Krebs (Citric Acid) Cycle

Definition

The citric acid cycle (CAC) – also known as the TCA cycle (tricarboxylic acid cycle) or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats and proteins into adenosine triphosphate (ATP) and carbon dioxide

Purpose

The main function of the Krebs cycle is to produce electron carriers that can be used in the last step of cellular respiration

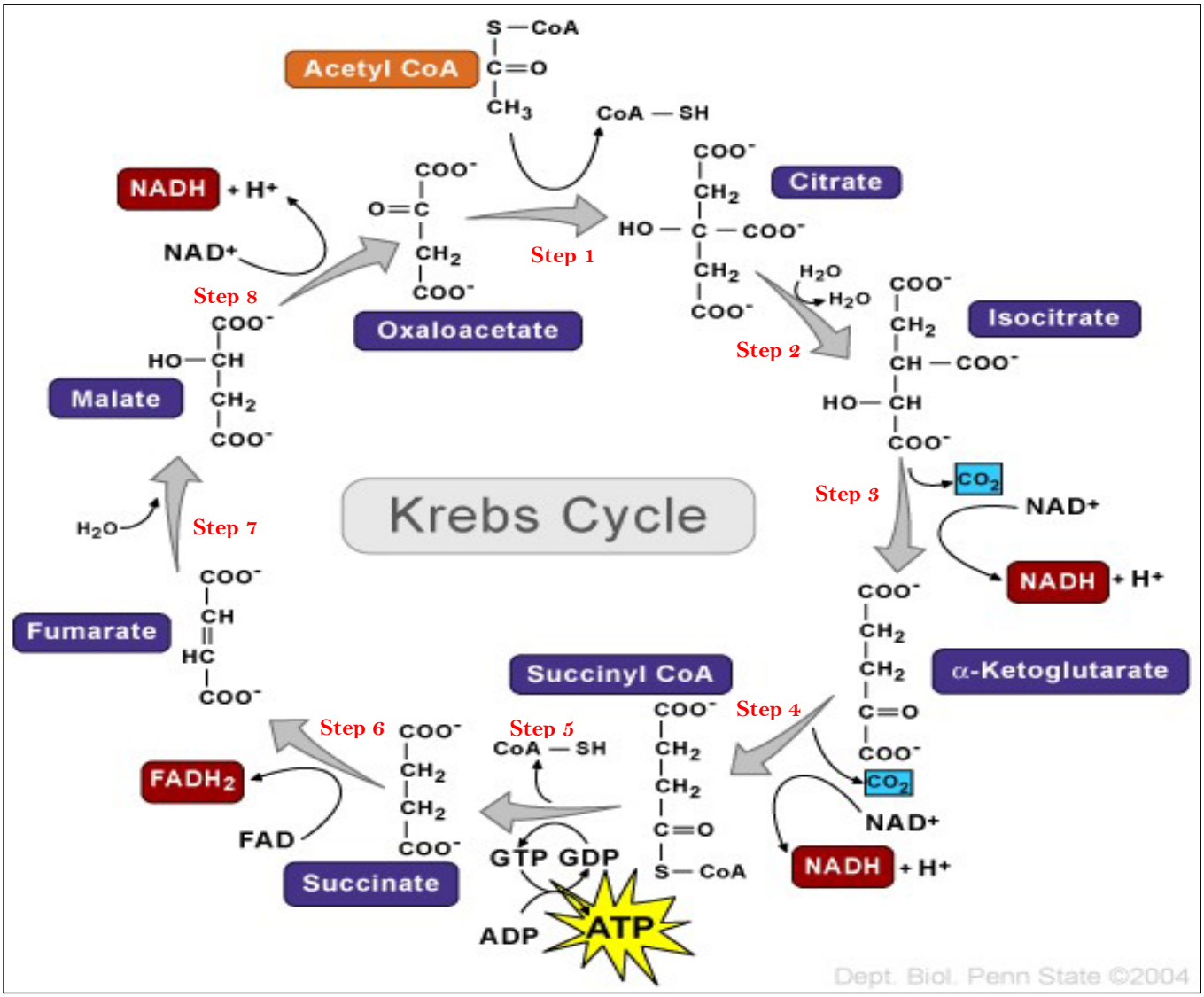
Location

The citric acid cycle takes place in the matrix of the mitochondria.

It is also known as TriCarboxylic Acid (TCA) cycle. In prokaryotic cells, the citric acid cycle occurs in the cytoplasm; in eukaryotic cells, the citric acid cycle takes place in the matrix of the mitochondria.

