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Citric Acid Cycle

Description

The Citric Acid Cycle or also called the Krebs cycle or tricarboxylic acid cycle is one of the most studied metabolic processes and Biochemistry topics both in Medicine and in Nursing and careers related to Health.

What is the Citric Acid Cycle?

The Citric Acid Cycle or Krebs Cycle is the final oxidation pathway in common for both carbohydrates, lipids, and proteins. Glucose, fatty acids, and amino acids have Acetyl-CoA or some intermediate of this cycle as their final product.

The Citric Acid Cycle is also a fundamental part of processes such as Glycolysis, Gluconeogenesis, Lipogenesis, and even the interconversion of amino acids.

The Citric Acid Cycle is the process of oxidation of Acetyl-CoA. Its purpose is the production of NADH and FADH2. Compounds necessary for the production of ATP in the respiratory chain.

Citric Acid Cycle and Glycolysis

The Citric Acid Cycle is the metabolic pathway that continues to Aerobic Glycolysis. The final product of Glycolysis is Pyruvate. This Pyruvate is captured by the enzyme Pyruvate Dehydrogenase, which converts it into Acetyl-CoA.

This process is called Pyruvate Oxidation. In this process, a CoA molecule is added and a CO2 molecule and NADH are produced.

Acetyl-CoA is the necessary precursor formed from Pyruvate to start the Citric Acid Cycle

Reactions of the Citric Acid Cycle

The Citric Acid Cycle consists of 10 chain reactions measured by 8 different enzymes. All reactions of the Citric Acid Cycle occur at the Mitochondrial level.

Citric Acid Cycle step by step

Each of the 10 reactions of the Krebs Cycle implies a change at the structural level of Citric Acid or Citrate. These changes may seem complicated at first, but here we explain them step by step.

Oxaloacetate to Citric Acid

The first enzyme of the Citric Acid Cycle is Citrate Synthetase. This enzyme uses Acetyl-CoA (2 carbons) and Oxalocaetato (4 carbons) to form Citric Acid or Citrate (6 Carbon). To achieve this, it transfers a Hydrogen of carbon 1 of Acetyl-CoA to the oxygen of carbon 3 of Oxaloacetate, forming OH. What breaks the double bond with said oxygen.

To stabilize, the molecule forms a bond between carbon 3 of Oxaloacetate and carbon 1 of Acetyl-CoA. Finally, this same enzyme uses a molecule of water (H2O) from the medium to transfer oxygen to the position of the CoA and thus separate it from the rest of the molecule. The CoA is loaded in the process with the 2 remaining Hydrogen of the Water molecule.

In this way, **the Oxaloacetate molecule is renamed Citrate** and begins the Citric Acid Cycle or Krebs Cycle.

Primera reaccion del Ciclo de Krebs

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First reaction of the Krebs Cycle

Citrate to Isocitrate

The passage from Citrate to Isocitrate occurs in 2 phases. At first, the Aconitase enzyme takes the OH group of carbon 2 and a Hydrogen of carbon 3. Forming a molecule of water (H2O). A double bond is formed between carbon 2 and 3 of the Citrate molecule, which is renamed **Cis-Aconitate**.

In a second reaction, the OH group is transferred from H2O to carbon 3 and Hydrogen to carbon 2. In essence, only one change occurs between the OH group and H +. An isomerization. Then the molecule goes from being called **Cis-Aconite to Isocitrate**

Citric Acid Cycle

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Both reactions catalyzed by the Aconitase enzyme are reversible and are actually an isomerization of Citrate.

Isocitrate to ?-ketoglutarate

The third reaction is mediated by the enzyme Isocitrate Dehydrogenase, which takes 2 hydrogen from carbon 3 of Isocitrate, including one from the OH group and transfers them to a molecule of NADH, forming NADH (NADH + H). Carbon 3 then forms a double bond with the remaining Oxygen and is renamed Oxalosucinate.

The same enzyme takes the Carboxyl group from carbon 2 of Oxalosucinate (Decarboxylation) and releases it in the form of Carbon Dioxide (CO2). At carbon 2, an H + from the medium is added to stabilize the molecule. This is then renamed ?-ketoglutarate.

Citric Acid Cycle

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?-ketoglutarate to Succinyl-CoA

In the fourth reaction of the Citric Acid Cycle, the enzyme ?-ketoglutarate dehydrogenase uses the CoA molecule with 2 H + released in the first reaction of the Krebs Cycle to charge a NAD. The CoA molecule then gives up its 2 Hydrogens and they are transferred to NAD, forming NADH + H

The same enzyme exchanges the Carboxyl group on carbon 3 of ?-ketoglutarate for the CoA molecule. Which converts the molecule to Succinyl-CoA. The Carboxyl is then released in the form of CO2.

Cuarta reaccion del Ciclo de Krebs

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Succinyl-CoA to Succinate

The fifth reaction of the Citric Acid Cycle is mediated by the enzyme Succinyl CoA synthetase, which has a GDP molecule and an Inorganic Phosphorus (Pi). This reaction seeks to bind the inorganic phosphorus with the GDP molecule.

