Glucose metabolism

INDRAPRASTHA INSTITUTE *of* INFORMATION TECHNOLOGY DELHI

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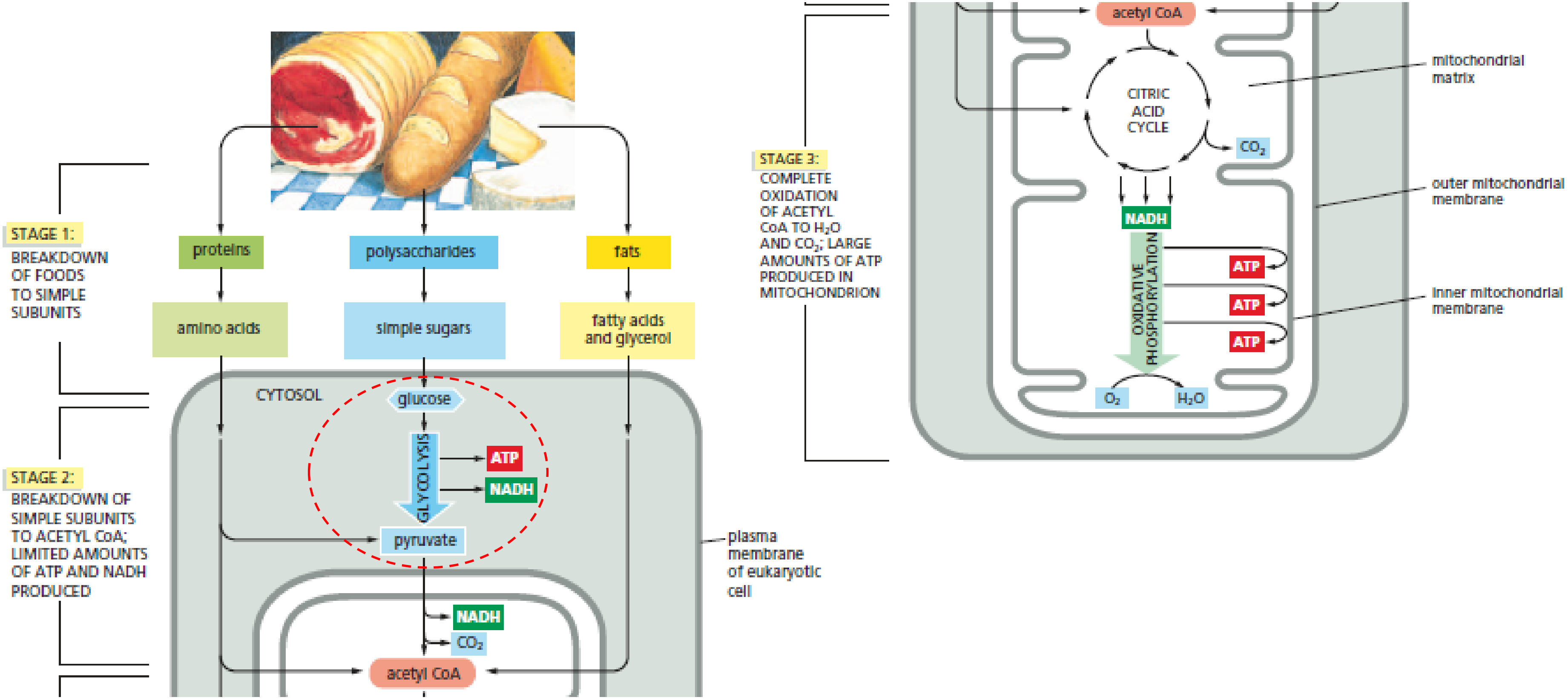
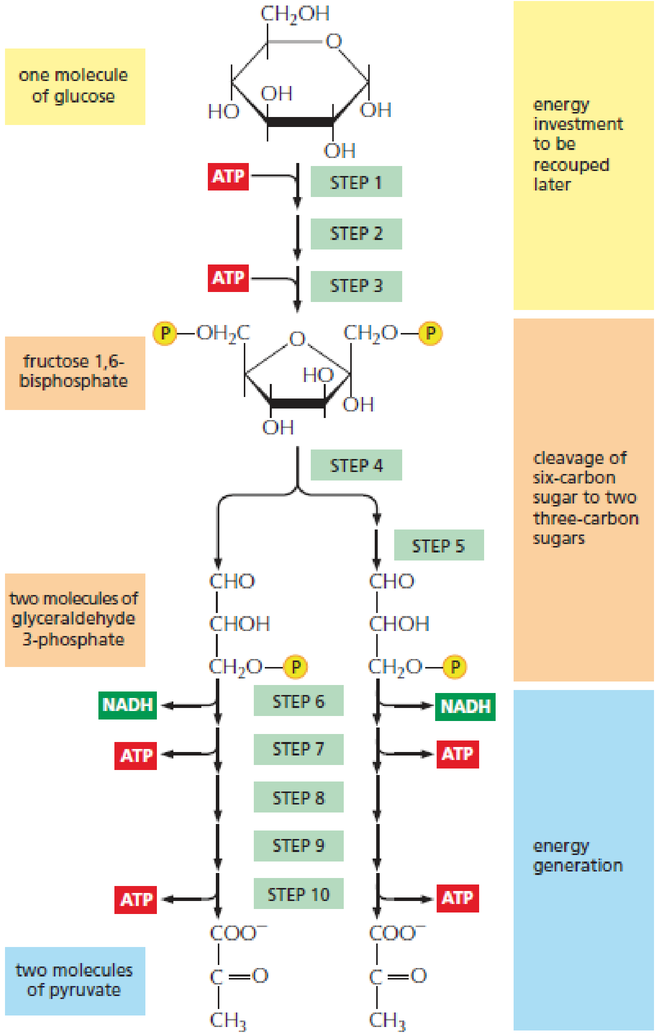
Glycolysis

Food molecules are broken down in three stages



Glycolysis - overview

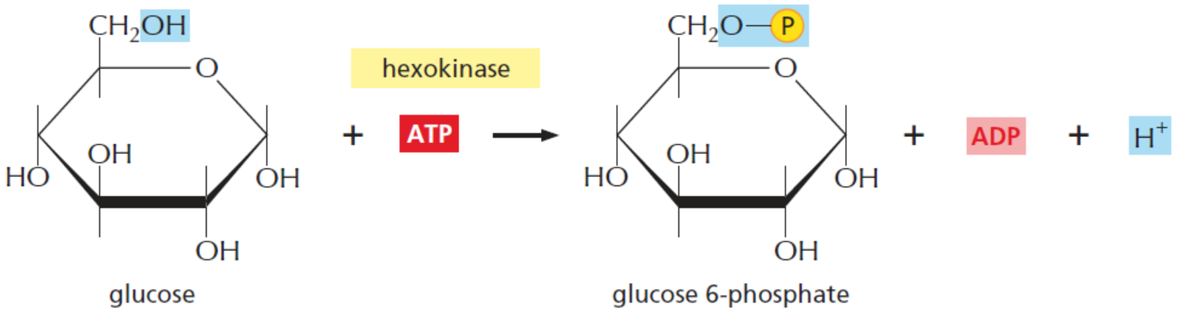


- Glycolysis is also sometimes referred to as the Embden–Meyerhof pathway.
- Much of the energy released by the breakdown of glucose is used to drive the synthesis of ATP molecules from ADP and Pi. This form of ATP synthesis, which takes place in steps 7 and 10 in glycolysis, is known as substrate-level phosphorylation because it occurs by the transfer of a phosphate group directly from a substrate molecule—one of the sugar intermediates—to ADP. By contrast, most phosphorylations in cells occur by the transfer of phosphate from ATP to a substrate molecule.

