

## Cellular Respiration: The Big Picture

Everyday activities require energy. Humans, like all living organisms, need to fuel their actions, similar to the way a car requires fuel to run. To fuel all of this physical work, our bodies break down food molecules and extract their energy. We rely on this process, called cellular respiration, to run smoothly so that we will have the energy needed to exert ourselves or just relax.

In cellular respiration, plants, animals, and all other living organisms harvest energy by breaking down energy-rich molecules. In this example, a bison ingests grass, digests the food, and delivers food molecules to cells of its body.

As energy is released by the reactions of cellular respiration, cells capture and store the energy in the bonds of ATP molecules, the chief energy currency of the cell. This plentiful, readily available stored energy in ATP can then be used as needed to fuel the activities of the organism.

Cellular respiration requires oxygen, which the animal inhales, and releases carbon dioxide, which the animal exhales. Water is also released during these reactions.

Cellular respiration is a bit like photosynthesis in reverse. Note that in photosynthesis, oxygen and sugar are products of the reaction, while they are inputs in cellular respiration. In cellular respiration, carbon dioxide and water are products of the reaction, while in photosynthesis they are inputs. In photosynthesis, the sun provides the energy to power the reactions, while in cellular respiration, the released energy is stored in the bonds of ATP.

Cellular respiration occurs in three basic steps—glycolysis, the Krebs cycle, and the electron transport chain. During these processes food molecules such as glucose are gradually broken down, and their energy is used to produce ATP.



### Glycolysis

Glycolysis is a series of chemical reactions in the cytoplasm of a cell in which glucose is essentially split in half. In the process, a small amount of energy is released and captured in ATP. For many organisms, glycolysis is just the first of three steps—together called cellular respiration—in which glucose is completely broken down and used to produce a much larger amount of ATP.

Glycolysis has two distinct phases: an "uphill" preparatory phase and a "downhill" payoff phase. One way to understand the two phases of glycolysis is to compare the process to a downhill bike ride. Glucose has a lot of potential energy. A cyclist at an uphill starting spot has a lot of potential energy, too. With little effort, the rider taps the potential energy and coasts to the downhill spot.

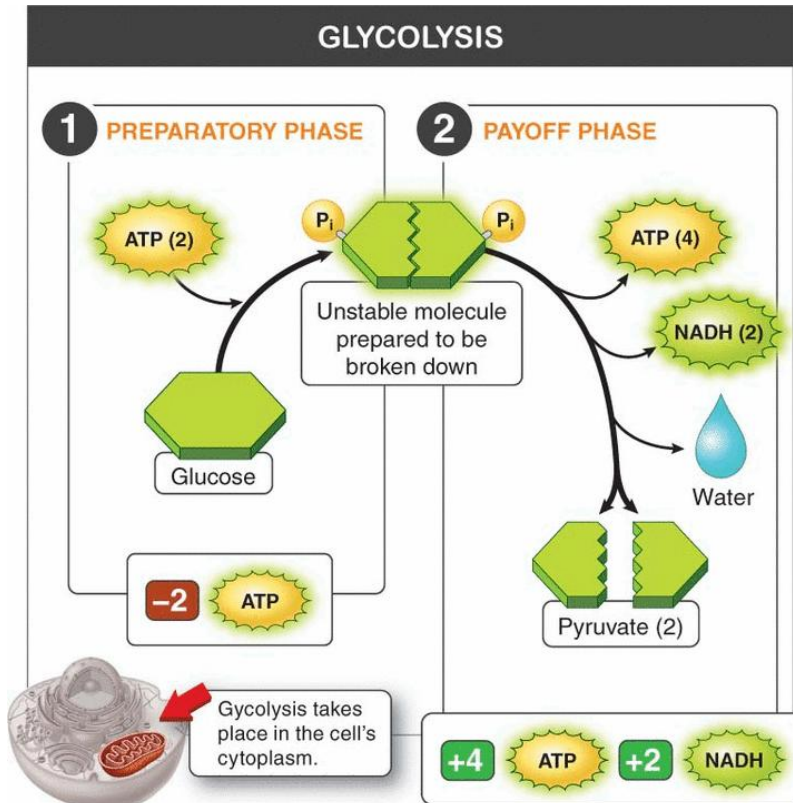
But sometimes, to reach a downhill spot, the cyclist must first go uphill—investing energy to get to the top of the hill. But on the way down, the cyclist gets back most of that energy investment, along with the reward of a longer ride.

