LIPID METABOLISM

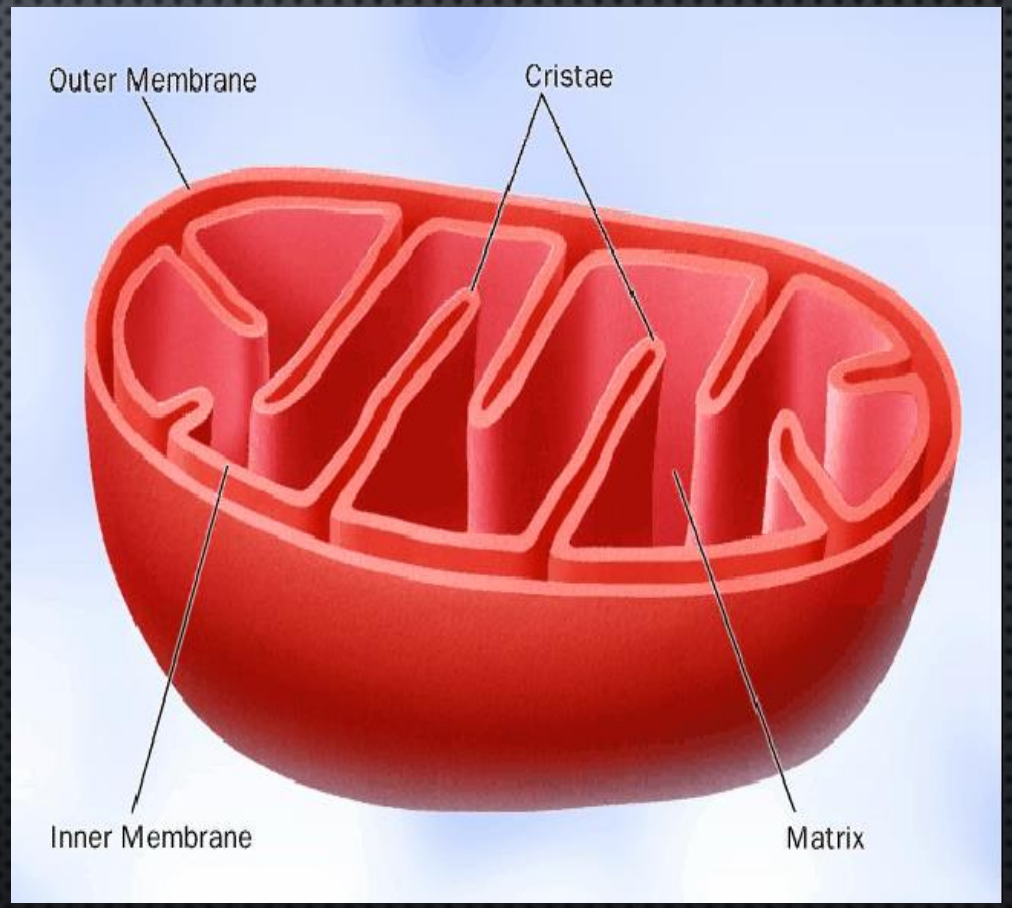
ASHCOPS

B OXIDATION

- DEF: OXIDATION & SPLITTING OF FATTY ACID TAKES PLACE AT THE B (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

2 transport of fatty acyl CoA across IMM

3 Reactions of b oxidation

SITE: CYTOSOL

MITOCHONDRIAL MATRIX

1. Activation of Fatty acids

