BIOCHEMISTRY

UNIT 3 NOTES

- LIPID METABOLISM
- AMINO ACID METABOLISM

Rx Pharma Education

Lipid Metabolism

- Lipids are generally the esters of Fatty Acids & Alcohols.
- Lipids constitutes about 15-20% of total body weight in humans
- They are present in our body in different forms like Triglycerides, Phospholipids, fatty acids etc.
- About 85-90% part of lipids in our body is Triglycerides which is stored in the Adipose Tissue.
- The synthesis and breakdown of Lipid is known as Lipid Metabolism that involves Lipogenesis & Oxidation of fatty acids.

β-Oxidation Of Fatty Acids

- Fatty Acids are obtained from breakdown of Lipids (Mainly Triglycerides)
- Oxidation of Fatty acid is the process that body uses to breakdown and use fatty acid as energy.
- The Fatty acids in the body are mostly oxidized by β-Oxidation.
- β Oxidation may be defined as oxidation of fatty acids on β-Carbon Atom.

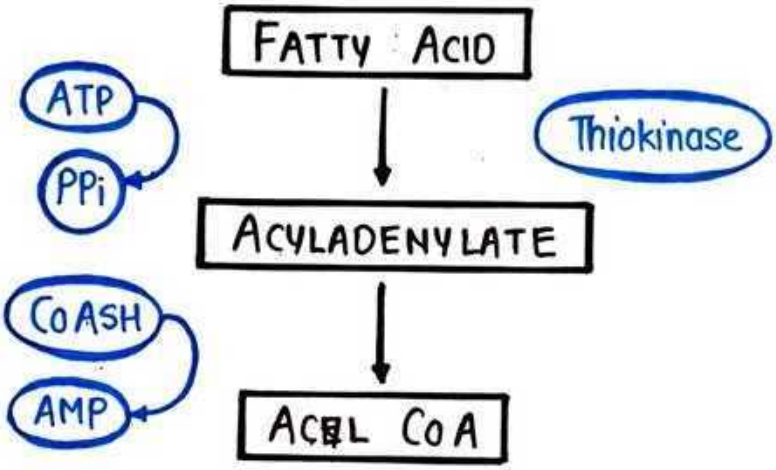
Stages Of β-Oxidation

β Oxidation of fatty acids occurs in three stages:

- Activation of Fatty Acids in cytosol
- Transport of Fatty Acid in Mitochondria.
- Proper β-Oxidation in Mitochondrial Matrix.

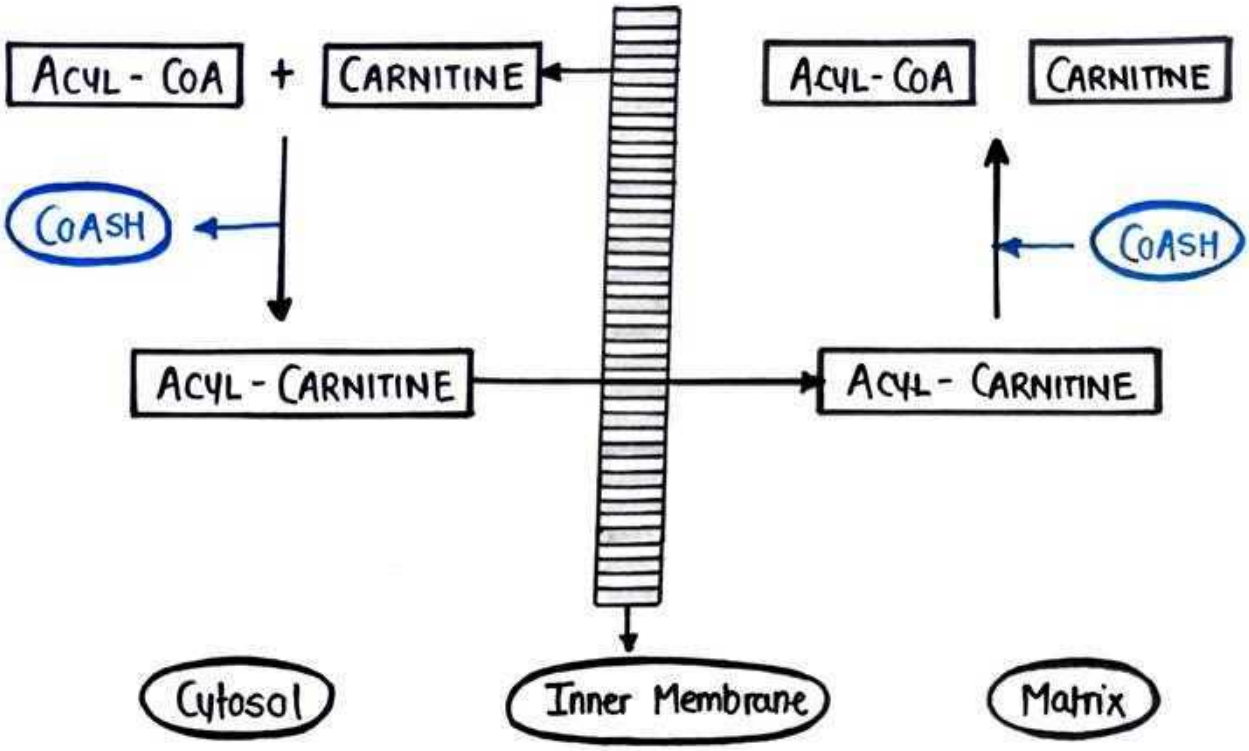
① Activation Of Fatty Acids

- Fatty acid activated into Acetyl Acyl CoA by Thiokinase.
- Reaction occurs in two steps & requires ATP, Mg^{2+} & CoA.
- In first step Fatty acids reacts with ATP & form Acyladenylate.
- In second step Acyladenylate combines with Coenzyme A & form Acyl Co A
- In activation 2 high energy phosphate utilized.



