Get Ready to Crack CSIR NET 2021 (Short notes on TCA Cycle)

Kreb's (TCA) Cycle

Location: Mitochondrial matrix

Pyruvate oxidation:

- In the presence of oxygen, further oxidation of pyruvate occurs in the mitochondrial matrix (cytosol in case of prokaryotes).
- In the mitochondrial matrix, the pyruvate first oxidizes into acetyl-CoA.
- The pyruvate dehydrogenase complex catalyses the conversion of pyruvate to acetyl-CoA.
- Pyruvate dehydrogenase is an assembly of three individual enzymes:
    1. Pyruvate dehydrogenase (E1)
    2. Dihydrolipoyl transacetylase (E2)
    3. Dihydrolipoyl dehydrogenase (E3)
- The oxidation of pyruvate to acetyl-CoA involves the coenzymes thiamine pyrophosphate (TPP), lipoic acid, FAD, NAD^+ and coenzyme ; acting in association with E1, E2 and E3 in the pyruvate dehydrogenase complex

Components of Pyruvate dehydrogenase complex:

Enzyme	Function	No. of polypeptides	Cofactors
Pyruvate dehydrogenase (E1)	Decarboxylation and oxidation of pyruvate	24	TPP
Dihydrolipoyl transacetylase (E2)	Catalyzes transfer of acetyl group to CoA	24	Lipoic acid, CoA
Dihydrolipoyl dehydrogenase (E3)	Reoxidizes dihydrolipomadie	12	NAD^+, FAD

Mechanism of action of pyruvate dehydrogenase complex:

- Firstly, E1 catalyzes the decarboxylation of pyruvate, producing hydroxyethyl-TPP and then the oxidation of the hydroxyethyl group to an acetyl group follows.
- The electrons from this oxidation reduce the disulfide of the lipoate bound to E2 and the acetyl group is transferred into thioester linkage with an -SH group of reduced lipoate.
- Therafter, E2 catalyzes the transfer of the acetyl group to coenzyme A, forming acetyl-CoA.
- Finally, E3 catalyzes the regeneration of the disulfide form of lipoate; electrons pass first to FAD and then to NAD^+.

Regulation of pyruvate dehydrogenase complex:

It is regulated by two ways:

- Allosteric regulation
- Covalent modification

Allosteric regulation:

- It is mediated by NADH and acetyl-CoA

Covalent modification:

- It occurs only in eukaryotes.
- It is mediated by phosphorylation/dephosphorylation.
- E2 is inhibited by acetyl-CoA and is activated by CoA
- E3 is inhibited by NADH and activated by NAD^+
- E1 subunit undergoes reversible phosphorylation/dephosphorylation

Inhibitors of pyruvate dehydrogenase:

Arsenite and mercuric ions

Step 1:

- The Kreb's cycle begins with the condensation of an oxaloacetate (four carbon unit) and the acetyl group of acetyl-CoA (two-carbon unit).
- Oxaloacetate reacts with acetyl-CoA and H_2O, yielding citrate and coenzyme A.
- This reaction (an aldol condensation) followed by a hydrolysis, is catalysed by citrate synthase.
- Citrate has no chiral centre but has the potential to react asymmetrically if an enzyme with which it interacts has an active site that is asymmetric.
- Such molecule is called prochiral molecule

Step 2:

- An isomerization reaction, wherein water is first removed and then added back, shifts the hydroxyl group from one carbon atom to its neighbour.
- The enzyme catalysing this step, aconitase (nonheme iron protein), is the target site for the toxic compound fluoroacetate (used as a pesticide).
- The citric acid cycle is halted by fluroacetate's metabolic conversion into fluorocitrate, which is a potent inhibitor of aconitase.

Step 3:

- Isocitrate is oxidized and decarboxylated to α-Ketoglutarate (also called oxoglutarate).
- In the first of the four sequential oxidation steps, the carbon carrying the hydroxyl group gets converted to a carbonyl group.
- The immediate product is unstable, losing CO_2 while still bound to the enzyme.
- The oxidative decarboxylation of isocitrate is catalysed by isocitrate dehydrogenase.

Step 4:

- A second oxidative decarboxylation reaction results in the formation of succinyl-CoA from α-Ketoglutarate.
- α-Ketoglutarate dehydrogenase catalyses this oxidative step and produces NADH, CO_2 and a high energy thioester bond to coenzyme A.

Step 5:

- The thioester bond cleavage of succinyl-CoA is paired with the phosphorylation of an ADP or a GDP(substrate-level phosphorylation).
- This step is catalysed by succinyl CoA synthetase (succinate thiokinase).
- ATP and GTP are energetically equivalent.
- Interestingly, it is the only step in TCA that directly yields a compound with high phosphoryl transfer potential through a substrate-level phosphorylation.
- Animal cells have two isozymes of succinyl-CoA synthetase, one specific for ADP and the other for GDP.
- The GTP formed by succinyl-CoA synthetase can donate its terminal phosphoryl group to ADP to form ATP, in a reversible reaction catalysed by nucleoside diphosphate kinase.
- In the cells of plants, bacteria and some animal tissues, an ATP molecule forms directly by substrate-level phosphorylation.