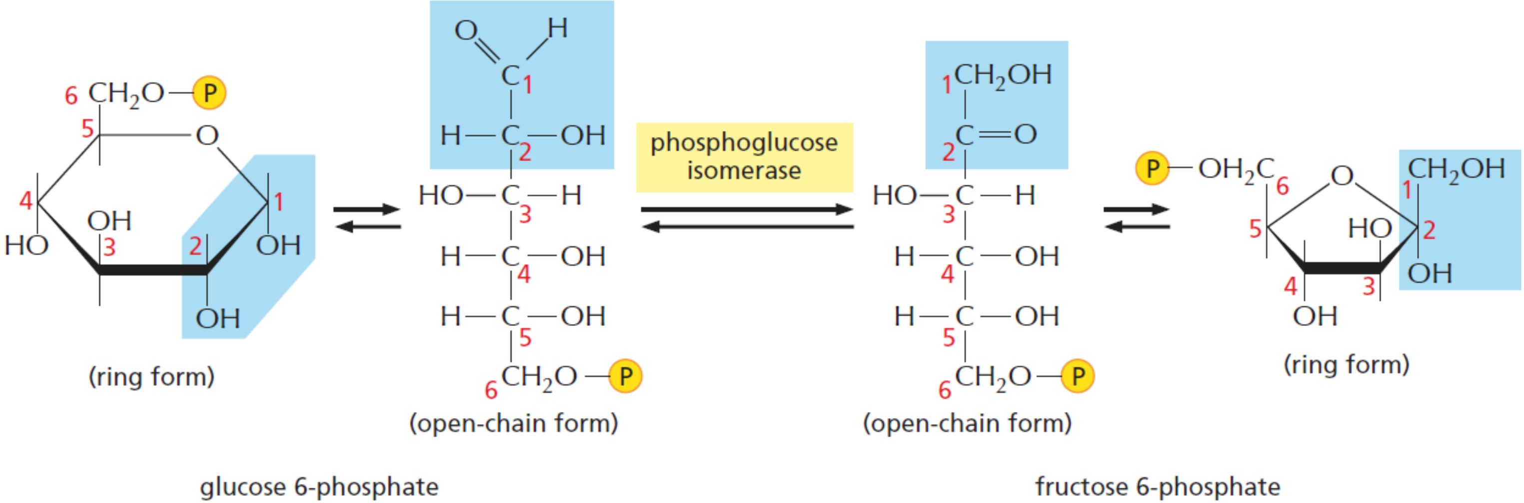
NET RESULT: GLUCOSE → 2 PYRUVATE + 2 ATP + 2 NADH

Glycolysis steps

Step 1 Glucose is phosphorylated by ATP to form a sugar phosphate. The negative charge of the phosphate prevents passage of the sugar phosphate through the plasma membrane, trapping glucose inside the cell.

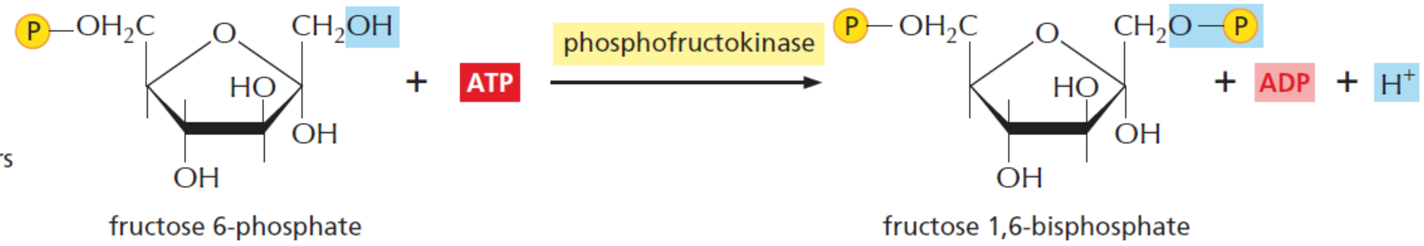


Step 2 A readily reversible rearrangement of the chemical structure (isomerization) moves the carbonyl oxygen from carbon 1 to carbon 2, forming a ketose from an aldose sugar.

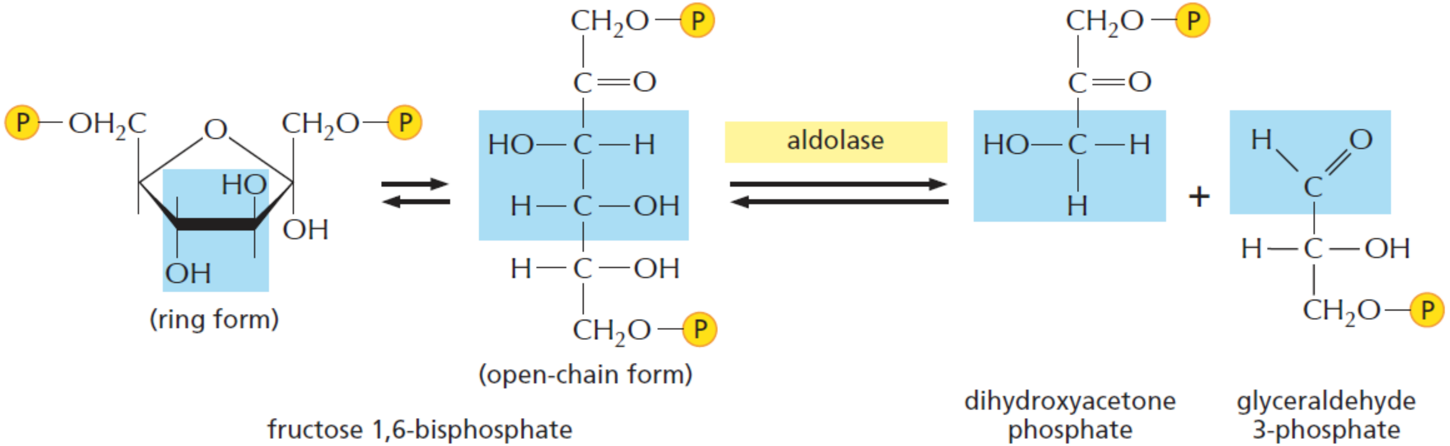


Glycolysis steps

Step 3 The new hydroxyl group on carbon 1 is phosphorylated by ATP, in preparation for the formation of two three-carbon sugar phosphates. The entry of sugars into glycolysis is controlled at this step, through regulation of the enzyme *phosphofructokinase*.

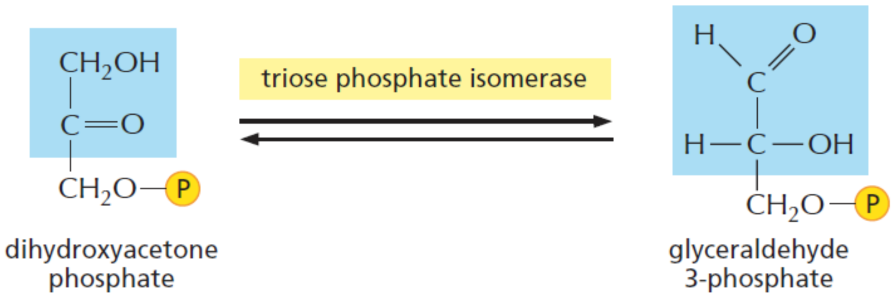


Step 4 The six-carbon sugar is cleaved to produce two three-carbon molecules. Only the glyceraldehyde 3-phosphate can proceed immediately through glycolysis.