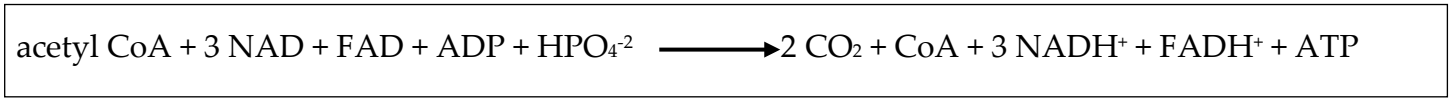
The cycle was first elucidated by scientist "**Sir Hans Adolf Krebs**" (1900 to 1981). He shared the Nobel Prize for physiology and Medicine in 1953 with Fritz Albert Lipmann, the father of ATP cycle.

The process oxidises glucose derivatives, fatty acids and amino acids to carbon dioxide (CO2) through a series of enzyme controlled steps. The purpose of the Krebs Cycle is to collect (eight) high-energy electrons from these fuels by oxidising them, which are transported by activated carriers NADH and FADH2 to the electron transport chain. The Krebs cycle is also the source for



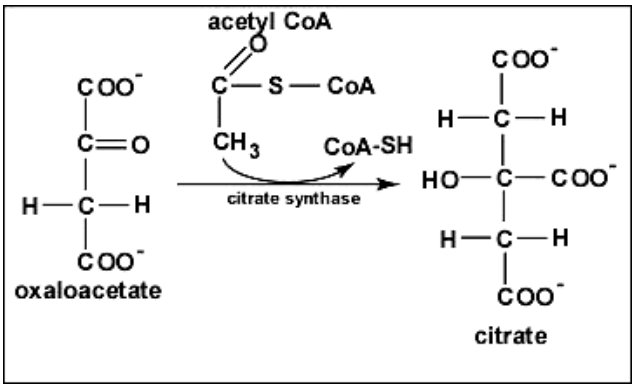
the precursors of many other molecules, and is therefore an amphibolic pathway (meaning it is both anabolic and catabolic).

The Net Equation



Reaction 1: Formation of Citrate

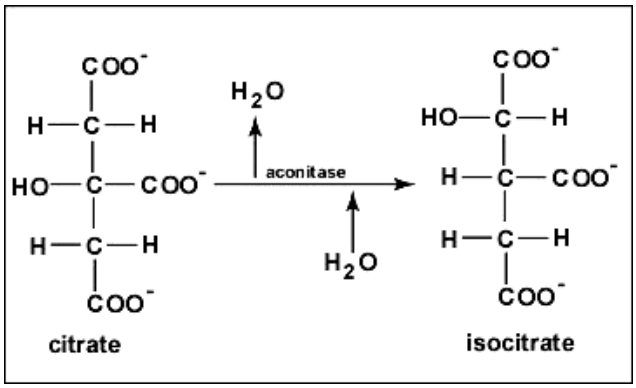
The first reaction of the cycle is the condensation of **acetyl-CoA** with **oxaloacetate** to form **citrate**, catalyzed by **citrate synthase**. Once oxaloacetate is joined with acetyl-CoA, a water molecule attacks the acetyl leading to the release of coenzyme A from the complex.



Reaction 2: Formation of Isocitrate

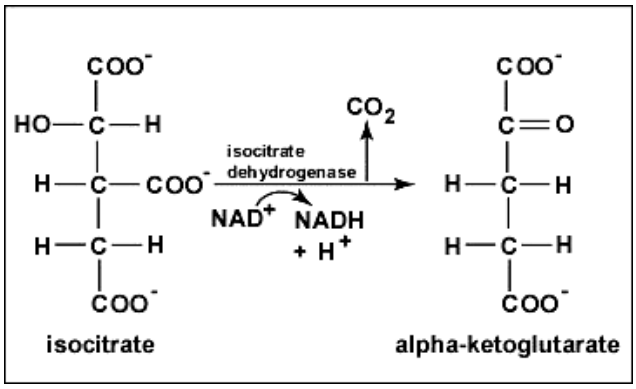
The **citrate** is rearranged to form an isomeric form, **isocitrate** by an enzyme **acontinase.**

In this reaction, **a water molecule is removed** from the citric acid and then put back on in another location. The overall effect of this conversion is that the –OH group is moved from the 3 to the 4′ position on the molecule. This transformation yields the molecule **isocitrate.**



