



TCA Cycle

TCA Cycle

- Also known as **Krebs cycle**
- TCA cycle essentially involves the oxidation of **acetyl CoA to CO₂ and H₂O.**
- TCA cycle –the **central metabolic pathway**
- The TCA cycle is the **final common oxidative pathway for carbohydrates, fats, amino acids.**

- **TCA cycle supplies energy & also provides many intermediates required for the synthesis of amino acids, glucose, heme etc.**
- **TCA cycle is the most important central pathway connecting almost all the individual metabolic pathways.**

- **Definition**
- **Citric acid cycle or TCA cycle or tricarboxylic acid cycle essentially involves the oxidation of acetyl CoA to CO_2 & H_2O .**
- **Location of the TCA cycle**
- **Reactions of occur in mitochondrial matrix, in close proximity to the ETC.**

Reactions of TCA cycle

- **Oxidative decarboxylation of pyruvate to acetyl CoA by PDH complex.**
- **This step is connecting link between glycolysis and TCA cycle.**

Reactions of TCA Cycle

- **Step:1 Formation of citrate**
- **Oxaloacetate condenses with acetyl CoA to form Citrate, catalysed by the enzyme citrate synthase**
- **Inhibited by:**
- **ATP, NADH, Citrate - competitive inhibitor of oxaloacetate.**

Steps 2 & 3 Citrate is isomerized to isocitrate

- **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-aconitase**

Steps 4 & 5 Formation of α -ketoglutarate

- **Isocitrate dehydrogenase (ICDH) catalyses the conversion of (oxidative decarboxylation) of isocitrate to oxalosuccinate & then to α -ketoglutarate.**
- **The formation of NADH & the liberation of CO_2 occur at this stage.**
- **Stimulated (cooperative) by isocitrate, NAD^+ , Mg^{2+} , ADP, Ca^{2+} (links with contraction).**
- **Inhibited by NADH & ATP**

Step: 6 Conversion of α -ketoglutarate to succinyl CoA

- **Occurs through oxidative decarboxylation, catalysed by α -ketoglutarate dehydrogenase complex.**
- **α -ketoglutarate dehydrogenase is an multienzyme complex.**
- **At this stage of TCA cycle, second NADH is produced & the second CO_2 is liberated.**

