14.2 Feeder pathways for glycolysis

p558

Dietary polysaccharides and disaccharides undergo hydrolysis to monosaccharides

Polysaccharides: starch and glycogen

Disaccharides: maltose, lactose, trehalose and sucrose

Monosaccharides: fructose, mannose and galactose

Dietary glycogen and starch breakdown

1. **Alpha-amylase**: Saliva, pancreatic juice

   endoglycosidase

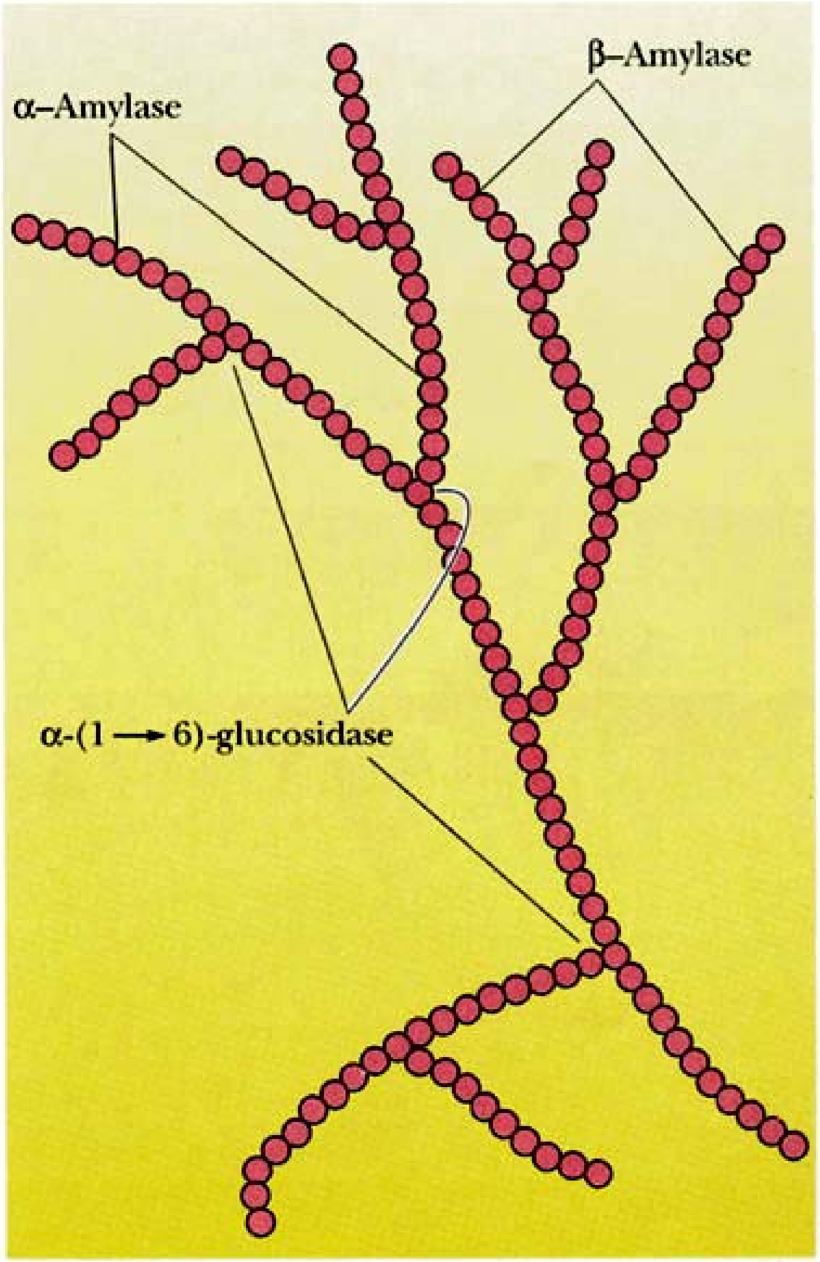
   substrates: amylose, amylopectin and glycogen