Glycolysis is similar. Although glucose is packed with energy, the energy is not readily released unless energy from ATP is first added. When ATP is added to the reaction, the resulting sugar molecule now has two phosphate groups, which makes it less stable than before—and ripe for chemical breakdown.

In the payoff phase, three reactions now yield energy. In one reaction, each of the halves from glucose is attached to a high-energy phosphate group, and each donates high-energy electrons, along with protons (also called hydrogen ions), to electron carriers called  $\text{NAD}^+$ .

The resulting NADH molecules are high-energy electron carriers that are used later in cellular respiration for an even greater energy payoff. The essential difference between  $\text{NAD}^+$  and NADH is that NADH carries one additional proton and two additional high-energy electrons.

As glycolysis continues and more bonds from the two halves of glucose are broken, the energy released is quickly recaptured by attaching phosphate groups to molecules of ADP, creating energy-rich ATP molecules.



Two molecules of water are also produced during glycolysis.

Near the end of glycolysis, two ADP molecules take the remaining phosphate groups, forming two additional ATP molecules. By the end of glycolysis, a molecule of glucose has been broken down into two molecules of pyruvate.

Glycolysis results in the production of 2 NADH and 4 ATP molecules. However, two ATP molecules were originally invested (represented by the two remaining ADP molecules), so glycolysis nets 2 ATP and 2 NADH molecules per molecule of glucose. However, much more energy still remains in the pyruvate molecules. Cells get much more "energy bang" for their "food buck" if they now perform the Krebs cycle and the electron transport chain.

## The Krebs Cycle

The second step in cellular respiration, called the Krebs cycle, picks up where glycolysis left off. Recall that in glycolysis, glucose is split into two molecules of pyruvate. Note that these two pyruvate molecules retain the original six carbon atoms from glucose, as well as most of glucose's energy.

Before the Krebs cycle can begin, the pyruvate molecules must be transported from the cytoplasm, where glycolysis occurs, into mitochondria, where the Krebs cycle takes place.

To prepare for the Krebs cycle, pyruvate is modified in three quick steps involving  $\text{NAD}^+$  and another molecule called coenzyme A. In one of these modifications, carbon dioxide is released from pyruvate and eventually exhaled from the body. In the other modifications, the 2-carbon molecule that remains is attached to coenzyme A, while a proton (also called a hydrogen ion) and high energy electrons are donated to  $\text{NAD}^+$ , yielding the high-energy electron carrier NADH. The new molecule is called acetyl-CoA. Because two pyruvate molecules emerged from glycolysis, two acetyl-CoA molecules and two NADH are now formed. Note that two of the six carbon atoms from glucose are now in the form of two carbon dioxide molecules.

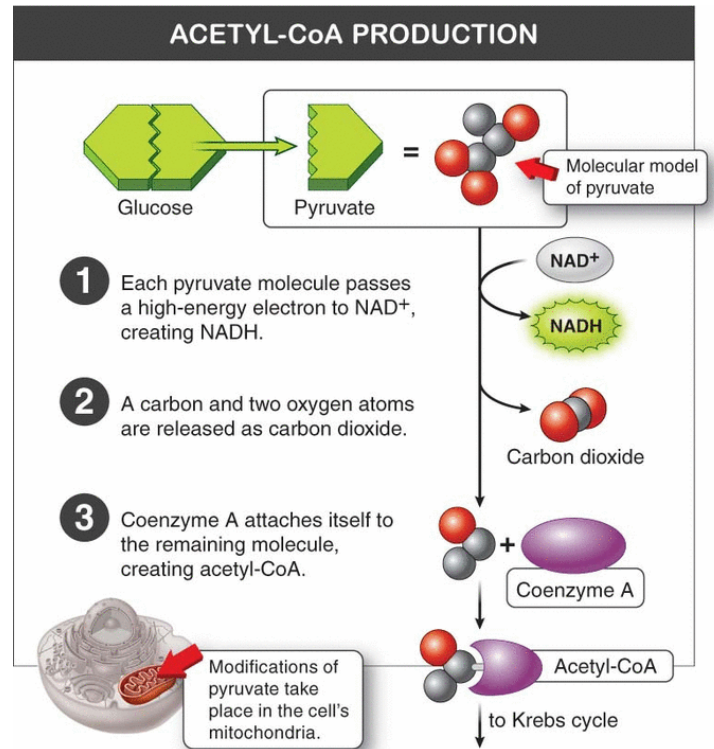
Acetyl-CoA enters the Krebs cycle, where the remaining four carbon atoms that originated from glucose will soon be released as carbon dioxide. In the first step of this pathway, acetyl-CoA combines with water and a molecule called oxaloacetate. The first outcome of the Krebs cycle is the production of a molecule with six carbon atoms—four from oxaloacetate and two that originated from glucose.