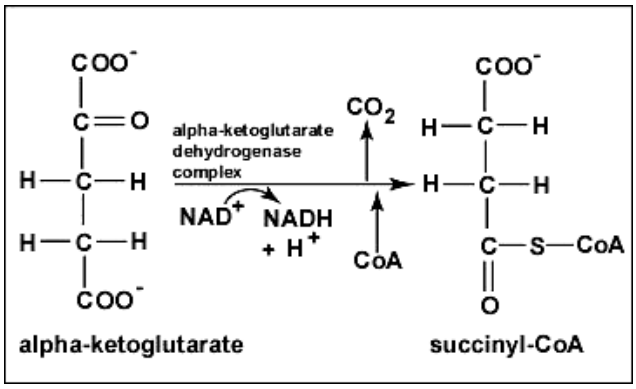
Reaction 3: Oxidation of Isocitrate to α-Ketoglutarate

In this step, isocitrate dehydrogenase catalyzes oxidative decarboxylation of **isocitrate** to form ***α*-ketoglutarate.** In the reaction, generation of NADH from NAD is seen. The enzyme **isocitrate dehydrogenase** catalyzes the oxidation of the –OH group at the 4′ position of isocitrate to yield an intermediate which then has a carbon dioxide molecule removed from it to yield **alpha-ketoglutarate**.



Reaction 4: Oxidation of α-Ketoglutarate to Succinyl-CoA

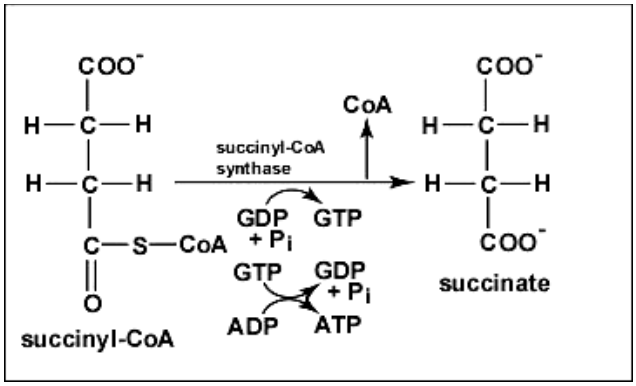
Alpha-ketoglutarate is oxidized, carbon dioxide is removed, and coenzyme A is added to form the 4-carbon compound **succinyl-CoA**. During this oxidation, NAD+ is reduced to NADH + H+. The enzyme that catalyzes this reaction is **alpha-ketoglutarate dehydrogenase.**



Reaction 5: Conversion of Succinyl-CoA to Succinate

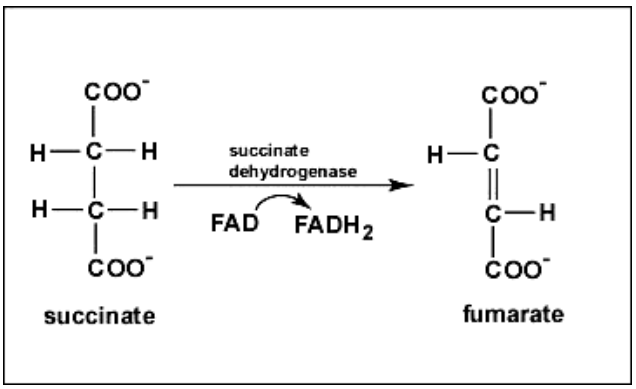
CoA is removed from **succinyl-CoA** to produce **succinate.**

The energy released is used to make guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and Pi by substrate-level phosphorylation. GTP can then be used to make ATP. The enzyme **succinyl-CoA synthase** catalyzes this reaction of the citric acid cycle.



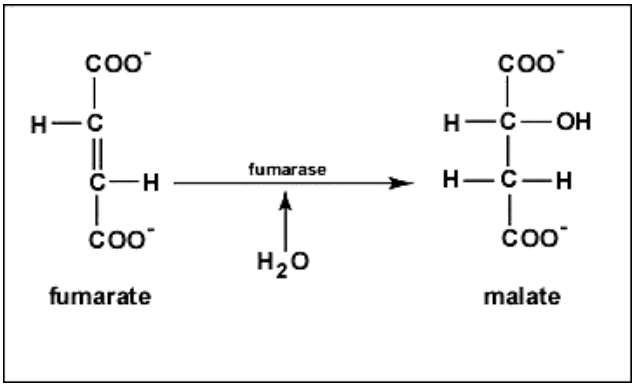
Reaction 6: Oxidation of Succinate to Fumarate

Succinate is oxidized to **fumarate**. During this oxidation, FAD is reduced to FADH2. The enzyme **succinate dehydrogenase** catalyzes the removal of two hydrogens from succinate.



