B.Sc-4th sem
Unit-4 (CC-410)

KREB'S CYCLE

BY

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TCA Cycle

- Also known as Krebs cycle
- TCA cycle essentially involves the oxidation of acetyl CoA to CO_2 and H_2O.
- 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-aconiase

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 occure 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

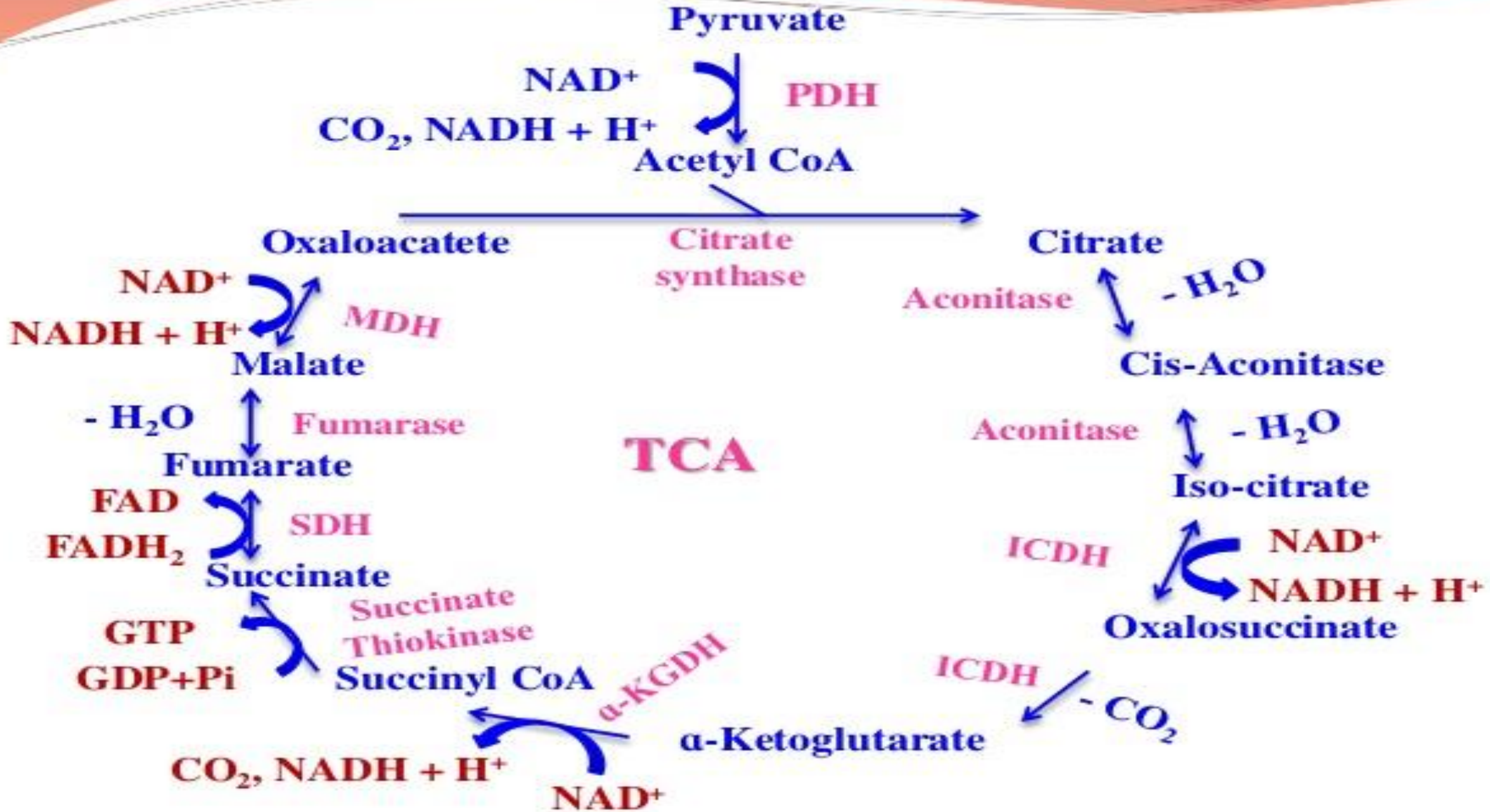
- Succinyl CoA is converted to succinate by succinate thiokinase.
- This reaction is coupled with the phosphorylation of GDP to GTP.
- This is a substrate level phosphorylation.
- GTP is converted to ATP by the enzyme nucleoside diphosphate kinase.

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.