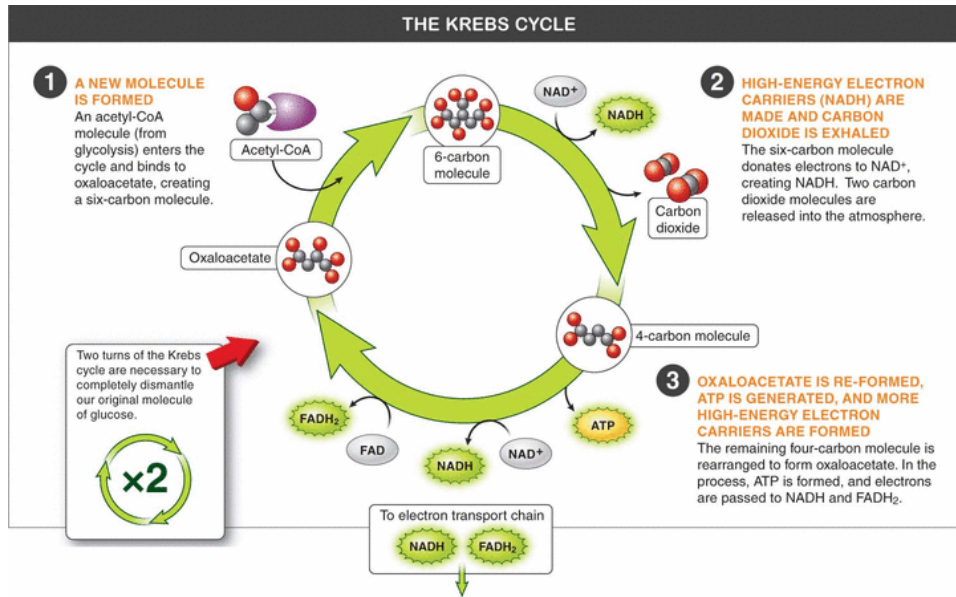
This six-carbon molecule is rearranged by the removal and then the addition of water. Another important outcome of the Krebs cycle occurs next, when the molecule is stripped of two molecules of carbon dioxide, which are exhaled. At the same time, high-energy electrons and protons are donated to molecules of  $\text{NAD}^+$ , creating NADH molecules.

Another important outcome of the Krebs cycle occurs in the next reaction, which draws energy from the remaining molecule to join inorganic phosphate and ADP into a molecule of ATP.

In addition to  $\text{NAD}^+$ , another molecule called FAD plays a role in as a high-energy electron carrier. The four-carbon molecule donates protons and high-energy electrons to these carriers. The molecule then becomes slightly rearranged by the addition of water, after which more electrons and a proton join with  $\text{NAD}^+$  to form NADH. The final outcome of the Krebs cycle is the re-formation of the cycle's starting molecule, oxaloacetate.

The entire cycle occurs again with the second acetyl-CoA molecule. As the second round continues, more NADH, more carbon dioxide, more ATP, and more  $\text{FADH}_2$  molecules result. If these molecules are added to those made from the preparation reactions, we can see that all six of the carbon atoms from glucose have been released in the form of carbon dioxide. Although a small amount of ATP has been formed in the Krebs cycle, it is the NADH and  $\text{FADH}_2$  molecules that represent the most energy for the cell.





