

7.2 | Glycolysis

By the end of this section, you will be able to do the following:

- Describe the overall result in terms of molecules produced during the chemical breakdown of glucose by glycolysis
- Compare the output of glycolysis in terms of ATP molecules and NADH molecules produced

As you have read, nearly all of the energy used by living cells comes to them in the bonds of the sugar glucose. **Glycolysis** is the first step in the breakdown of glucose to extract energy for cellular metabolism. In fact, nearly all living organisms carry out glycolysis as part of their metabolism. The process does not use oxygen directly and therefore is termed **anaerobic**. Glycolysis takes place in the cytoplasm of both prokaryotic and eukaryotic cells. Glucose enters heterotrophic cells in two ways. One method is through secondary active transport in which the transport takes place against the glucose concentration gradient. The other mechanism uses a group of integral proteins called **GLUT proteins**, also known as glucose transporter proteins. These transporters assist in the facilitated diffusion of glucose.

Glycolysis begins with the six-carbon ring-shaped structure of a single glucose molecule and ends with two molecules of a three-carbon sugar called **pyruvate**. Glycolysis consists of two distinct phases. The first part of the glycolysis pathway traps the glucose molecule in the cell and uses energy to modify it so that the six-carbon sugar molecule can be split evenly into the two three-carbon molecules. The second part of glycolysis extracts energy from the molecules and stores it in the form of ATP and NADH—remember: this is the reduced form of NAD.

First Half of Glycolysis (Energy-Requiring Steps)

Step 1. The first step in glycolysis (**Figure 7.6**) is catalyzed by hexokinase, an enzyme with broad specificity that catalyzes the phosphorylation of six-carbon sugars. Hexokinase phosphorylates glucose using ATP as the source of the phosphate, producing glucose-6-phosphate, a more reactive form of glucose. This reaction prevents the phosphorylated glucose molecule from continuing to interact with the GLUT proteins, and it can no longer leave the cell because the negatively charged phosphate will not allow it to cross the hydrophobic interior of the plasma membrane.

Step 2. In the second step of glycolysis, an isomerase converts glucose-6-phosphate into one of its isomers, fructose-6-phosphate (this isomer has a phosphate attached at the location of the sixth carbon of the ring). An **isomerase** is an enzyme that catalyzes the conversion of a molecule into one of its isomers. (This change from phosphoglucose to phosphofructose allows the eventual split of the sugar into two three-carbon molecules.)

Step 3. The third step is the phosphorylation of fructose-6-phosphate, catalyzed by the enzyme phosphofructokinase. A second ATP molecule donates a high-energy phosphate to fructose-6-phosphate, producing fructose-1,6-bisphosphate. In this pathway, phosphofructokinase is a rate-limiting enzyme. It is active when the concentration of ADP is high; it is less active when ADP levels are low and the concentration of ATP is high. Thus, if there is “sufficient” ATP in the system, the pathway slows down. This is a type of end product inhibition, since ATP is the end product of glucose catabolism.

Step 4. The newly added high-energy phosphates further destabilize fructose-1,6-bisphosphate. The fourth step in glycolysis employs an enzyme, aldolase, to cleave fructose-1,6-bisphosphate into two three-carbon isomers: dihydroxyacetone phosphate and glyceraldehyde-3-phosphate.

Step 5. In the fifth step, an isomerase transforms the dihydroxyacetone-phosphate into its isomer, glyceraldehyde-3-phosphate. Thus, the pathway will continue with two molecules of a glyceraldehyde-3-phosphate. At this point in the pathway, there is a net investment of energy from two ATP molecules in the breakdown of one glucose molecule.