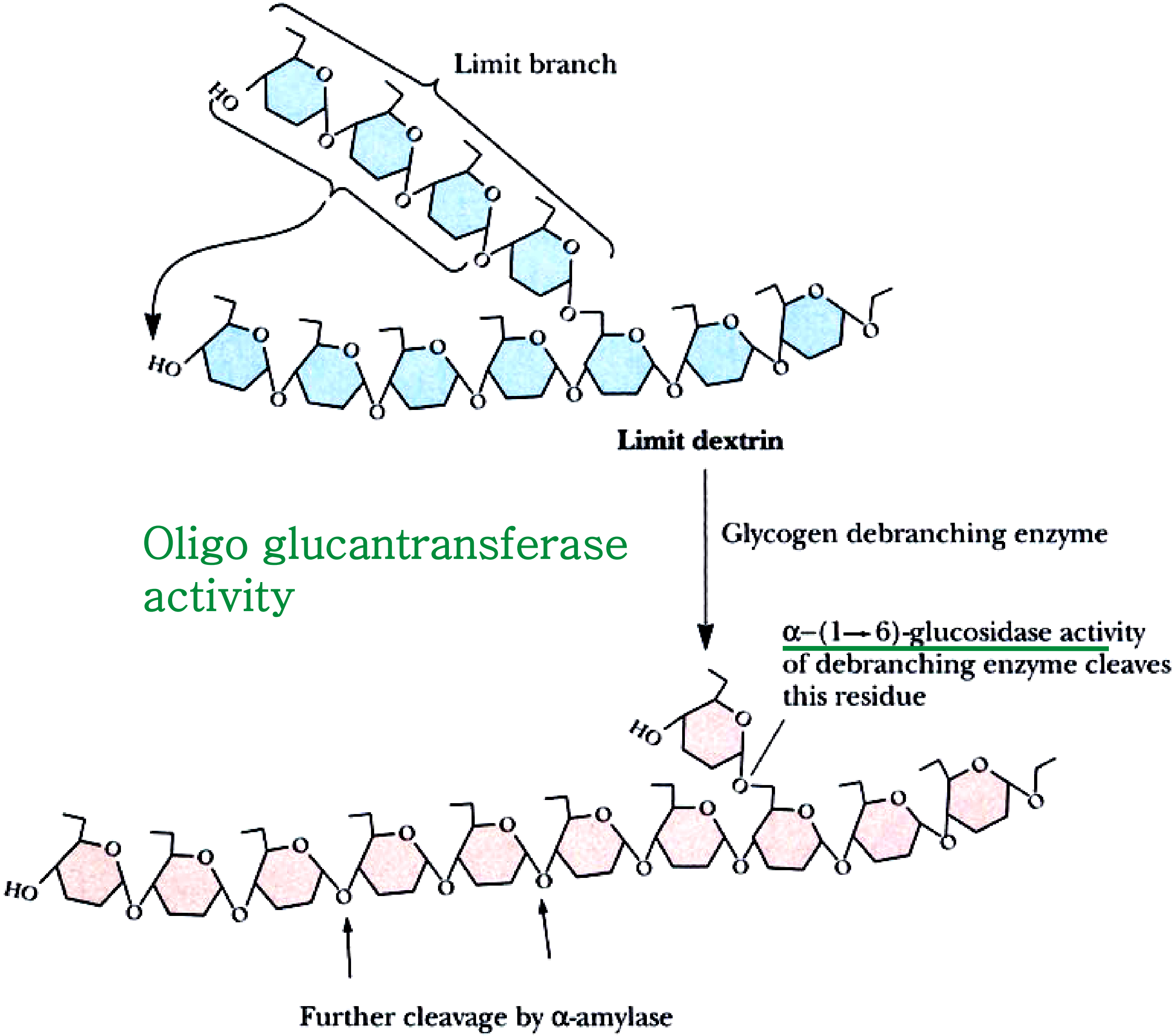
   products: maltose and maltotriose

2. Beta-amylase, in plant

   exoglycosidase

In this hydrolysis reaction water is the attacking species





Digestive breakdown of starch and glycogen is an unregulated process

The reaction of debranching enzyme

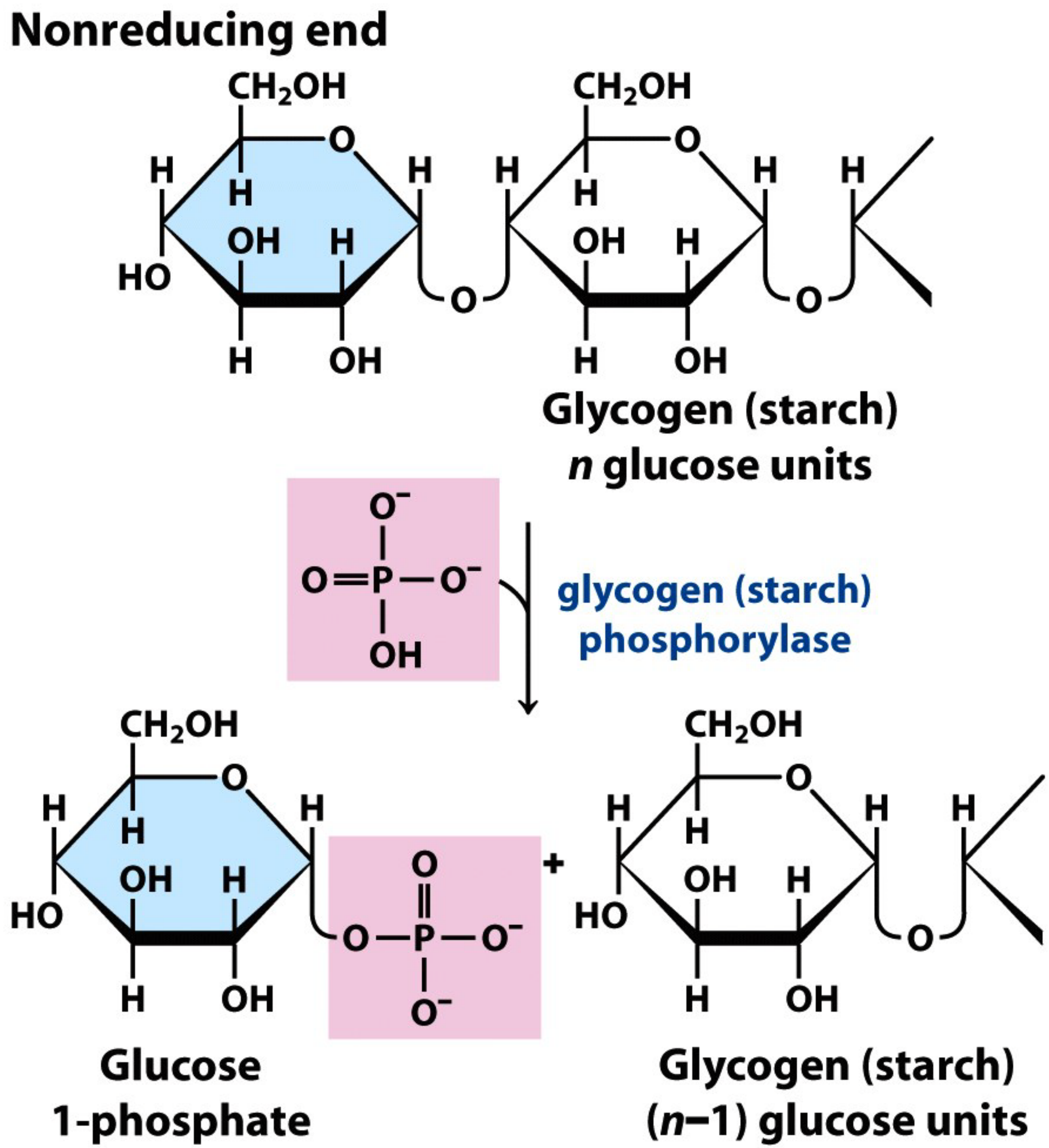


Figure 14-11

Endogenous glycogen and starch are degraded by phosphorolysis

$$\text{Maltose} + H_2O \xrightarrow{\text{maltase}} \text{2D-glucose}$$

$$\text{Trehalose} + H_2O \xrightarrow{\text{trehalase}} \text{2D-glucose}$$

$$\text{Lactose} + H_2O \xrightarrow{\text{lactase}} \text{D-glucose} + \text{D-galactose}$$

$$\text{Sucrose} + H_2O \xrightarrow{\text{sucrase}} \text{D-glucose} + \text{D-fructose}$$