Transport Of Activated Fatty Acid In Mitochondria

- Acyl group of Acyl Co A transferred to carnitine and the reaction is catalysed by Carnitine Acyl Transferase - I
- Acyl- carnitine is transported across the membrane to the mitochondrial matrix by specific carrier protein.
- Acyl carnitine again converted into Acyl Co-A inside the mitochondrial matrix by Carnitine Acyl Transferase - II.



PROPER B- OXIDATION OF FATTY ACIDS

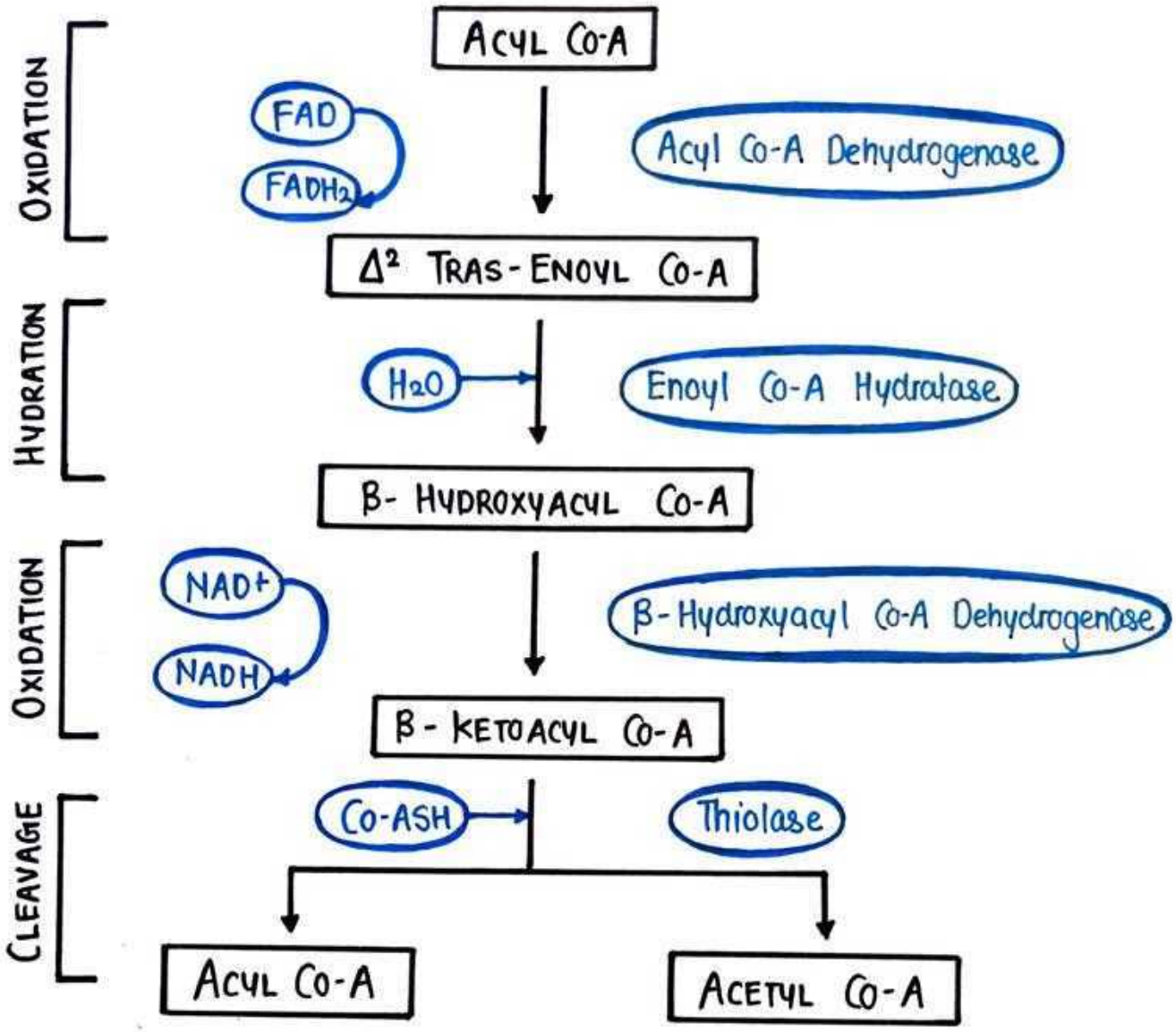
It occurs in following 4 steps :

- **Oxidation** : Acyl Co A undergoes Dehydrogenation by a flavoenzyme Acyl Co A Dehydrogenase.

- **Hydration** : Enoyl Co A cause the hydration of double bond to form β - hydroxyacyl Co-A

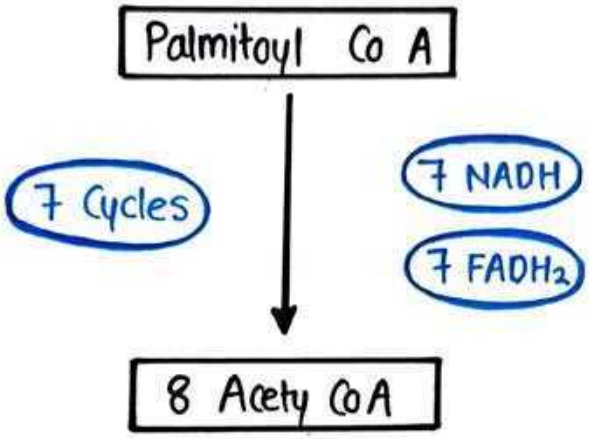
- **Oxidation** : In the second oxidation β- hydroxyacyl Co-A converted into β- ketoacyl Co-A & reaction is catalysed by β- hydroxyacyl Co A dehydrogenase.

