

Glycolysis

Glucose is stored in polymeric form as starch in plants and as glycogen (a multibranched polysaccharide) in animals. The breakdown of these polymers provides glucose monomers that can be catabolized to release energy. The conversion of the six-carbon glucose to the three-carbon pyruvate, a pathway we now call **glycolysis**, occurs in **ten steps**.

Glycolysis does not require molecular oxygen.

Glycolysis, along with other metabolic pathways, exhibits the following properties:

1. Each step of the pathway is catalyzed by a distinct enzyme.
2. The free energy consumed or released in certain reactions is transferred by molecules such as ATP and NADH.
3. The rate of the pathway can be controlled by altering the activity of individual enzymes.

Phase 1-5: preparatory phase (investing free energy in form of two ATP molecules)

1. **Glucose Phosphorylation:** A phosphate group is added to glucose, trapping it inside the cell and committing it to glycolysis.
2. **Isomerization:** Glucose is rearranged into fructose-6-phosphate, preparing for the cleavage reaction.
3. **Phosphorylation:** Another phosphate group is added to fructose-6-phosphate, adding energy for the upcoming split.
4. **Cleavage:** The 6-carbon fructose-1,6-bisphosphate is cleaved into two 3-carbon molecules: glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP).
5. **Isomerization:** Dihydroxyacetone phosphate is converted into its isomer, glyceraldehyde-3-phosphate, ensuring two identical molecules for the next steps.

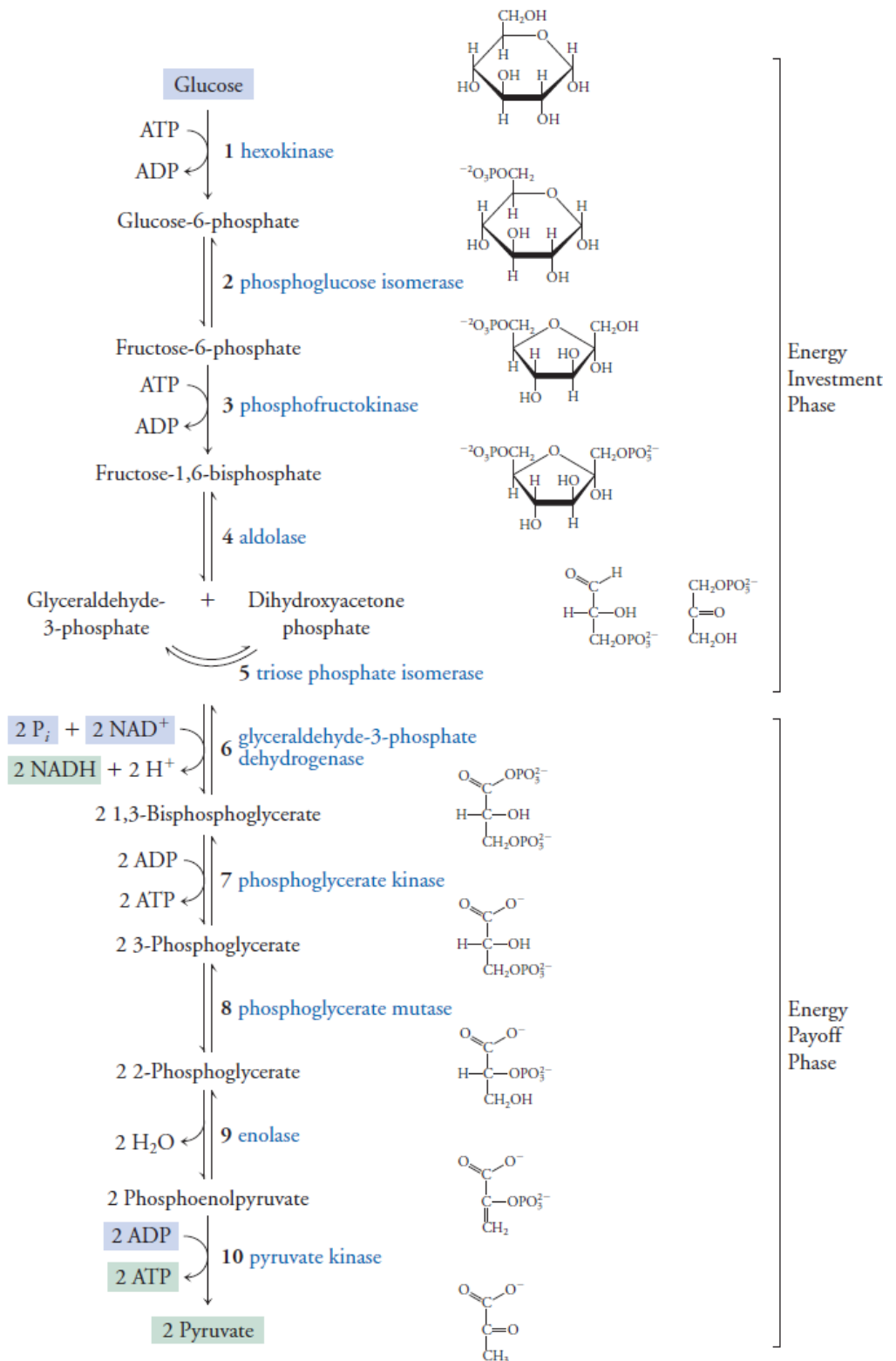
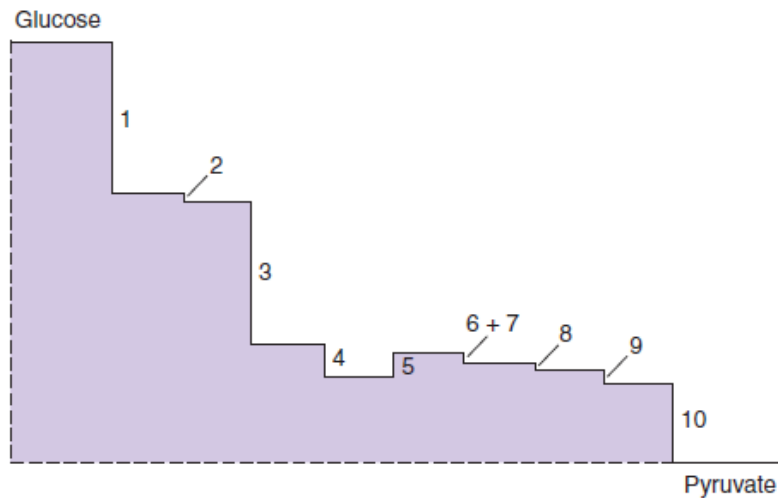


