

21.7: The Citric Acid Cycle

Learning Objectives

- Describe the reactions of the citric acid cycle.
- Describe the function of the citric acid cycle and identify the products produced.

The acetyl group enters a cyclic sequence of reactions known collectively as the citric acid cycle (or **Krebs cycle** or tricarboxylic acid [TCA] cycle). The cyclical design of this complex series of reactions, which bring about the oxidation of the acetyl group of acetyl-CoA to carbon dioxide and water, was first proposed by Hans Krebs in 1937. (He was awarded the 1953 Nobel Prize in Physiology or Medicine.) Acetyl-CoA's entrance into the citric acid cycle is the beginning of stage III of catabolism. The citric acid cycle produces adenosine triphosphate (ATP), reduced nicotinamide adenine dinucleotide (NADH), reduced flavin adenine dinucleotide (FADH₂), and metabolic intermediates for the synthesis of needed compounds.

Steps of the Citric Acid Cycle

At first glance, the citric acid cycle appears rather complex (Figure 21.7.1). All the reactions, however, are familiar types in organic chemistry: hydration, oxidation, decarboxylation, and hydrolysis. Each reaction of the citric acid cycle is numbered, and in Figure 21.7.1, the two acetyl carbon atoms are highlighted in red. Each intermediate in the cycle is a carboxylic acid, existing as an anion at physiological pH. All the reactions occur within the mitochondria, which are small organelles within the cells of plants and animals.