Step: 7 Formation of succinate

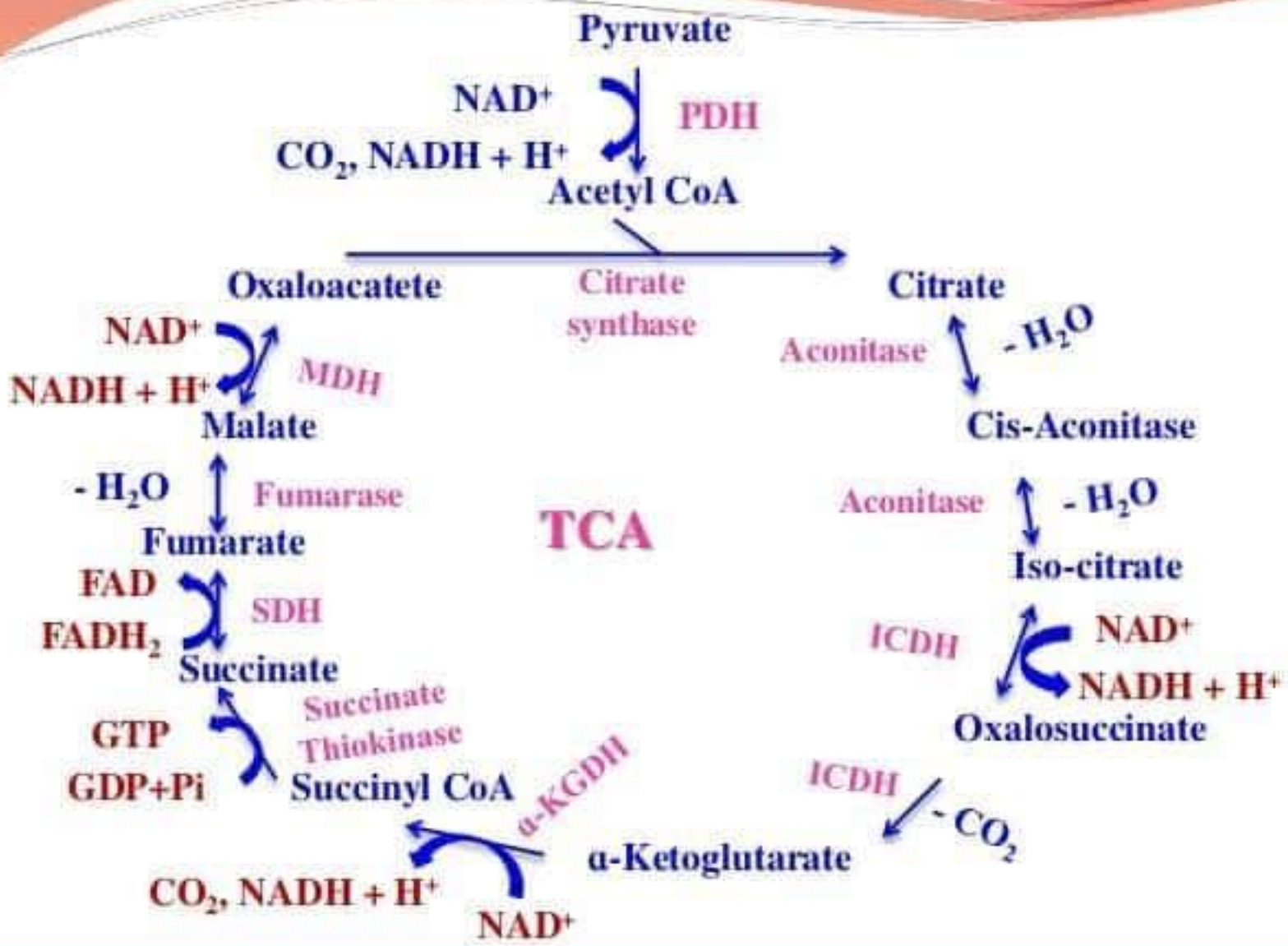
- **Succinyl CoA is converted to succinate by succinate thiokinase.**
- **This reaction is coupled with the phosphorylation of GDP to GTP.**
- **This is a substrate level phosphorylation.**
- **GTP is converted to ATP by the enzyme nucleoside diphosphate kinase.**

Step: 8 Conversion of succinate to fumarate

- **Succinate is oxidized by succinate dehydrogenase to fumarate.**
- **This reaction results in the production of FADH_2 .**
- **Step: 9 Formation of malate: The enzyme fumarase catalyses the conversion of fumarate to malate with the addition of H_2O .**

Step: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.**



Regeneration of oxaloacetate

- **The TCA cycle basically involves the oxidation of acetyl CoA to CO_2 with the simultaneous regeneration of oxaloacetate.**
- **There is no net consumption of oxaloacetate or any other intermediate in the cycle.**

Significance of TCA cycle

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

Requirement of O_2 by TCA cycle

- There is no direct participation of O_2 in TCA cycle.
- Operates only under aerobic conditions.
- This is due to, NAD^+ & FAD required for the operation of the cycle can be regenerated in the respiratory chain only in presence of O_2 .
- Therefore, **citric acid cycle is strictly aerobic.**

Energetics of TCA Cycle

- **Oxidation of 3 NADH by ETC coupled with oxidative phosphorylation results in the synthesis of 9ATP.**
- **FADH₂ leads to the formation of 2ATP.**
- **One substrate level phosphorylation.**
- **Thus, a total of 12 ATP are produced from one acetyl CoA.**

