TCA CYCLE

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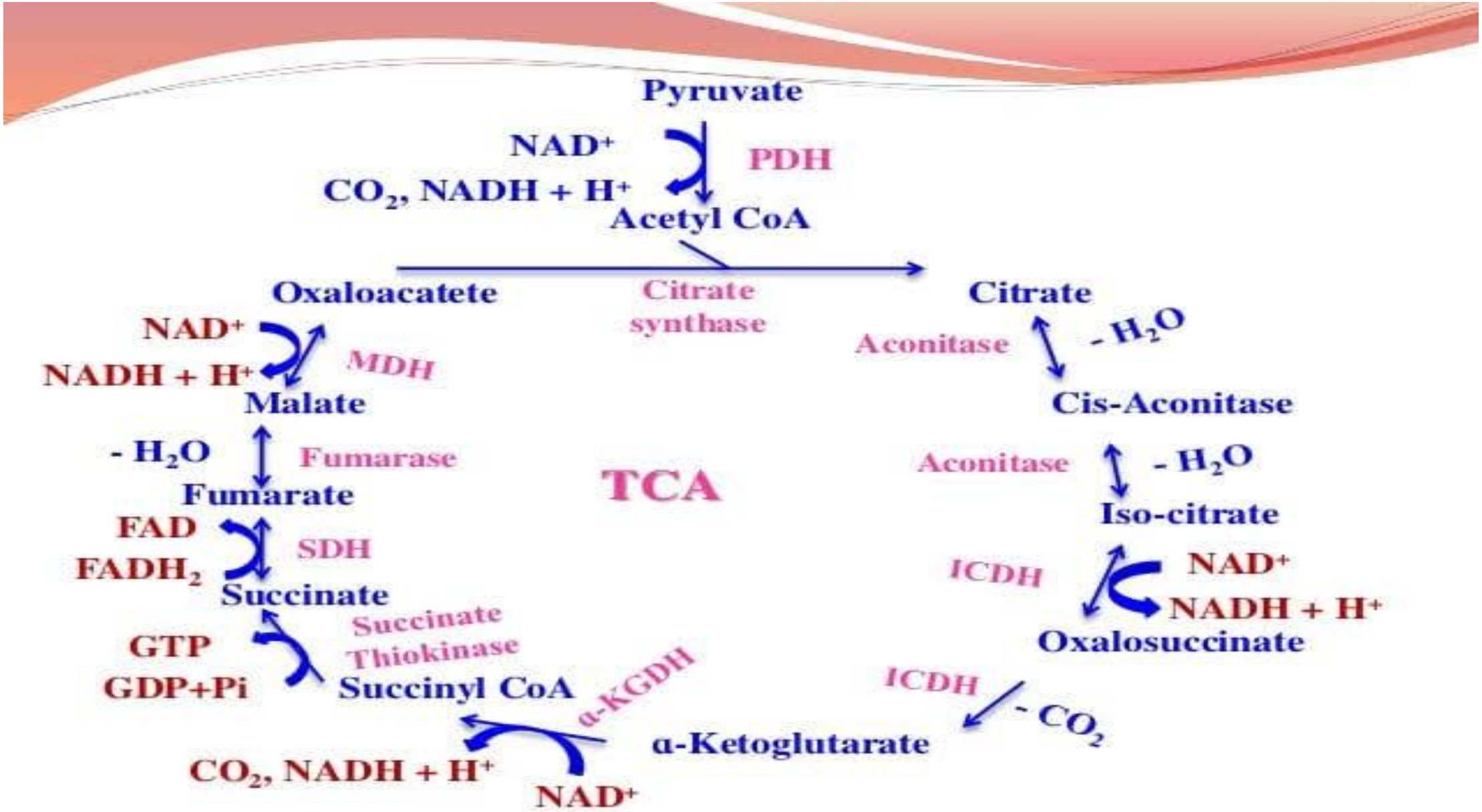
INTRODUCTION