These electron carriers enter the next phase of cellular respiration, called the electron transport chain. NADH and  $\text{FADH}_2$  molecules must give up their extra electrons to the electron transport chain so that they may revert back to  $\text{NAD}^+$  and FAD and help in the Krebs cycle again. The electron transport chain uses the energy from the electrons to produce a large number of ATP molecules. Note that

the electron transport chain absolutely requires oxygen to operate. Because the Krebs cycle relies on a functioning electron transport chain to accept electrons from NADH and  $\text{FADH}_2$ , the Krebs cycle will shut down along with the electron transport chain if oxygen disappears.

*Aerobic training can cause our bodies to produce more mitochondria in muscle cells. Why might this be beneficial?*

An increase in mitochondria means that the cell has more cellular machinery to perform the Krebs cycle and the electron transport chain. Because so much ATP is produced in the electron transport chain, such an increase in mitochondria can provide the cell with more energy to sustain physical activity, provided oxygen is available.

## The Electron Transport Chain

The last step in cellular respiration, called the electron transport chain, takes place in mitochondria. This step is essential for producing enough ATP for animals and many other organisms to survive. The first two steps in cellular respiration—glycolysis and the Krebs cycle—produced a small amount of ATP from the breakdown of glucose. These steps also produced NADH and  $\text{FADH}_2$  molecules. Through the electron transport chain, the cell can now use the energy in NADH and  $\text{FADH}_2$  molecules to make many more molecules of ATP.

The mitochondrion has two membranes, an outer membrane and an inner membrane, and is essentially a bag within a bag. The proteins of the electron transport chain reside in the inner membrane. Both NADH and  $\text{FADH}_2$  donate electrons to the chain. We will use NADH as an example.

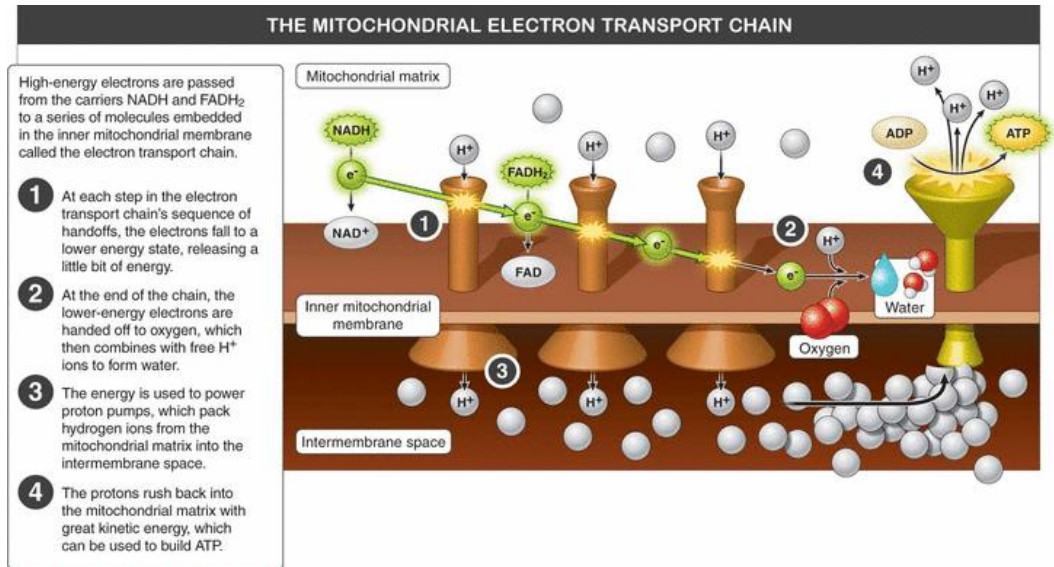
As electrons move from one complex to another in the chain, they transfer some of their energy to proteins that pump protons, also known as hydrogen ions, across the membrane. With each transfer, the electrons lose energy, which is used to pump more protons. The process of electron transfer results in a difference in the concentration of protons on the two sides of the membrane. This concentration difference—called a gradient—is a form of potential energy.