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

- **Acyl CoA synthetase / Thiokinase**

Fatty acid + CoASH → Fatty acyl CoA

ATP → AMP + PPi

2. TRANSPORT OF FATTYACYL COA TO MITOCHONDRIA

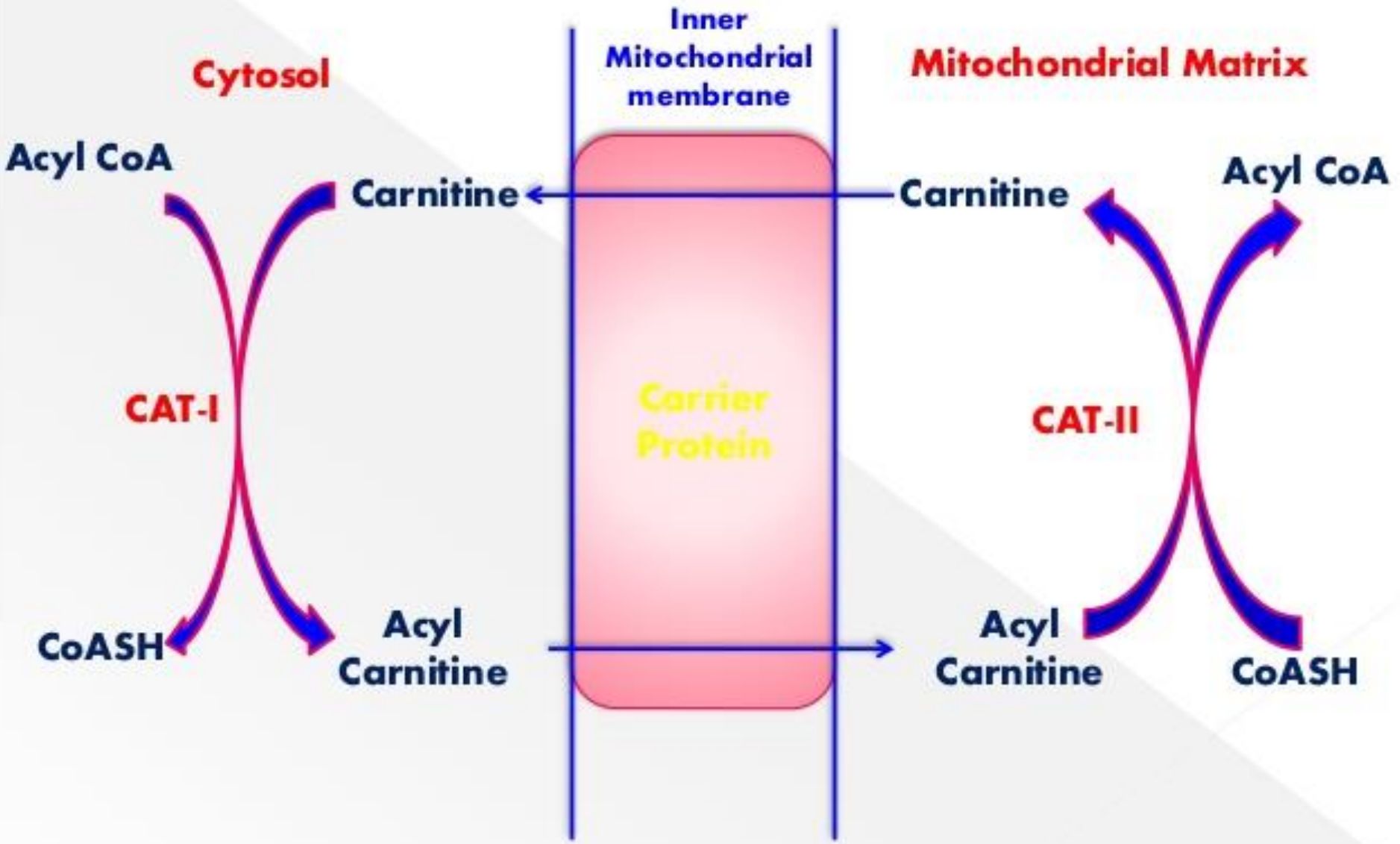
- LONG CHAIN FATTY ACYL COA CANNOT PASS THROUGH INNER MITOCHONDRIAL MEMBRANE
- A TRANSPORTER, *CARNITINE* IS INVOLVED