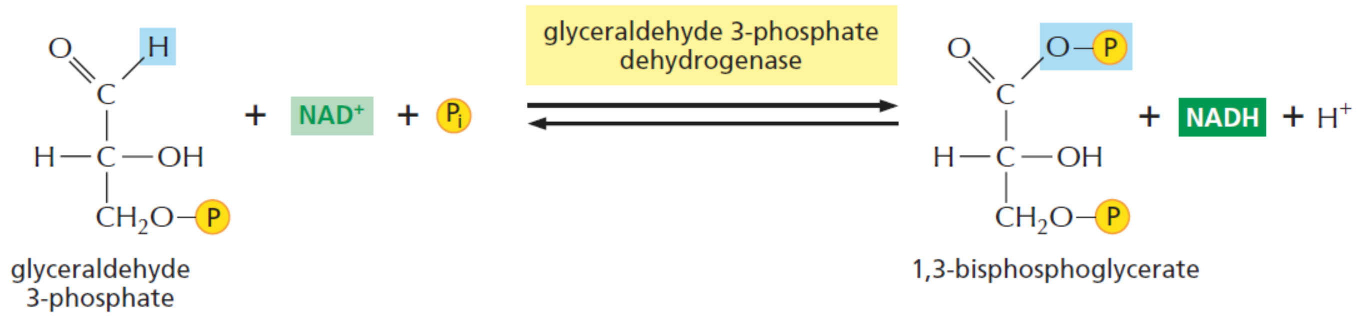


Glycolysis steps

Step 5 The other product of step 4, dihydroxyacetone phosphate, is isomerized to form glyceraldehyde 3-phosphate.

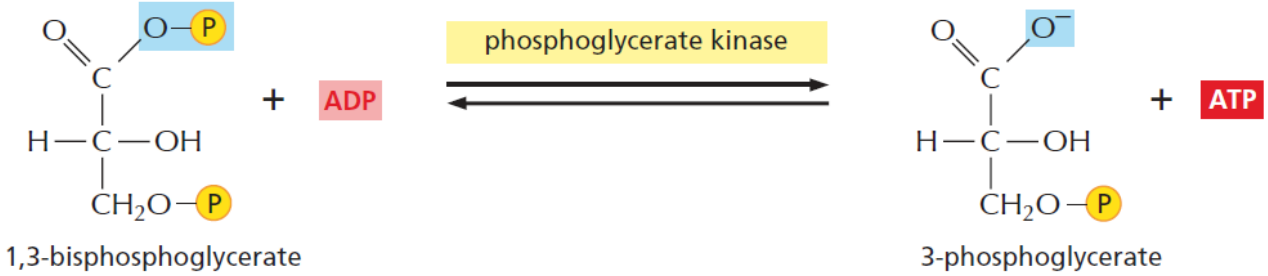


Step 6 The two molecules of glyceraldehyde 3-phosphate are oxidized. The energy-generation phase of glycolysis begins, as NADH and a new high-energy anhydride linkage to phosphate are formed

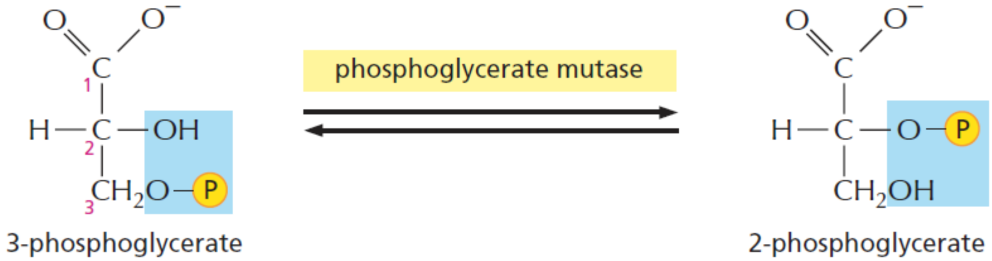


Glycolysis steps

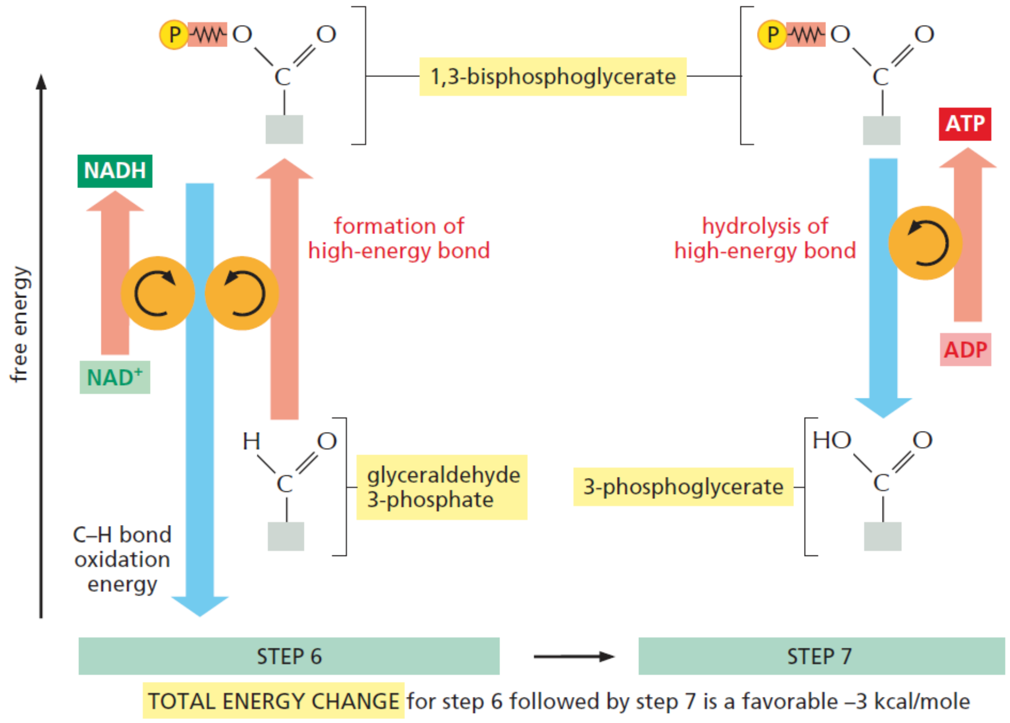
Step 7 The transfer to ADP of the high-energy phosphate group that was generated in step 6 forms ATP.



Step 8 The remaining phosphate ester linkage in 3-phosphoglycerate, which has a relatively low free energy of hydrolysis, is moved from carbon 3 to carbon 2 to form 2-phosphoglycerate.