Figure 13-2 The reactions of glycolysis. The substrates, products, and enzymes corresponding to the 10 steps of the pathway are shown. Shading indicates the substrates (purple) and products (green) of the pathway as a whole. ➕ See Animated Figure. Overview of glycolysis.

Phase 6-10: energy-producing phase

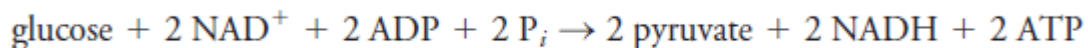
6. **Oxidation and Phosphorylation:** Glyceraldehyde-3-phosphate is oxidized, losing electrons and gaining a phosphate group, generating ATP and NADH.
7. **Substrate-level Phosphorylation:** A high-energy phosphate group is transferred from a phosphorylated intermediate to ADP, forming ATP.
8. **Substrate-level Phosphorylation (repeat):** The same process as phase 7 occurs again with the other glyceraldehyde-3-phosphate molecule, producing another ATP.
9. **Enolization:** Pyruvate is formed from phosphoenolpyruvate, losing water and gaining a double bond, becoming more reactive.
10. **Pyruvate Kinase:** A final phosphate group is transferred from phosphoenolpyruvate to ADP, forming ATP and yielding pyruvate as the end product of glycolysis.



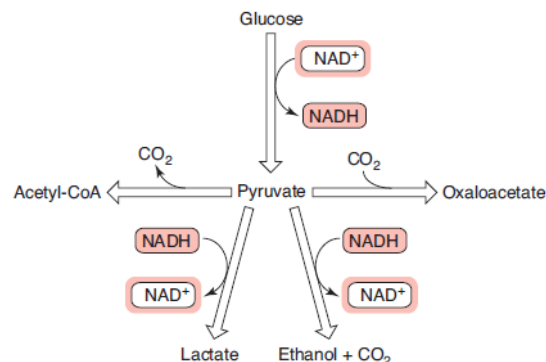
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Glycolysis

Figure 13-7 Graphical representation of the free energy changes of glycolysis. Three steps have large negative values of ΔG ; the remaining steps are near equilibrium ($\Delta G \approx 0$). The height of each step corresponds to its ΔG value in heart muscle, and the numbers correspond to glycolytic enzymes. Keep in mind that ΔG values vary slightly among tissues. [Data from Newsholme, E. A., and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).]

This catabolic pathway is accompanied by the phosphorylation of **two molecules of ADP** (to produce 2 ATP) and the reduction of **two molecules of NAD⁺**. The net equation for the pathway (ignoring water and protons) is,



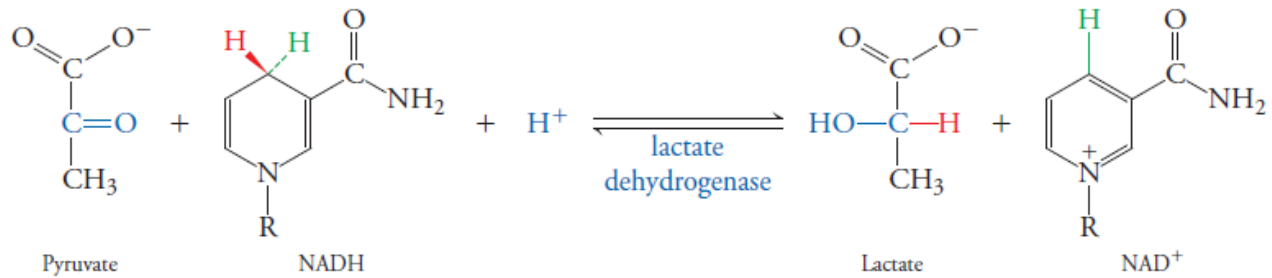
Anaerobic glucose catabolism during exercise and Lactate