- **Cleavage** : It is the final step of β-oxidation in which β- ketoacyl Co A cleaved into Acyl Co-A & Acetyl Co-A in the presence of thiolase enzyme.


Oxidation
Acyl Co-A
FAD
FADH2
Acyl Co-A Dehydrogenase
Δ2 Tras-Enoyl Co-A
Hydration
H2O
Enoyl Co-A Hydratase
β- Hydroxyacyl Co-A
Oxidation
NAD+
NADH
β-Hydroxyacyl Co-A Dehydrogenase
β- Ketoacyl Co-A
Cleavage
Co-ASH
Thiolase
Acyl Co-A
Acetyl Co-A

ENERGETICS OF β- OXIDATION

- Generally Palmitic acid is used for the process of β-oxidation of fatty acid
- Now Palmitic acid is a 16 carbon compound that undergoes 7 cycle of β oxidation & form 8 Acetyl Co-A



- 1 Acetyl Co A = 10 ATP
- 1 NADH = 2.5 ATP
- 1 $FADH_2$ = 1.5 ATP

- Now in β- Oxidation of Palmitic acid, we have

- 8 Acetyl Co A = 10 X 8 → 80 ATP
- 7 NADH = 2.5 X 7 → 17.5 ATP
- 7 $FADH_2$ = 1.5 X 7 → 10.5 ATP

- Now Total ATP = 80 + 17.5 + 10.5 → 108 ATP
- But since 2 ATP is utilized in the activation, hence net ATP will be 108 - 2 = 106

NET ATP → 106

De Novo Synthesis Of Fatty Acids

- De novo synthesis is also known as Biosynthesis of Fatty Acids.
- It occurs in the cytosol of Liver, kidney & Adipose Tissue.
- The enzymes required for de novo synthesis present in the Cytosol (Cytoplasm)
- Now, generally most of the times, the Fatty Acid that is synthesized during De novo synthesis is Palmitic Acid.

Requirments

- Acetyl Co-A (C-atom source)
- NADPH (As reducing equivalent)
- ATP (For Energy supply)

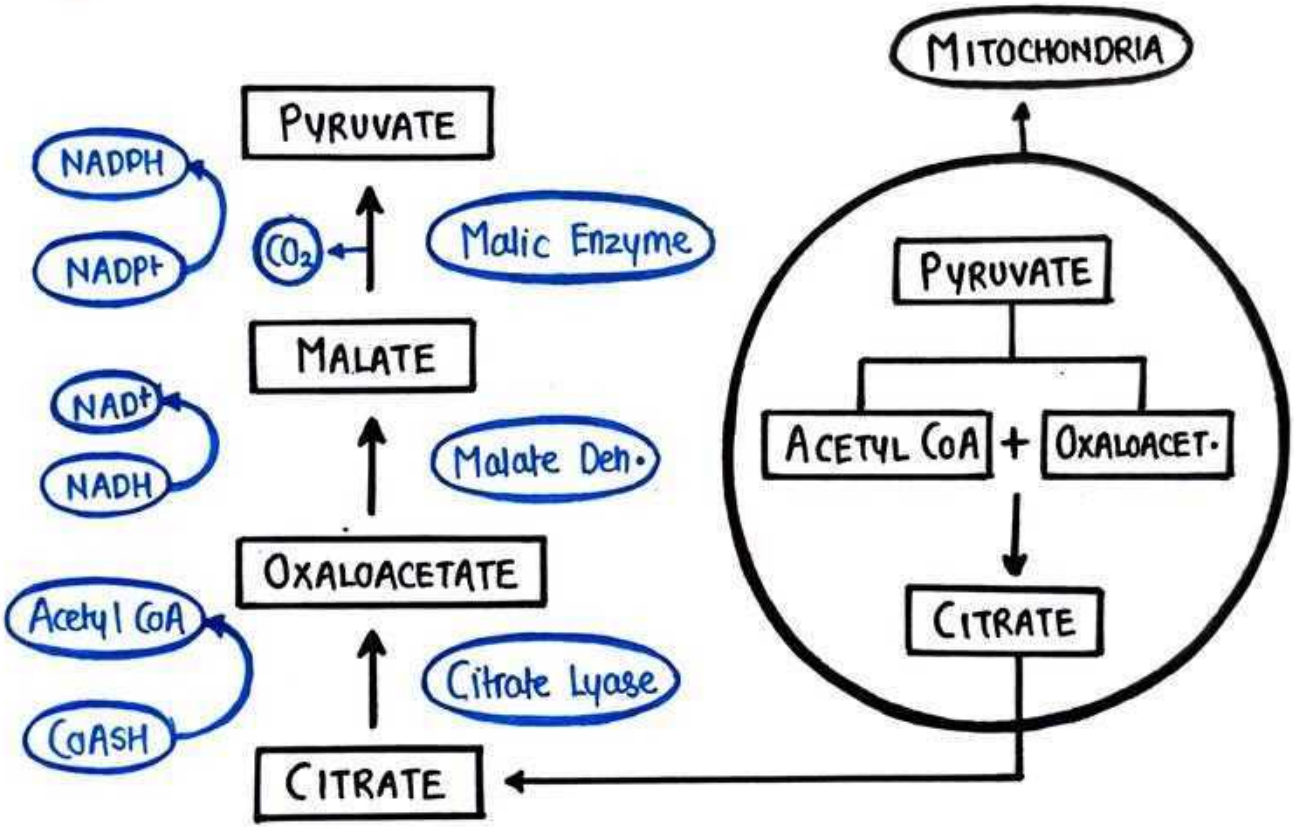
Stages Of De-Novo Synthesis

The de-novo synthesis of Fatty Acids occurs in 3 stages:

