Summary of chapter 16 (p.449-488)

Glycolysis is the sequence of reactions that metabolizes one molecule of glucose to two molecules of pyruvate with the concomitant net production of two molecules of ATP. This process is anaerobic (i.e., it does not require O_2) because it evolved before substantial amounts of oxygen accumulated in the atmosphere. Pyruvate can be further processed anaerobically to lactate (*lactic acid fermentation*) or ethanol (*alcoholic fermentation*). Under aerobic conditions, pyruvate can be completely oxidized to CO_2, generating much more ATP. Because glucose is such a precious fuel, metabolic products, such as
pyruvate and lactate, are salvaged to synthesize glucose in the process of *gluconeogenesis.* Although glycolysis and gluconeogenesis have some enzymes in common, the two pathways are not simply the reverse of each other. In particular, the highly exergonic, irreversible steps of glycolysis are
bypassed in gluconeogenesis. The two pathways are reciprocally regulated so that glycolysis and gluconeogenesis do not take place simultaneously in the same cell to a significant extent.

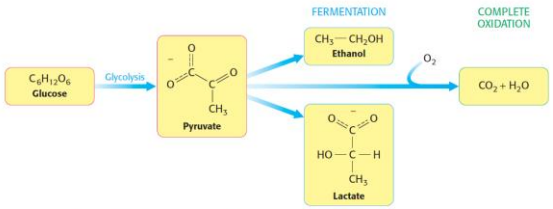


Figure 16.1 Some fates of glucose.

Glucose is a common and important fuel. In mammals, glucose is the only fuel that the brain uses under nonstarvation conditions and the only fuel that red blood cells can use at all.
Why is glucose instead of some other monosaccharide such a prominent fuel? We can speculate on the reasons. First, glucose is one of several monosaccharides formed from formaldehyde under prebiotic conditions, and so it may have been available as a fuel source for primitive biochemical systems. Second, glucose has a low tendency, relative to other monosaccharides, to nonenzymatically glycosylate proteins. In their open-chain forms, monosaccharides contain carbonyl groups that can react with the amino groups of proteins to form Schiff bases, which rearrange to form a more stable amino–ketone linkage. Such nonspecifically modified proteins often do not function effectively. Glucose has a strong tendency to exist in the ring conformation and, consequently, relatively little tendency to modify proteins. Recall that all the hydroxyl groups in the ring conformation of b-glucose are equatorial, contributing to the sugar's high relative stability.
We now begin our consideration of the glycolytic pathway. This pathway is common to virtually all cells, both prokaryotic and eukaryotic. In eukaryotic cells, glycolysis takes place in the cytoplasm.

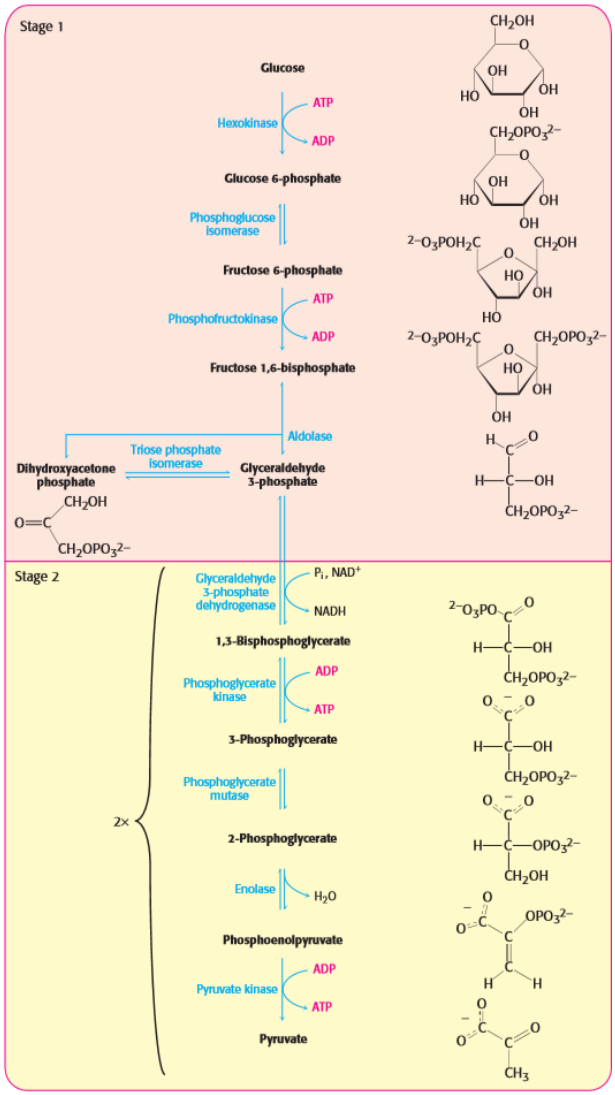
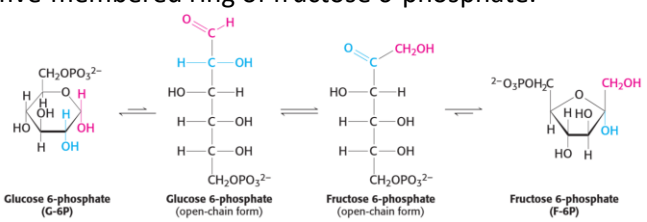


Figure 16.2 Stages of glycolysis. The glycolytic pathway can be divided into two stages: (1) glucose is trapped, destabilized, and cleaved into two interconvertible three-carbon molecules generated by cleavage of six-carbon fructose; and (2) ATP is generated.

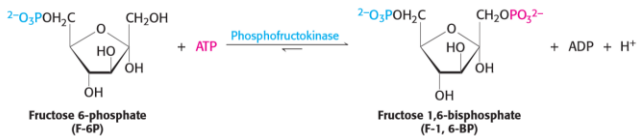
Stage 1 is the trapping and preparation phase. No ATP is generated in this stage. Stage 1 begins with the conversion of glucose into fructose 1,6-bisphosphate, which consists of three steps: a phosphorylation, an isomerization, and a second phosphorylation reaction. The strategy of these initial steps in glycolysis is to trap the glucose in the cell and form a compound that can be readily cleaved into phosphorylated three-carbon units. Stage 1 is completed with the cleavage of the fructose 1,6-bisphosphate into two three-carbon fragments. These resulting three-carbon units are readily interconvertible. In stage 2, ATP is harvested when the three-carbon fragments are oxidized to pyruvate.

Hexokinase traps glucose in the cell and begins glycolysis: Glucose enters cells through specific transport proteins (p. 477) and has one principal fate: it is phosphorylated by ATP to form glucose 6-phosphate. This step is notable for two reasons: (1) glucose 6-phosphate cannot pass through the membrane because it is not a substrate for the glucose transporters, and (2) the addition of the phosphoryl group acts to destabilize glucose, thus facilitating its further metabolism. The transfer of the phosphoryl group from ATP to the hydroxyl group on carbon 6 of glucose is catalyzed by hexokinase. Kinases are enzymes that catalyze the transfer of a phosphoryl group from ATP to an acceptor. Hexokinase, like adenylate kinase (Section 9.4) and all other kinases, requires Mg2+ (or another divalent metal ion such as Mn2+) for activity. The divalent metal ion forms a complex with ATP. The binding of glucose induces a large conformational change in the enzyme. Hexokinase consists of two lobes, which move toward each other when glucose is bound. The cleft between the lobes closes, and the bound glucose becomes surrounded by protein, except for the hydroxyl group of carbon 6, which will accept the phosphoryl group from ATP. The glucose-induced structural changes are significant in two respects. First, the environment around the glucose becomes more nonpolar, which favors reaction between the hydrophilic hydroxyl group of glucose and the terminal phosphoryl group of ATP. Second, the conformational changes enable the kinase to discriminate against H2O as a substrate. The closing of the cleft keeps water molecules away from the active site. If hexokinase were rigid, a molecule of H2O occupying the binding site for the OCH2OH of glucose could attack the ɣ phosphoryl group of ATP, forming ADP and P_i. Substrate-induced cleft closing is a general feature of kinases.

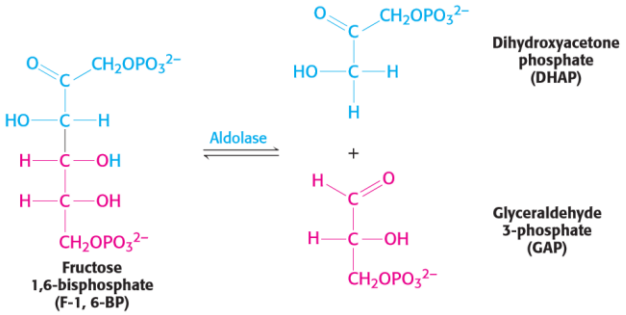
Fructose 1,6-bisphosphate is generated from glucose 6-phosphate. The enzyme must first open the six-membered ring of glucose 6-phosphate, catalyze the isomerization, and then promote the formation of the five-membered ring of fructose 6-phosphate.