Lactate intolerance

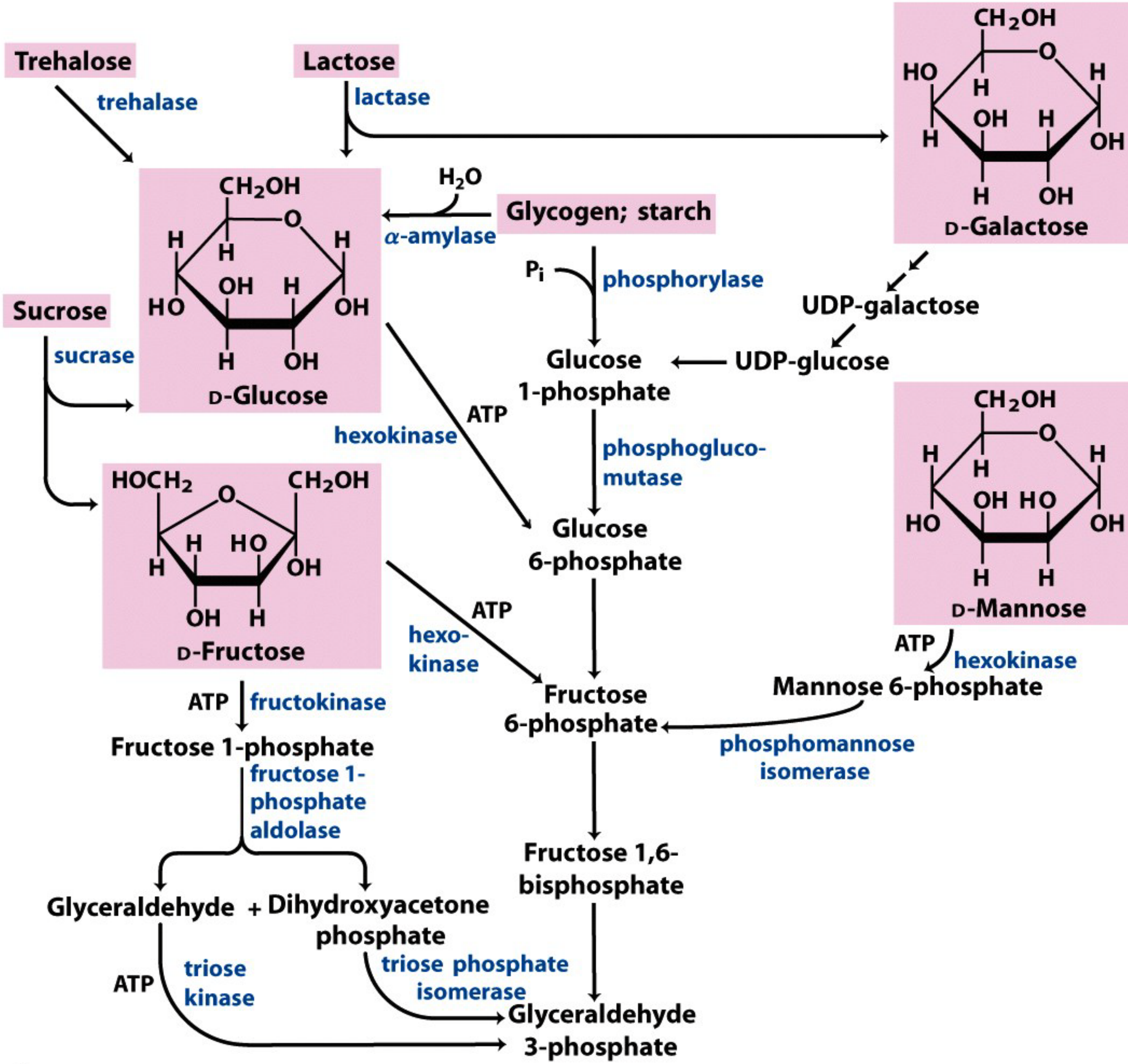


Figure 14-10

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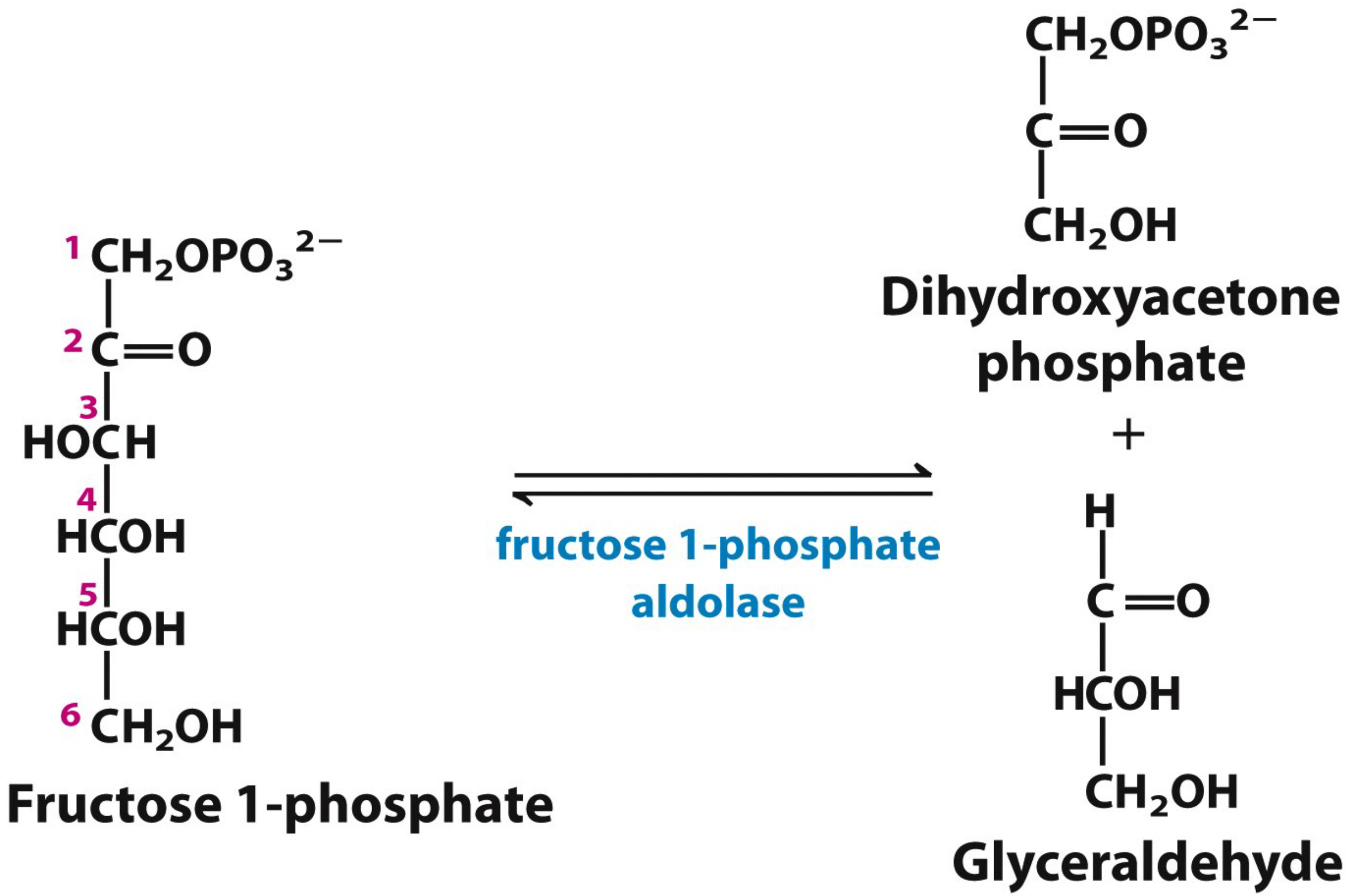

