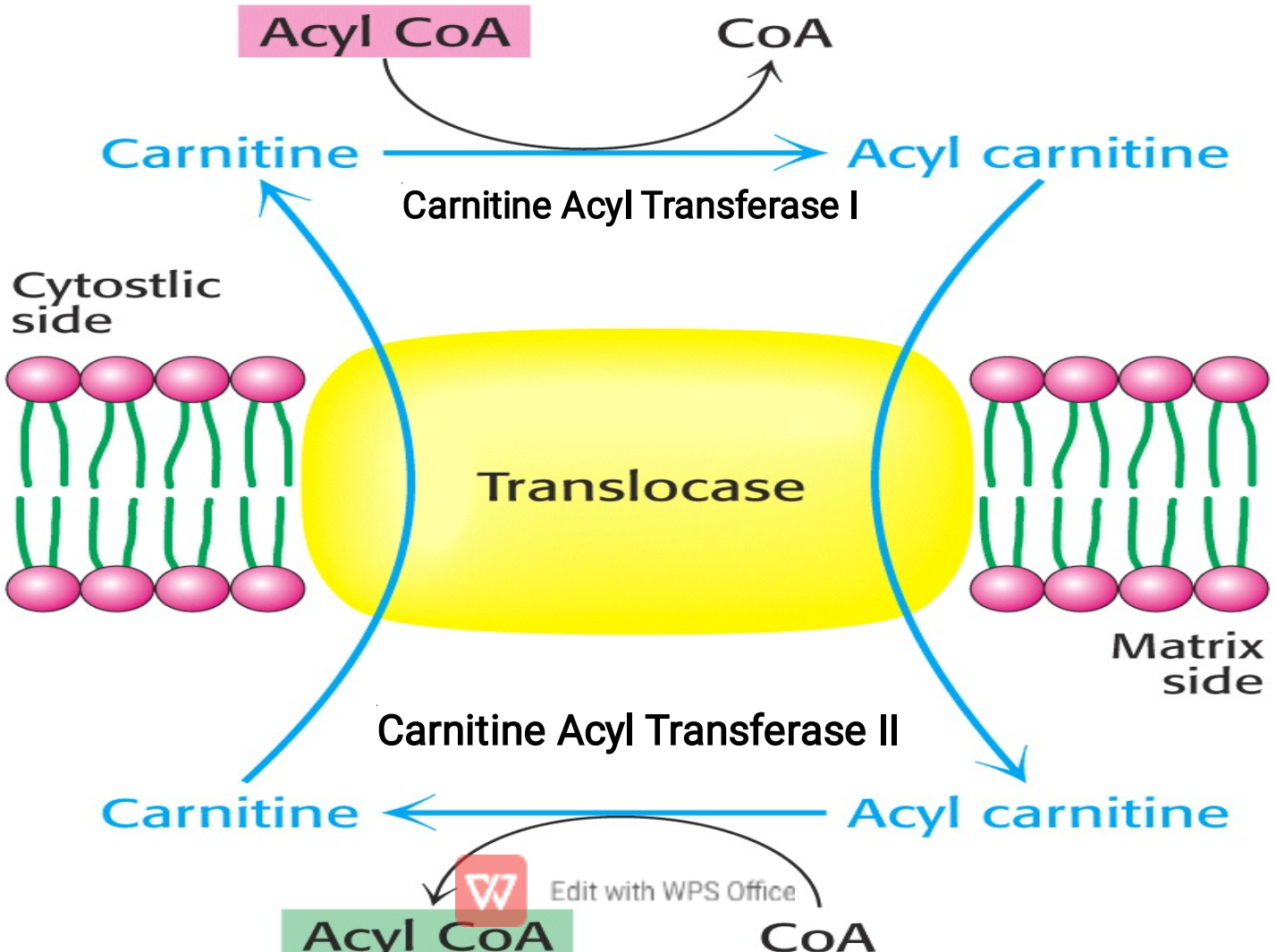
- Carnitine is beta hydroxy gamma trimethyl ammonium butyrate
- It is obtained from lysine and methionine
- It is synthesized in liver and kidney