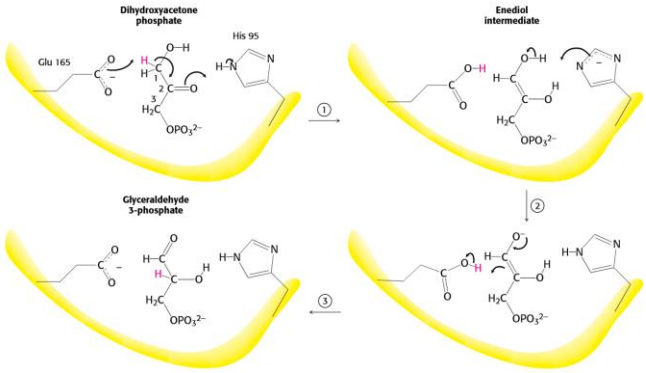
A second phosphorylation reaction follows the isomerization step. Fructose 6-phosphate is phosphorylated at the expense of ATP to fructose 1,6-bisphosphate. This reaction is catalyzed by phosphofructokinase (PFK), an **allosteric** enzyme that sets the pace of glycolysis. As we will learn, this enzyme plays a central role in the metabolism of many molecules in all parts of the body.



The newly formed fructose 1,6-bisphosphate is cleaved into glyceraldehyde 3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), completing stage 1 of glycolysis



Glyceraldehyde 3-phosphate is on the direct pathway of glycolysis, whereas dihydroxyacetone phosphate is not. These compounds are isomers that can be readily interconverted. At equilibrium, 96% of the triose phosphate is dihydroxyacetone phosphate. However, the reaction proceeds readily from dihydroxyacetone phosphate to glyceraldehyde 3-phosphate because the subsequent reactions of glycolysis remove this product.



We come now to the second stage of glycolysis, a series of steps that harvest some of the energy contained in glyceraldehyde 3-phosphate as ATP. The initial reaction in this sequence is the conversion of glyceraldehyde 3-phosphate into 1,3-bisphosphoglycerate (1,3-BPG), a reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase. 1,3-Bisphosphoglycerate is an acyl phosphate, which is a mixed anhydride of phosphoric

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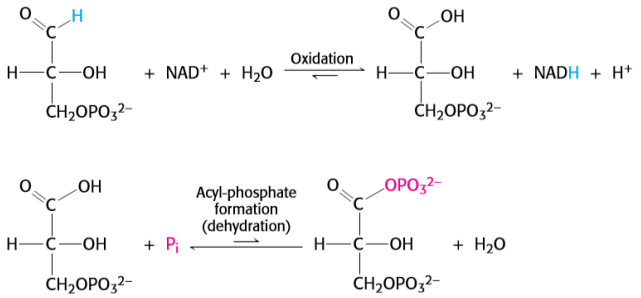
acid and a carboxylic acid. Such compounds have a high phosphoryl-transfer potential; one of its phosphoryl groups is transferred to ADP in the next step in glycolysis.



The first reaction is thermodynamically quite favorable, with a standard free-energy change, ΔG of approximately -50 kJ /mol whereas the second reaction is quite unfavorable.

These two processes must be coupled so that the favorable aldehyde oxidation can be used to drive the formation of the acyl phosphate. How are these reactions coupled? The key is an intermediate, formed as a result of the aldehyde oxidation, that is linked to the enzyme by a thioester bond. The thioester intermediate is higher in free energy than the free carboxylic acid is. The favorable oxidation and unfavorable phosphorylation reactions are coupled by the thioester intermediate, which preserves much of the free energy released in the oxidation reaction. This thioester intermediate has a free energy close to that of the reactants.

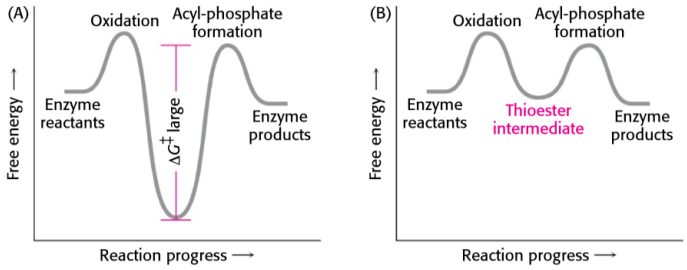


FIGURE 16.6 Free-energy profiles for glyceraldehyde oxidation followed by acyl-phosphate formation. (A) A hypothetical case with no coupling between the two processes. The second step must have a large activation barrier, making the reaction very slow. (B) The actual case with the two reactions coupled through a thioester intermediate.

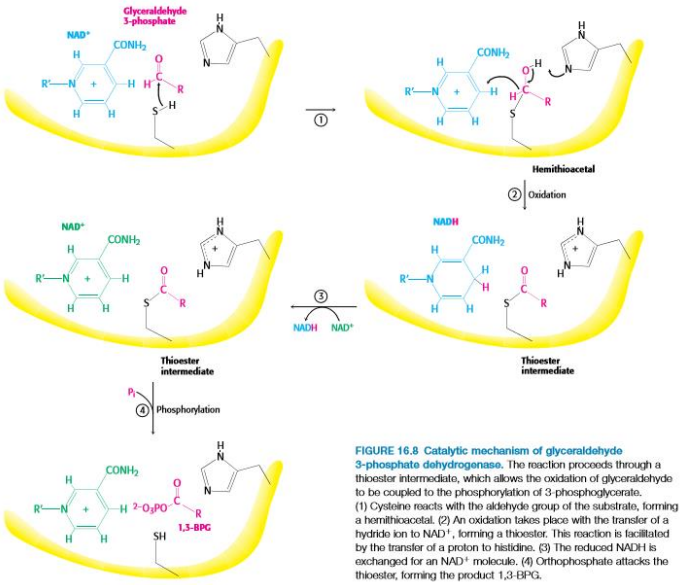
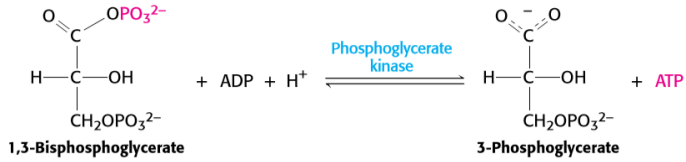
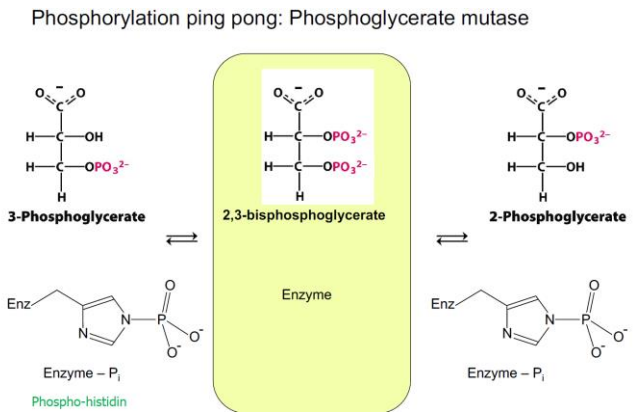


FIGURE 16.8 Catalytic mechanism of glyceraldehyde 3-phosphate dehydrogenase. The reaction proceeds through a thioester intermediate, which allows the oxidation of glyceraldehyde to be coupled to the phosphorylation of 3-phosphoglycerate. (1) Cysteine reacts with the aldehyde group of the substrate, forming a hemithioacetal. (2) An oxidation takes place with the transfer of a hydride ion to NAD^+, forming a thioester. This reaction is facilitated by the transfer of a proton to histidine. (3) The reduced NADH is exchanged for an NAD^+ molecule. (4) Orthophosphate attacks the thioester, forming the product 1,3-BPG.

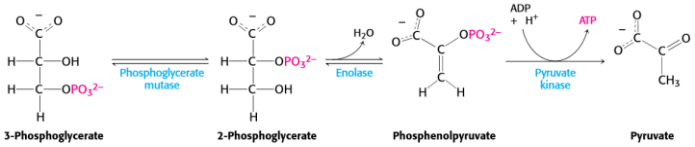
1 ,3-Bisphosphoglycerate is an energy-rich molecule with a greater phosphoryl-transfer potential than that of ATP (Section 15.2). Thus, 1,3BPG can be used to power the synthesis of ATP from ADP.





the formation of ATP in this manner is referred to as substrate-level phosphorylation.

In the remaining steps of glycolysis, 3-phosphoglycerate is converted into pyruvate, and a second molecule of ATP is formed from ADP.



the high phosphoryl-transfer potential of phosphoenolpyruvate arises primarily from the large driving force of the subsequent enol–ketone conversion. Hence, pyruvate is formed, and ATP is

generated concomitantly. The virtually irreversible transfer of a phosphoryl group from phosphoenolpyruvate to ADP is catalyzed by pyruvate kinase.