Unnumbered 14 p545a

Triose kinase

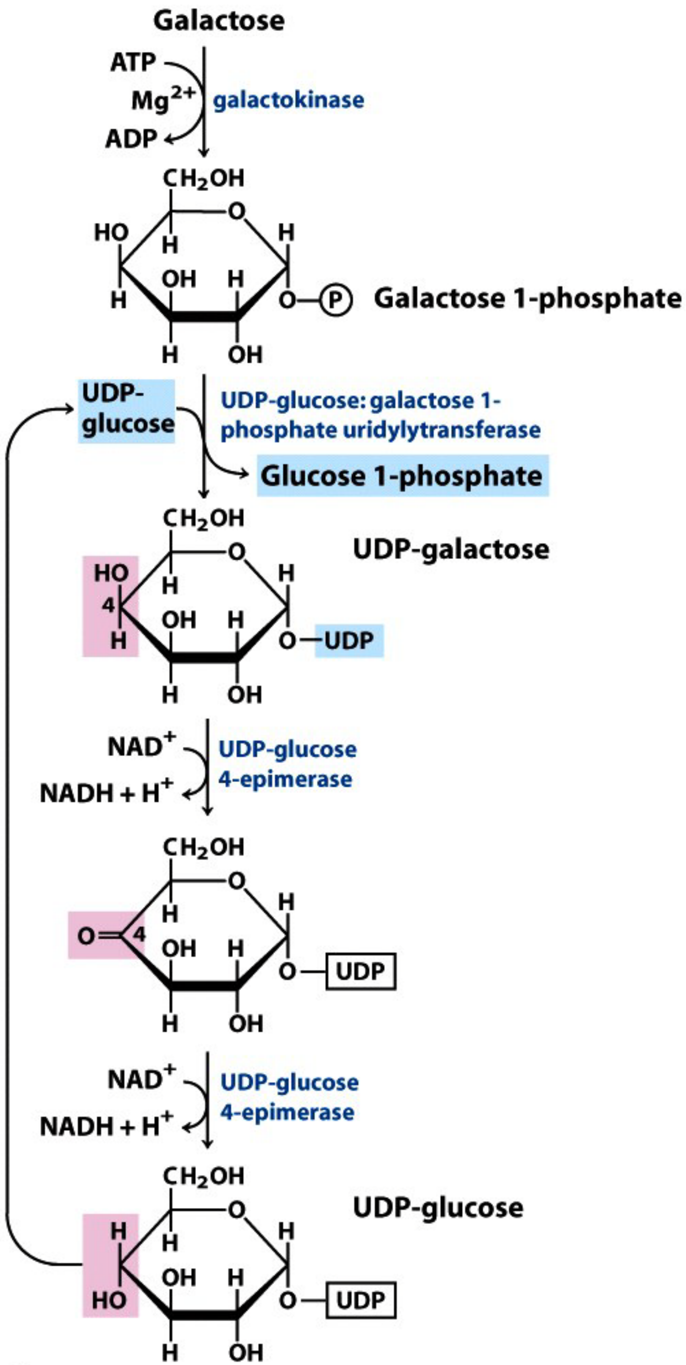

Figure 14-12

Conversion of galactose to glucose 1-phosphate