- Production of Acetyl Co A & NADPH
- Conversion of Acetyl Co A to Malonyl Co A
- Reactions of Fatty Acid Synthase complex

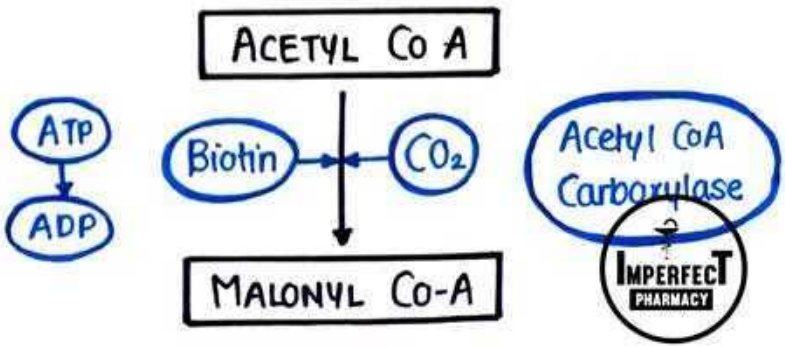
PRODUCTION OF ACETYL CoA & NADPH

- Acetyl CoA is produced in the mitochondria from Pyruvate.
- Acetyl CoA alone cannot cross the mitochondrial membrane, hence it condenses with oxaloacetate to form Citrate.
- Citrate is freely transported to cytosol where it releases the acetyl Co A while oxaloacetate → Malate → Pyruvate & generates NADPH.



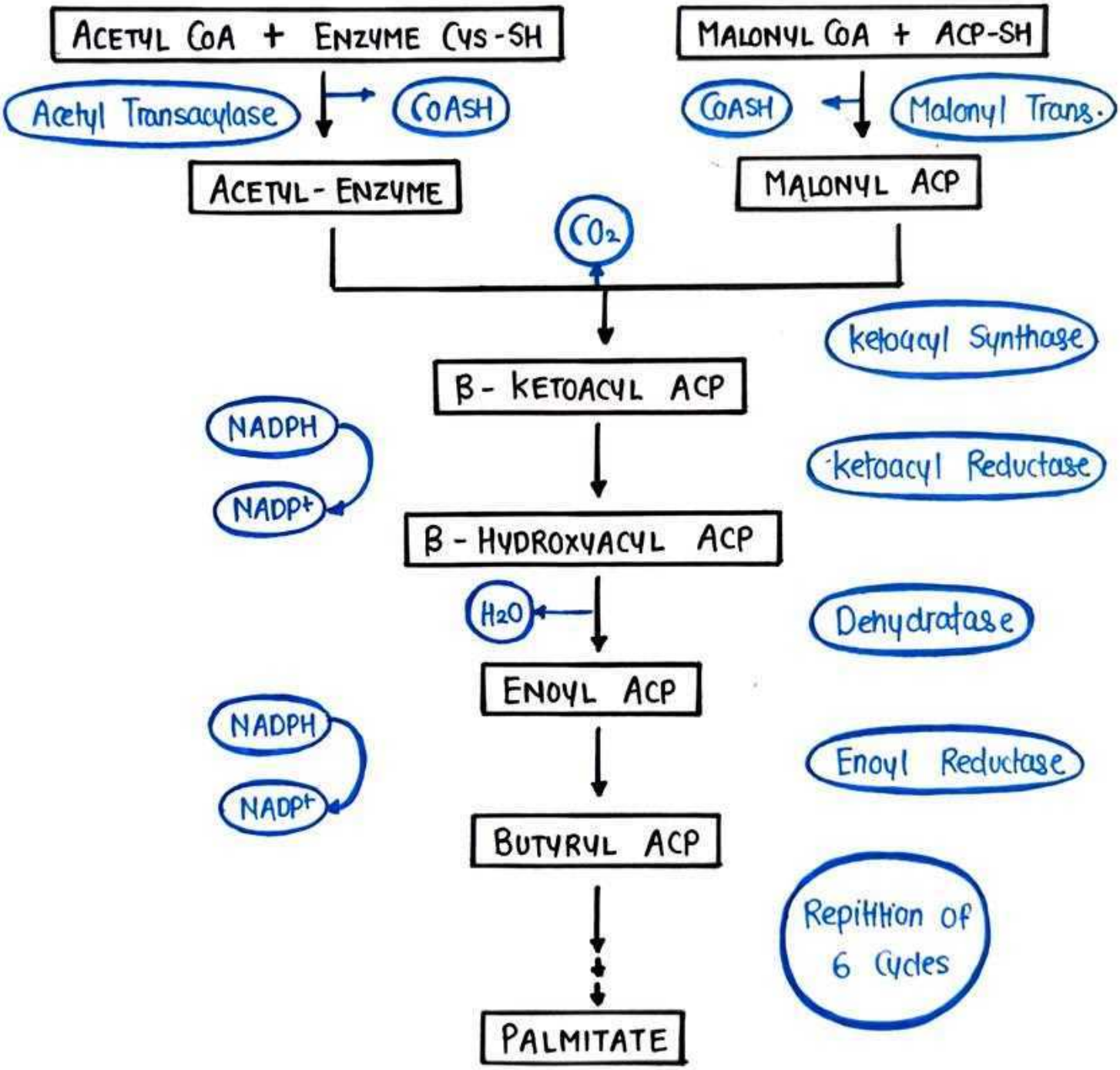
CONVERSION OF ACETYL Co-A TO MALONYL CoA