CARNITINE

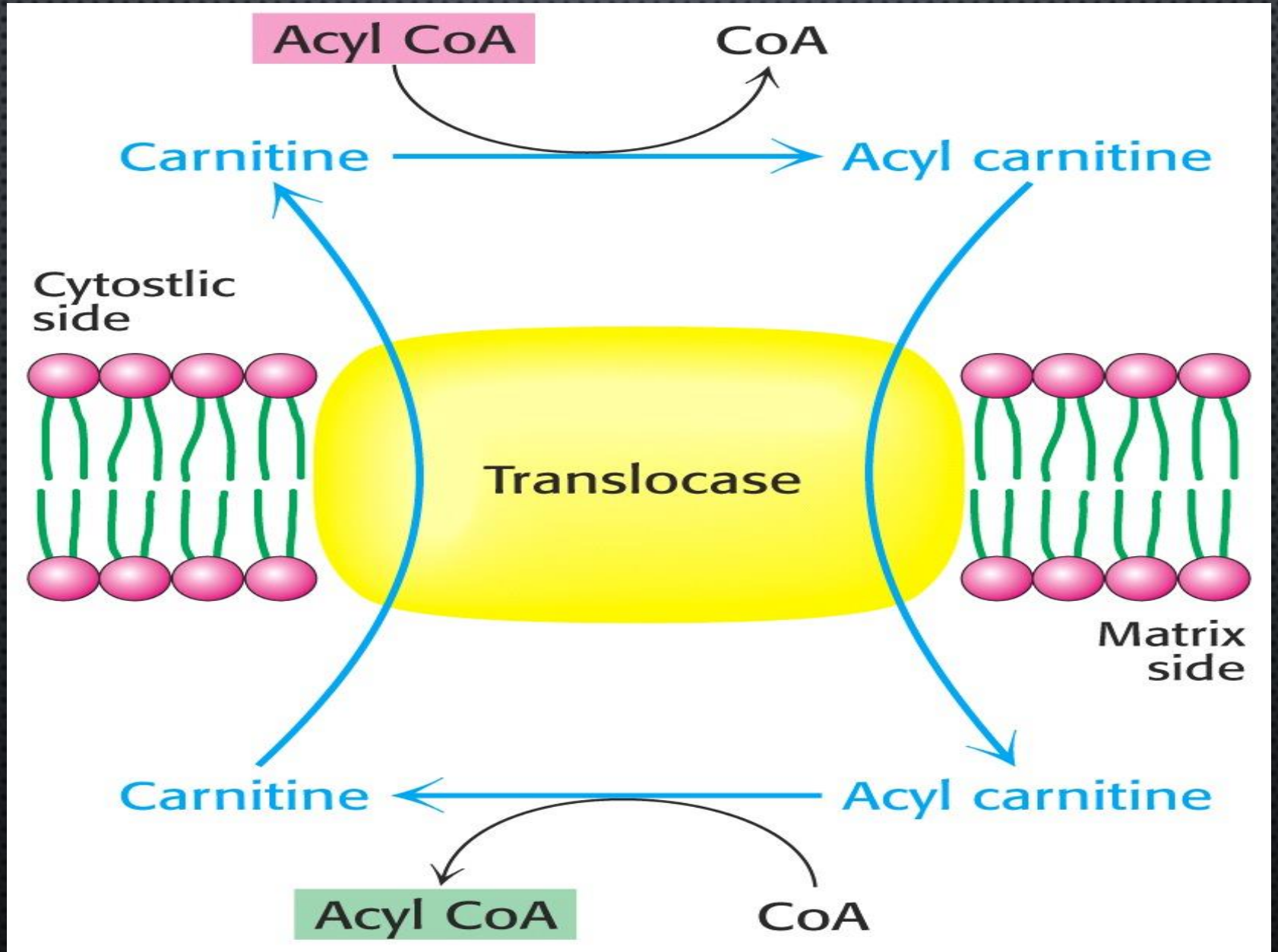
- DEF: CARRIER MOLECULE INVOLVED IN THE TRANSPORT OF LONG CHAIN FATTY ACYL COA ACROSS THE INNER MITOCHONDRIAL MEMBRANE FOR B OXIDATION