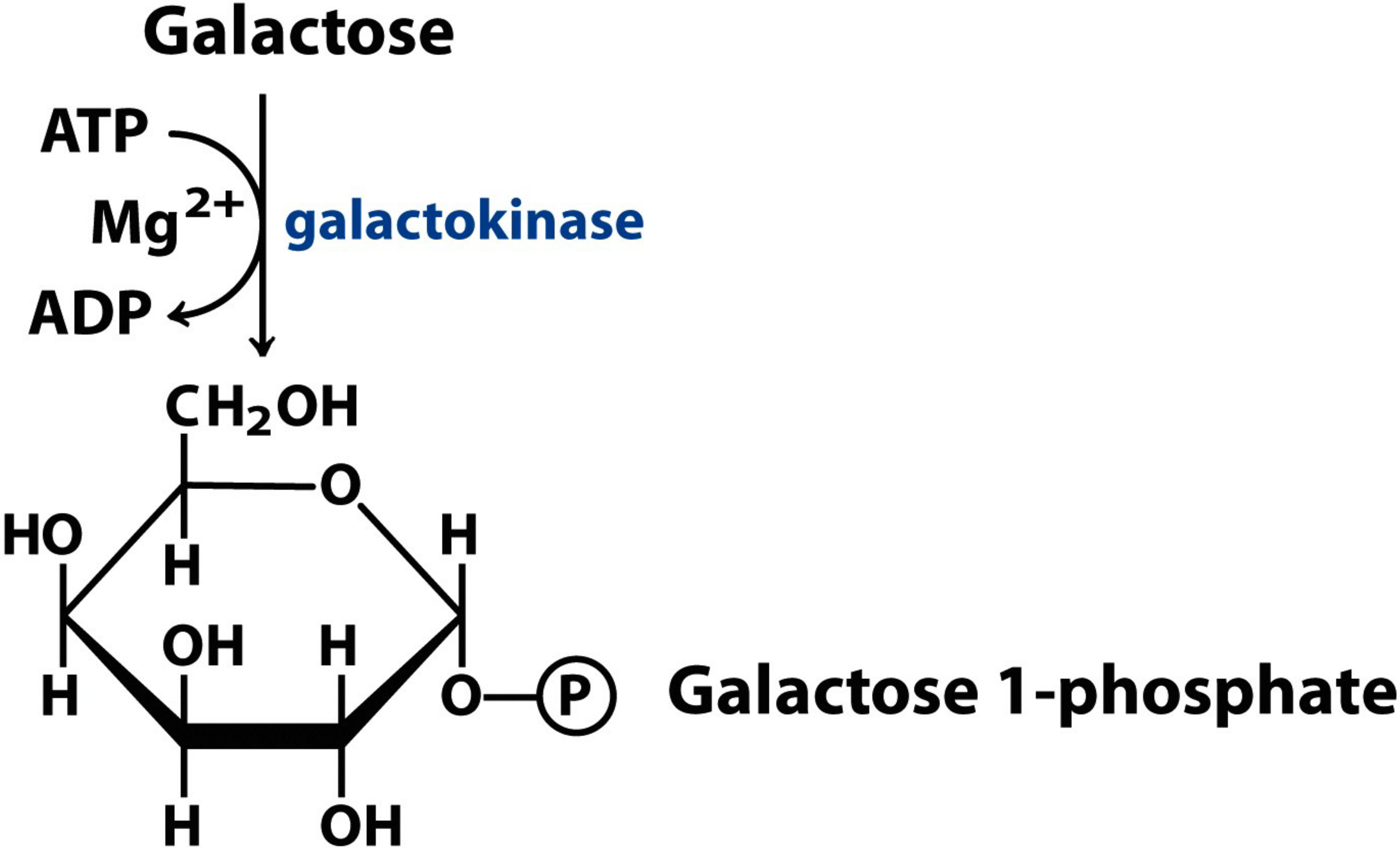

Figure 14-12 part 1
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