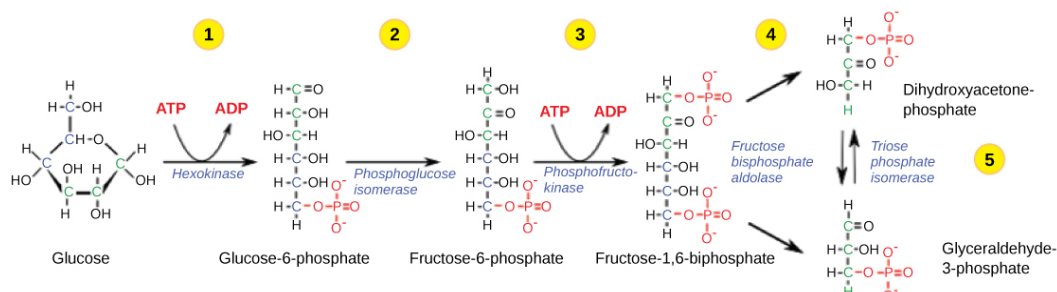


Figure 7.6 The first half of glycolysis uses two ATP molecules in the phosphorylation of glucose, which is then split into two three-carbon molecules.

Second Half of Glycolysis (Energy-Releasing Steps)

So far, glycolysis has cost the cell two ATP molecules and produced two small, three-carbon sugar molecules. Both of these molecules will proceed through the second half of the pathway, and sufficient energy will be extracted to pay back the two ATP molecules used as an initial investment and produce a profit for the cell of two additional ATP molecules and two even higher-energy NADH molecules.

Step 6. The sixth step in glycolysis (**Figure 7.7**) oxidizes the sugar (glyceraldehyde-3-phosphate), extracting high-energy electrons, which are picked up by the electron carrier NAD^+ , producing NADH. The sugar is then phosphorylated by the addition of a second phosphate group, producing 1,3-bisphosphoglycerate. Note that the second phosphate group does not require another ATP molecule.

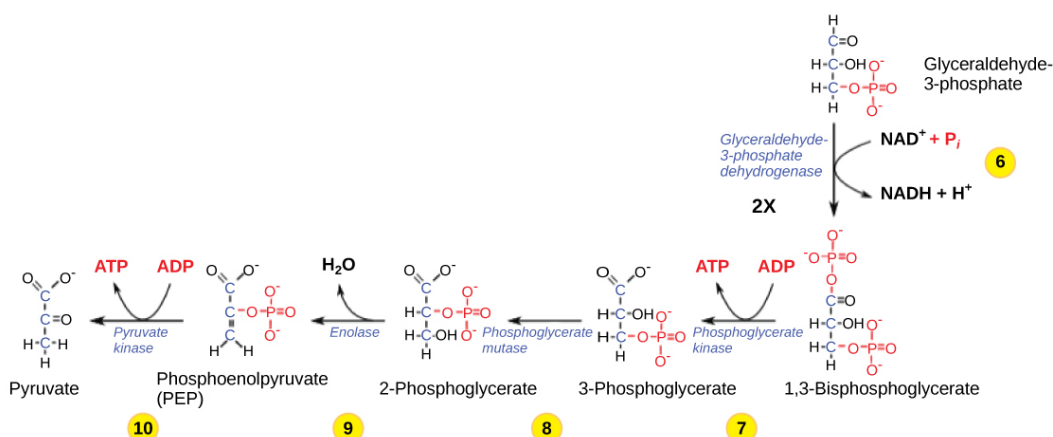


Figure 7.7 The second half of glycolysis involves phosphorylation without ATP investment (step 6) and produces two NADH and four ATP molecules per glucose.

Here again is a potential limiting factor for this pathway. The continuation of the reaction depends upon the availability of the oxidized form of the electron carrier, NAD^+ . Thus, NADH must be continuously oxidized back into NAD^+ in order to keep this step going. If NAD^+ is not available, the second half of glycolysis slows down or stops. If oxygen is available in the system, the NADH will be oxidized readily, though indirectly, and the high-energy electrons from the hydrogen released in this process will be used to produce ATP. In an environment without oxygen, an alternate pathway (fermentation) can provide the oxidation of NADH to NAD^+ .

Step 7. In the seventh step, catalyzed by phosphoglycerate kinase (an enzyme named for the reverse reaction), 1,3-bisphosphoglycerate donates a high-energy phosphate to ADP, forming one molecule of ATP. (This is an example of substrate-level phosphorylation.) A carbonyl group on the 1,3-bisphosphoglycerate is oxidized to a carboxyl group, and 3-phosphoglycerate is formed.