Substrate level phosphorylation



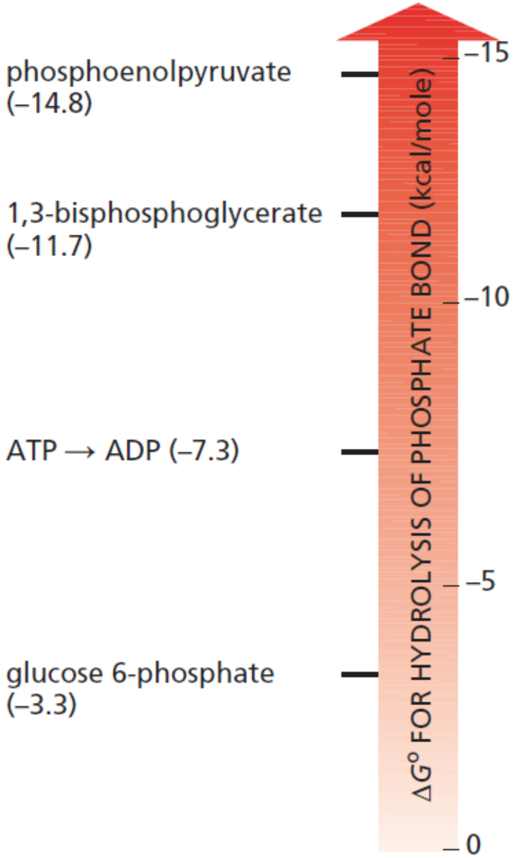
Blue arrows - energetically favorable reactions

Red arrows - energetically costly

In step 6, the energy released by the energetically favorable oxidation of a C–H bond in glyceraldehyde 3-phosphate (blue arrow) is large enough to drive two energetically costly reactions: the formation of both NADH and a high-energy phosphate bond in 1,3-bisphosphoglycerate.

The subsequent energetically favorable hydrolysis of that high-energy phosphate bond in step 7 then drives the formation of ATP.

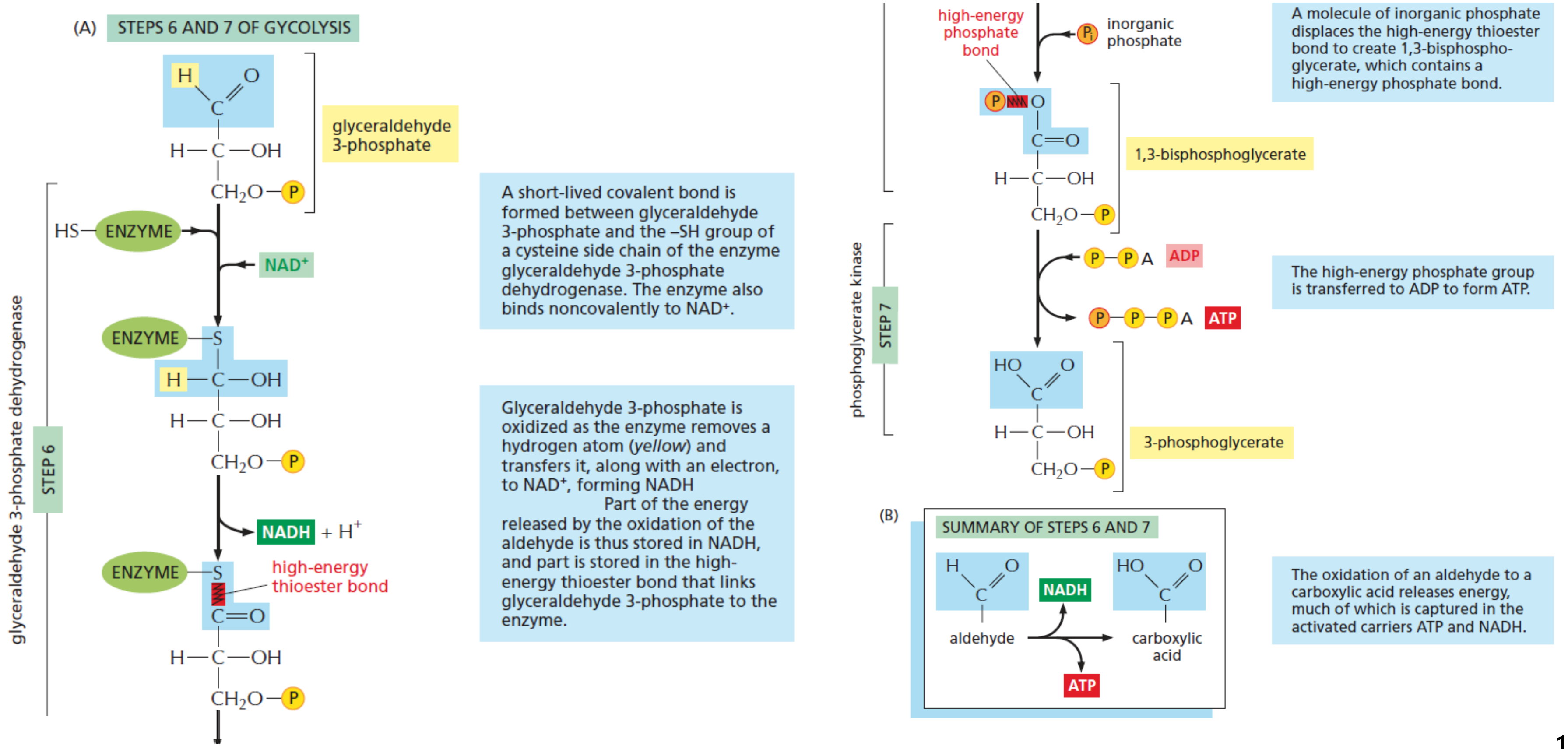
Substrate level phosphorylation



The transfer of a phosphate group from one molecule to another is energetically favorable if the standard free-energy change (ΔG°) for hydrolysis of the phosphate bond is more negative for the donor molecule than for the acceptor.

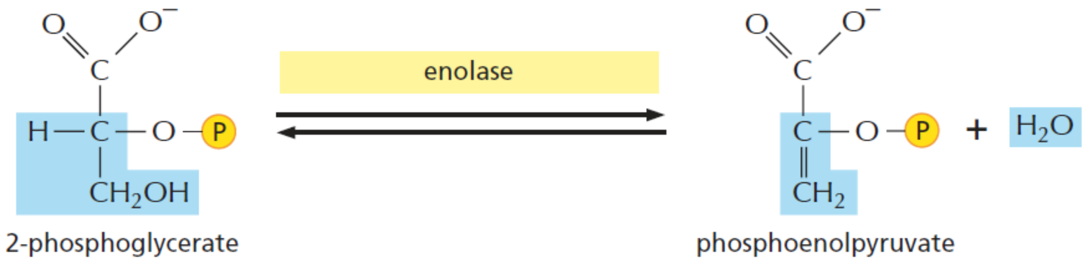
Thus, a phosphate group is readily transferred from 1,3-bisphosphoglycerate to ADP to form ATP .