To achieve this, Inorganic Phosphorus displaces CoA from carbon 4 and binds inorganic Phosphorus instead. This is a temporary process, because the same enzyme takes the phosphate group andleaves only the oxygen forming GTP.

This process causes the Succinyl CoA molecule to be called Succinate.

Quinta reaccion

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However, can use ADP as a receptor for the phosphate group instead of GDP. Forming in this case ATP.

Succinate to Fumarate

The sixth reaction of the Krebs Cycle is given by the enzyme Succinate Dehydrogenase. This enzyme uses a compound FAD, which seeks to receive 2 Hydrogens. Therefore, in this reaction, 2 hydrogens are stolen from carbon 2 and 3 of the Succinate, forming FADH2.

To stabilize the molecule, it forms a double bond between carbon 2 and 3. Now it is called Fumarate.

Citric Acid Cycle

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Fumarate to L-Malate

The seventh reaction of the Krebs Cycle takes place by means of the enzyme Fumarate Hydratase. As its name indicates, this enzyme uses a Water molecule (H2O) to transfer an OH group to carbon 3 and a Hydrogen to carbon 2 of the Fumarate. This addiction breaks the previously formed double bond. Then the **Fumarate is renamed L-Malate**.

Septima reaccion

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L-Malate to Oxaloacetate

The Eighth reaction of the Krebs Cycle converts Malate to Oxaloacetate. The enzyme responsible for this reaction is Malate dehydrogenase. This enzyme has a molecule of NAD. So it takes 2 Hydrogens from carbon 3 of Malate, including one from the OH group. This 2 hydrogen then pass to the NAD molecule forming NADH (NADH + H).

The Malate molecule must then create a double bond with the Oxygen that remains from the OH group. In this way, it is called Oxaloacetate.

Octava reaccion

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The Oxaloacetate formed is then ready to restart the Citric Acid Cycle.

Products of the Citric Acid Cycle

Each Acetyl-CoA molecule that is combined with an Oxaloacetate to form Citric Acid produces:

- 1 GTP molecule
- 3 Molecules of NADH + H
- 1 Molecule of FADH2
- 2 Molecules of Carbon Dioxide (CO2)

It is important to remember that in Glycolysis 2 Pyruvates are produced as a final product. So 2 Acetyl-CoA is actually produced and entered into the Citric Acid Cycle

Therefore, for each Glucose molecule that undergoes Aerobic Glycolysis, they are produced in the Citric Acid Cycle.

- 2 GTP molecule
- 6 Molecules of NADH + H
- 2 Molecule of FADH2
- 4 CO2 molecules

Energy production in the Citric Acid Cycle

The ultimate goal of the Krebs Cycle is energy production. However, in the entire cycle, only one molecule of GTP or ATP is produced.

The greatest energy production is actually achieved through the production of NADH and FADH.

Each molecule of NADH that passes into the respiratory chain and is oxidized produces 3 ATP. While each molecule of FADH produces 2 ATP.

So for each molecule of Acetyl CoA that is oxidized in the Citric Acid Cycle, 3 NADH and 1 FADH are produced. What gives rise to 12 ATP in the respiratory chain (3 NADH x 3 = 9 + 1 FADH X2 = 2 + 1 GTP / ATP = 12 ATP) Therefore for each Glucose molecule that manages to reach the Citric Acid Cycle and later oxidation in the respiratory chain produces 24 ATP.

Aerobic Glycolysis produces a total of 36 ATP at the end of the respiratory chain. Which are broken down as follows: **2 net ATP of the Glycolysis**, **4 ATP in the form of NADH of the Glycolysis**, **6 ATP in the form of NADH in the oxidation of Pyruvate**, **2 GDP / ATP of the Citric Acid Cycle,** and **22 ATP in the form of oxidized NADH and FADH in the Respiratory Chain**.

Citric Acid Cycle Summary

With little time? Here I leave you the most important of the Krebs Cycle and the 8 summarized reactions.

Summary Reactions of the Citric Acid Cycle

The first reaction of the Citric Acid Cycle is the synthesis of Citrate or Citric Acid. What happens by the enzyme Citrate Synthetase. Which combines Acetyl-CoA with Oxaloacetate.

Citrate is dehydrated by the Aconitase enzyme. What forms Cis-Aconite. This Cis-Aconitate molecule undergoes Hydration by the same Aconitase enzyme and gives rise to Isocitrate.

Isocitrate is converted to Oxalosuccinate by the enzyme Isocitrate Dehydrogenase. In this reaction, a molecule of NADH is produced.

The same enzyme Isocitrate Dehydrogenase generates a Decarboxylation of Oxalosuccinate, converting it into ?-ketoglutarate. In this reaction, a CO2 molecule is produced.

The ?-ketoglutarate is then taken up by the ?-ketoglutarate dehydrogenase enzyme and undergoes oxidative decarboxylation. Which gives rise to the compound called Succinyl-CoA. In addition, a CO2 molecule and another NADH molecule are produced.

