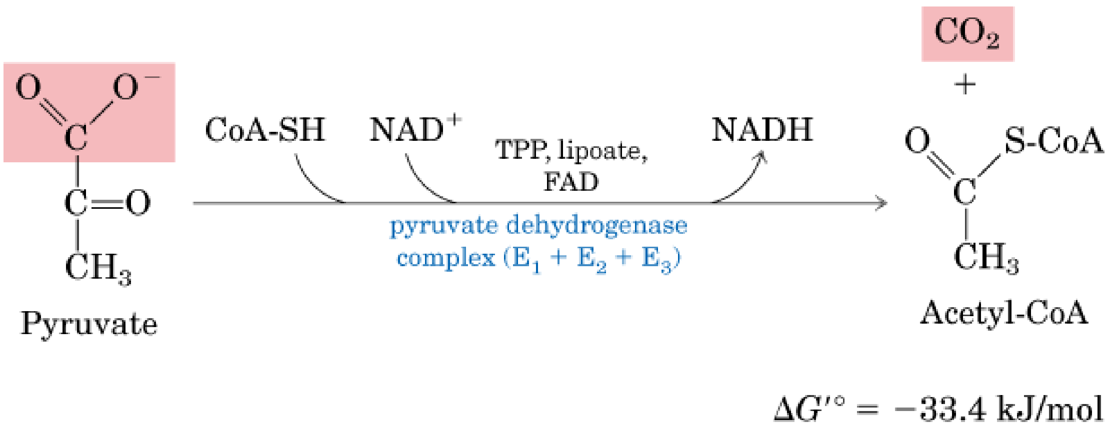
Citric Acid cycle or Tricarboxylic Acid cycle or Krebs Cycle

Reactions of Glycolysis are localized in Cytosol, and do not require any oxygen.
whereas pyruvate dehydrogenase and TCA cycle reactions take place in mitochondria where oxygen is utilized to generate ATP by oxydative phosphorylation.Consumption of oxygen (respiration) depends on the rate of PDC and TCA reactions.

Reaction of pyruvate dehydrogenase complex (PDC)



