Role of Krebs Cycle (Unit III)

* The Kreb cycle or citric acid cycle is the most important metabolic pathway for the energy supply to the body
* About 65-70% of the ATP is synthesized in Krebs cycle
* Kreb cycle essentially involves the oxidation of acetyl CoA to CO_2 and H_2O. This cycle utilizes about two third of total oxygen consumed by the body.
* Kreb cycle is the final common oxidative pathway for carbohydrates, fats & amino acids.
* It is the most important central pathway connecting almost all individual metabolic pathway.
* The cycle was proposed by Hans Adolf Krebs in 1937, based on the studies of oxygen consumption in pigeon breast muscle.
* The cycle is named in his honour.
* The enzyme of TCA cycle are located in mitochondrial matrix, in close proximity to the electron transport chain. This enables the synthesis of ATP by oxidative phosphorylation.

Reaction of Kreb cycle

*1. Formation of citrate

- The cycle proper starts with the condensation of acetyl CoA and oxaloacetate, catalysed by the enzyme citrate syntinase.

2&3. Citrate is isomerized to isocitrate by the enzyme aconitase. This is achieved in a two stage reaction of dehydration followed by hydration through the formation of an intermediate - cis aconitate.

4&5. Formation of α-Ketoglutarate

The enzyme isocitrate dehydrogenase catalyses the conversion (oxidative decarboxylation) of isocitrate to oxalosuccinate & then to α-Ketoglutarate. The formation of NADH & the liberation of CO_2 occur.

6. Conversion of α-Ketoglutarate to succinyl CoA.

- It occurs through oxidative decarboxylation, catalysed by α-Ketoglutarate dehydrogenase complex. This enzyme is dependent on 5 cofactors - TPP, lipoamide, NAD^+, FAD & CoA. The reaction is analogous to the conversion of pyruvate to acetyl CoA. At this stage of the Kreb cycle, second NADH & CO_2 is produced.

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7. Formation of Succinate

Succinyl CoA is converted to succinate by succinate thiokinase. This reaction is coupled with the phosphorylation of GDP to GTP. This is a substrate level phosphorylation. GTP is converted to ATP by the enzyme nucleoside diphosphate kinase.

$$GTP + ADP \longrightarrow GDP + ATP$$

8. Conversion of succinate to fumarate

Succinate is oxidized by succinate dehydrogenase to fumarate. This reaction results in the production of $FADH_2$ & not NADH

9 Formation of malate

The enzyme fumarase catalyses the conversion of fumarate to malate with the addition of H_2O.

10. Conversion of malate to Oxaloacetate

Malate is then oxidized to oxaloacetate by malate dehydrogenase. The third & final synthesis of NADH occurs at this stage

The Oxaloacetate is regenerated which can combine with another molecule of acetyl CoA & continue the cycle.