- 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

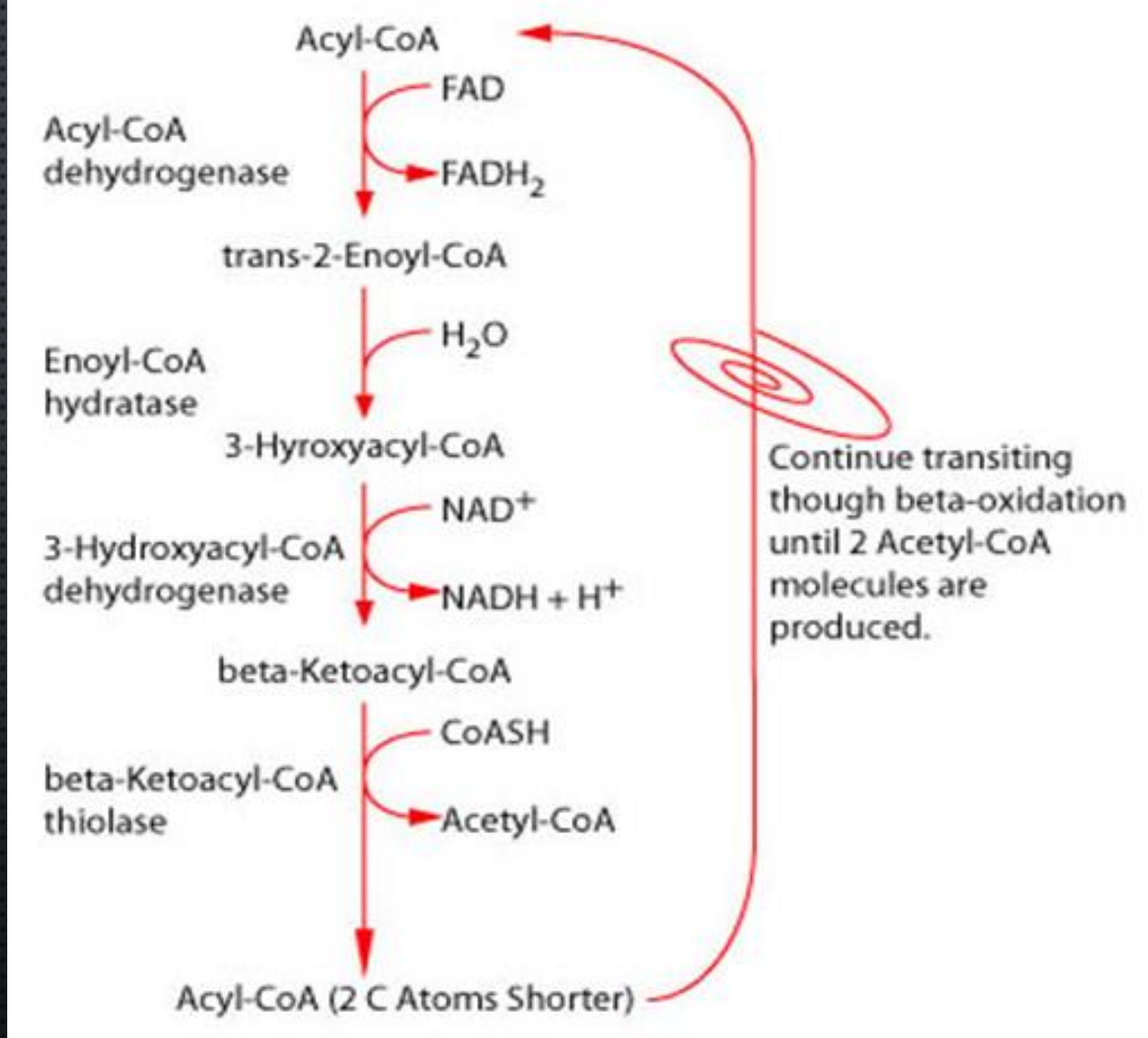


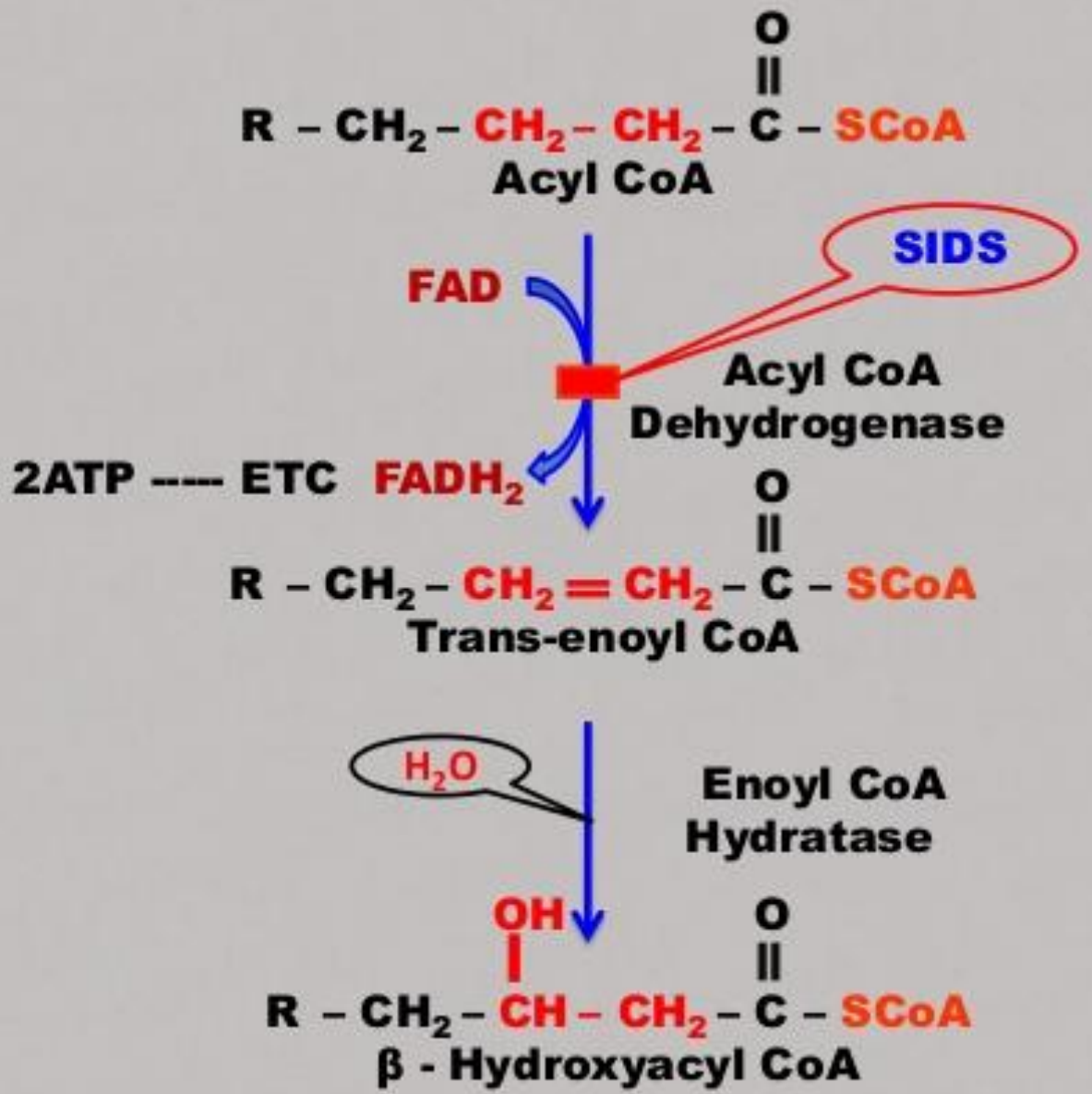
Carnitine shuttle

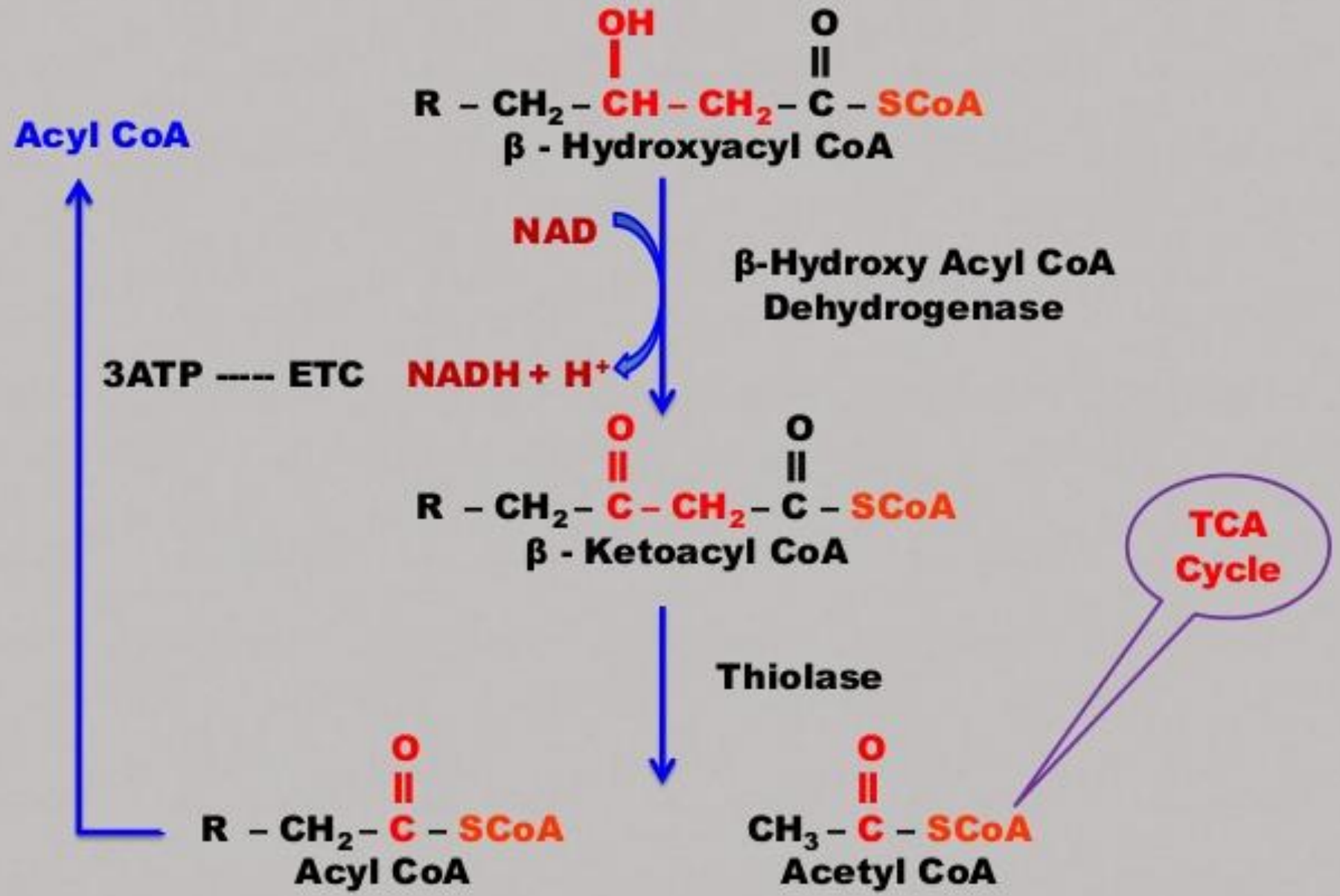


3. REACTIONS OF β - OXIDATION

1. FAD DEPENDENT DEHYDROGENATION (OXIDATION)
2. HYDRATION
3. NAD^+ DEPENDENT DEHYDROGENATION (OXIDATION)
4. THIOLYTIC CLEAVAGE TO REMOVE ACETYL COA


Acyl-CoA
FAD
Acyl-CoA dehydrogenase
$FADH_2$
trans-2-Enoyl-CoA
H_2O
Enoyl-CoA hydratase
3-Hyroxyacyl-CoA
NAD^+
3-Hydroxyacyl-CoA dehydrogenase
$NADH + H^+$
beta-Ketoacyl-CoA
CoASH
beta-Ketoacyl-CoA thiolase
Acetyl-CoA
Acyl-CoA (2 C Atoms Shorter)
Continue transiting though beta-oxidation until 2 Acetyl-CoA molecules are produced.


R – CH2 – CH2 – CH2 – C – SCoA
Acyl CoA
FAD
SIDS
Acyl CoA
Dehydrogenase
2ATP ---- ETC FADH2
R – CH2 – CH2 = CH2 – C – SCoA
Trans-enoyl CoA
H2O
Enoyl CoA
Hydratase
OH
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
O
R – CH2 – C – SCoA
Acyl CoA
CH3 – C – SCoA
Acetyl CoA

ENERGETICS (B - 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 = 106 ATP**
  FOR INITIAL ACTIVATION

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

More b oxidation

uptake of FA into

mitochondria

Controlled by CAT 1

⊖

Malonyl CoA

(substrate for FA synthesis)