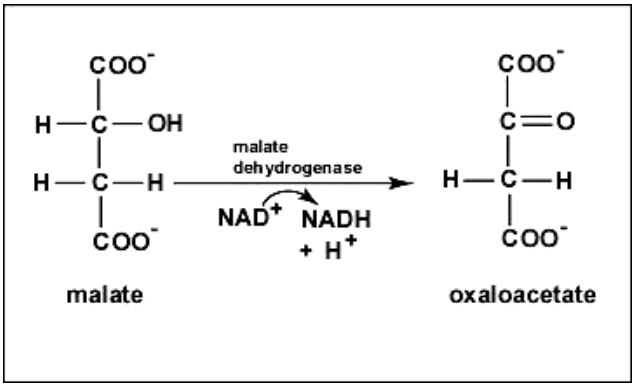
Reaction 7: Hydration of Fumarate to Malate

The reversible hydration of **fumarate** to **L-malate** is catalyzed by **fumarase (fumarate hydratase).** **Fumarase** continues the rearrangement process by adding **Hydrogen** and **Oxygen** back into the substrate that had been previously removed.



Reaction 8: Oxidation of Malate to Oxaloacetate

Malate is oxidized to produce **oxaloacetate**, the starting compound of the citric acid cycle by **malate dehydrogenase**. During this oxidation, NAD+ is reduced to NADH + H+.



ATP Generation

Total ATP = 12 ATP

- 3 NAD+ = 9 ATP
- 1 FAD = 2 ATP
- 1 ATP = 1 ATP

Reviewing the whole process, the Krebs cycle primarily transforms the acetyl group and water, into carbon dioxide and energized forms of the other reactants.

Energy yield per pyruvate molecule i.e one acetyl CoA is

Step No.	*Reaction*	*Method of ATP Formation*	*ATP Yield Per Mole*
3	Isocitrate → α-ketoglutarate + CO_2	Respiratory chain oxidation of NADH	3
4	α-ketoglutarate → Succinyl-CoA + CO_2	Respiratory chain oxidation of NADH	3
5	Succinyl-CoA + ADP + P*i* → Succinate + ATP	Oxidation at substrate level	1
6	Succinate → Fumarate	Respiratory chain oxidation of $FADH_2$	2
8	Malate → Oxaloacetate	Respiratory chain oxidation of NADH	3
		Total gain of ATP = 12	

Significance of Krebs Cycle

1. Intermediate compounds formed during Krebs cycle are used for the synthesis of biomolecules like amino acids, nucleotides, chlorophyll, cytochromes and fats etc.
2. Intermediate like succinyl CoA takes part in the formation of chlorophyll.
3. Amino Acids are formed from α- Ketoglutaric acid, pyruvic acids and oxaloacetic acid.
4. Krebs cycle (citric Acid cycle) releases plenty of energy (ATP) required for various metabolic activities of cell.
5. By this cycle, carbon skeleton are got, which are used in process of growth and for maintaining the cells.