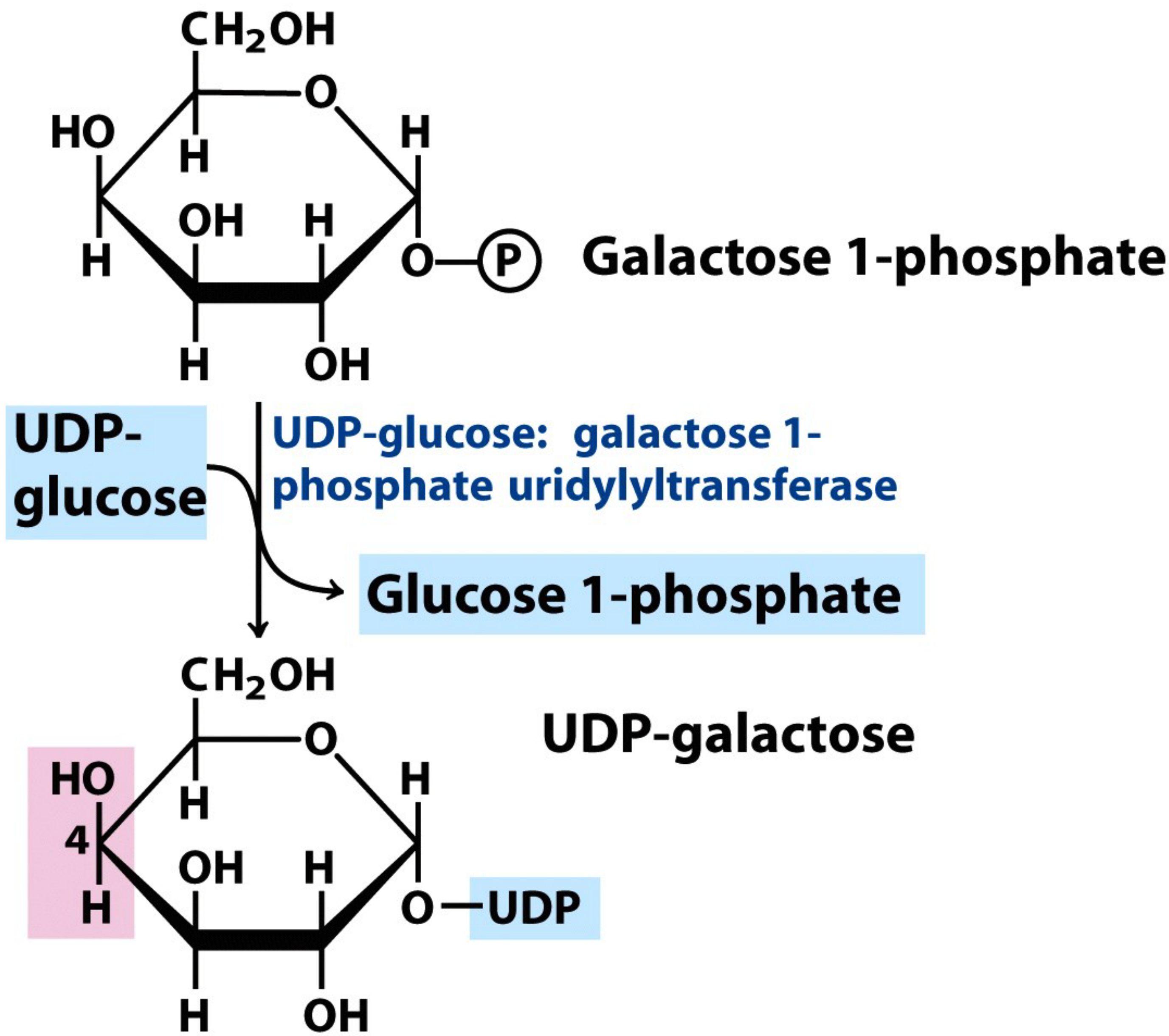

Figure 14-12 part 2

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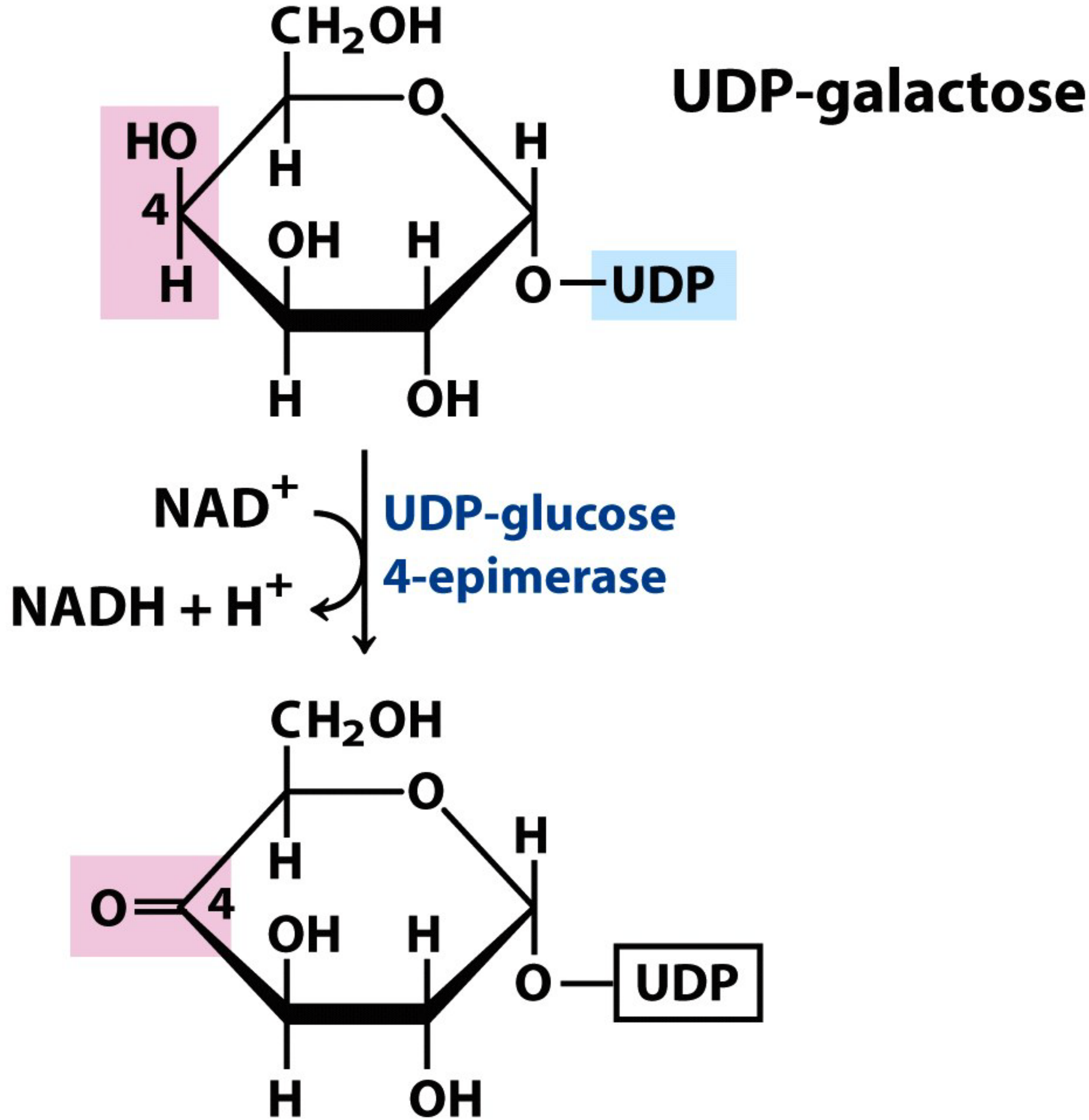