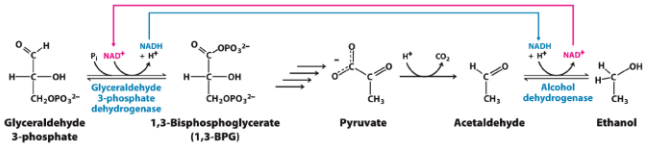
Two ATP molecules are formed in the conversion of glucose into pyruvate

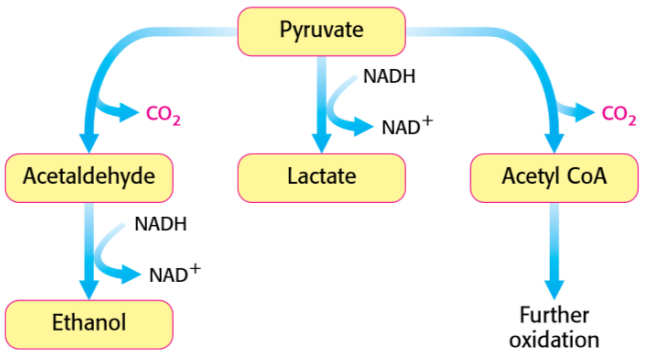
The net reaction in the transformation of glucose into pyruvate is

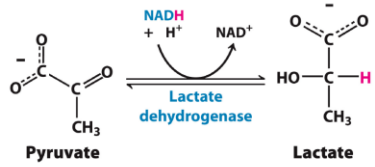
$$\text{Glucose} + 2\,P_i + 2\,ADP + 2\,NAD^+ \rightarrow 2\,\text{pyruvate} + 2\,ATP + 2\,NADH + 2\,H^+ + 2\,H_2O$$

Thus, *two molecules of ATP are generated in the conversion of glucose into two molecules of pyruvate.* The reactions of glycolysis are summarized in Table 16.1.

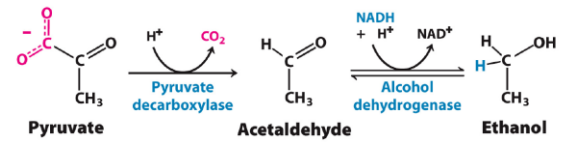
The conversion of glucose into two molecules of pyruvate has resulted in the net synthesis of ATP. However, an energy-converting pathway that stops at pyruvate will not proceed for long, because redox balance has not been maintained. Consequently, NAD^+ must be regenerated for glycolysis to proceed. Thus, the final process in the pathway is the regeneration of NAD^+ through the metabolism of pyruvate.







Lactate and ethanol are "redox-balanced" with glucose.



Fructose is converted into glycolytic intermediates by fructokinase

Although glucose is the most widely used monosaccharide, others also are important fuels. Let us consider how fructose is funneled into the glycolytic pathway (Figure 16.13). There are no catabolic pathways for metabolizing fructose, and so the strategy is to convert this sugar into a metabolite of Glucose.

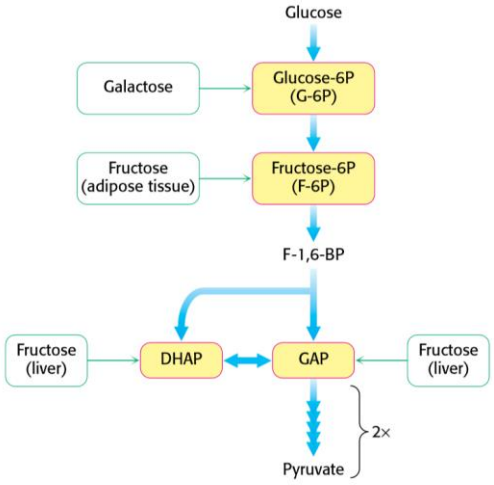
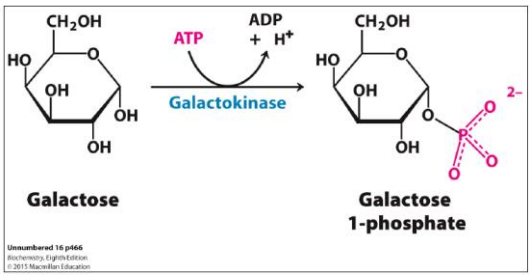
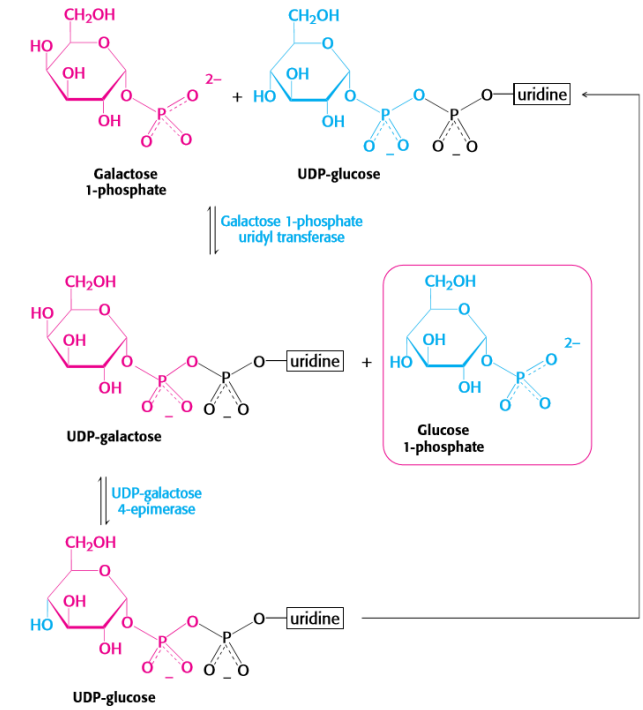


FIGURE 16.13 Entry points in glycolysis for fructose and galactose.

Galactose is converted into glucose 6-phosphate

Like fructose, galactose is an abundant sugar that must be converted into metabolites of glucose.





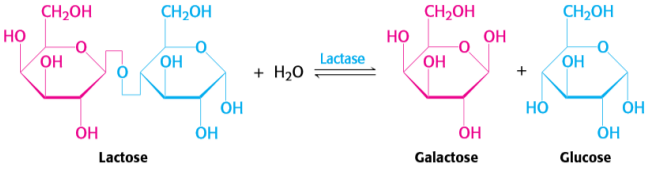
$$\text{Galactose} + ATP \rightarrow \text{glucose 1-phosphate} + ADP + H^+$$

Phosphoglucomutase

$$\text{Glucose 1-phosphate} \rightleftharpoons \text{glucose 6-phosphate}$$

Many adults are intolerant of milk because they are deficient in lactase

Many adults are unable to metabolize the milk sugar lactose and experience gastrointestinal disturbances if they drink milk. Lactose intolerance, or hypolactasia, is most commonly caused by a deficiency of the enzyme lactase, which cleaves lactose into glucose and galactose.



16.2 The Glycolytic Pathway Is Tightly Controlled

The glycolytic pathway has a dual role: it degrades glucose to generate ATP and it provides building blocks for biosynthetic reactions. The rate of conversion of glucose into pyruvate is regulated to meet these two major cellular needs. In metabolic pathways, enzymes catalyzing essentially irreversible reactions are potential sites of control. In glycolysis, the reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase are virtually irreversible, and each of them serves as a control site.

Phosphofructokinase is the most important control site in the mammalian glycolytic pathway (Figure 16.16). High levels of ATP allosterically inhibit the enzyme. ATP binds to a specific regulatory site that is distinct from the catalytic site. The binding of ATP lowers the enzyme's affinity for fructose 6-phosphate. Thus, a high concentration of ATP converts the hyperbolic binding curve of fructose 6-phosphate into a sigmoidal one (Figure 16.17). AMP reverses the inhibitory action of ATP, and so the activity of the enzyme increases when the ATP/AMP ratio is lowered. In other words, glycolysis is stimulated as the energy charge falls. A decrease in pH also inhibits phosphofructokinase activity by augmenting the inhibitory effect of ATP.

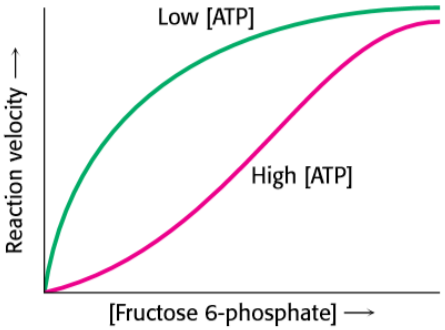


FIGURE 16.17 Allosteric regulation of phosphofructokinase. A high level of ATP inhibits the enzyme by decreasing its affinity for fructose 6-phosphate.

Why is AMP and not ADP the positive regulator of phosphofructokinase? When ATP is being utilized rapidly, the enzyme adenylate kinase (Section 9.4) can form ATP from ADP by the following reaction:

$$\text{ADP} + \text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}$$

Thus, some ATP is salvaged from ADP, and AMP becomes the signal for the low-energy state. Moreover, the use of AMP as an allosteric regulator provides an especially sensitive control. We can understand why by considering, first, that the total adenylate pool ([ATP], [ADP], [AMP]) in a cell is constant over the short term and, second, that the concentration of ATP is greater than that of ADP and the concentration of ADP is, in turn, greater than that of AMP. Consequently, small-percentage changes in [ATP] result in larger-percentage changes in the concentrations of the other adenylate nucleotides. This magnification of small changes in [ATP] to larger changes in [AMP] leads to tighter control by increasing the range of sensitivity of phosphofructokinase.