Pyruvate
NAD+
CO2, NADH + H+
PDH
Acetyl CoA
Oxaloacatete
Citrate synthase
Citrate
NAD+
NADH + H+
MDH
Malate
Aconitase
- H2O
Cis-Aconitase
- H2O
Fumarase
Fumarate
Aconitase
- H2O
Iso-citrate
TCA
FAD
FADH2
SDH
Succinate
ICDH
NAD+
NADH + H+
Oxalosuccinate
Succinate Thiokinase
GTP
GDP+Pi
Succinyl CoA
α-KGDH
ICDH
- CO2
α-Ketoglutarate
CO2, NADH + H+
NAD+

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.
- $FADH_2$ leads to the formation of 2ATP.
- One substrate level phosphorylation.
- Thus, a total of 12 ATP are produced from one acetyl CoA.

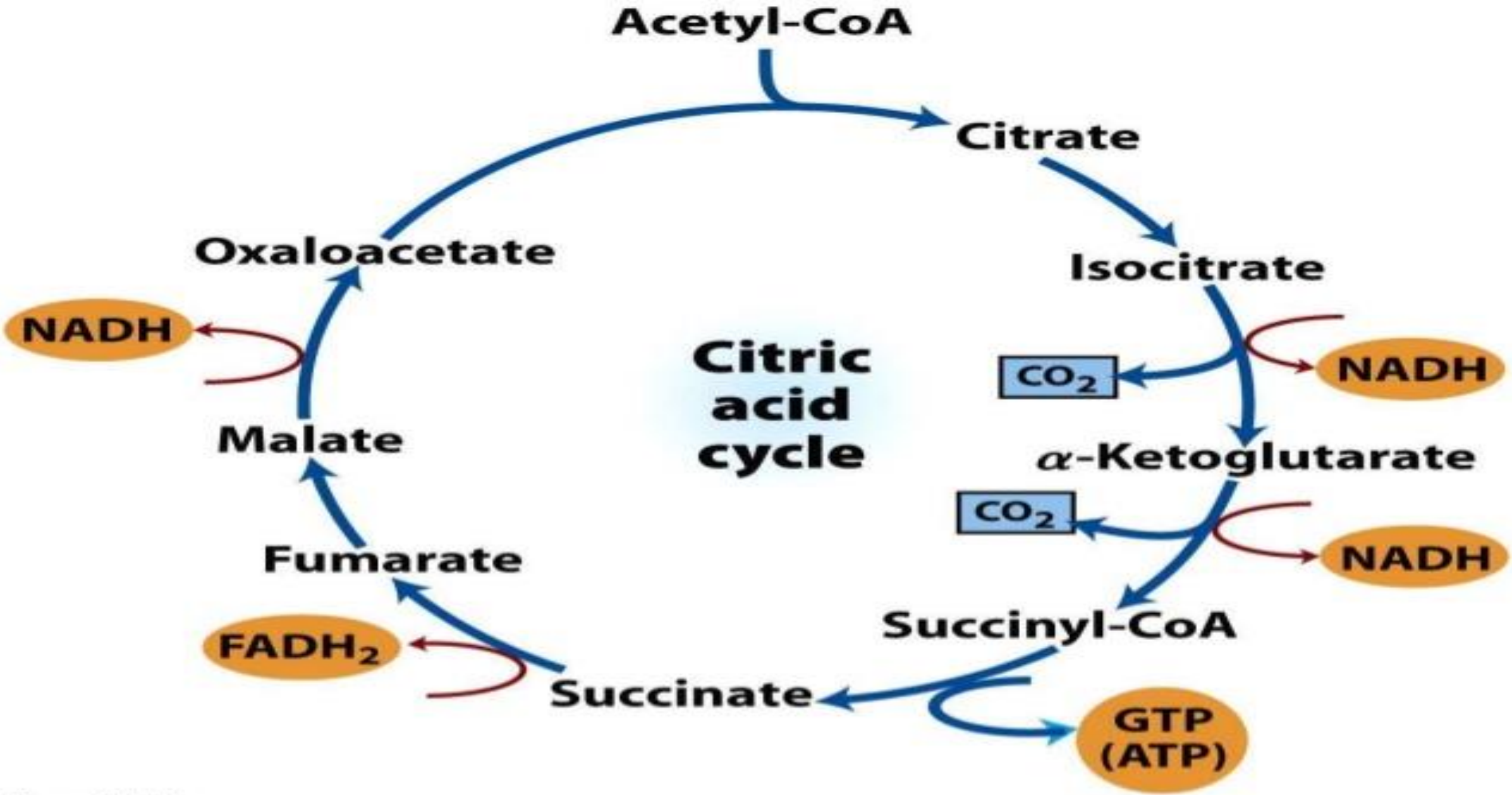


Figure 16-13
Lehninger Principles of Biochemistry, Fifth Edition

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.**

Transamination

- **Transamination is a process where an amino acid transfers its amino group to a keto group and itself gets converted to a keto acid.**
- **The formation of Alpha ketoglutarate & oxaloacetate occures by this mechanism.**

Thank You