Figure 14-12 part 3
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inverse

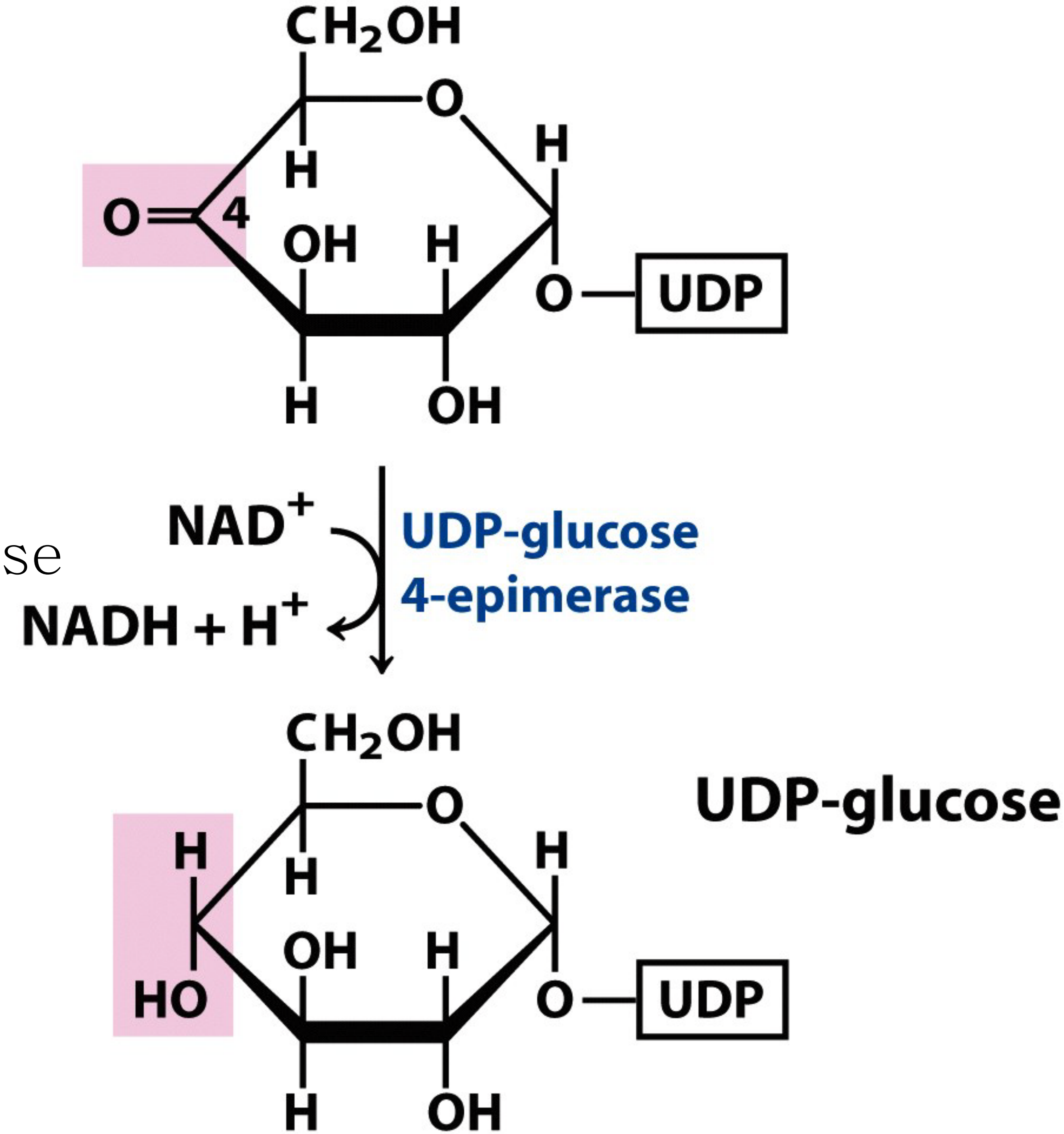

Figure 14-12 part 4
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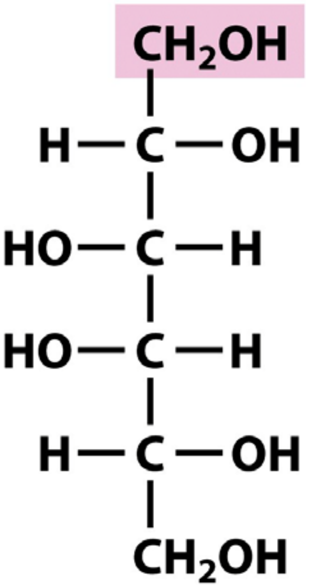
A defect in any of the three enzymes in this pathway causes galactosemia in humans