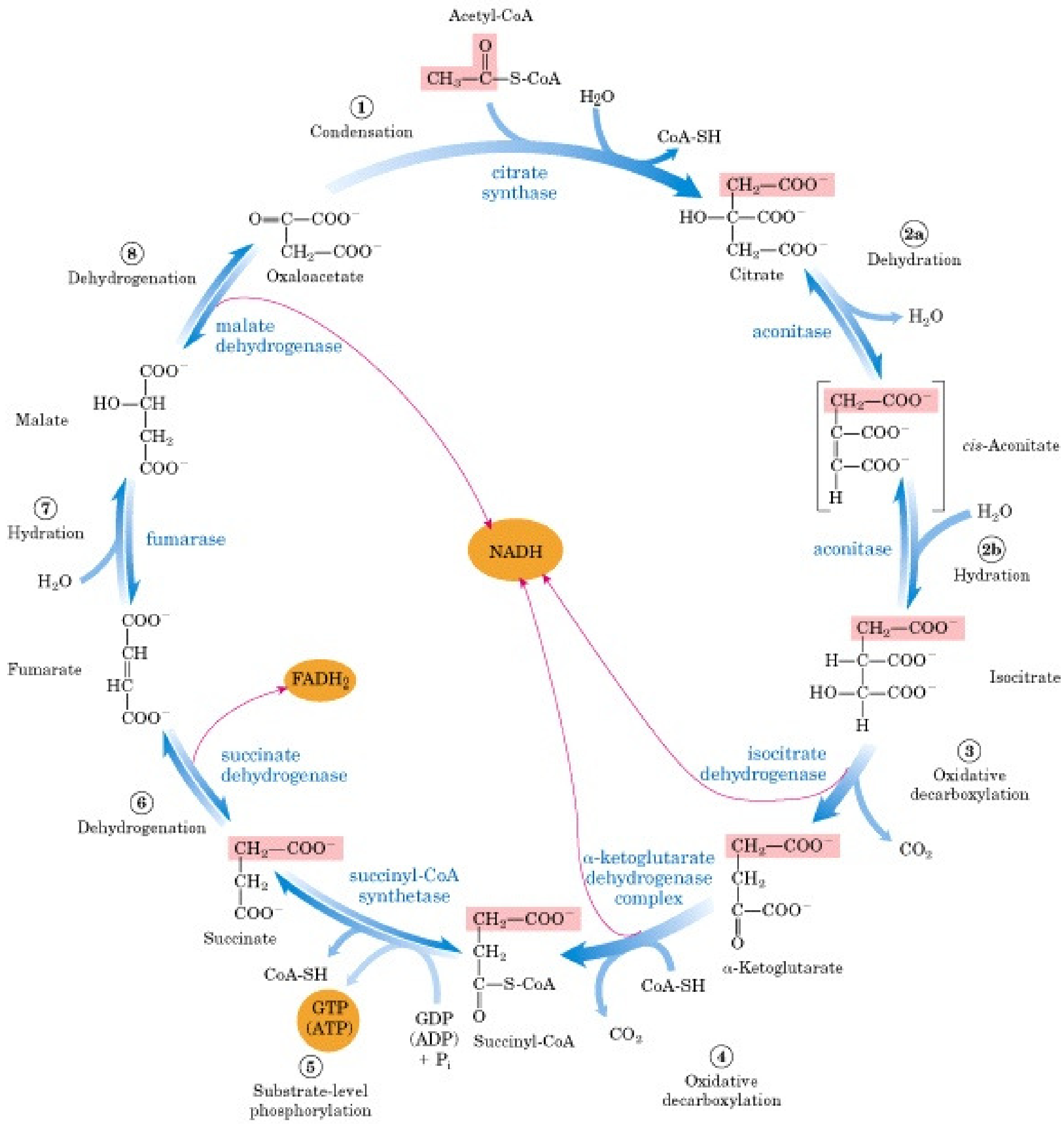
Pyruvate dehydrogenase Complex (PDC): It is a multi-enzyme complex containing three enzymes associated together noncovalently:
E-1 : Pyruvate dehydrogenase , uses Thiamine pyrophosphate as cofactor bound to E1
E-2 : Dihydrolipoyl transacetylase, Lipoic acid bound, CoA as substrate
E-3 : Dihydrolipoyl Dehydrogenase FAD bound, NAD+ as substrate

Advantages of multienzyme complex:

1. Higher rate of reaction: Because product of one enzyme acts as a substrate of other, and is available for the active site of next enzyme without much diffusion.
2. Minimum side reaction.
3. Coordinated control.

Reactions of TCA cycle: 8 reactions:

- Citrate synthase
- Aconitase
- Iso-citrate dehydrogenase
- ketoglutarate dehydrogenase
- Succinyl-Coenzyme A synthetase
- Succinate dehydrogenase
- Fumerase
- Malate dehydrogenase



Reactions of Citric Acid Cycle

1. Citrate synthase: Formation of Citroyl CoA intermediate.
   Binding of Oxaloacetate to the enzyme results in conformational change which facilitates the binding of the next substrate, the acetyl Coenzyme A. There is a further conformational change which leads to formation of products. This mechanism of reaction is referred as induced fit model.
2. Aconitase: This enzyme catalyses the isomerization reaction by removing and then adding back the water (H and OH) to cis-aconitate in at different positions.Isocitrate is consumed rapidly by the next step thus deriving the reaction in forward direction.
3. Isocitrate dehydrogenase: There are two isoforms of this enzyme, one uses NAD+ and other uses NADP+ as electron acceptor.
4. α-Ketoglutarate dehydrogenase: This is a complex of different enzymatic activities similar to the pyruvate dyhdogenase complex. It has the same mechanism of reaction with E1, E2 and E3 enzyme units. NAD+ is an electron acceptor.
5. **Succinyl CoA synthatse:** Sccinyl CoA, like Acetyl CoA has a thioester bond with very negative free energy of hydrolysis. In this reaction, the hydrolysis of the thioester bond leads to the formation of phosphoester bond with inorganic phosphate. This phosphate is transferred to Histidine residue of the enzyme and this high energy, unstable phosphate is finally transferred to GDP resulting in the generation of GTP.