- MCFA & SCFA do not need carnitine for transport , so easily oxidized

Carnitine transport system

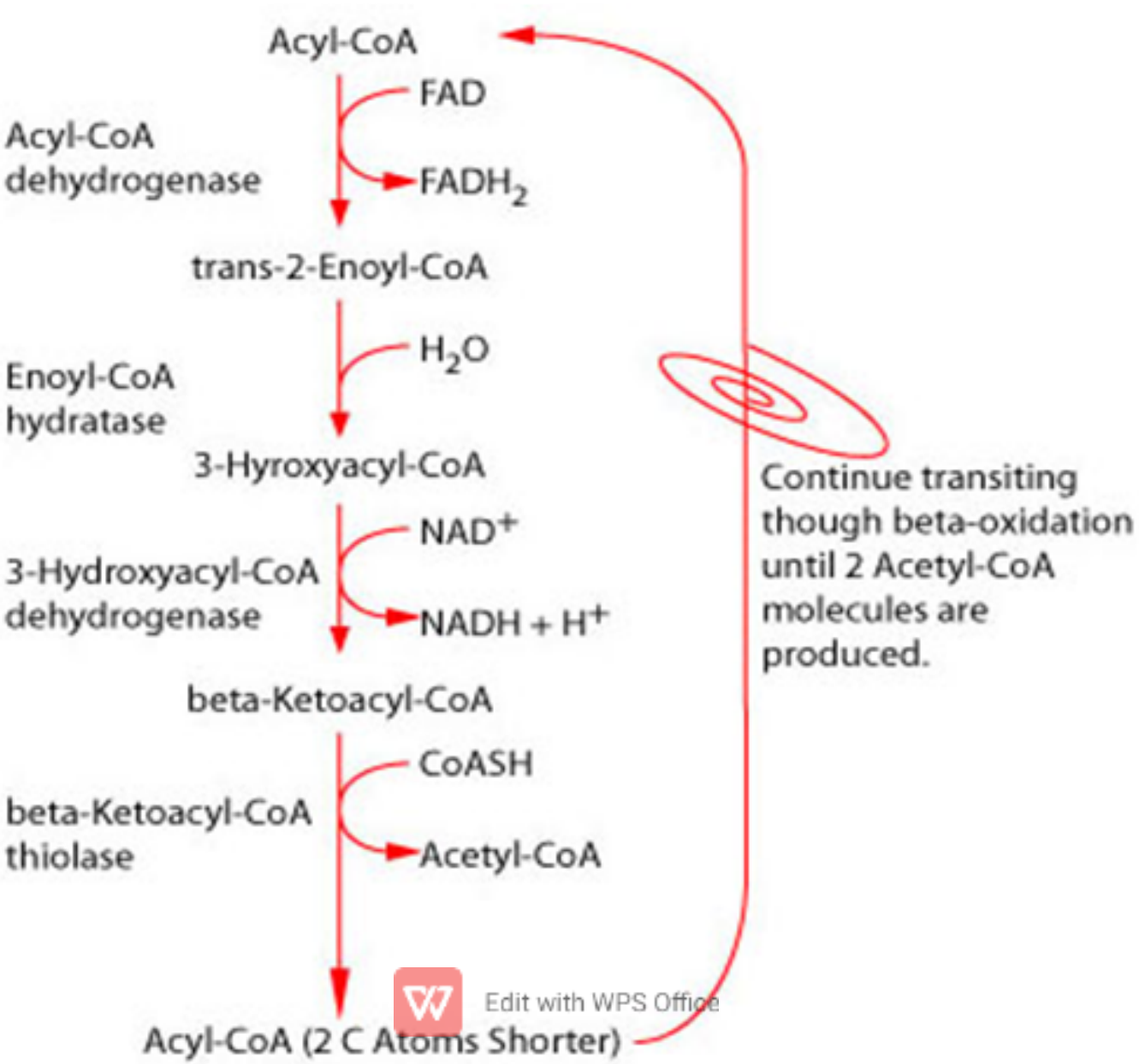


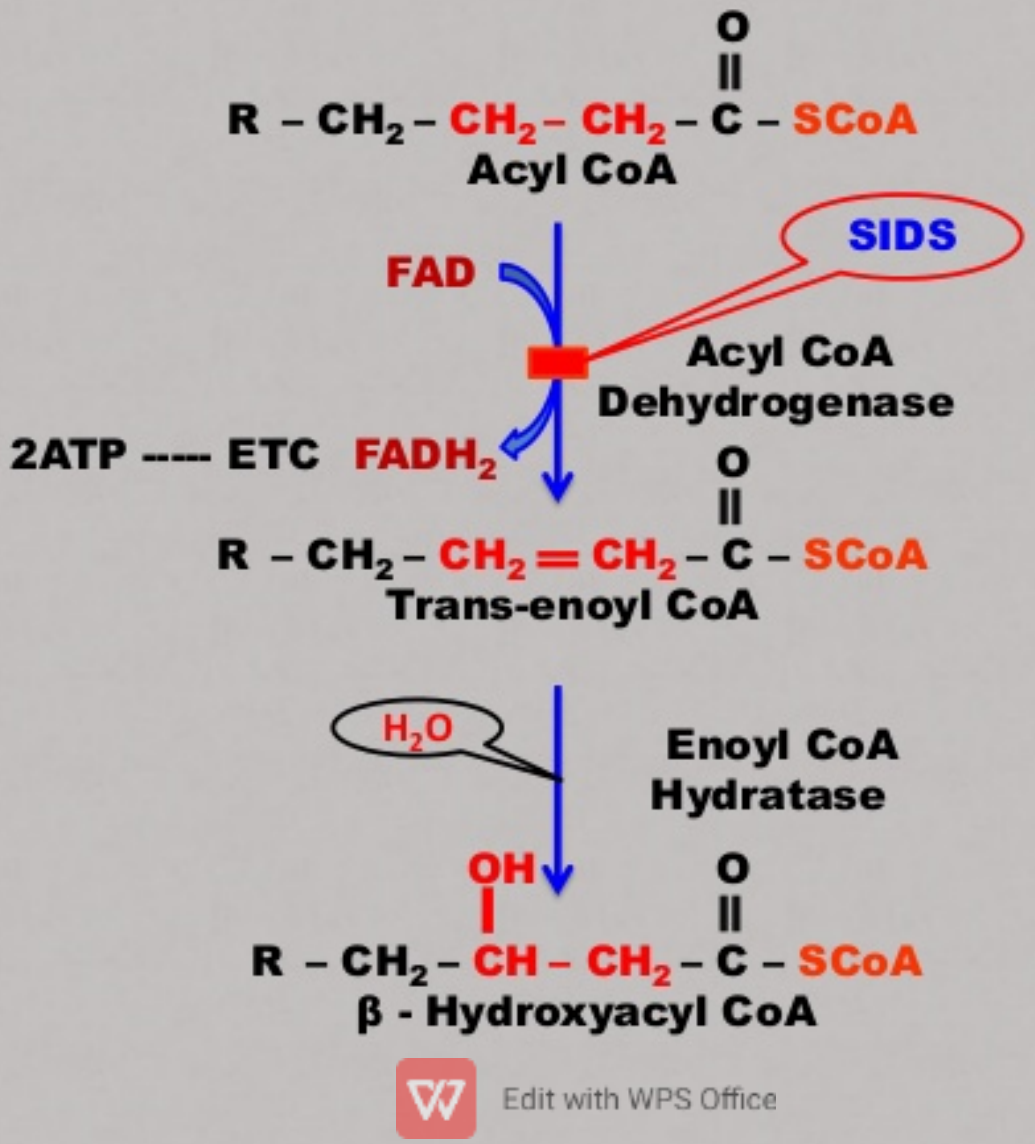
Carnitine shuttle

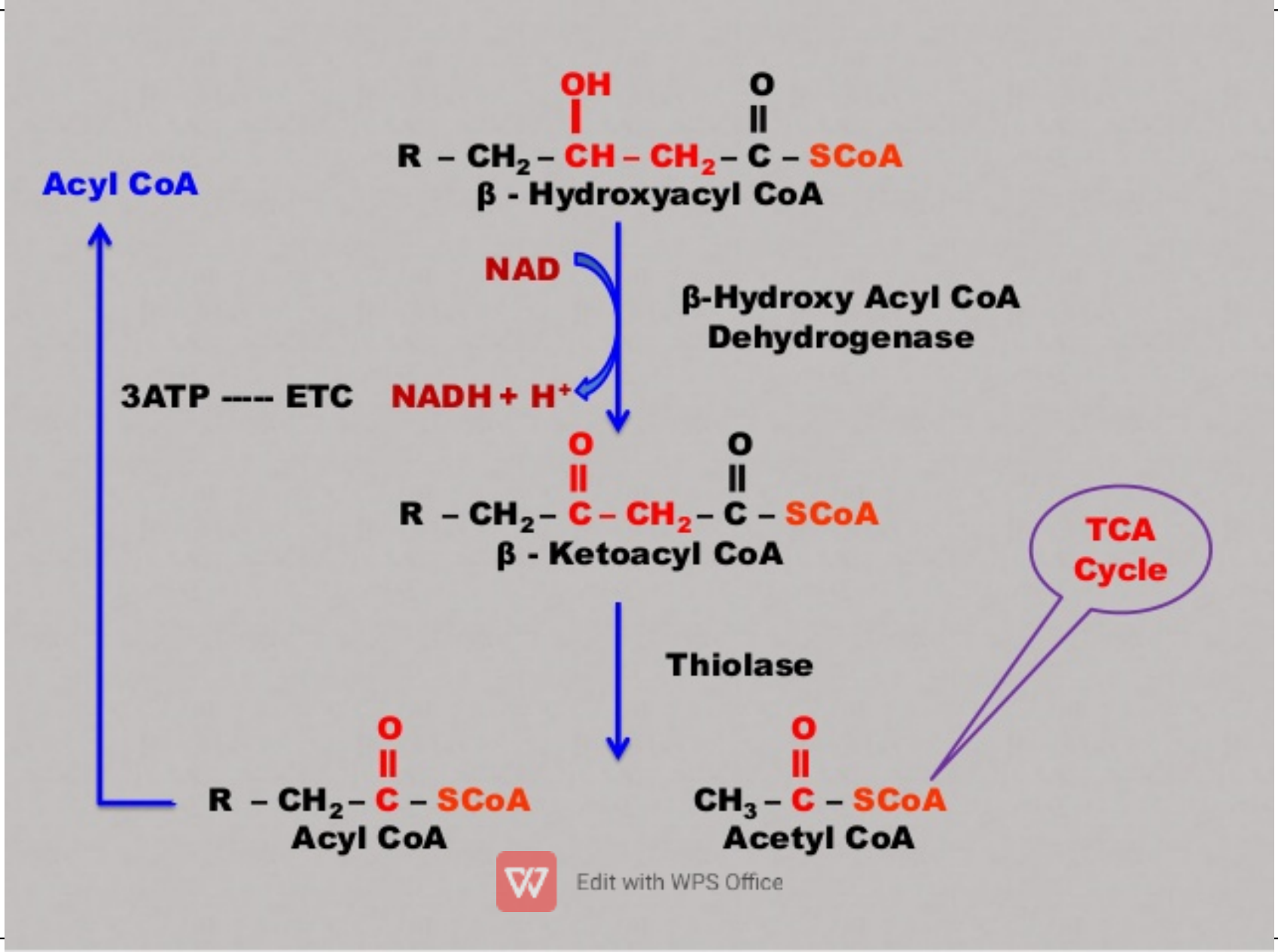


3. Reactions of β - oxidation

1. FAD dependent dehydrogenation (oxidation)
2. Hydration
3. NAD^+ dependent dehydrogenation (oxidation)
4. Thiolytic cleavage to remove acetyl CoA






Acyl CoA
R – CH2 – CH – CH2 – C – SCoA
β - Hydroxyacyl CoA
NAD
β-Hydroxy Acyl CoA
Dehydrogenase
3ATP ---- ETC
NADH + H+
R – CH2 – C – CH2 – C – SCoA
β - Ketoacyl CoA
TCA
Cycle
Thiolase
R – CH2 – C – SCoA
Acyl CoA
CH3 – C – SCoA
Acetyl CoA
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Energetics (β – oxidation of 16C palmitate)