- Acetyl Co A carboxylase to Malonyl Co-A by acetyl CoA carboxylase
- Process requires ATP, & biotin for CO_2 fixation



REACTIONS OF FATTY ACID SYNTHASE COMPLEX

- The reactions of fatty acid synthesis is performed by a Multifunctional Enzyme called 'Fatty Acid Synthase Complex'
- It is a Multi enzyme complex that performs following reactions:



KETONE BODIES

- Ketone bodies are metabolic products that produce energy during metabolism.
- They are produced by liver.
- Ketone bodies are water soluble and energy yeilding compounds that mainly produce energy during ~~metaboli~~ starvation and diabetes mellitus.
- There are mainly 3 types of ketone bodies :

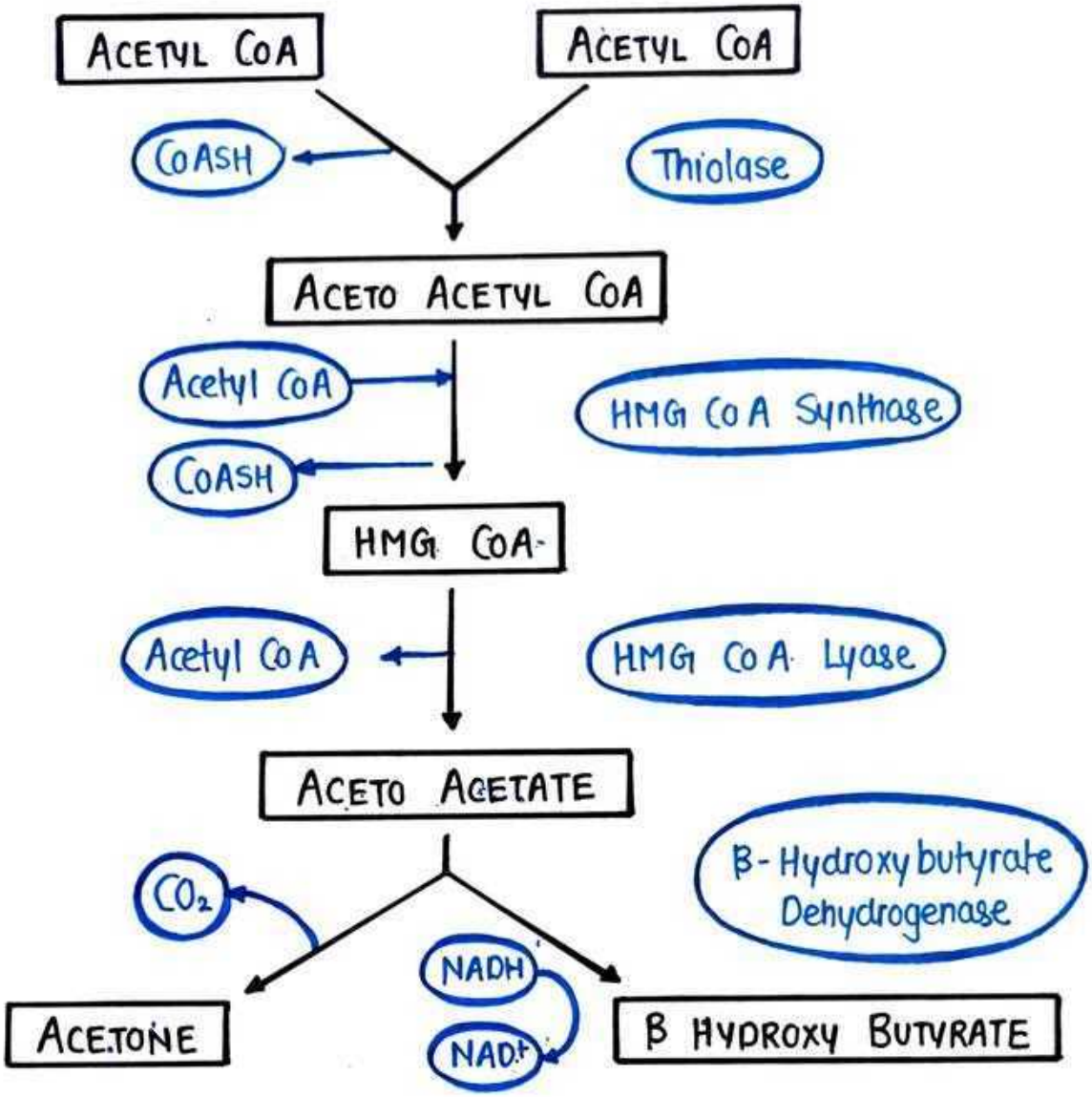
① Acetone
② Aceto- acetate
③ β- Hydroxybutyrate

- Now in the above 3 only first two are true ketone because β- Hydroxybutyrate doesn't posses a keto group.

FORMATION OF KETONE BODIES / KETOGENESIS

The formation of ketone bodies also known as ketogenesis occurs in the mitochondrial matrix of Liver. ketogenesis involves the following reactions :

- Acetoacetyl CoA formed by condensation of two moles of Acetyl CoA.
- Acetoacetyl CoA combines with 1 more molecule of Acetyl CoA & converted into HMG CoA (also known as β- Hydroxy - β - methyl glutaryl CoA) in the presence of HMG CoA synthase.
- HMG CoA cleaves into Aceto - acetate & Acetyl CoA.
- Now Acetoacetone can undergo spontaneous decarboxylation to form Acetone & it can be reduced to form β- hydroxybutyrate.