6. Succinate Dehydrogenase: Oxidation of succinate to fumarate. This is the only citric acid cycle enzyme that is tightly bound to the inner mitochondrial membrane. It is an FAD dependent enzyme. Malonate has similar structure to Succinate, and it competitively inhibits SDH.

7. Fumarase: Hydration of Fumarate to malate: It is a highly stereospecific enzyme. Cis-Maleate (the cis form of fumarate) is not recognized by this enzyme.

8. L-Malate dehydrogenase: Oxidation of malate to oxaloacetate: It is an NAD+dependent enzyme. Reaction is pulled in forward direction by the next reaction (citrate synthase reaction) as the oxaloacetate is depleted at a very fast rate.

Conservation of energy of oxidation in the CAC: The two carbon acetyl group generated in PDC reaction enter the CAC, and two molecules of CO2 are released in on cycle. Thus there is complete oxidation of two carbons during one cycle. Although the two carbons which enter the cycle become the part of oxaloacetate, and are released as CO2 only in the third round of the cycle. The energy released due to this oxidation is conserved in the reduction of 3 NAD+, 1 FAD molecule and synthesis of one GTP molecule which is converted to ATP.

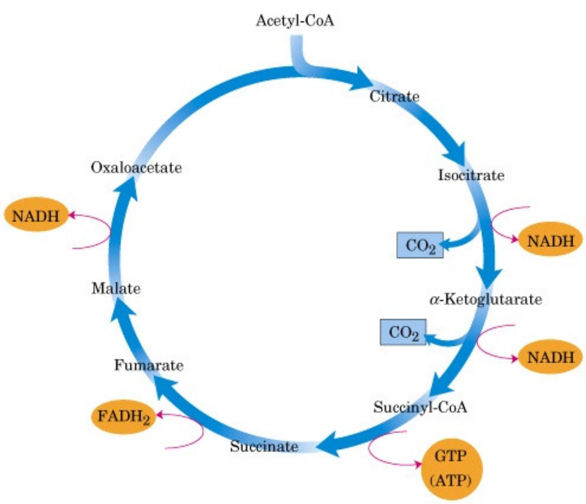


table 16–1

Stoichiometry of Coenzyme Reduction and ATP Formation in the Aerobic Oxidation of Glucose via Glycolysis, the Pyruvate Dehydrogenase Reaction, the Citric Acid Cycle, and Oxidative Phosphorylation

Reaction	Number of ATP or reduced coenzymes directly formed	Number of ATP ultimately formed*
Glucose ⟶ glucose 6-phosphate	−1 ATP	−1
Fructose 6-phosphate ⟶ fructose 1,6-bisphosphate	−1 ATP	−1
2 Glyceraldehyde 3-phosphate ⟶ 2 1,3-bisphosphoglycerate	2 NADH	3–5
2 1,3-Bisphosphoglycerate ⟶ 2 3-phosphoglycerate	2 ATP	2
2 Phosphoenolpyruvate ⟶ 2 pyruvate	2 ATP	2
2 Pyruvate ⟶ 2 acetyl-CoA	2 NADH	5
2 Isocitrate ⟶ 2 α-ketoglutarate	2 NADH	5
2 α-Ketoglutarate ⟶ 2 succinyl-CoA	2 NADH	5
2 Succinyl-CoA ⟶ 2 succinate	2 ATP (or 2 GTP)	2
2 Succinate ⟶ 2 fumarate	2 $FADH_2$	3
2 Malate ⟶ 2 oxaloacetate	2 NADH	5
Total		30–32

*This is calculated as 2.5 ATP per NADH and 1.5 ATP per $FADH_2$. A negative value indicates consumption.