- 8 Acetyl CoA X 10 = 80 ATP
(oxidized in TCA cycle)
- 7 FADH2 X 1.5 = 10.5 ATP
(oxidized in ETC)
- 7 NADH X 2.5 = 17.5 ATP (oxidized in ETC)
- TOTAL = 108 ATP
- **Less 2 high energy bonds for initial activation** = **106 ATP**

Significance

- Tissues which derive most of the energy from FA at least during fasting : Heart, skeletal muscle & liver
- Note: Adult brain cannot use FA as a source of energy

- Clinical significance

- 1. Carnitine deficiency:
- Causes: - dietary deficiency / Preterm infants

Signs/ symptoms:-

- hypoglycemic encephalopathy
- Muscle weakness
- hepatomegaly

Biochemical basis for hypoglycemia: -

↓ FA oxdn.

↓ ATP for gluconeogenesis

↓ Acetyl CoA for activation of Pyruvate carboxylase

2. Translocase deficiency

- defective metabolism of LCFA
- Muscle cramps precipitated by exercise & high fat diet

3. Jamaican vomiting sickness

- Unripe ackee fruits have toxin – hypoglycin
- Enzyme inhibited : Acyl CoA dehydrogenase
- Hypoglycemia, vomiting

Regulation

Availability of FFA

Controlled by

Glucagon : insulin ratio

Ratio high in

starvation & DM

More FFA from adipose synthesis

More β oxidation

uptake of FA into mitochondria

Controlled by CAT 1

Θ

Malonyl CoA

(substrate for FA synthesis)