Hexokinase. Phosphofructokinase is the most prominent regulatory enzyme in glycolysis, but it is not the only one. Hexokinase, the enzyme catalyzing the first step of glycolysis, is inhibited by its product, glucose 6-phosphate. High concentrations of this molecule signal that the cell no longer requires glucose for energy or for the synthesis of glycogen, a storage form of glucose), and the glucose will be left in the blood. A rise in glucose 6-phosphate concentration is a means by which phosphofructokinase communicates with hexokinase. When phosphofructokinase is inactive, the concentration of fructose 6-phosphate rises. In turn, the level of glucose 6-phosphate rises because it is in equilibrium with fructose 6-phosphate.

Hence, the inhibition of phosphofructokinase leads to the inhibition of hexokinase.

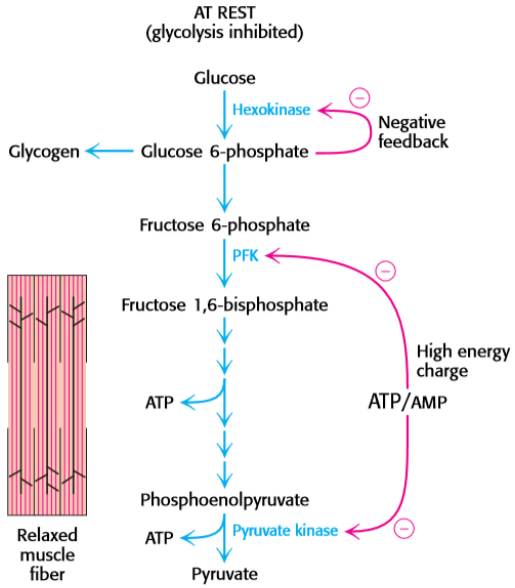
Why is phosphofructokinase rather than hexokinase the pacemaker of glycolysis? The reason becomes evident on noting that glucose 6-phosphate is not solely a glycolytic intermediate. In muscle, glucose 6-phosphate can also be converted into glycogen. The first irreversible reaction unique to the glycolytic pathway, the committed step (Section 10.1), is the phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate. Thus, it is highly appropriate for phosphofructokinase to be the primary control site in glycolysis. In general, the enzyme catalyzing the committed step in a metabolic sequence is the most important control element in the pathway

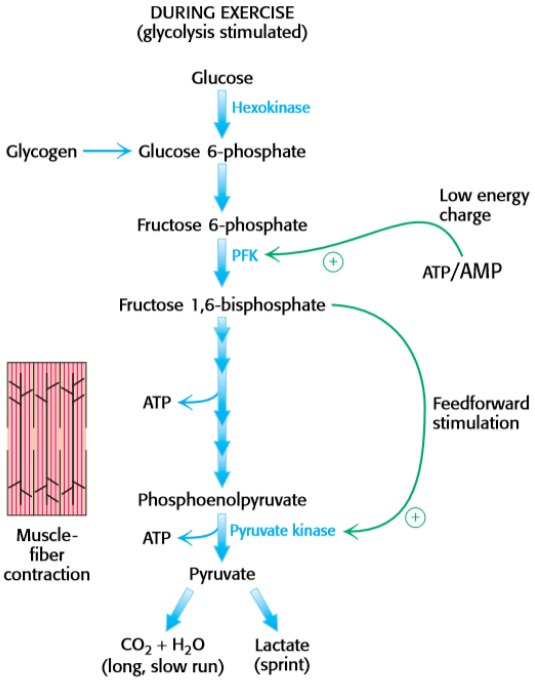
Pyruvate kinase. Pyruvate kinase, the enzyme catalyzing the third irreversible step in glycolysis, controls the outflow from this pathway. This final step yields ATP and pyruvate, a central metabolic intermediate that can be oxidized further or used as a building block. ATP allosterically inhibits pyruvate kinase to slow glycolysis when the energy charge is high. When the pace of glycolysis increases, fructose 1,6-bisphosphate, the product of the preceding irreversible step in glycolysis, activates the kinase to enable it to keep pace with the oncoming high flux of intermediates.

Phosphofructokinase:

Glycolysis in the liver furnishes carbon skeletons for biosyntheses, and so a signal indicating whether building blocks are abundant or scarce should also regulate phosphofructokinase. In the liver, phosphofructokinase is inhibited by citrate, an early intermediate in the citric acid cycle (Chapter 17). A high level of citrate in the cytoplasm means that biosynthetic precursors are abundant, and so there is no need to degrade additional glucose for this purpose. Citrate inhibits phosphofructokinase by enhancing the inhibitory effect of ATP.

The signal molecule fructose 2,6-bisphosphate (F-2,6-BP) is a potent activator of phosphofructokinase. The concentration of fructose 6-phosphate rises when blood- glucose concentration is high, and the abundance of fructose 6-phosphate accelerates the synthesis of F-2,6-BP (Figure 16.20). Hence, an abundance of fructose 6-phosphate leads to a higher concentration of F-2,6-BP. The binding of fructose 2,6-bisphosphate increases the affinity of phosphofructokinase for fructose 6-phosphate and diminishes the inhibitory effect of ATP. Glycolysis is thus accelerated when glucose is abundant. Such a process is called feedforward stimulation.





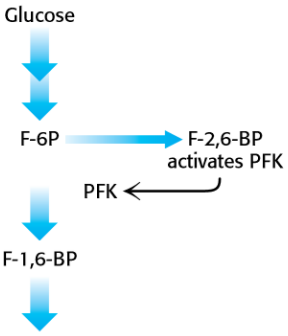


FIGURE 16.19 Regulation of phosphofructokinase by fructose 2,6-bisphosphate. In high concentrations, fructose 6-phosphate (F-6P) activates the enzyme phosphofructokinase (PFK) through an intermediary, fructose 2,6-bisphosphate (F-2,6-BP).

Gluconeogenesis:

The synthesis of glucose from noncarbohydrate precursors is a process called gluconeogenesis. Maintaining levels of glucose is important because the brain depends on glucose as its primary fuel and red blood cells use glucose as their only fuel. Gluconeogenesis is especially important during a longer period of fasting or starvation. The gluconeogenic pathway converts pyruvate into glucose. Noncarbohydrate precursors of glucose are first converted into pyruvate or enter the pathway at later intermediates such as oxaloacetate and dihydroxyacetone phosphate (Figure 16.24). The major noncarbohydrate precursors are lactate, amino acids, and glycerol. Lactate is formed by active skeletal muscle when the rate of glycolysis exceeds the rate of oxidative metabolism. Lactate is readily converted into pyruvate by the action of lactate dehydrogenase.

The major site of gluconeogenesis is the liver, with a small amount also taking place in the kidney. Little gluconeogenesis takes place in the brain, skeletal muscle, or heart muscle. Rather, gluconeogenesis in the liver and kidney helps to maintain the glucose level in the blood so that the brain and muscle can extract sufficient glucose from it to meet their metabolic demands.