The oxygen that we breathe is essential for electron transport. Oxygen is exceptionally electron greedy and snatches electrons from the end of the electron transport chain. After grabbing electrons, it combines with protons to form water.

From the operation of the electron transport chain, a concentration gradient of protons forms across the membrane. Like water held behind a dam, given the opportunity, the protons will tend to flow across the membrane barrier. A complex in the membrane provides a passageway for the protons, and uses the energy from the proton flow to power the production of ATP. The protons will tend to flow in this direction until the concentrations are the same on both sides of the membrane—that is, until the gradient disappears. If the electron transport chain stops for any reason, such as a lack of oxygen to capture electrons at the end of the chain, the gradient will quickly disappear, turning off ATP production.

The  $\text{NAD}^+$  molecules left over from the electron transport chain are later recycled back to glycolysis and the Krebs cycle, where they will capture more high-energy electrons from food molecules.

ATP, produced in plenty during this last stage of cellular respiration, contains energy that had its origin in a molecule of glucose. Along the way, the energy took many forms, including the energy held by electron carriers, the energy released



by transporting electrons in the electron transport chain, and the energy stored in a concentration gradient across a membrane. In the form of ATP, the energy originally in the bonds of glucose can be used to fuel cellular work.

*Why is cyanide such a deadly poison?*

Cyanide is a deadly poison because it cripples the electron transport chain. Cyanide binds to the last complex in the chain and, in so doing, blocks oxygen from binding.

Recall that during the operation of the electron transport chain,  $\text{NADH}$  donates electrons to the beginning of the chain. The process of electron transport fuels the pumping of protons across the membrane. However, with cyanide already bound, oxygen cannot grab the electrons at the end of the chain. Therefore, no new electrons from  $\text{NADH}$  can be added at the beginning.

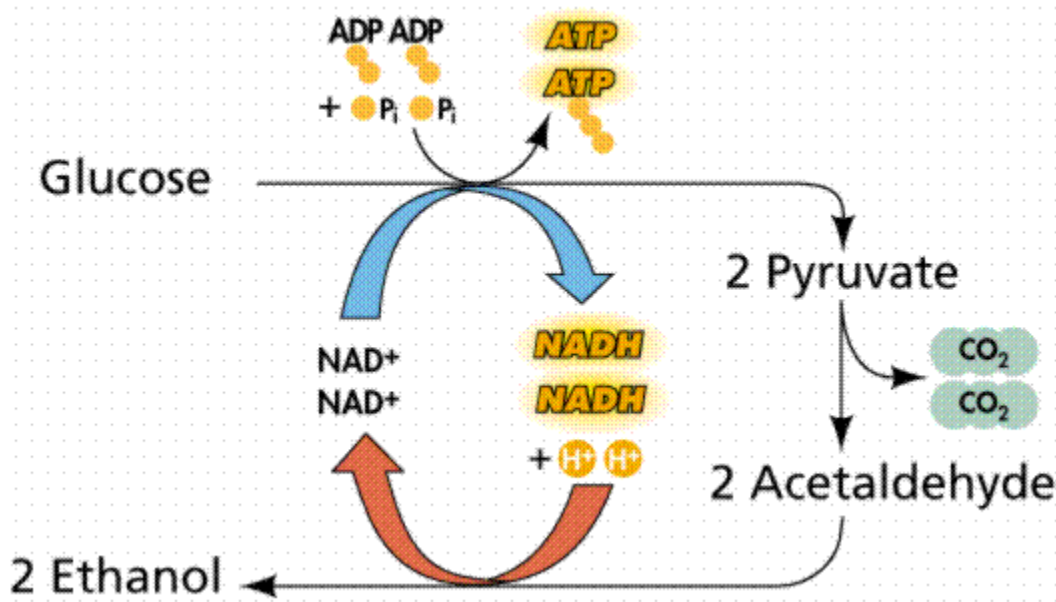
Under these conditions, electron transport and proton pumping grind to a halt. Without the active pumping of protons to one side of the membrane, the proton concentrations on both sides soon equalize.