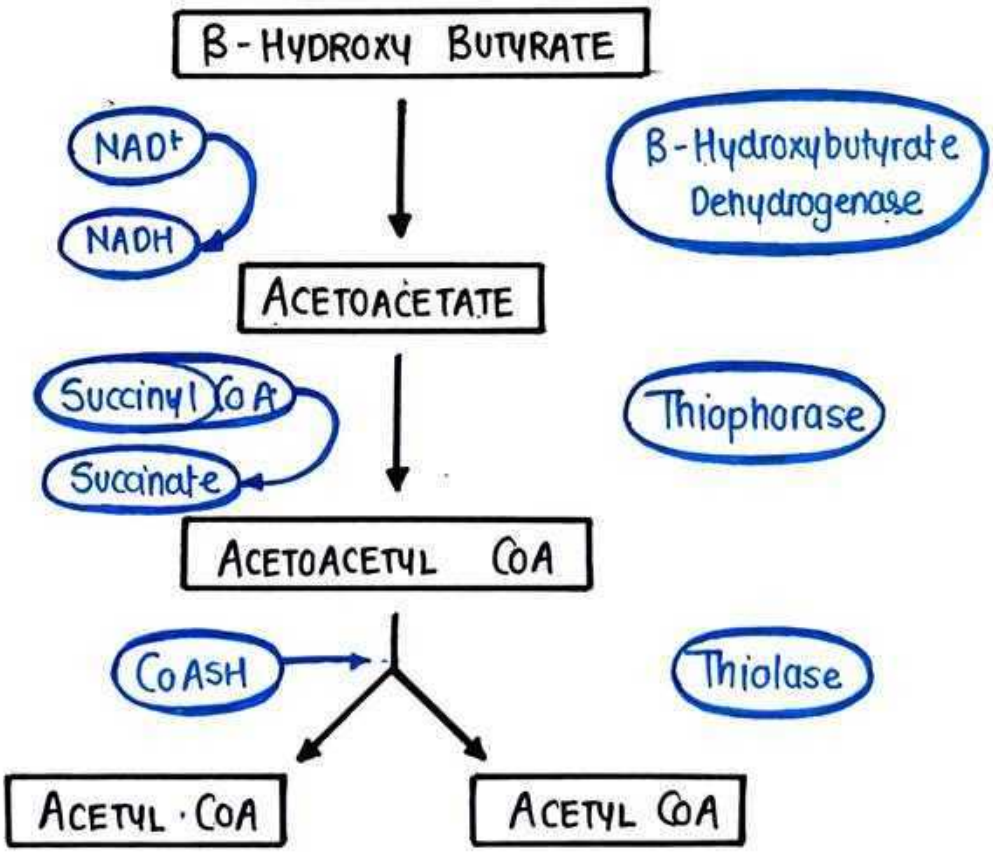


UTILIZATION OF KETONE BODIES

- The utilization of ketone bodies occurs through the process of ketolysis.
- ketolysis is the process of converting ketone bodies into Acetyl CoA to generate energy.
- ketone bodies are important source of energy for skeletal muscles, cardiac muscles, renal cortex etc.
- It is utilized during starvation & Diabetes Mellitus.
- ketolysis is just opposite to ketogenesis.

STEPS OF KETOLYSIS

- β-Hydroxybutyrate is first converted to Acetoacetate.
- Acetoacetate is activated to Acetoacetyl CoA by the thiophorase enzyme present in mitochondria.
- The CoA is denoted by Succinyl CoA
- Thiophorase is absent in liver, hence they are not utilized by liver cells.
- Acetyl CoA cleaves into two ~~enzyme~~ ~~of~~ moles of Acetyl CoA by Thiolase enzyme.



KETOACIDOSIS

- Both Acetoacetate & β-Hydroxybutyrate are strong acids.
- Now increase in their concentration in blood can cause ketoacidosis.
- ketoacidosis can be further divided into two types :

① Alcoholic ketoacidosis
② Diabetic ketoacidosis

ALCOHOLIC KETOACIDOSIS

- It occurs due to intake of alcohol for prolonged time.
- Excessive alcohol consumption can cause Malnourishment.
- Malnourished Alcoholic person has greatre chances of developing Alcoholic ketoacidosis

DIABETIC KETOACIDOSIS

- Diabetic ketoacidosis occurs due to decrease in insulin level of body
- Diabetic ketoacidosis is a dangerous condition that may result in coma & even death, if not treated.
- Diabetic ketoacidosis required a rapid treatment.
- Insulin Therapy is the most useful treatment for diabetic ketoacidosis.