Succinyl-CoA is taken up by the enzyme Succinyl CoA synthetase. This enzyme generates a Hydrolysis of Succinyl-CoA giving rise to Succinate.

In this process, a phosphate group is transferred to a GDP molecule, giving rise to GTP. This same enzyme can use ADP as a receptor for the phosphate group, forming ATP instead. In addition, in this reaction, the CoA molecule (CoA-SH) is released from the Succinyl-CoA compound.

The next reaction is dehydration mediated by the enzyme Succinate Dehydrogenase. Which turns Succinate into Fumarate. In this reaction, FADH is also formed

The Fumarate is then oxidized by the enzyme Fumarate Hydratase giving rise to L-Malate..

The L-Malate is then oxidized by the enzyme Malate dehydrogenase, which gives rise to Oxaloacetate. In this reaction a molecule of NADH is formed

Oxaloacetate is taken up again by the enzyme Citrate Synthase and the Citric Acid Cycle begins again.

Citric Acid Cycle Diagram

Citric Acid Cycle

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Diagram of the Krebs Cycle and its reactions

Citric Acid Cycle Enzymes

In total there are 8 enzymes that participate in the Krebs Cycle:

1. Citrate Synthase: Joins Oxaloacetate with Acetyl-CoA forming Citrate.
2. Aconitase: Converts Citrate to Cis-Aconite and then to Isocitrate.
3. Isocitrate Dehydrogenase: Oxidizes Isocitrate converting it to Oxalosuccinate and later to ?-ketoglutarate.

4. ?-ketoglutarate dehydrogenase: Decarboxylates ?-ketoglutarate to convert it to Succinyl-CoA.
5. Succinyl CoA Synthetase: Hydrolyzes Succinyl-CoA to transform it into Succinate.
6. Succinate Dehydrogenase: Oxidizes Succinate to convert it to Fumarate.
7. Fumarate Hydratase: Converts Fumarate to L-Malate.
8. Malate Dehydrogenase: Oxidizes L-Malate and converts it to Oxaloacetate.

Biomedical Importance

The Krebs Cycle is the final route of various oxidation reactions for Carbohydrates, Lipids and Porteins. This is because both Glucose, fatty acids and most amino acids are oxidized to Acetyl-CoA. Which, as we already learned, is the precursor for the formation of Citrate or Citric Acid.

Citric Acid Cycle FAQs

Are you about to have a Biochemistry or Biology exam? and the Citric Acid or Krebs Cycle comes in that exam … Don’t worry, here are a series of frequently asked questions. Careful! More than one comes on your exam.

General Questions about the Citric Acid Cycle

These are the typical questions related to the generalities of the Citric Acid Cycle.

Where does the Citric Acid Cycle occur?

R /. It occurs in cells at the mitochondrial level.

How much ATP is produced?

R /. This is a trick question. In essence, in the Citric Acid Cycle or Krebs only 1 GTP is produced. Which then turns into ATP. So in a practical way the answer would be that only 1 GTP is produced.

But … this is the catch. The question may refer to how many ATP are produced in the Respiratory Cycle and Chain. In this case, the answer would be 24 ATP. And if the question made reference to how many ATP are produced from Glycolysis then it would be 36 ATP.

My advice, if this question is very ambiguous, ask your teacher to specify or detail the question.

How many reactions occur in the whole cycle?

R /. In total there are 10 reactions in the Krebs Cycle but only 8 enzymes.

So some authors consider that only 8 reactions actually occur. But remember that in the first enzymes they carry out 2 reactions each, so there are 10 reactions in total.

How many enzymes are involved?

R /. In total there are 8 enzymes that participate in the Citric Acid Cycle. You can see the complete list of enzymes here.

By what other name is the Citric Acid Cycle known?

Alternative names are Citric Acid Cycle and Tricarboxylic Acid Cycle..

Who discovered the Krebs Cycle?

The Krebs Cycle was discovered by Hans Adolf Krebs in 1937 (who also received the Nobel Prize in 1953)

Is the Krebs Cycle anabolic or catabolic?

None. The Citric Acid Cycle is Amphibolic. This means that it is a process that involves both catabolic and anabolic reactions.

Does Pyruvic Acid or Pyruvate directly enter the Citric Acid Cycle?

No. Pyruvate must first be converted to Acetyl CoA in order to enter the Krebs Cycle. This process is called Pyruvate Oxidation.

[su_box title="????? **Key Aspects of the Krebs Cycle ?**" box_color="#004cd4?]

- The objective of the Krebs Cycle is the production of NADH and FADH, compounds necessary for the formation of ATP in the respiratory chain.
- A total of 8 enzymes are involved and there are a total of 10 reactions.
- ***A total of 2 GTP, 6 NADH are produced. 2 FADH and 4 CO2***??
- For each Glucose molecule that enters the Krebs Cycle and subsequent oxidation in the respiratory chain, 24 ATP is produced

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