Gluconeogenesis is not a reversal of glycolysis

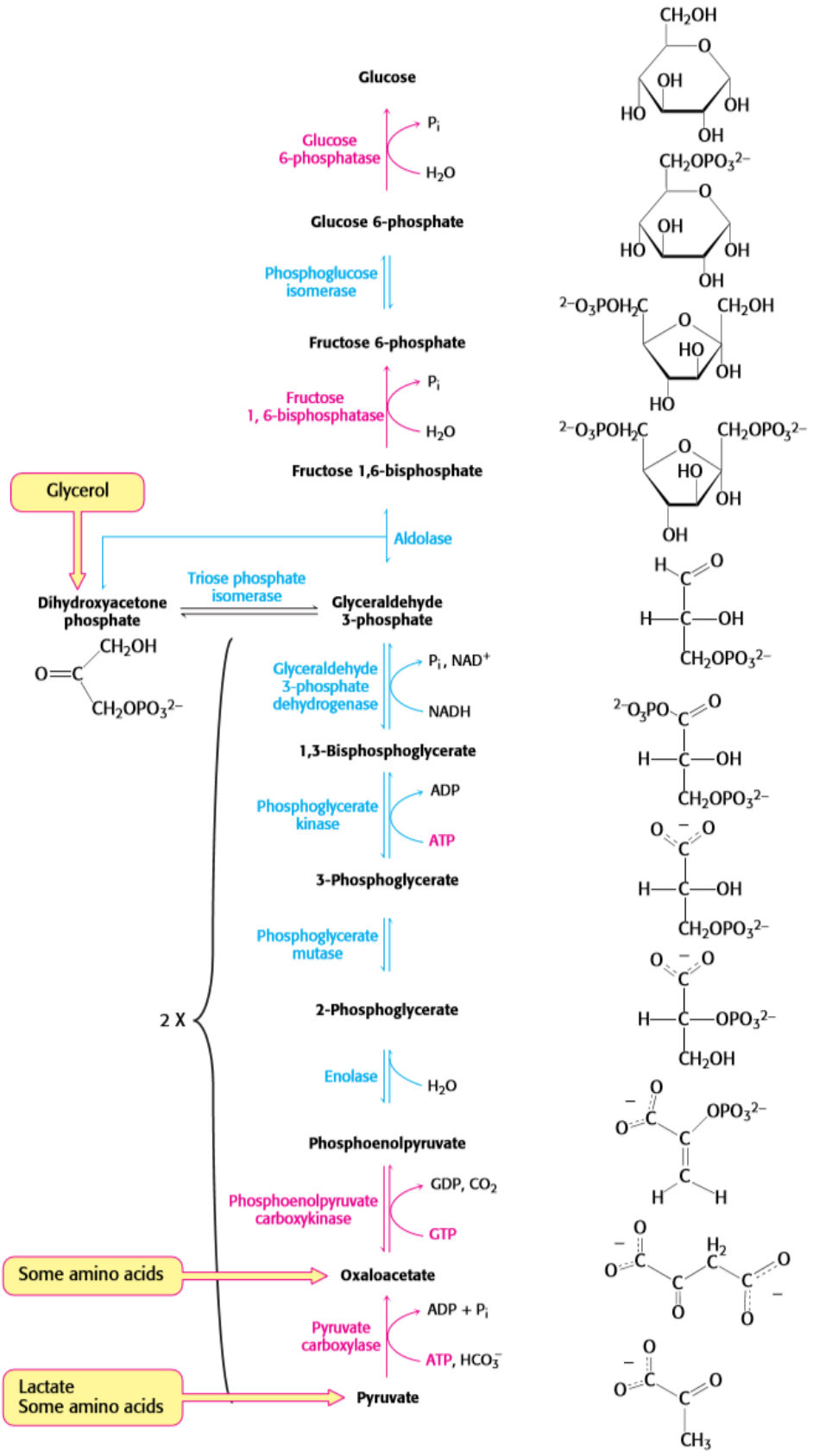


FIGURE 16.24 Pathway of gluconeogenesis. The reactions and enzymes unique to gluconeogenesis are shown in red. The other reactions are common to glycolysis. The enzymes for gluconeogenesis are located in the cytoplasm, except for pyruvate carboxylase (in the mitochondria) and glucose 6-phosphatase (membrane bound in the endoplasmic reticulum). The entry points for lactate, glycerol, and amino acids are shown.

In glycolysis, glucose is converted into pyruvate; in gluconeogenesis, pyruvate is converted into glucose. However, gluconeogenesis is not a reversal of glycolysis. Several reactions must differ because the equilibrium of glycolysis lies far on the side of pyruvate

formation. The actual free energy change for the formation of pyruvate from glucose is about -90 kJ/mol under typical cellular conditions. Most of the decrease in free energy in glycolysis takes place in the three essentially irreversible steps catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase. In gluconeogenesis, these virtually irreversible reactions of glycolysis must be bypassed.

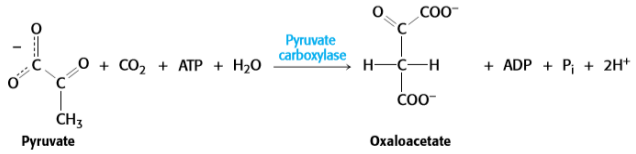
$$\text{Glucose} + \text{ATP} \xrightarrow{\text{Hexokinase}} \text{Glucose 6-phosphate} + \text{ADP}$$
$$\Delta G = -33\ \text{kJ mol}^{-1}\ (-8.0\ \text{kcal mol}^{-1})$$

$$\text{Fructose 6-phosphate} + \text{ATP} \xrightarrow{\text{Phosphofructokinase}} \text{fructose 1,6-bisphosphate} + \text{ADP}$$
$$\Delta G = -22\ \text{kJ mol}^{-1}\ (-5.3\ \text{kcal mol}^{-1})$$

$$\text{Phosphoenolpyruvate} + \text{ADP} \xrightarrow{\text{Pyruvate kinase}} \text{pyruvate} + \text{ATP}$$
$$\Delta G = -17\ \text{kJ mol}^{-1}\ (-4.0\ \text{kcal mol}^{-1})$$

The conversion of pyruvate into phosphoenol-pyruvate begins with the formation of oxaloacetate

he first step in gluconeogenesis is the carboxylation of pyruvate to form oxaloacetate at the expense of a molecule of ATP, a reaction catalyzed by pyruvate carboxylase. This reaction occurs in the mitochondria.



Pyruvate carboxylase requires biotin, a covalently attached prosthetic group, which serves as the carrier of activated CO_2.

Oxalacetate must be transported to the cytoplasm to complete the synthesis of phosphoenolpyruvate. However since oxaloacetate can't leave the mitochondrium, it is first reduced to malate.

Malate is transported across the mitochondrial membrane and reoxidized to oxaloacetate by a cytoplasmic NAD^+ linked malate dehydrogenase.

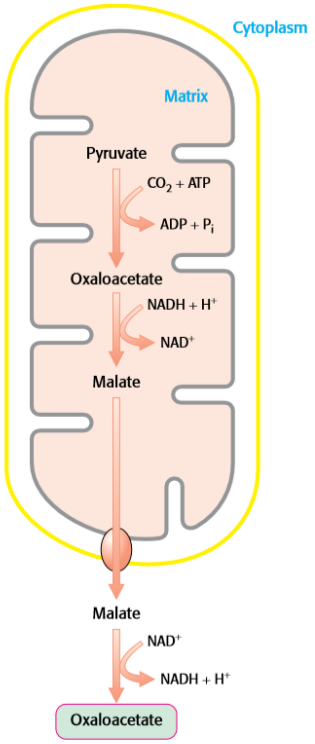
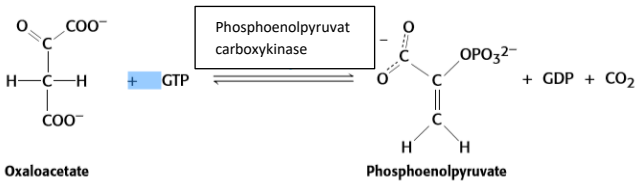


FIGURE 16.27 Compartmental cooperation. Oxaloacetate used in the cytoplasm for gluconeogenesis is formed in the mitochondrial matrix by the carboxylation of pyruvate. Oxaloacetate leaves the mitochondrion by a specific transport system (not shown) in the form of malate, which is reoxidized to oxaloacetate in the cytoplasm.

oxaloacetate is simultaneously decarboxylated and phosphorylated by phosphoenolpyruvate carboxykinase (PEPCK) to generate phosphoenolpyruvate. The phosphoryl donor is GTP. <u>The CO_2 that was added to pyruvate by pyruvate carboxylase comes off in this step</u> *(Prof. Locher/Stryer asked question about where a radioactively marked $C(O_2)$ will be found after gluconeogenesis → not at all, the $C(O_2)$ is removed again and doesn't appear in glucose).*



The sum of the reactions catalyzed by pyruvate carboxylase and phosphoenolpyruvate carboxykinase is

$$\text{Pyruvate} + \text{ATP} + \text{GTP} + \text{H}_2\text{O} \longrightarrow \text{phosphoenolpyruvate} + \text{ADP} + \text{GDP} + \text{P}_i + 2\,\text{H}^+$$

This pair of reactions bypasses the irreversible reaction catalyzed by pyruvate kinase in glycolysis.

Why is a carboxylation and a decarboxylation required to form phosphoenolpyruvate from pyruvate? Recall that, in glycolysis, the presence of a phosphoryl group traps the unstable enol isomer of pyruvate as phosphoenolpyruvate (p. 461). However, the addition of a phosphoryl group to pyruvate is a highly unfavorable reaction: In gluconeogenesis, the use of the carboxylation and decarboxylation steps results

in a much more favorable deltaG°'. Decarboxylations often drive reactions that are otherwise highly endergonic. This metabolic motif is used in the citric acid cycle (Chapter 17), the pentose phosphate pathway (Chapter 20), and fatty acid synthesis (Section 22.4).

The conversion of fructose 1,6-bisphosphate into fructose 6-phosphate and orthophosphate is an irreversible step

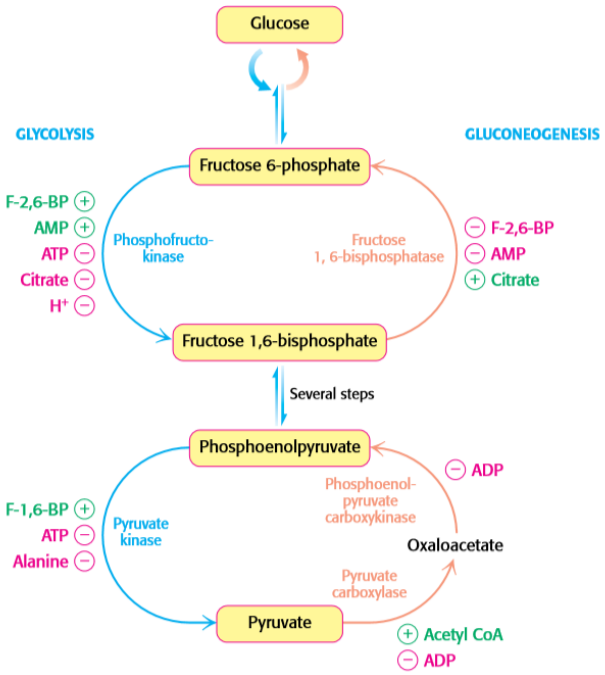
On formation, phosphoenolpyruvate is metabolized by the enzymes of glycolysis but in the reverse direction. These reactions are near equilibrium under intracellular conditions; so, when conditions favor gluconeogenesis, the reverse reactions will take place until the next **irreversible step** is reached. This step is the **hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate and P_i**.