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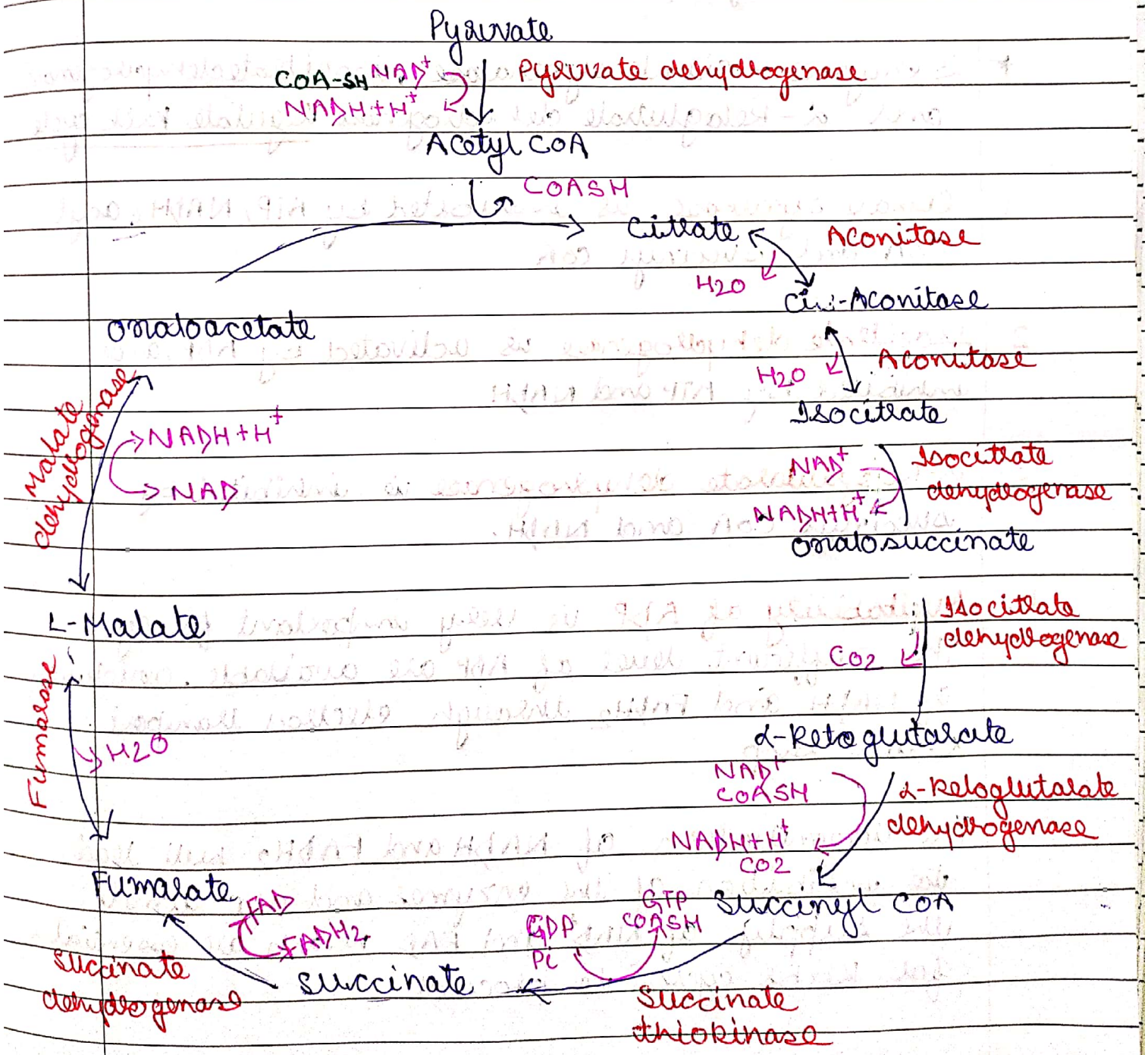
$$Acetyl\ CoA + 3NAD^+ + FAD + GDP + Pi + 2H_2O \rightarrow 2CO_2 + 3NADH + 3H^+ + FADH_2 + GTP + CoA$$



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Regulation of Krebs cycle

* The cellular demands of ATP are crucial in controlling the rate of citric acid cycle

* The regulation is brought about either by enzymes or the level of ADP.

* 3 enzymes – Citrate synthase, isocitrate dehydrogenase, and α-Ketoglutrate dehydrogenase regulate Krebs cycle.

1. Citrate synthase is inhibited by ATP, NADH, acyl CoA and succinyl CoA

2. Isocitrate dehydrogenase is activated by ADP, and inhibited by ATP and NADH

3. α-Ketoglutarate dehydrogenase is inhibited by succinyl CoA and NADH.

4. Availability of ADP is very important for cycle. The sufficient level of ADP are available, oxidation of NADH and $FADH_2$ through electron transport chain stop

The accumulation of NADH and $FADH_2$ will lead the inhibition of the enzymes and also limits the supply of NAD^+ and FAD which are essential for Krebs cycle to proceed

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Energetics of Krebs cycle

- During the process of oxidation of acetyl CoA via Krebs cycle 4 reducing (3 as $NADH$ and one as $FADH_2$) are produced
- Oxidation of 3 $NADH$ by ETC coupled with oxidative phosphorylation results the synthesis of 9 ATP
- $FADH_2$ leads to the formation of 2 ATP.
- One substrate level phosphorylation
- Thus, a total 12 ATP are produced from one acetyl CoA.

Role of Krebs cycle

- Complete oxidation of acetyl CoA.
- ATP generation.
- Final common oxidative pathway.
- Fat is burned on the wick of carbohydrates.
- Excess carbohydrates are converted as neutral fats.
- No net synthesis of carbohydrate from fat.
- Carbon skeleton of amino acids finally enter Krebs cycle.