Substrate level phosphorylation

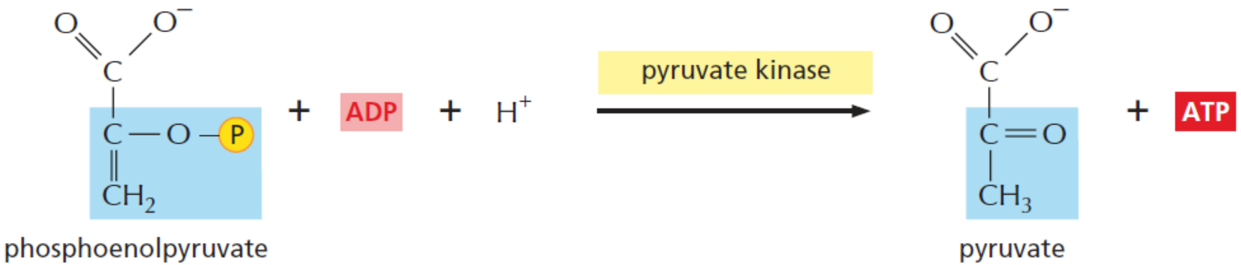


Glycolysis steps

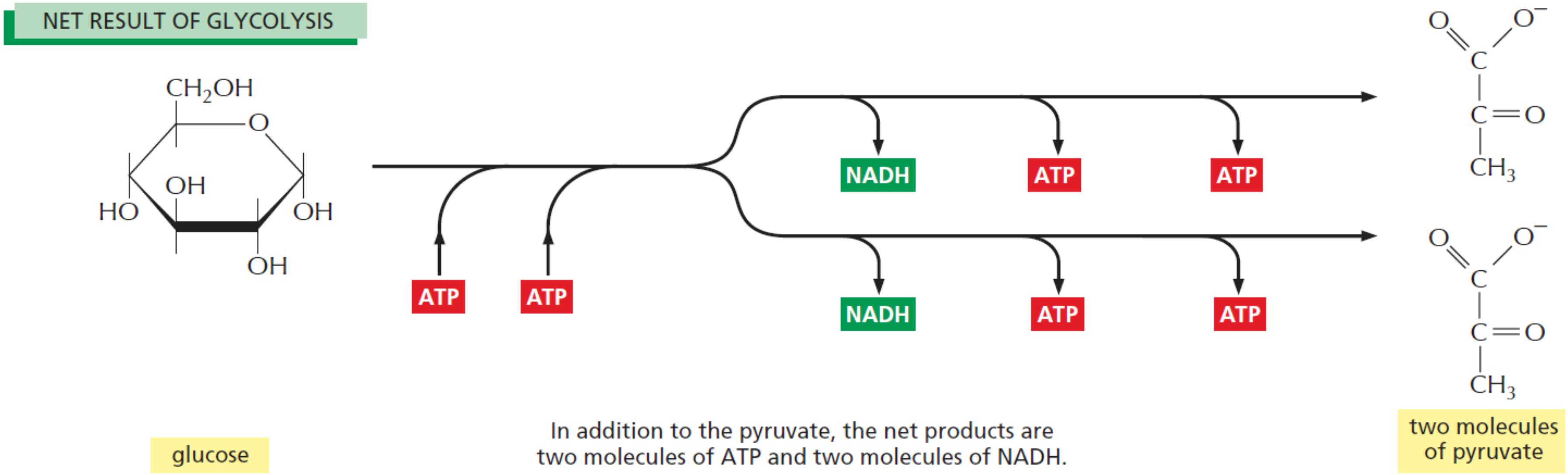
Step 9 The removal of water from 2-phosphoglycerate creates a high-energy enol phosphate linkage.



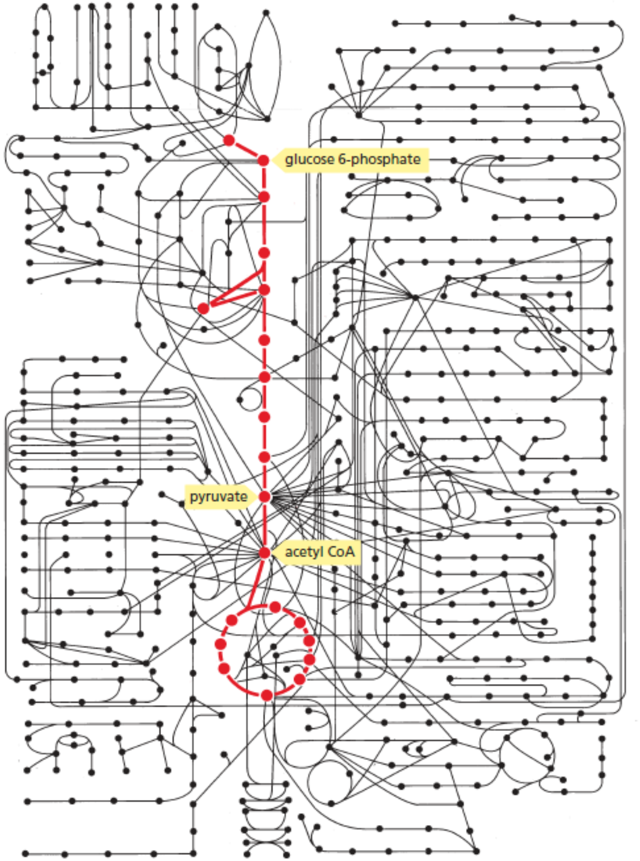
Step 10 The transfer to ADP of the high-energy phosphate group that was generated in step 9 forms ATP, completing glycolysis.



Glycolysis steps



Regulation of Glycolysis



- For all these pathways to work together smoothly, as is required to allow the cell to survive and to respond to its environment, the choice of which pathway each metabolite will follow must be carefully regulated at every branch point.
- A cell must decide whether to route key metabolites into anabolic or catabolic pathways—in other words, whether to use them to build other molecules or burn them to provide immediate energy.

Regulation of Glycolysis

The same substrate is often a part of many different pathways.

For example,

(i) The pyruvate dehydrogenase complex converts pyruvate to acetyl CoA.

(ii) During fermentation, lactate dehydrogenase converts it to lactate.

(iii) A third enzyme converts pyruvate to oxaloacetate.

(iv) It is also used for the synthesis of amino acid alanine.

An elaborate network of control mechanisms regulates and coordinates the activity of the enzymes that catalyze the myriad metabolic reactions that go on in a cell.

Activity of enzymes can be controlled by covalent modification—such as the addition or removal of a phosphate group, and by the binding of small regulatory molecules, often a metabolite.

Regulation of Glycolysis

- Both types of regulation—positive and negative—control the activity of key enzymes involved in the breakdown and synthesis of glucose.
- Animals need an ample supply of glucose. Active muscles need glucose to power their contraction, and brain cells depend almost completely on glucose for energy. During periods of fasting or intense physical exercise, the body's glucose reserves get used up faster than they can be replenished from food. One way to increase available glucose is to synthesize it from pyruvate by a process called gluconeogenesis.
- Gluconeogenesis makes use of many of the same enzymes as glycolysis. It simply runs them in reverse. For example, the isomerase that converts glucose 6-phosphate to fructose 6-phosphate in step 2 of glycolysis will readily catalyze the reverse reaction.
- Three steps in glycolysis that so strongly favor the direction of glucose breakdown that they are effectively irreversible.

Regulation of Glycolysis

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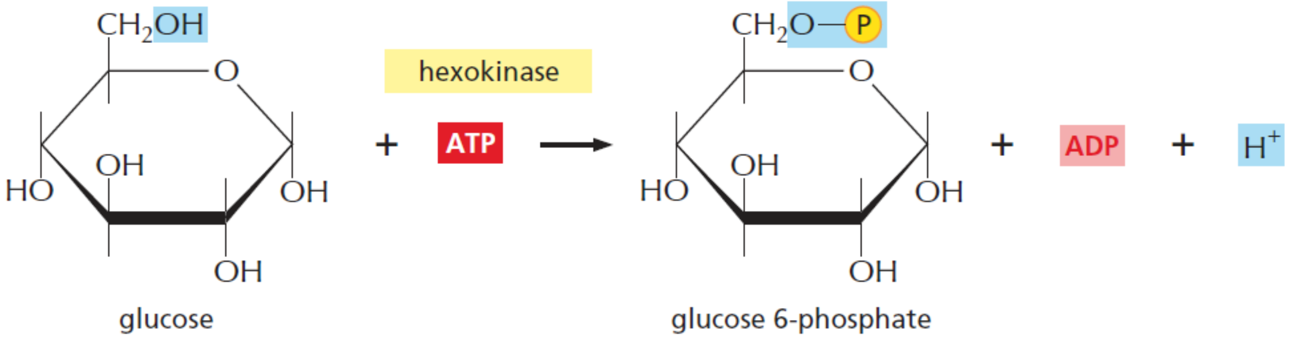