The generation of free glucose is an important control point.

The fructose 6-phosphate generated by fructose 1,6-bisphosphatase is readily converted into glucose 6-phosphate. In most tissues, gluconeogenesis ends here. Free glucose is not generated; rather, the glucose 6-phosphate is processed in some other fashion, notably to form glycogen. One advantage to ending gluconeogenesis at glucose 6-phosphate is that, unlike free glucose, the molecule is not transported out of the cell. The enzyme responsible for the conversion of glucose 6-phosphate into glucose, glucose 6-phosphatase, is present only in tissues whose metabolic duty is to maintain blood-glucose homeostasis—tissues that release glucose into the blood. These tissues are the liver and to a lesser extent the kidney.

Gluconeogenesis and Glycolysis Are Reciprocally Regulated

Gluconeogenesis and glycolysis are coordinated so that, within a cell, one pathway is relatively inactive while the other is highly active.



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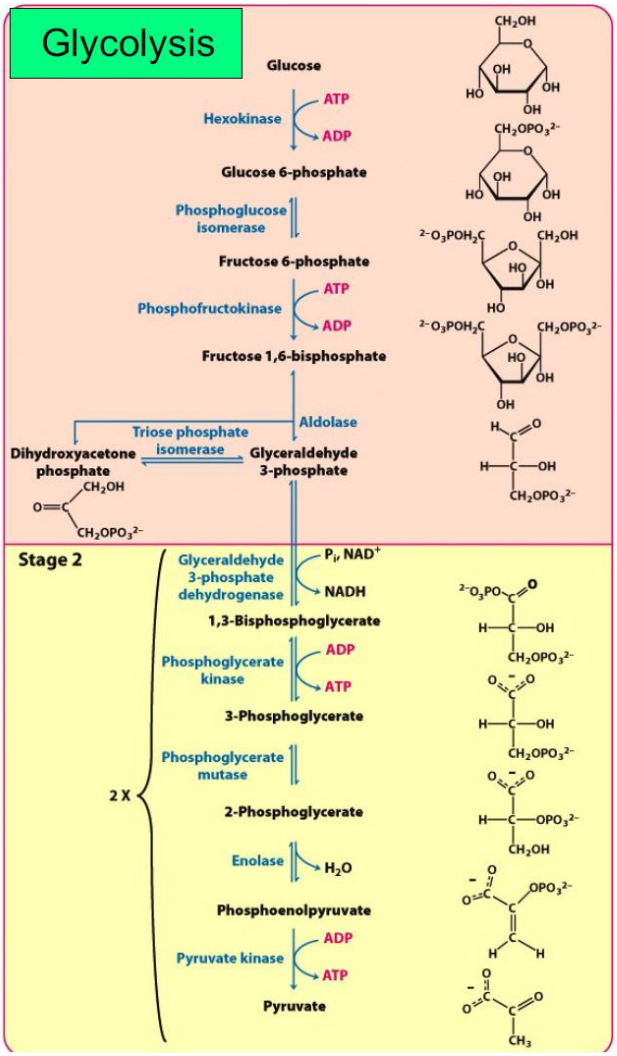

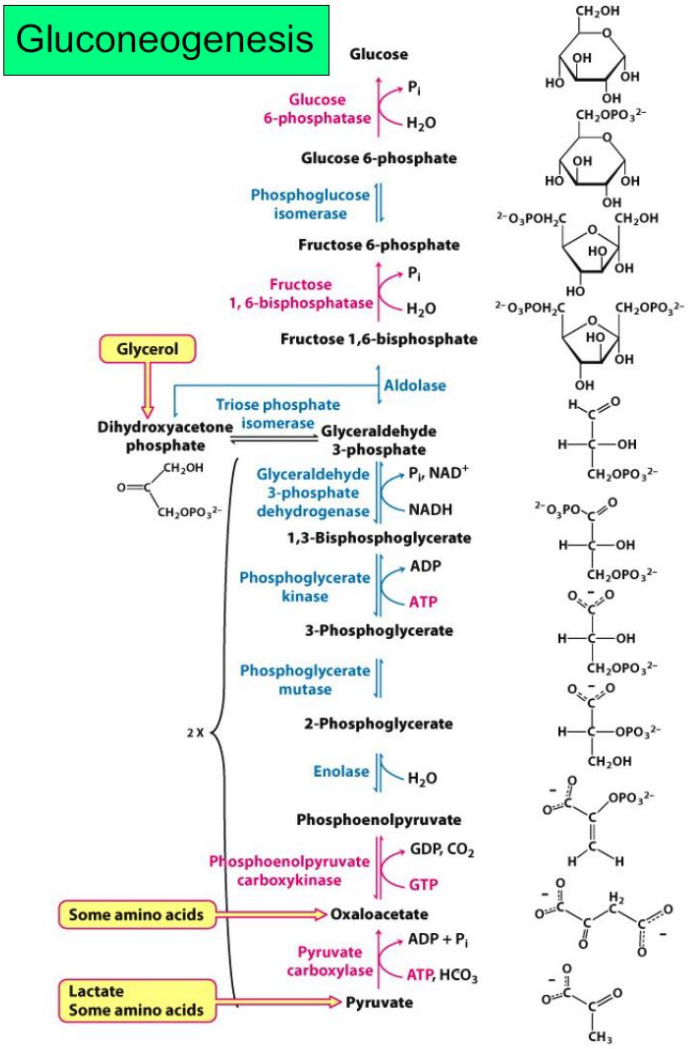

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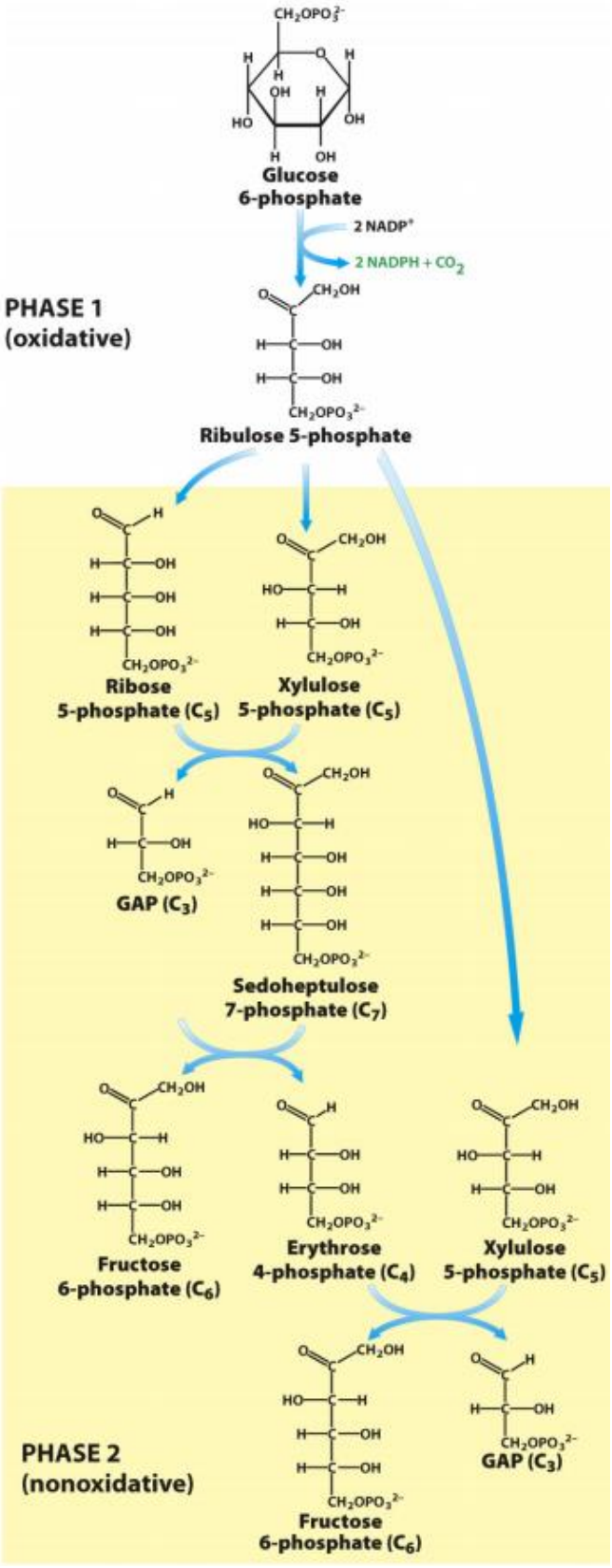
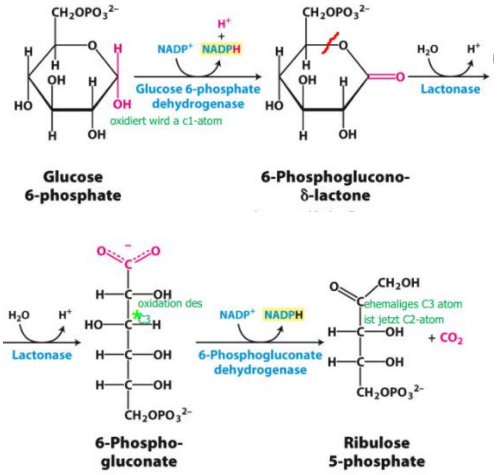
Pentose phosphate pathway