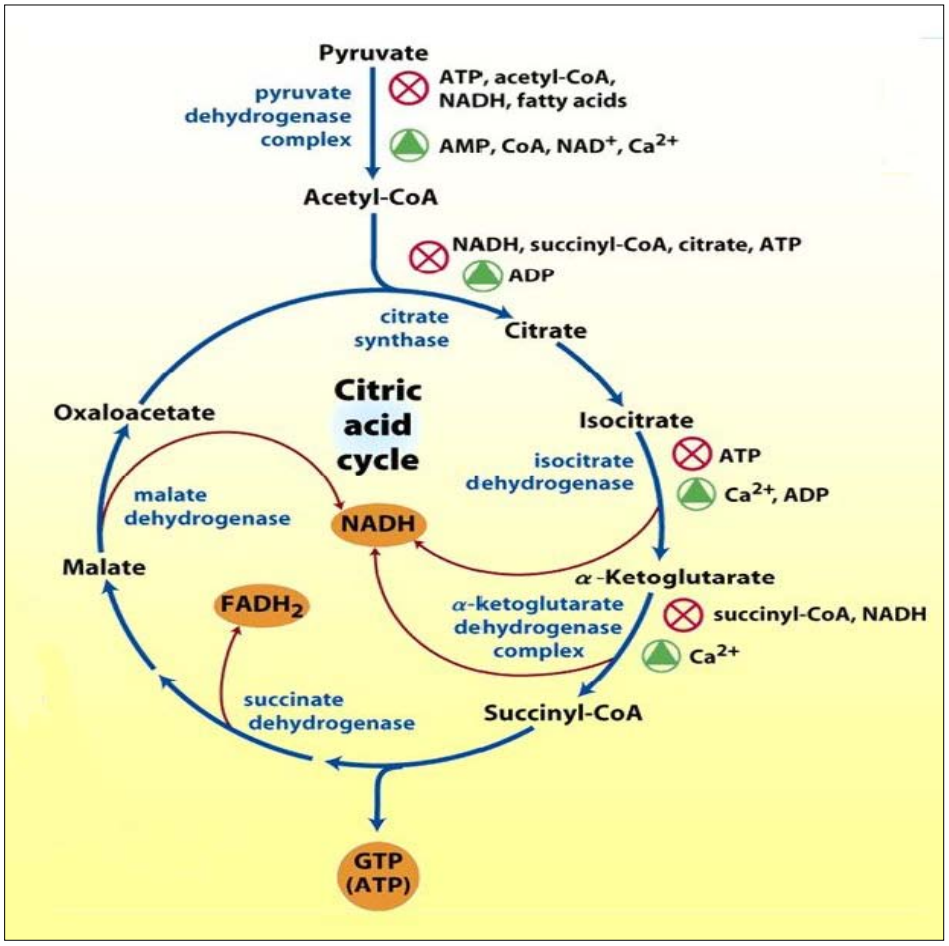
Regulation of Citric acid cycle

Several factors serve to control the rate of reactions sequence in the Citric acid cycle. These are described below:

1. **Substrate level:**
   - One of the controlling features for any reaction sequence is the availability of the various substrates involved in it.
   - The relatively restricted concentration of OAA puts in emphasizes on its role in controlling the input of Acetyl-CoA into the cycle.
   - Regulation of the rate of this reaction would control activity in the enzyme cycle.
2. **Enzyme level:**
   - All mitochondria from widely different sources possess constant relative proportions of the various enzymes, including the characteristic dehydrogenases of the citric acid cycle.

- The observations suggest that there exists a genetic mechanism for the control of the synthesis or the integration of the key mitochondrial enzymes in the course of mitochondriogenesis.
- The genetic mechanism may involve a single operon containing all necessary structural genes to control enzyme biosynthesis.

3. **Respiratory control:**
   - Respiration rate depends, not only on the nature and concentration of the substrates to be oxidized but also on the coupling of respiration to phosphorylation.
   - Intact mitochondria are usually 'tightly' coupled so that their rate of respiration is actually controlled by the ratio [ADP]/[ATP].
   - When this ratio is high, respiration is promoted.
   - In contrast, low ratios (i.e., high ATP concentrations) decline respiration.
   - Added ATP can even inhibit respiration because they bring about reversed electron flow.
   - These phenomena are now known as respiratory control.
4. **Accessibility of Cycle Intermediates:**
   - The activity of the citric acid cycle is also controlled by its accessibility to acetyl-CoA of intermediates of the cycle.
   - The mitochondrial membrane itself provides a means for the admission of some substrates and the exclusion of others.
   - A few examples are given below :
     - Mitochondrial succinate dehydrogenase is freely available to succinate from outside the mitochondria but not to fumarate.
     - Furthermore, added fumarate is also not freely accessible to the mitochondrial fumarase.
5. **Ketosis:**
   - The accumulation of ketone bodies, acetoacetate, and acetone formed by the liver in diabetics result from the production of more acetyl-CoA than can be cyclized via the Krebs cycle or other synthetic reactions.
   - Under these conditions, the rate of Krebs cycle slows down probably due to hormonal action since ketone body formation (i.e., ketosis) is affected by hormones of the hypophysis and adrenal cortex.
6. **Control of enzyme activity:**
   - Three enzymes-namely Citrate synthase, Isocitrate dehydrogenase and α-ketoglutarate dehydrogenase-reguIate Citric acid cycle.
     - Citrate synthase is inhibited by ATP, NADH, acetyl CoA, and succinyl CoA.
     - lsocitrate dehydrogenase is activated by ADP and inhibited by ATP and NADH.
     - α-Ketoglutarate dehydrogenase is inhibited by succinyl CoA and NADH.


Pyruvate
pyruvate dehydrogenase complex
ATP, acetyl-CoA, NADH, fatty acids
AMP, CoA, NAD+, Ca2+
Acetyl-CoA
NADH, succinyl-CoA, citrate, ATP
ADP
citrate synthase
Citrate
Citric acid cycle
Oxaloacetate
Isocitrate
isocitrate dehydrogenase
ATP
Ca2+, ADP
malate dehydrogenase
NADH
Malate
α-Ketoglutarate
FADH2
α-ketoglutarate dehydrogenase complex
succinyl-CoA, NADH
Ca2+
succinate dehydrogenase
Succinyl-CoA
GTP (ATP)