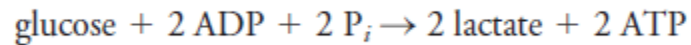
(Fates of pyruvate)

In a highly active muscle cell, glycolysis rapidly provides ATP to power muscle contraction, **but the pathway also consumes NAD⁺** (which are crucial electron carriers) at the glyceraldehyde-3-phosphate dehydrogenase step (**Step 6**).

Reoxidizing NADH by oxygen is too slow. To compensate, NAD⁺ needed for rapid ATP production is replenished by the enzyme lactate dehydrogenase, which reduces pyruvate to lactate, allowing muscle to function anaerobically for a few minutes:

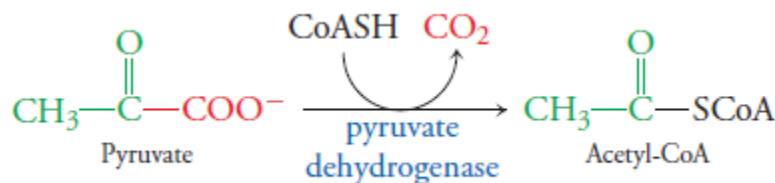


The net reaction is:



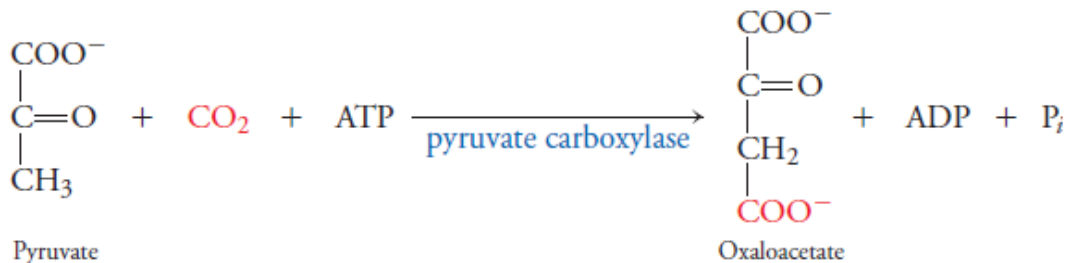
Acetyl-CoA

The further catabolism of pyruvate begins with its decarboxylation to form a two-carbon acetyl group linked to coenzyme A, Acetyl-CoA – a substrate for the TCA cycle.



Oxaloacetate

Pyruvate is also the precursor of oxaloacetate, a four-carbon molecule that is an intermediate in the synthesis of several amino acids. It is also one of the intermediates of the citric acid cycle. Oxaloacetate is synthesized by the action of pyruvate carboxylase:



Pyruvate can be converted to glucose by **glycolytic enzymes operating in reverse** and by **enzymes that bypass the irreversible steps of glycolysis**.

Gluconeogenesis

Gluconeogenesis, occurring mainly in the liver and kidneys, is the synthesis of glucose from non-carbohydrate sources.

Purpose: Vital for maintaining blood glucose levels during fasting or low-carbohydrate states.

Substrates: Utilizes substrates like lactate, glycerol, and amino acids, converting them into glucose.

Irreversible Steps (Steps 1, 3, 10 in Glycolysis): Bypasses three irreversible steps in glycolysis using specific enzymes, including pyruvate carboxylase (Step 1), phosphoenolpyruvate carboxykinase (Step 3), and fructose-1,6-bisphosphatase (Step 10).

Role of Oxaloacetate: Oxaloacetate, a crucial intermediate, combines with acetyl-CoA to form citrate in the citric acid cycle and serves as a starting point for gluconeogenesis.

Energy Cost: Demands ATP and GTP, making it energetically demanding.

Reciprocal Regulation with Glycolysis: Regulated to avoid futile cycling, ensuring a balance with glycolysis.

Hormonal Control (e.g., cortisol, glucagon): Influenced by hormones such as cortisol (stress hormone) and glucagon (raises blood glucose levels).

Integration with Metabolism: Connected with the citric acid cycle and fatty acid metabolism for overall metabolic balance.

Physiological Importance: Ensures a constant glucose supply for tissues, especially the brain, during nutrient scarcity or fasting.

Storage

Dietary glucose and the glucose produced by gluconeogenesis are stored in the liver and other tissues as glycogen. Glycogen degradation is thermodynamically spontaneous; thus, glycogen synthesis requires the input of free energy.