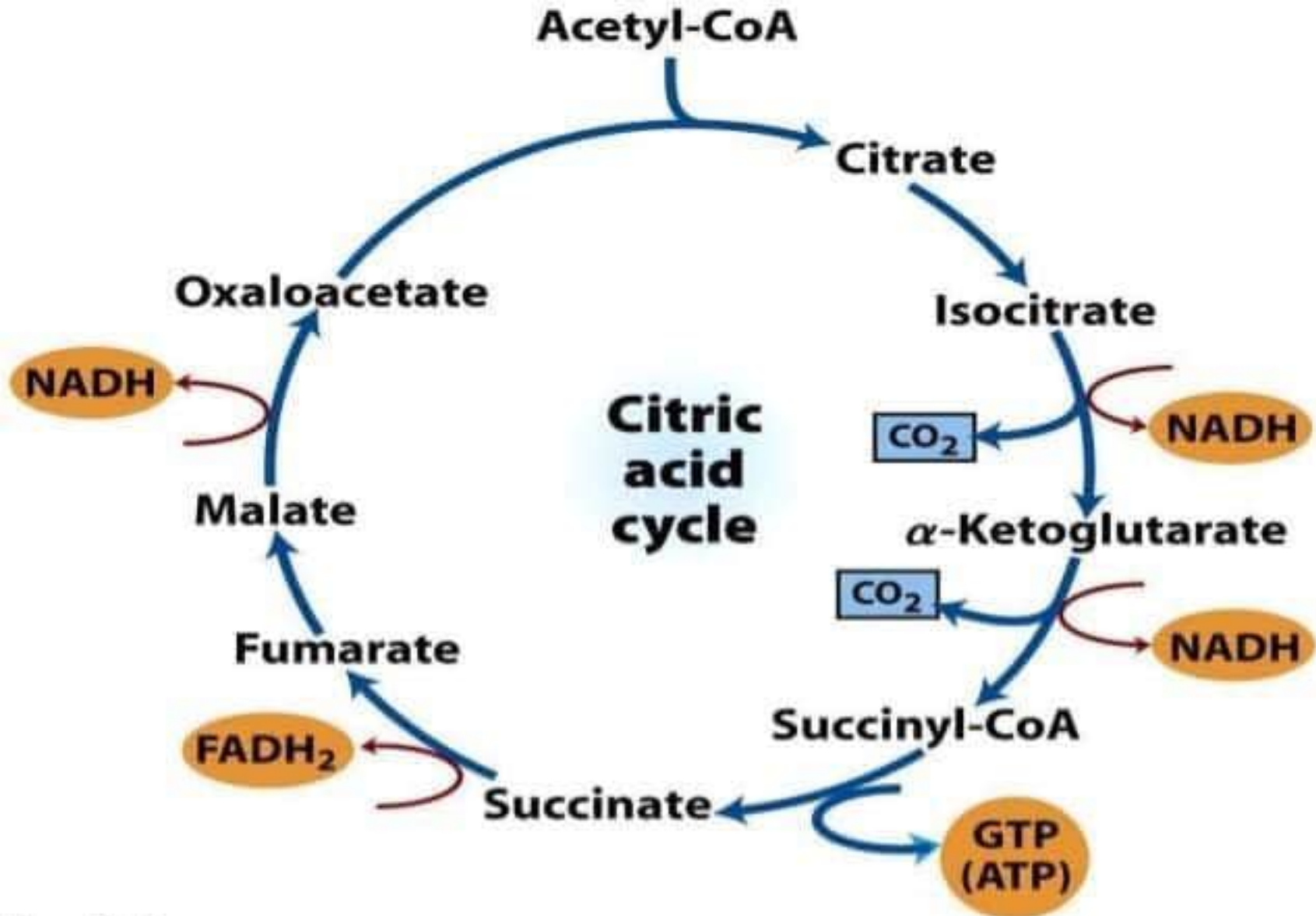


Figure 16-13
Lehninger Principles of Biochemistry, Fifth Edition
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Regulation of TCA Cycle

- **Three regulatory enzymes**

- 1. Citrate synthase**

- 2. Isocitrate dehydrogenase**

- 3. α -ketoglutarate dehydrogenase**

- **Citrate synthase** is inhibited by ATP, NADH, acyl CoA & succinyl CoA.
- **Isocitrate dehydrogenase** is activated by ADP & inhibited by ATP and NADH
- **α -ketoglutarate dehydrogenase** is inhibited by succinyl CoA & NADH.
- **Availability of ADP** is very important for TCA cycle to proceed.