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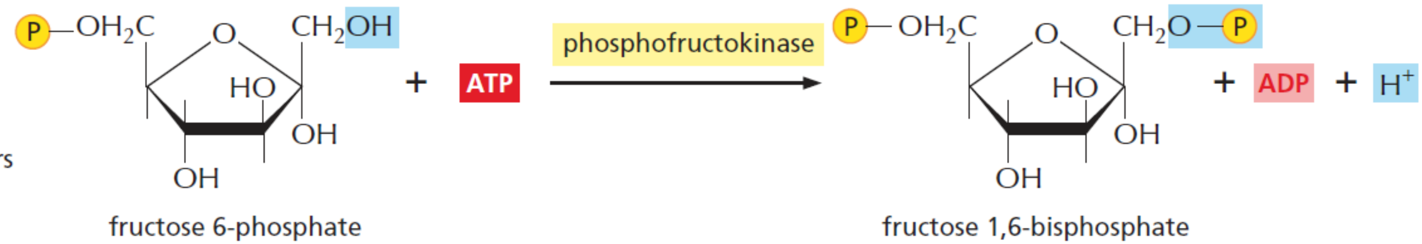

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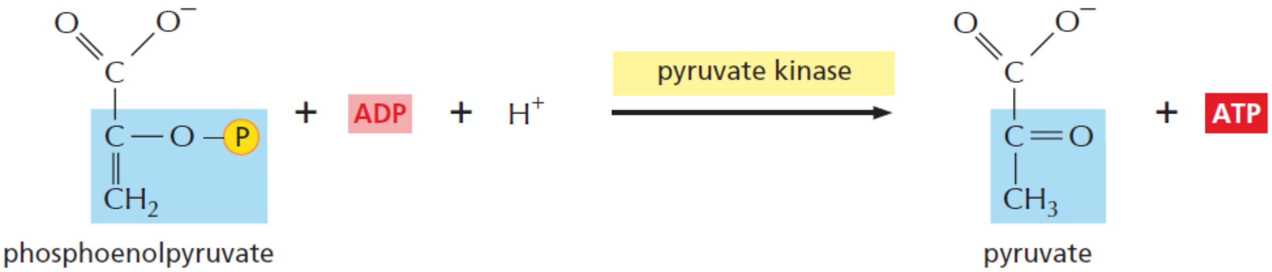
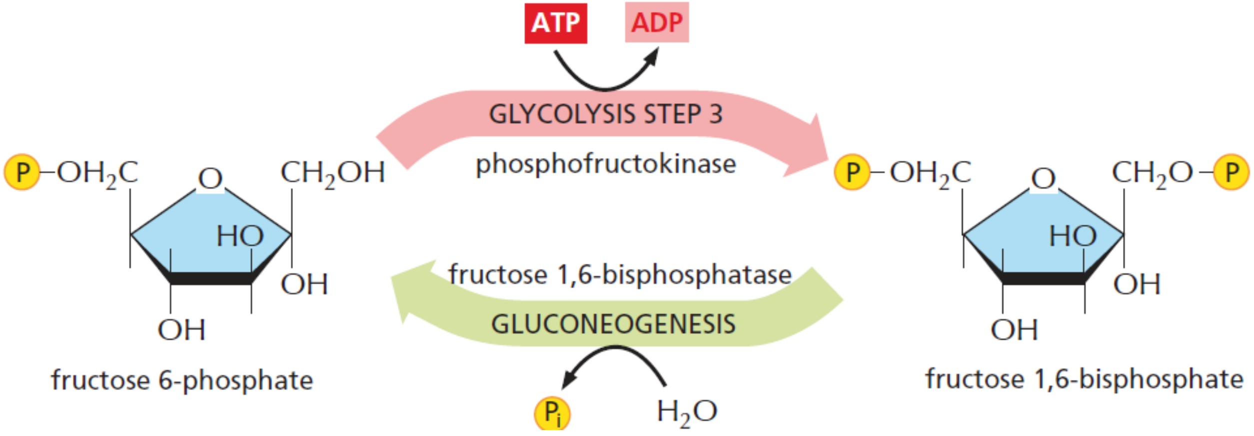


To get around these one-way steps, gluconeogenesis uses a special set of enzymes to catalyze a set of bypass reactions.



Regulation of Glycolysis

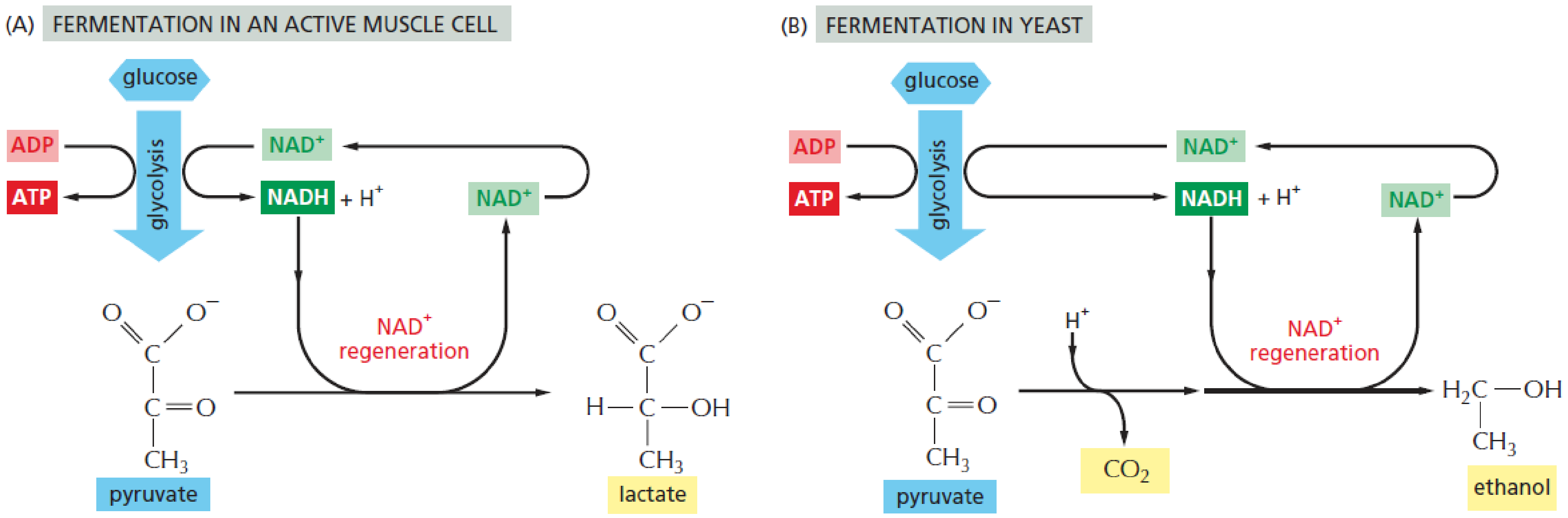
- The activity of the enzyme phosphofructokinase is allosterically regulated by the binding of a variety of metabolites, which provide both positive and negative feedback regulation.
- The enzyme is activated by byproducts of ATP hydrolysis—including ADP, AMP, and inorganic phosphate—and it is inhibited by ATP.
- When ATP is depleted and its metabolic byproducts accumulate, phosphofructokinase is turned on and glycolysis proceeds to generate ATP; when ATP is abundant, the enzyme is turned off and glycolysis shuts down.
- The enzyme that catalyzes the reverse reaction, fructose 1, 6–bisphosphatase, is regulated by the same molecules but in the opposite direction. Thus, this enzyme is activated when phosphofructokinase is turned off, allowing gluconeogenesis to proceed.
- Production of a single molecule of glucose by gluconeogenesis consumes four molecules of ATP and two molecules of GTP. Thus, a cell must tightly regulate the balance between glycolysis and gluconeogenesis.