CHOLESTROL

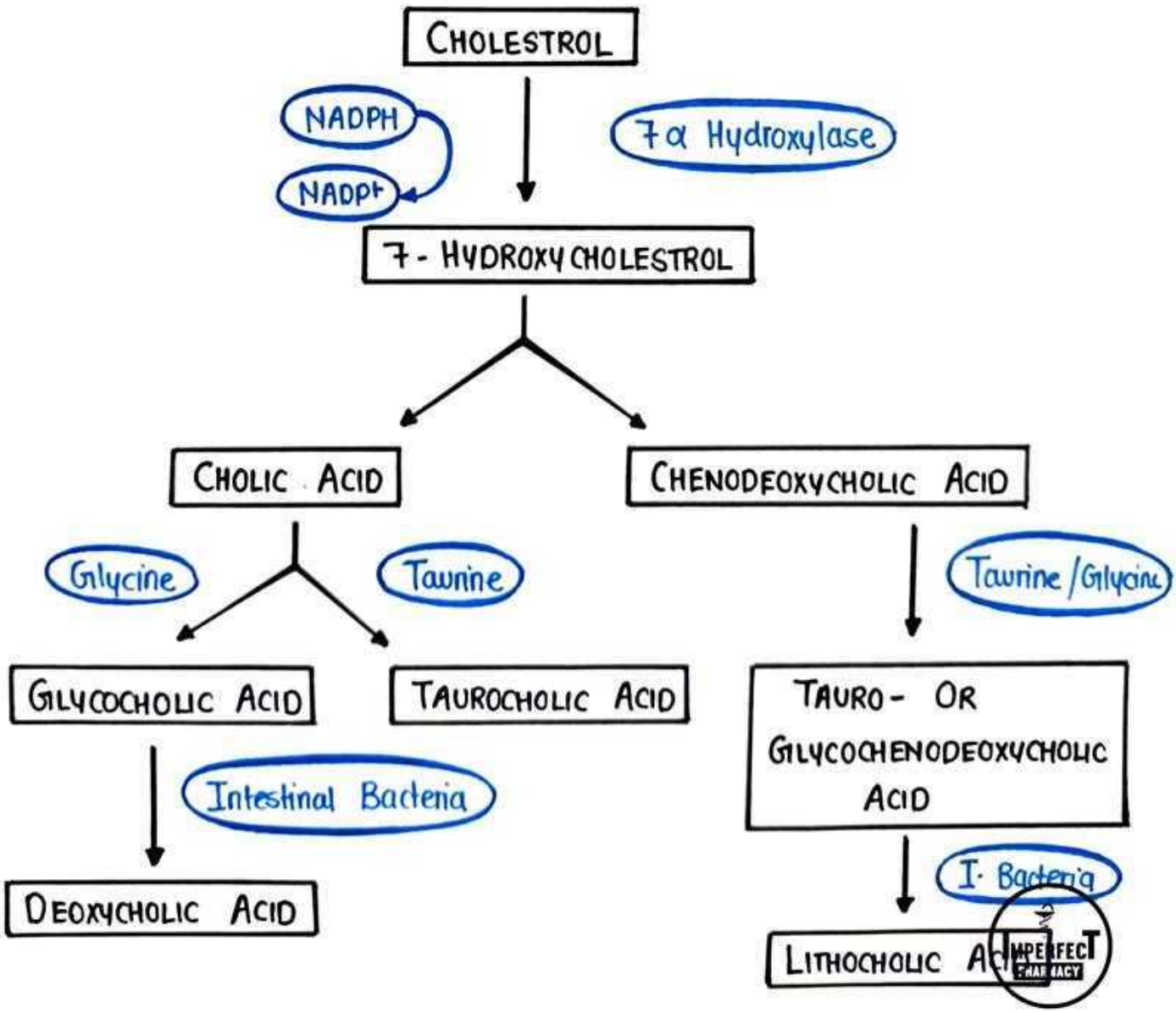
- Cholestrol primarily belongs to a group of compounds known as sterols.
- It is the major component of cell membrane in human body.
- It is a type of lipid present in our body.
- It is naturally synthesized in our body in Liver and can also be obtained from external sources.
- It is present in the foods of animal origin and absent in the food of plant origin.

BIOLOGICAL SIGNIFICANCE OF CHOLESTROL

- It is the major structural component of cell membrane.
- It is the most essential ingredient in the structure of Lipoproteins
- It is the precursor of bile acid.
- It is the precursor of vitamin D.
- It is also the precursor of various steroidal harmones like progesteron, androgens, corticosteroids etc.
- Fatty acids are transported to liver as cholestrol esters.
- It insulates nerve fibres.
- Although cholestrol has various biological significance but its high concentration can leads to Atherosclerosis.

Conversion Of Cholestrol Into Bile Acid

- The synthesis of bile acid (bile juice) takes place in liver.
- bile acids promotes absorbtion of lipids & fat soluble vitamins.
- Cholestrol first converted into 7- Hydroxycholestrol in the presence of 7α Hydroxylase.
- 7- Hydroxycholestrol breaks into cholic acid & chenodeoxycholic acid & these are the primary bile acids.
- On conjugation with glycine or taurine, conjugated bile acids (Glycocholic and Taurocholic acid) are formed.
- Finally in the presence of bacterial enzymes, secondary bile acid forms.