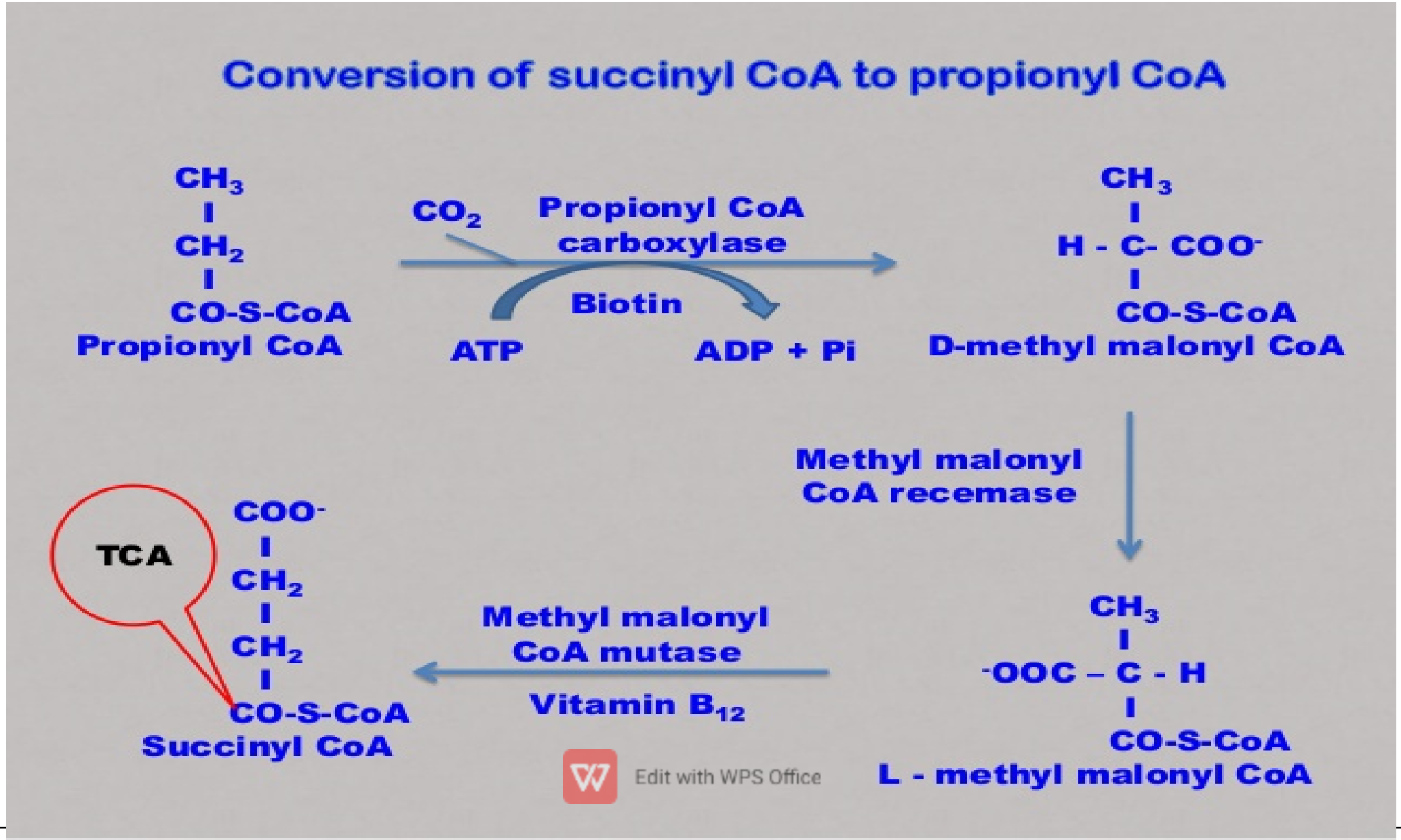
So FA oxidation &

cannot occur at same

Oxidation of Odd chain Fatty acids
(Source – milk)

- Oxidized by β – oxidation
- In the final round
  - one **acetyl CoA** &
  - one **3-carbon propionyl CoA** is formed

Propionyl CoA from odd chain FA is the only part of a FA that is glucogenic


Conversion of succinyl CoA to propionyl CoA
CH3
CH2
CO-S-CoA
Propionyl CoA
CO2
Propionyl CoA carboxylase
Biotin
ATP
ADP + Pi
CH3
H - C- COO-
CO-S-CoA
D-methyl malonyl CoA
Methyl malonyl CoA recemase
CH3
-OOC – C - H
CO-S-CoA
L - methyl malonyl CoA
Methyl malonyl CoA mutase
Vitamin B12
TCA
COO-
CH2
CH2
CO-S-CoA
Succinyl CoA
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Methyl Malonic Aciduria

- This is a condition where excess methyl malonic acid is excreted through urine
- Two forms: B12 responsive
  B12 non-responsive

First group has defective formation of adenosyl B12.

Second group : deficient in enzyme – Methyl malonyl CoA mutase

Clinical features: Ketoacidosis & mental retardation.

Oxidation of VLCFA

- Occurs in Peroxisomes
- modified form of β-oxidation
- β-oxidation sequence ends at octanoyl CoA
- Further β-oxidation in mitochondria
- FADH2 formed is used to produce H2O2 in peroxisomes

Zellweger's syndrome

- Defect: Absence of functional peroxisomes
- Death by age- 6 months

- (Note: peroxisomes are responsible for the synthesis of plasmalogens, bile acid & for shortening VLCFA)
- Biochemical findings :
- accumulation of VLCFA in brain, liver & kidney – cerebrohepatorenal syndrome
- Reduced plasmalogens and bile acid synthesis

Alpha -Oxidation

- **Def: Oxidation of fatty acids by removing one carbon atom at a time, from the carboxyl end as CO_2**
- **FA does not need activation**
- **Neither consumes nor generates energy**
- occurs in branched chain FA which have a methyl group at branch point.– blocks β-oxidation eg. Phytanic acid (present in chlorophyll, milk & animal fat)

Refsum's Disease

- Def: Metabolic disorder where α- oxidation is defective
- Enz deficient :- **α – hydroxylase**
- Biochemical finding: Phytanic acid accumulates in brain, blood & other tissues

- C/F : Severe neurological symptoms –

- **Peripheral neuropathy**
- cerebellar ataxia
- retinitis pigmentosa
- ichthyosis

Omega Oxidation

- Def: Minor pathway taking place in microsomes, where ω carbon of FA gets oxidized
- Important when β-oxidation is defective