Step 6:

- FAD removes two hydrogen atoms from succinate in what constitutes the third oxidative step in the TCA cycle.
- The enzyme catalysing this step, succinate dehydrogenase is strongly inhibited by malonate, a structural analogue of succinate and is a classic example of a competitive inhibitor.

Step 7:

- The addition of water to fumarate positions a hydroxyl group next to a carbonyl carbon.

Step 8:

- In the last of four oxidation steps in the cycle, the carbon carrying the hydroxyl group is converted to a carbonyl group, regenerating the oxaloacetate needed for step 1.
- NAD^+ linked malate dehydrogenase catalyses the oxidation of malate to oxaloacetate.

Overall reaction:

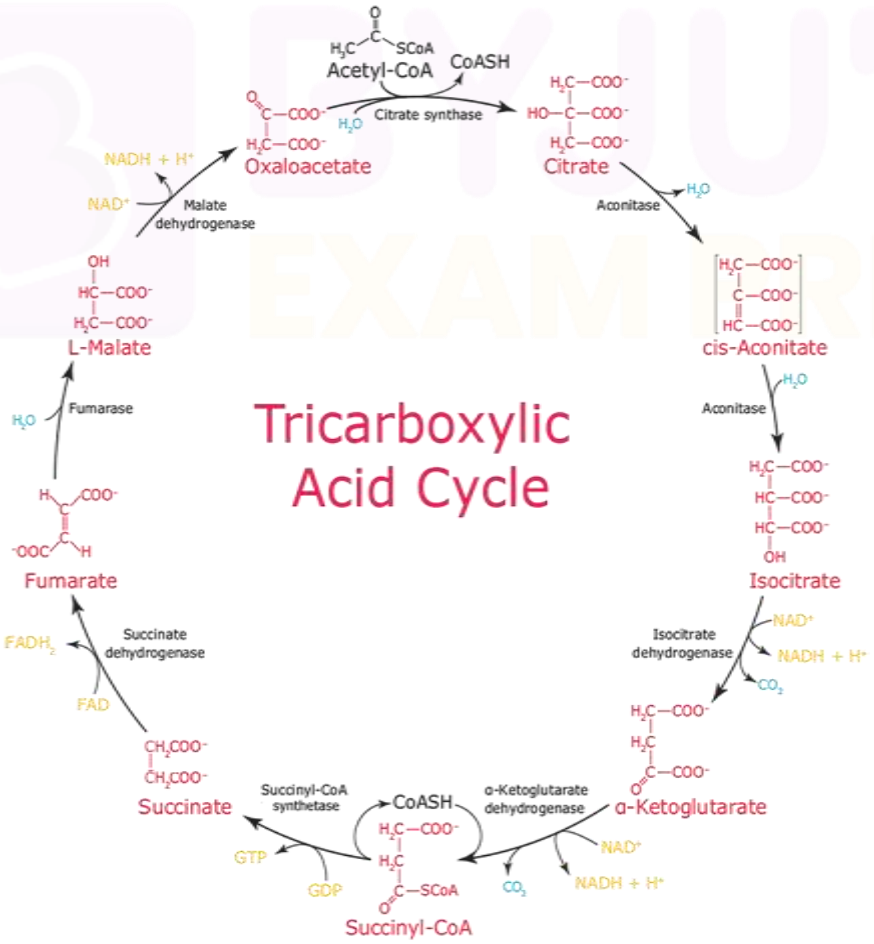
$$\text{Acetyl-CoA} + 3NAD^+ + FAD + GDP + 3H_2O \longrightarrow 2CO_2 + 3NADH + FADH_2 + GTP + H_2O$$

The energy yield from two pyruvate molecules when oxidized to $6CO_2$ via the pyruvate dehydrogenase complex and the citric acid cycle, and the electrons are transferred to O_2 via oxidative phosphorylation as many as 25 ATP are obtained.

Energetics of TCA cycle:

Reaction	Method of ATP production	No. of ATP generated
Isocitrate dehydrogenase	1 NADH enter ETC	2.5 ATPs
α-Ketoglutarate dehydrogenase	1 NADH enter ETC	2.5 ATPs
Succinate dehydrogenase	Substrate-level phosphorylation	1 ATPs
Succinate dehydrogenase	1 $FADH_2$ enter ETC	1.5 ATPs
Malate dehydrogenase	1 NADH enter ETC	2.5 ATPs
Total number of ATP per turn of TCA cycle		10 ATPs

To sum up, three molecules of NADH and one of $FADH_2$ are produced for each molecule of acetyl-CoA catabolized in one turn of the cycle.



The TCA cycle

Regulation of TCA cycle:

- Long chain acyl CoA and ATP inhibit citrate synthase.
- ATP and NADH have an inhibitory effect on Isocitrate dehydrogenase.
- Succinate dehydrogenase is inhibited by oxaloacetate.
- High ADP and high NAD^+ are the activators of TCA cycle.
- High ATP/ADP and high NADH/NAD^+ ratio are inhibitors of TCA cycle.

Inhibitors of TCA cycle:

- Aconitase is non-competitively inhibited by fluoroacetate.
- α-Ketoglutarate dehydrogenase non-competitively inhibited by arsenite.
- Succinate dehydrogenase is competitively inhibited by malonate.

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