UREA CYCLE

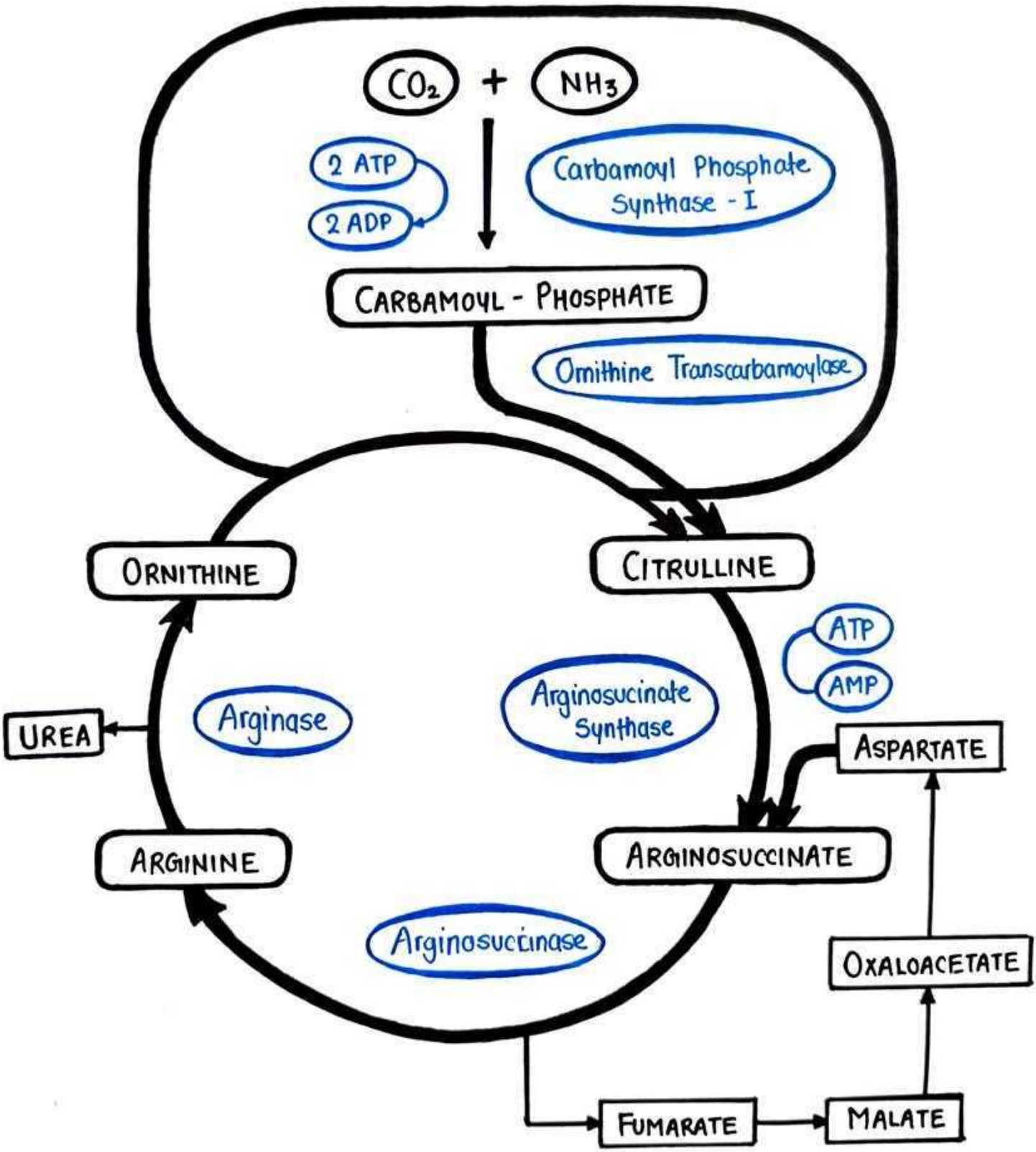
- Urea cycle is defined as the cyclic process in which Ammonia is converted into Urea.
- Urea cycle is also defined as the first cyclic process or first metabolism pathway discovered by Hans krebs and kurt Henseleit, hence also known as 'krebs Henseleit Cycle'. It is also called Ornithine Cycle.
- Urea synthesis occurs only in Liver and after that it is further transported to kidney through blood & excreted out from body.

Enzymes Involved In Urea Cycle

Urea cycle involves Five enzymes as follows

① Carbamoyl Phosphate Synthase I
② Ornithine Transcarbamoylase
③ Arginosuccinate Synthase
④ Arginosuccinase
⑤ Arginase

- Now in the above five enzymes, First 2 are found in mitochondria while rest 3 are found in cytosol of liver.
- Arginase is the enzyme only found in Liver, hence urea synthesis or Urea Cycle occurs only in liver.


CO_2 + NH_3
2 ATP
2 ADP
Carbamoyl Phosphate Synthase - I
CARBAMOYL - PHOSPHATE
Ornithine Transcarbamoylase
ORNITHINE
CITRULLINE
ATP
AMP
Arginase
Arginosucinate Synthase
UREA
ASPARTATE
ARGININE
ARGINOSUCCINATE
Arginosuccinase
OXALOACETATE
FUMARATE
MALATE

STEPS OF UREA CYCLE

① Synthesis Of Carbamoyl Phosphate

- NH_3 condensed with CO_2 and activated in the presence of Carbamoyl Phosphate Synthase - I to form Carbamoyl Phosphate
- This step consumes 2 ATP and is irreversible.

② Formation Of Citrulline

- Citrulline is synthesized from Carbamoyl Phosphate and Ornithine by Ornithine Transcarbamoylase
- Ornithine is again regenerated & Urea cycle continues.

③ Synthesis Of Arginosucinate

- Citrulline condenses with Aspartate to produce Arginosuccinate in the presence of Arginosuccinate Synthase.
- ATP is converted into AMP & Pyrophosphate (PPi).

④ Formation Of Arginine

- Arginosuccinate cleaves to produce Arginine & Fumarate in the presence of Arginosuccinase.
- Arginine is used as immediate precursor of Urea.

⑤ Formation Of Urea

- Arginine finally in the presence of Arginase converted into Urea and ornithine.
- Ornithine again used in Urea Cycle while Urea is excreted out from body through kidney.

Energetics Of Urea Cycle

- In Urea cycle 4 ATP molecules are consumed & it is irreversible process.
- Two ATP are utilized for synthesis of Carbamoyl Phosphate.
- One ATP is converted to AMP to produce Arginosuccinate which is equal to 2 ATP.

Metabolic Disorders Of Urea Cycle

- In healthy people, the normal blood Urea concentration is 10-40 mg/dl, now increase in blood-urea level can leads to various metabollic disbalances in our body.
- Urea cycle disorders are various genetic disorders occurs due to deficiency in enzymes involved in Urea Cycle.
- The Five most common disorders are as follows :

① Hyper Ammonemia Type I : Carbamoyl Phosphate Synthase I
② Hyper Ammonemia Type II : Ornithine Transcarbamoylase
③ Citrullinemia : Arginosuccinate Synthase
④ Arginosuccinic Aciduria : Arginosuccinase
⑤ Hyperargininemia : Arginase