Fermentations can produce ATP in the absence of oxygen

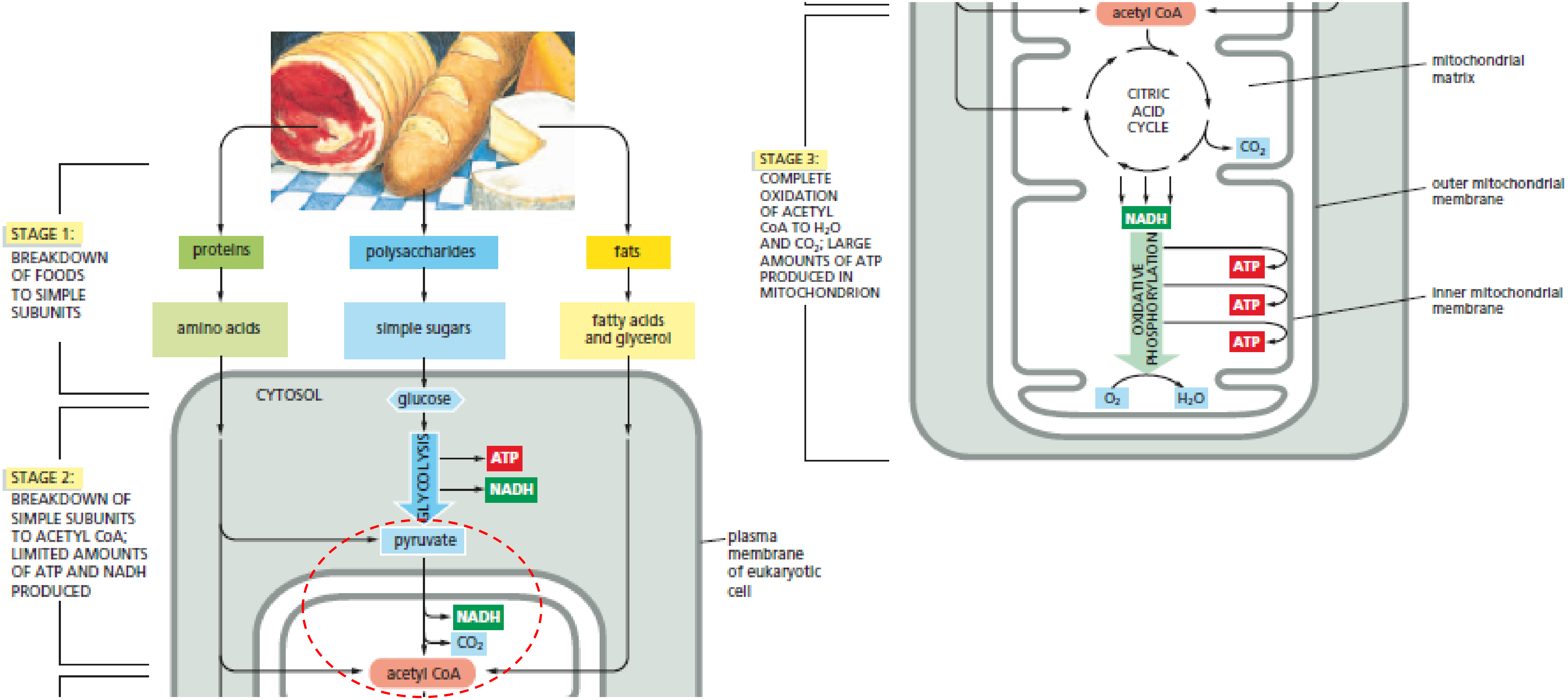
- Over the course of glycolysis, two molecules of NADH are formed per molecule of glucose.
- In aerobic organisms, these NADH molecules donate their electrons to the electron-transport chain in the inner mitochondrial membrane. Such electron transfers release energy as the electrons fall from a state of higher energy to a lower one.
- The electrons that are passed along the electron-transport chain are ultimately passed on to O_2, forming water. In giving up its electrons, NADH is converted back into NAD^+, which is then available to be used again for glycolysis. In the absence of oxygen, NAD^+ can be regenerated by an alternate type of energy-yielding reaction called a fermentation.

Fermentations can produce ATP in the absence of oxygen

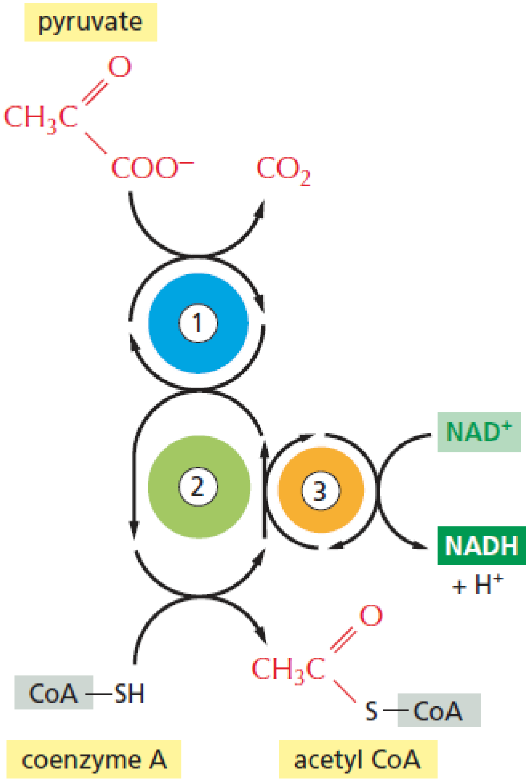
For many anaerobic microorganisms, which can grow and divide in the absence of oxygen, glycolysis is the principal source of ATP. The same is true for certain animal cells, such as skeletal muscle cells, which can continue to function at low levels of oxygen.