Step 8. In the eighth step, the remaining phosphate group in 3-phosphoglycerate moves from the third carbon to the second carbon, producing 2-phosphoglycerate (an isomer of 3-phosphoglycerate). The enzyme catalyzing this step is a mutase (isomerase).

Step 9. Enolase catalyzes the ninth step. This enzyme causes 2-phosphoglycerate to lose water from its structure; this is a dehydration reaction, resulting in the formation of a double bond that increases the potential

energy in the remaining phosphate bond and produces phosphoenolpyruvate (PEP).

Step 10. The last step in glycolysis is catalyzed by the enzyme pyruvate kinase (the enzyme in this case is named for the reverse reaction of pyruvate's conversion into PEP) and results in the production of a second ATP molecule by substrate-level phosphorylation and the compound pyruvic acid (or its salt form, pyruvate). Many enzymes in enzymatic pathways are named for the reverse reactions, since the enzyme can catalyze both forward and reverse reactions (these may have been described initially by the reverse reaction that takes place in vitro, under nonphysiological conditions).



Gain a better understanding of the breakdown of glucose by glycolysis by visiting this [site \(http://openstaxcollege.org//glycolysis\)](http://openstaxcollege.org//glycolysis) to see the process in action.

Outcomes of Glycolysis

Glycolysis begins with glucose and produces two pyruvate molecules, four new ATP molecules, and two molecules of NADH. (Note: two ATP molecules are used in the first half of the pathway to prepare the six-carbon ring for cleavage, so the cell has a *net gain of two ATP molecules* and two NADH molecules for its use). If the cell cannot catabolize the pyruvate molecules further, it will harvest only two ATP molecules from one molecule of glucose. Mature mammalian red blood cells do not have mitochondria and thus are not capable of **aerobic respiration**—the process in which organisms convert energy in the presence of oxygen—and glycolysis is their sole source of ATP. If glycolysis is interrupted, these cells lose their ability to maintain their sodium-potassium pumps, and eventually, they die.

The last step in glycolysis will not occur if pyruvate kinase, the enzyme that catalyzes the formation of pyruvate, is not available in sufficient quantities. In this situation, the entire glycolysis pathway will proceed, but only two ATP molecules will be made in the second half. Thus, pyruvate kinase is a rate-limiting enzyme for glycolysis.

7.3 | Oxidation of Pyruvate and the Citric Acid Cycle

By the end of this section, you will be able to do the following:

- Explain how a circular pathway, such as the citric acid cycle, fundamentally differs from a linear biochemical pathway, such as glycolysis
- Describe how pyruvate, the product of glycolysis, is prepared for entry into the citric acid cycle

If oxygen is available, aerobic respiration will go forward. In eukaryotic cells, the pyruvate molecules produced at the end of glycolysis are transported into the mitochondria, which are the sites of cellular respiration. There, pyruvate is transformed into an acetyl group that will be picked up and activated by a carrier compound called coenzyme A (CoA). The resulting compound is called **acetyl CoA**. CoA is derived from vitamin B5, pantothenic acid. Acetyl CoA can be used in a variety of ways by the cell, but its major function is to deliver the acetyl group derived from pyruvate to the next stage of the pathway in glucose catabolism.

Breakdown of Pyruvate

In order for pyruvate, the product of glycolysis, to enter the next pathway, it must undergo several changes. The conversion is a three-step process ([Figure 7.8](#)).

Step 1. A carboxyl group is removed from pyruvate, releasing a molecule of carbon dioxide into the surrounding medium. This reaction creates a two-carbon hydroxyethyl group bound to the enzyme (pyruvate dehydrogenase). We should note that this is the first of the six carbons from the original glucose molecule to be removed. (This step proceeds twice because there are *two* pyruvate molecules produced at the end of glycolysis for every molecule of glucose metabolized anaerobically; thus, two of the six carbons will have been removed at