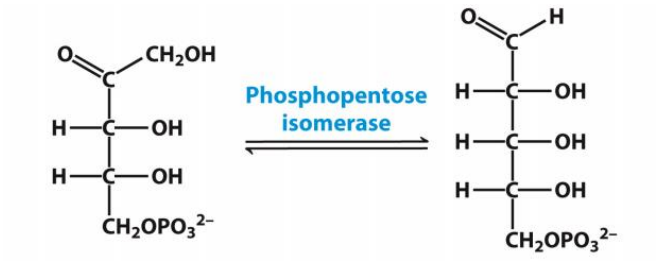


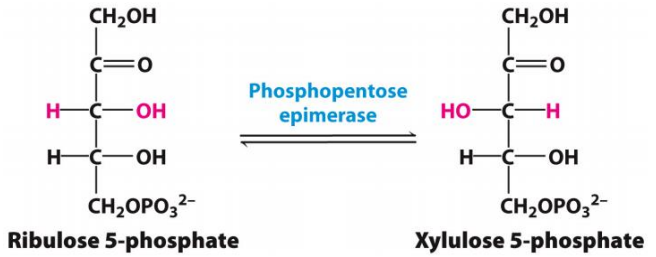
Bildung von Ribulose 5-phosphat (R-5-P) aus G-6-P:



Output dieser 3 Schritte: 1 CO_2, 2 NADPH, R-5-P.

Ribulose 5-phosphat wird zu Ribose 5-phosphate umgewandelt (Phosphopentose isomerase) oder zu Xylulose 5-phosphat (Phosphopentose epimerase).





Fragment shuffling:

$$C_5 + C_5 \xrightleftharpoons{\text{Transketolase}} C_3 + C_7$$

$$C_3 + C_7 \xrightleftharpoons{\text{Transaldolase}} C_6 + C_4$$

$$C_4 + C_5 \xrightleftharpoons{\text{Transketolase}} C_6 + C_3$$

Net: 3 C_5 → 2 C_6 + C_3

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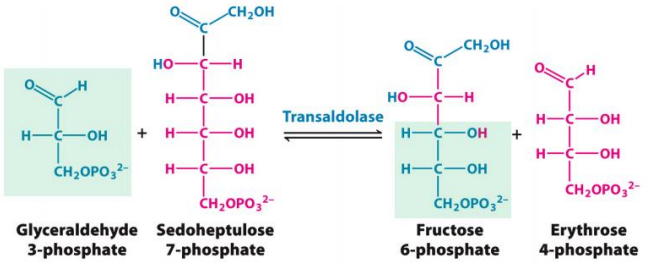
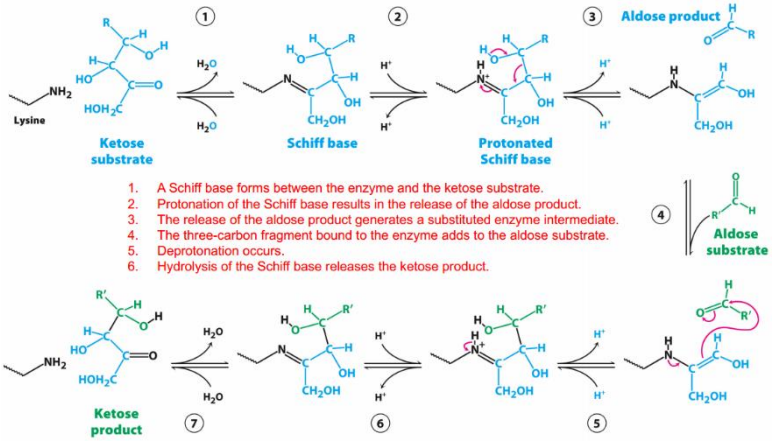
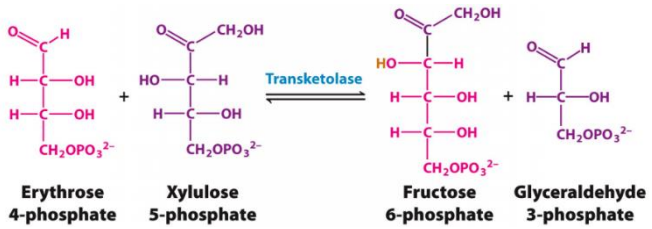
Transaldolase converts a ketose to a covalently bound Schiff base, breaks the bond between the α and β carbons, and transfers the remaining piece onto an aldolase.



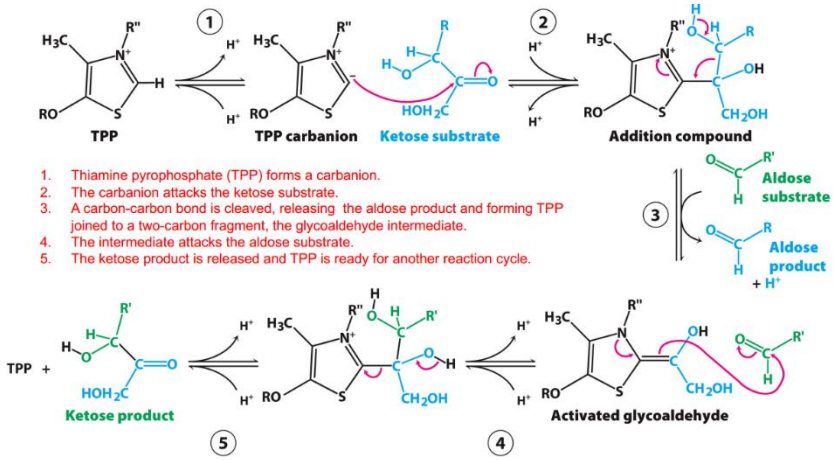
Transaldolase reaction mechanism:



Transketolase also processed ketones, but uses "Umpolung" (**TPP cofactor**) to break the bond between the carbonyl and α carbons, then transfers the remaining bit onto an aldolase.

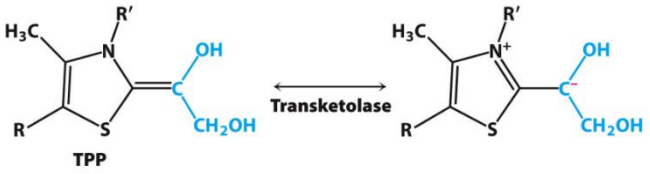


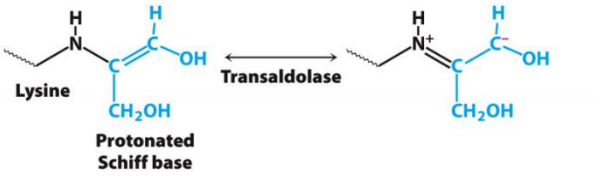
Transketolase reaction mechanism:



Essential mechanistic differences between transaldolase and transketolase:

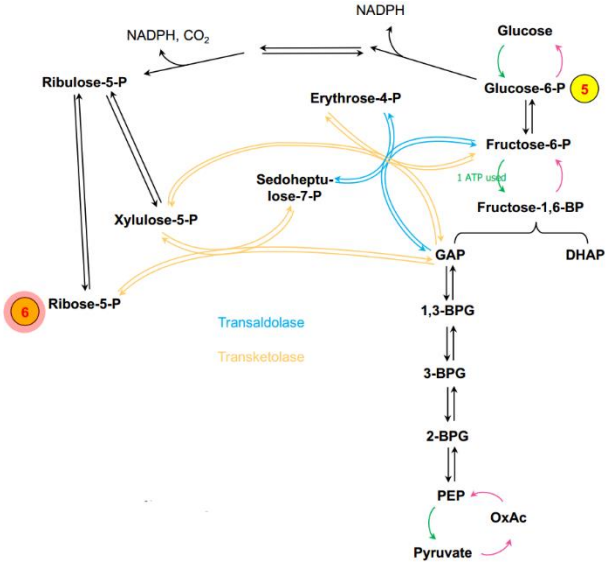
- Distinct stabilization of carbanionic intermediates.
- Distinct position of C–C break.





Stochiometry of pentose phosphate pathway (nicht vollständig, Prof. Locher hat nicht alle Slides hochgeladen).