- The citric acid cycle (Krebs cycle or tricarboxylic acid-TCA 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.
- Citric acid cycle essentially involves the oxidation of acetyl CoA to CO2 and H2O.
- Krebs cycle is the most important central pathway connecting almost all the individual metabolic pathways (either directly or indirectly).
- The citric acid cycle was proposed by Hans Adolf Krebs in 1937

LOCATION OF TCA CYCLE:

- The enzymes of TCA cycle are located in mitochondrial matrix, in close proximity to the electron transport chain.
- Krebs cycle basically involves the combination of a two carbon acetyl CoA with a four carbon oxaloacetate to produce a six carbon tricarboxylic acid.
- Oxaloacetate is considered to play a catalytic role in citric acid 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
GTP
GDP+Pi
Succinate Thiokinase
Succinyl CoA
ICDH
- CO2
α-KGDH
α-Ketoglutarate
CO2, NADH + H+
NAD+

OVERALL REACTION OF TCA CYCLE

- Acetyl CoA + 3 NAD+ + FAD + GDP + Pi + 2H2O ------> 2CO2 + 3NADH + 3H+ + FADH2 + GTP + CoA
- Regeneration of oxaloacetate in TCA cycle:
- The TCA cycle basically involves the oxidation of acetyl CoA to CO2 with simultaneous regeneration of oxaloacetate.
- There is no direct participation of oxygen in Krebs cycle. However, the cycle operates only under aerobic conditions.

ENERGETICS OF TCA CYCLE

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

REGULATION OF TCA 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 levels of ADP.
- Three enzymes-namely **citrate synthase**, **isocitrate dehydrogenase** and **alpha-ketoglutarate dehydrogenase** reguIate citric acid cycle.

1. Citrate synthase is inhibited by ATP, NADH, acetyl CoA and succinyl CoA.
2. lsocitrate dehydrogenase is activated by ADP, and inhibited by ATP and NADH.

- 3.alpha-Ketoglutarate dehydrogenase is inhibited by succinyl CoA and NADH.
- 4. Availability of ADP is very important for the citric acid cycle to proceed.
- This is due to the fact that unless sufficient levels of ADP are available, oxidation (coupled with phosphorylation of ADP to ATP) of NADH and FADH2 through electron transport chain stops.
- The accumulation of NADH and FADH2 will lead to inhibition of the enzymes and also limits the supply of NAD+ and FAD which are essential for TCA cycle to proceed.

AMPHIBOLIC NATURE OF THE CITRIC ACID CYCLE

- Krebs cycle is both catabolic and anabolic in nature, hence regarded as amphibolic.
- TCA cycle is actively involved in gluconeogenesis, transamination and deamination.

The most important synthetic (anabolic) reactions connected with TCA cycle are :

1 . Oxaloacetate and alpha-ketoglutarate, respectively, serve as precursors for the synthesis of aspartate and glutamate which, in turn, are required for the synthesis of other non-essential amino acids, purines and pyrimidines.

2. Succinyl CoA is used for the synthesis of porphyrins and heme.

3. Mitochondrial citrate is transported to the cytosol, where it is cleaved to provide acetyl CoA for the biosynthesis of fatty acids, sterols etc.

ANAPLEROSIS OR ANAPLEROTIC REACTIONS

- The reactions concerned to replenish or to fill up the intermediates of citric acid cycle are called anaplerotic reactions or anaplerosis (Greek : fill up).

1. Pyruvate carboxylase catalyses the conversion of pyruvate to oxaloacetate.

This is an ATP dependent carboxylation reaction.

Pyruvate + CO_2 + ATP $\longrightarrow$ Oxaloacetate+ ADP+ Pi

2. Pyruvate is converted to malate by NADP+ dependent malate dehydrogenase (malic enzyme).

Pyruvate +CO_2 + NADPH + H+ $\longrightarrow$ Malate + NADPH+ + H_2O

3. Transamination is a process wherein an amino acid transfers its amino group to a keto acid and itself gets converted to a keto acid. The formation of a-ketoglutarate and oxaloacetate occurs by this mechanism.

4. alpha-Ketoglutarate can also be synthesized from glutamate by glutamate dehydrogenase action.

THANK YOU