No longer do protons rush through the ATP-producing complex, and no more ATP is produced. Cells can't live long on the small quantity of ATP made by glycolysis, so without the ATP that comes from the electron transport chain, cells die.

## Anaerobic Pathways

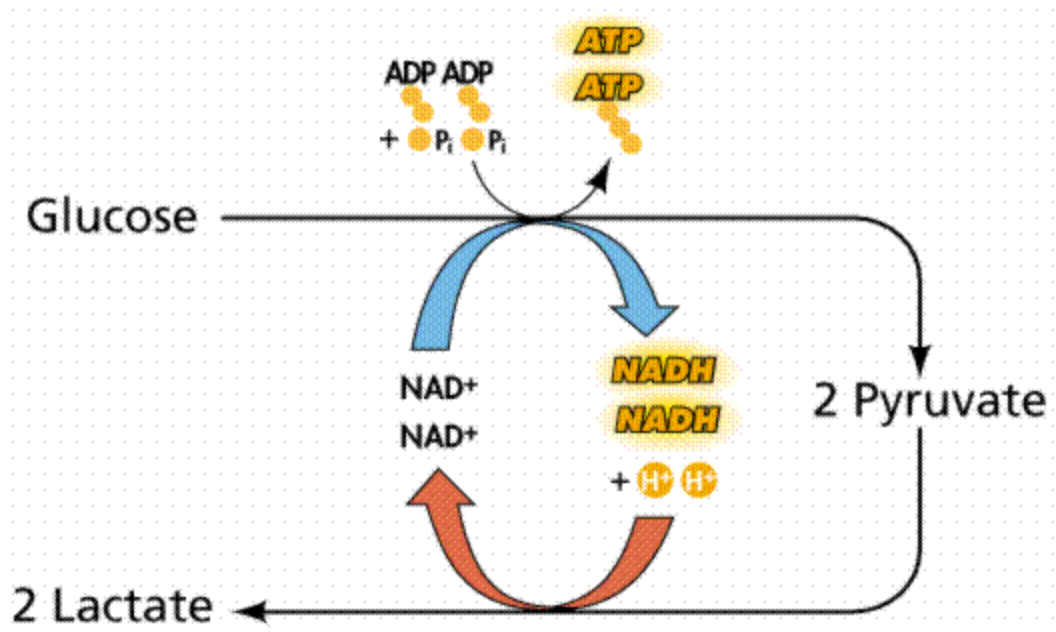
Under anaerobic conditions, the absence of oxygen, pyruvic acid can be routed by the organism into one of three pathways: lactic acid fermentation, alcohol fermentation, or cellular (anaerobic) respiration. Humans cannot ferment alcohol in their own bodies, we lack the genetic information to do so. These biochemical pathways, with their myriad reactions catalyzed by reaction-specific enzymes all under genetic control, are extremely complex. We will only skim the surface at this time and in this course.

Alcohol [fermentation](#) is the formation of alcohol from sugar. Yeast, when under anaerobic conditions, convert glucose to pyruvic acid via the glycolysis pathways, then go one step farther, converting pyruvic acid into ethanol, a C-2 compound.



Fermentation of ethanol. Image from Purves et al., *Life: The Science of Biology*, 4th Edition, by Sinauer Associates ([www.sinauer.com](http://www.sinauer.com)) and WH Freeman ([www.whfreeman.com](http://www.whfreeman.com))

Many organisms will also ferment pyruvic acid into, other chemicals, such as lactic acid. Humans ferment lactic acid in muscles where oxygen becomes depleted, resulting in localized anaerobic conditions. This lactic acid causes the muscle stiffness couch-potatoes feel after beginning exercise programs. The stiffness goes away after a few days since the cessation of strenuous activity allows aerobic conditions to return to the muscle, and the lactic acid can be converted into ATP via the normal aerobic respiration pathways.



Fermentation of lactate (lactic acid). Image from Purves et al., *Life: The Science of Biology*, 4th Edition, by Sinauer Associates ([www.sinauer.com](http://www.sinauer.com)) and WH Freeman ([www.whfreeman.com](http://www.whfreeman.com))