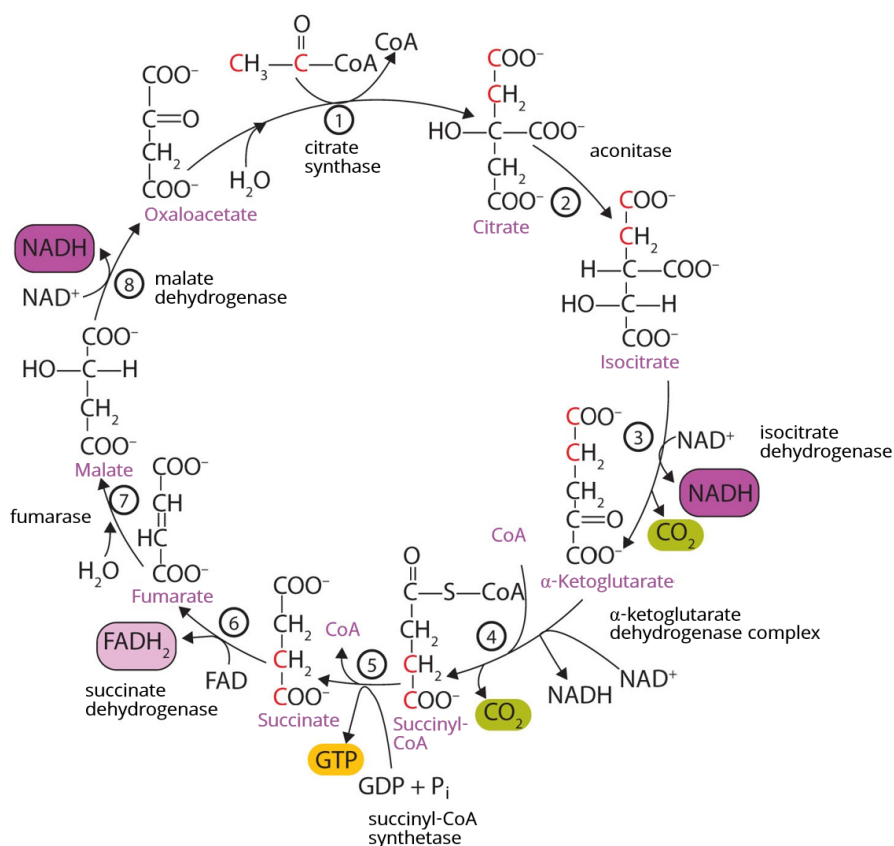


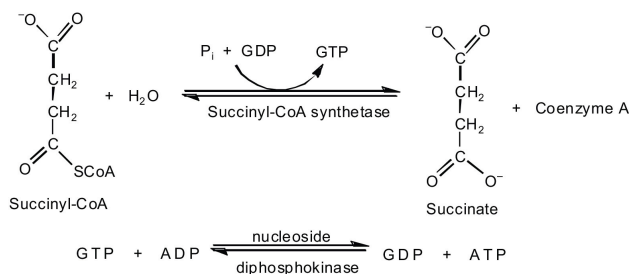
Figure 21.7.1: Reactions of the Citric Acid Cycle

- In the first step, acetyl-CoA enters the citric acid cycle, and the acetyl group is transferred onto oxaloacetate, yielding citrate. Note that this step releases coenzyme A. The reaction is catalyzed by *citrate synthase*.
- In the next step, *aconitase* catalyzes the isomerization of citrate to isocitrate. In this reaction, a tertiary alcohol, which cannot be oxidized, is converted to a secondary alcohol, which can be oxidized in the next step.

3. Isocitrate then undergoes a reaction known as oxidative decarboxylation because the alcohol is oxidized and the molecule is shortened by one carbon atom with the release of carbon dioxide (decarboxylation). The reaction is catalyzed by *isocitrate dehydrogenase*, and the product of the reaction is α -ketoglutarate. An important reaction linked to this is the reduction of the coenzyme nicotinamide adenine dinucleotide (NAD^+) to NADH. The NADH is ultimately reoxidized, and the energy released is used in the synthesis of ATP, as we shall see.
4. The fourth step is another oxidative decarboxylation. This time α -ketoglutarate is converted to succinyl-CoA, and another molecule of NAD^+ is reduced to NADH. The *α -ketoglutarate dehydrogenase complex* catalyzes this reaction. This is the only irreversible reaction in the citric acid cycle. As such, it prevents the cycle from operating in the reverse direction, in which acetyl-CoA would be synthesized from carbon dioxide.

So far, in the first four steps, two carbon atoms have entered the cycle as an acetyl group, and two carbon atoms have been released as molecules of carbon dioxide. The remaining reactions of the citric acid cycle use the four carbon atoms of the succinyl group to resynthesize a molecule of oxaloacetate, which is the compound needed to combine with an incoming acetyl group and begin another round of the cycle.

In the fifth reaction, the energy released by the hydrolysis of the high-energy thioester bond of succinyl-CoA is used to form guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and inorganic phosphate in a reaction catalyzed by *succinyl-CoA synthetase*. This step is the only reaction in the citric acid cycle that directly forms a high-energy phosphate compound. GTP can readily transfer its terminal phosphate group to adenosine diphosphate (ADP) to generate ATP in the presence of *nucleoside diphosphokinase*.



Succinate dehydrogenase then catalyzes the removal of two hydrogen atoms from succinate, forming fumarate. This oxidation-reduction reaction uses flavin adenine dinucleotide (FAD), rather than NAD^+ , as the oxidizing agent. Succinate dehydrogenase is the only enzyme of the citric acid cycle located within the inner mitochondrial membrane. We will see soon the importance of this.

In the following step, a molecule of water is added to the double bond of fumarate to form L-malate in a reaction catalyzed by *fumarase*.

One revolution of the cycle is completed with the oxidation of L-malate to oxaloacetate, brought about by *malate dehydrogenase*. This is the third oxidation-reduction reaction that uses NAD^+ as the oxidizing agent. Oxaloacetate can accept an acetyl group from acetyl-CoA, allowing the cycle to begin again.



Video: "The Citric Acid Cycle: An Overview". In the matrix of the mitochondrion, the Citric Acid Cycle uses Acetyl CoA molecules to produce energy through eight chemical reactions. This animation provides an overview of the pathway and its products. NDSU VCell Production's animation; for more information please see <http://vcell.ndsu.edu/animations>.

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