So FA oxidation & synthesis

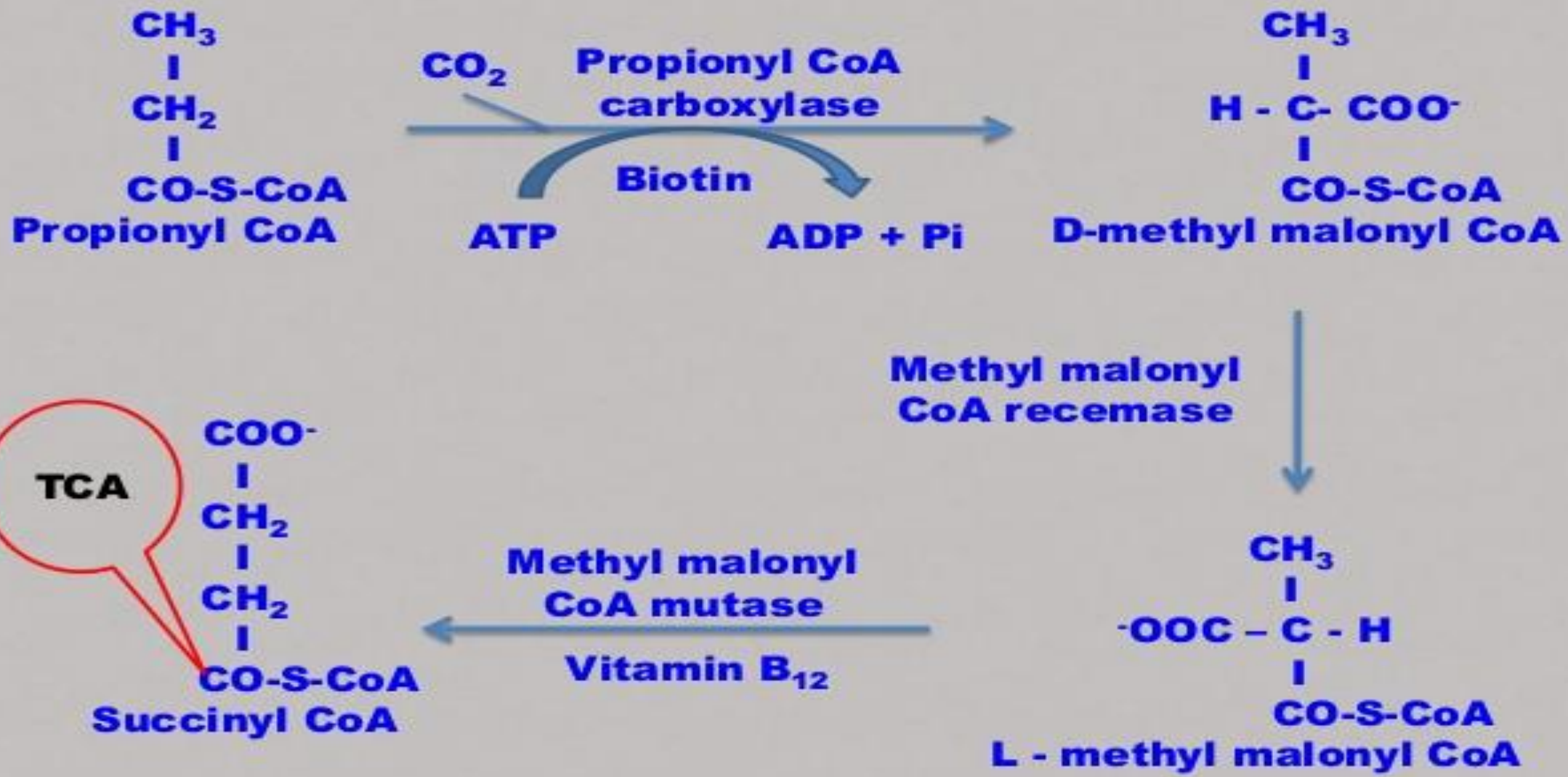
cannot occur at same time

OXIDATION OF ODD CHAIN FATTY ACIDS

- OXIDIZED BY B - OXIDATION
- IN THE FINAL ROUND (SOURCE – MILK)
  - 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



OXIDATION OF VLCFA

- Occurs in Peroxisomes
- modified form of B-oxidation
- B-oxidation sequence ends at octanoyl CoA
- Further B-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 b-oxidation eg. Phytanic acid (present in chlorophyll, milk & animal fat)

REFSUM'S DISEASE

- DEF: METABOLIC DISORDER WHERE A- OXIDATION IS DEFECTIVE
- ENZ DEFICIENT :- A – 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 b-oxidation is defective