5 G-6-P + ATP → 6 Ribose 5-phosphat + ADP.



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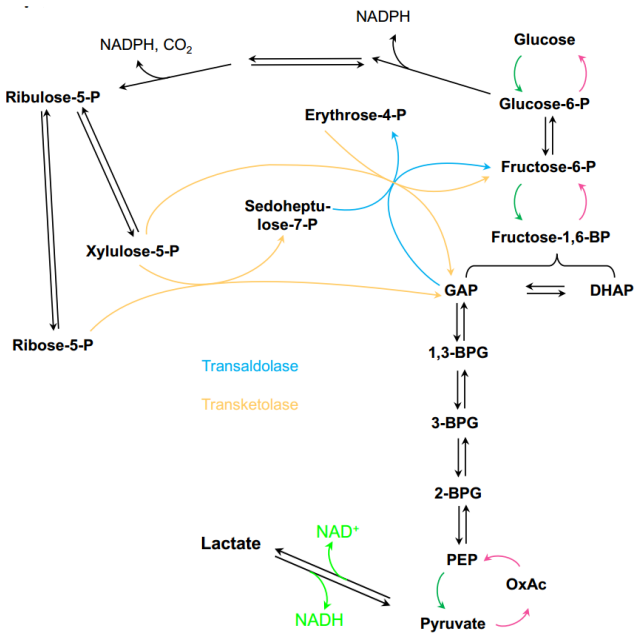
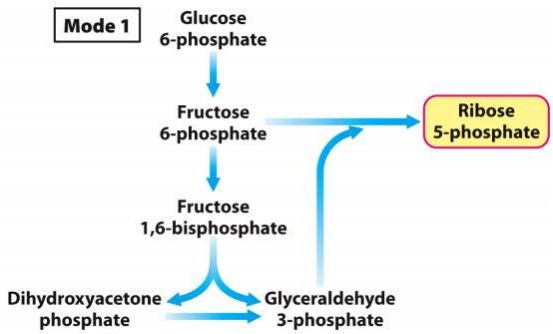
The flow of G-6-P depends on the need for NADPH, ribose-5-phosphate and ATP, the pentose phosphate pathway can operate in distinct modes that result from various combinations of the oxidative phase, the nonoxidative phase, glycolysis and gluconeogenesis.

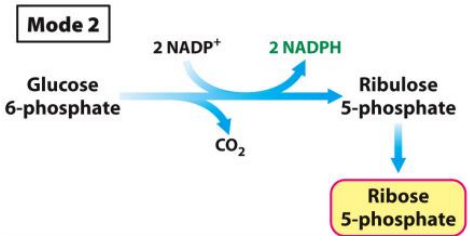


There are **four** different **modes** of pentose phosphate pathway:

1. Ribose 5-phosphate needs exceed the needs for NADPH.
2. The NADPH and ribose 5-phosphate needs are balanced.
3. More NADPH is needed than ribose 5-phosphate.
4. NADPH and ATP are both required.

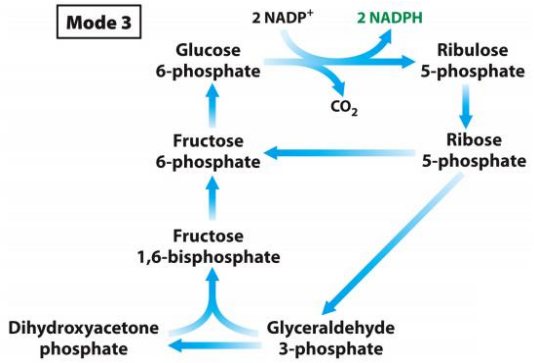


GAP and F-6-P (Gluconeogenesis) in combination with transaldolase and transketolase generate ribose-5-P. Glucose-6-P dehydrogenase is inactive. Ribose-5-P is used for DNA synthesis.

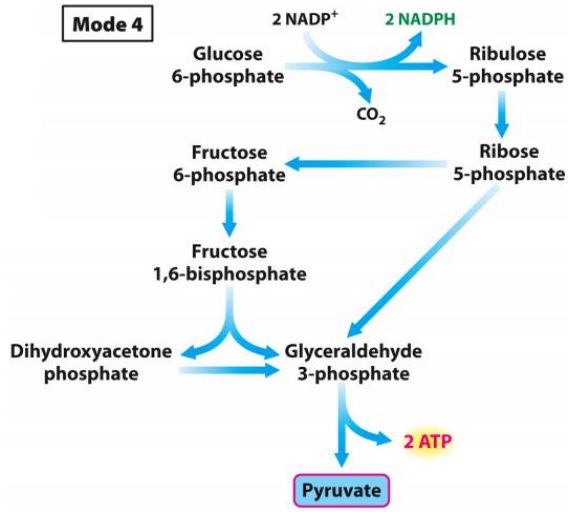


Glucose-6-P dehydrogenase is active, but transaldolase and transketolase are relatively inactive because most ribose-5-P is used for DNA synthesis and the concentrations of ribose-5-P and xylulose-5-P are low.

Generated NADPH has multiple purposes: Fatty acid -, cholesterol-, neurotransmitter-, and nucleotide biosynthesis; Detoxification (NADPH is required to recover reduced glutathione (GSH), which is needed to “destroy” reactive oxygen species).



G-6-P dehydrogenase is active, and transaldolase and transketolase convert most of the ribose-5-P and xylulose-5-P into GAP and F-6-P (for gluconeogenesis to G-6-P). For example, erythrocytes use this for their large NADPH needs.



G-6-P dehydrogenase ist active, and transaldolase and transketolase convert most of the ribose-5-P and xylulose-5-P into GAP and F-6-P (for glycolysis).

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Übersicht zu den bisher behandelten Stoffwechselwegen:

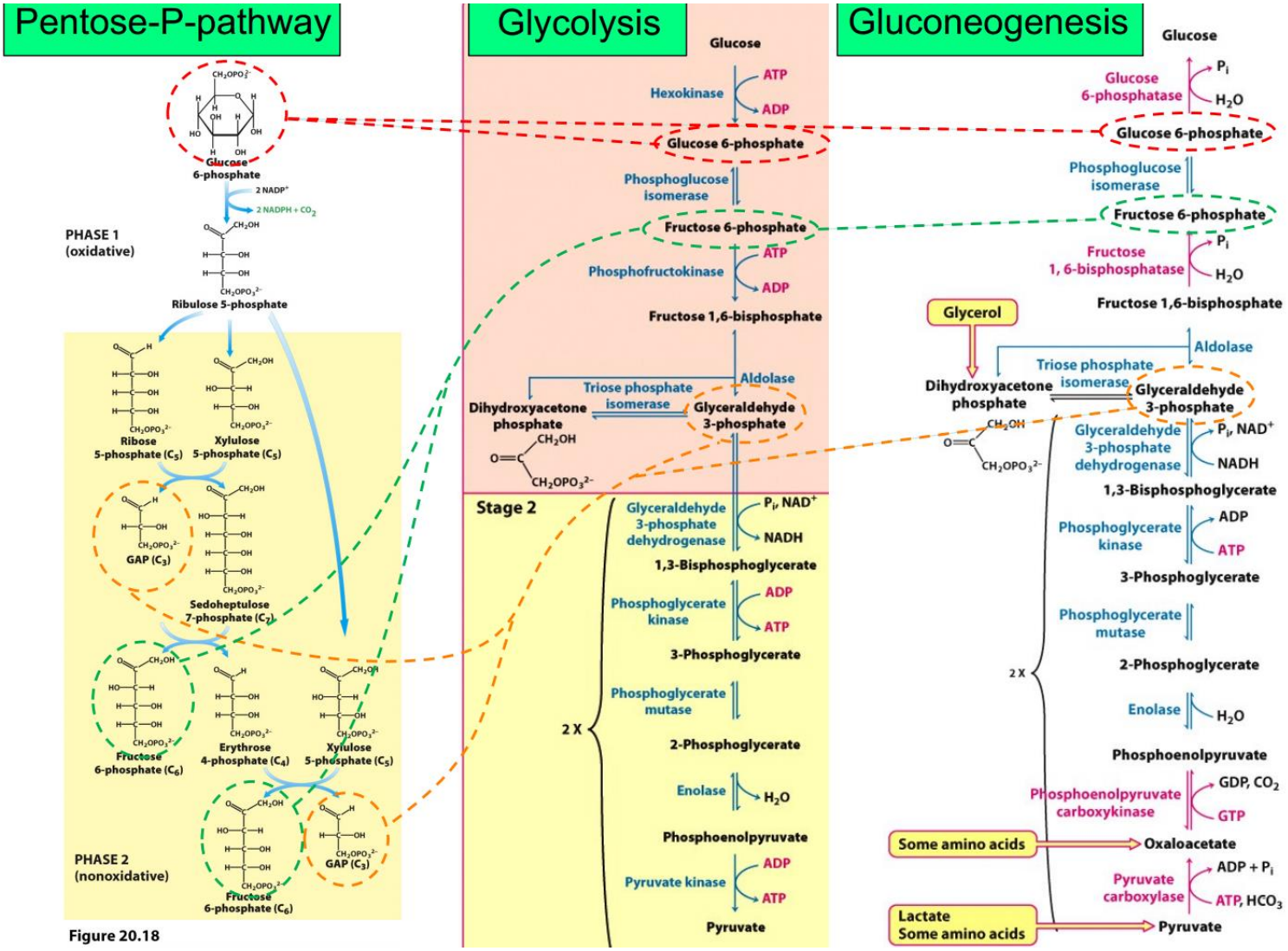

Figure 20.18