Food molecules are broken down in three stages

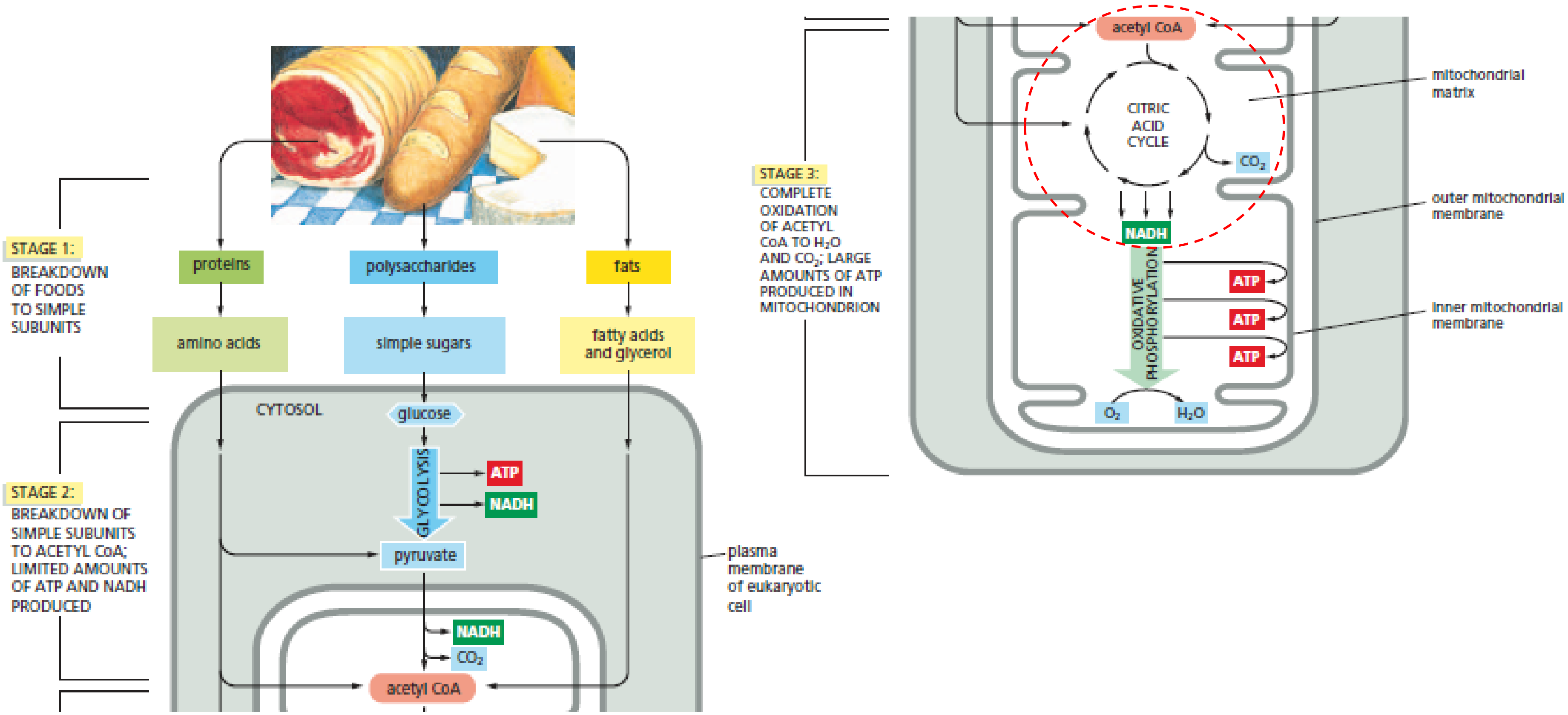


Pyruvate is converted to acetyl COA in the mitochondria



- In aerobic metabolism in eukaryotic cells, the pyruvate produced by glycolysis is actively pumped into the mitochondrial matrix.
- There, it is rapidly decarboxylated by a giant complex of three enzymes, called the pyruvate dehydrogenase complex [pyruvate dehydrogenase (1), dihydrolipoyl transacetylase (2), and dihydrolipoyl dehydrogenase (3)].
- The products of pyruvate decarboxylation are CO_2 (a waste product), NADH, and acetyl CoA.
- Fat is a major source of energy for most non-photosynthetic organisms, including humans. Like the pyruvate derived from glycolysis, the fatty acids derived from fat are also converted into acetyl CoA in the mitochondrial matrix.

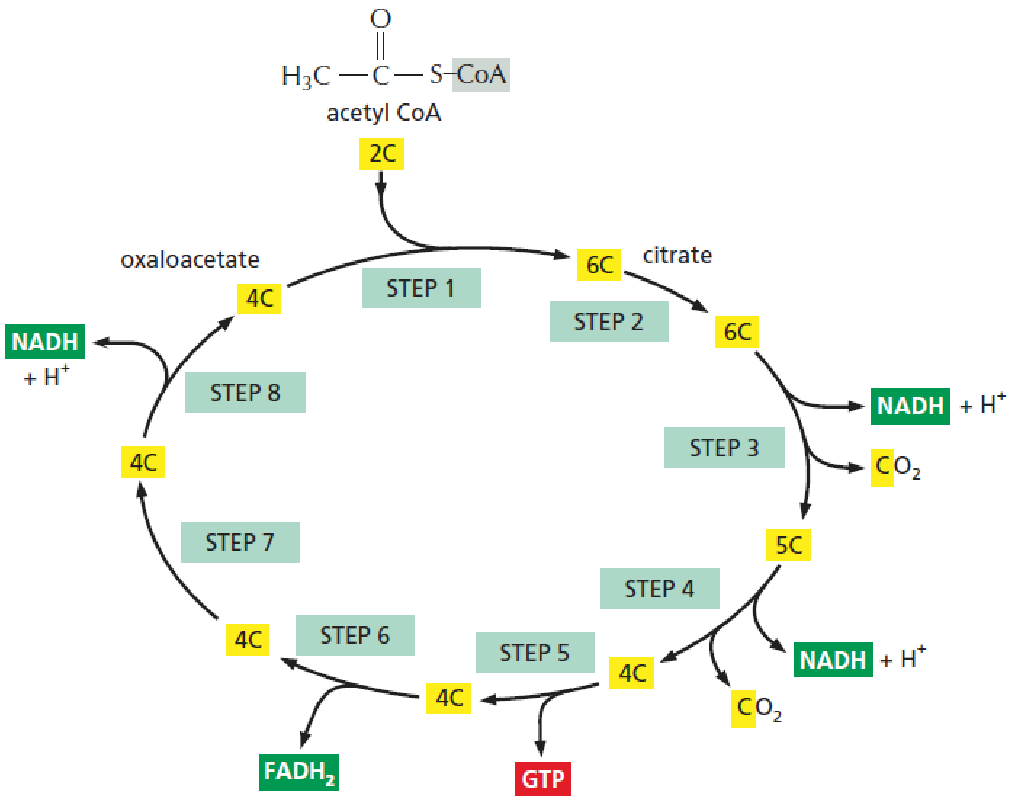
Food molecules are broken down in three stages



The Citric Acid Cycle

- Catabolism does not end with the production of acetyl CoA.
- In the process of converting food molecules to acetyl CoA, only a small part of their stored energy is extracted and converted into ATP, NADH, or $FADH_2$. Most of that energy is still locked up in acetyl CoA.
- The next stage in cell respiration is the citric acid cycle, in which the acetyl group in acetyl CoA is oxidized to CO_2 and H_2O in the mitochondrial matrix.
- Citric acid cycle is also called the tricarboxylic acid cycle or the Krebs cycle.
- The citric acid cycle catalyzes the complete oxidation of the carbon atoms of the acetyl groups in acetyl CoA, converting them into CO_2. The acetyl group is not oxidized directly, however. Instead, it is transferred from acetyl CoA to a larger four-carbon molecule, oxaloacetate, to form the six-carbon tricarboxylic acid, citric acid. The citric acid molecule (also called citrate) is then progressively oxidized, and the energy of this oxidation is harnessed to produce activated carriers. The chain of eight reactions forms a cycle, because the oxaloacetate that began the process is regenerated at the end.

The Citric Acid Cycle



NET RESULT: ONE TURN OF THE CYCLE PRODUCES THREE NADH, ONE GTP, AND ONE $FADH_2$, AND RELEASES TWO MOLECULES OF CO_2

In addition to three molecules of NADH, each turn of the cycle also produces one molecule of $FADH_2$ (reduced flavin adenine dinucleotide) from FAD and one molecule of the ribonucleoside triphosphate GTP (guanosine triphosphate) from GDP.

GTP is a close relative of ATP, and the transfer of its terminal phosphate group to ADP produces one ATP molecule in each cycle. Like NADH, $FADH_2$ is a carrier of high-energy electrons and hydrogen.