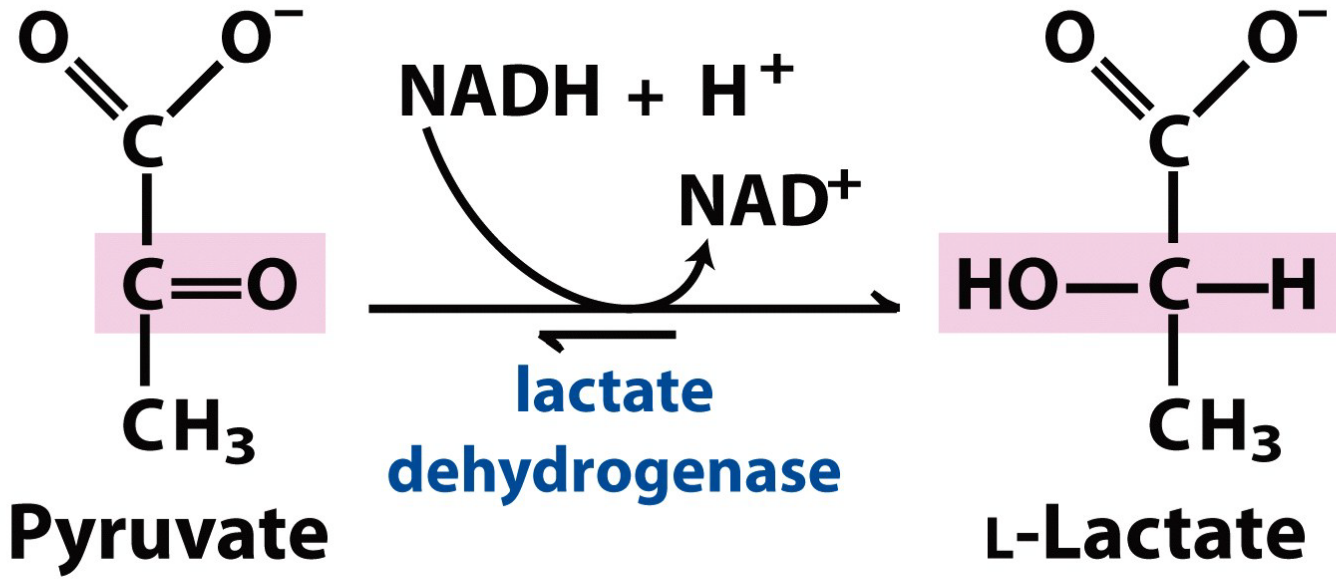


D-Galactitol

Unnumbered 14 p545b

Deposition of galactitol causes cataracts in infants

14.3 Fates of pyruvate under anaerobic conditions: fermentation



$\Delta G'^{\circ} = -\ 25.1\ \text{kJ/mol}$

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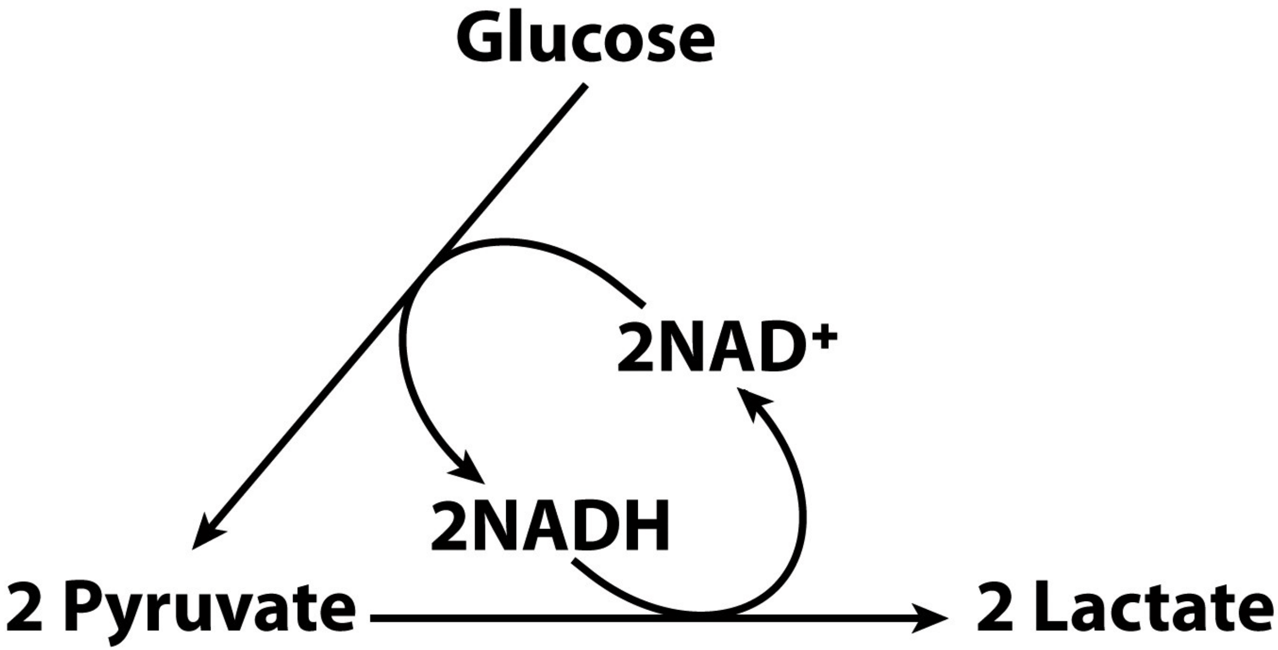
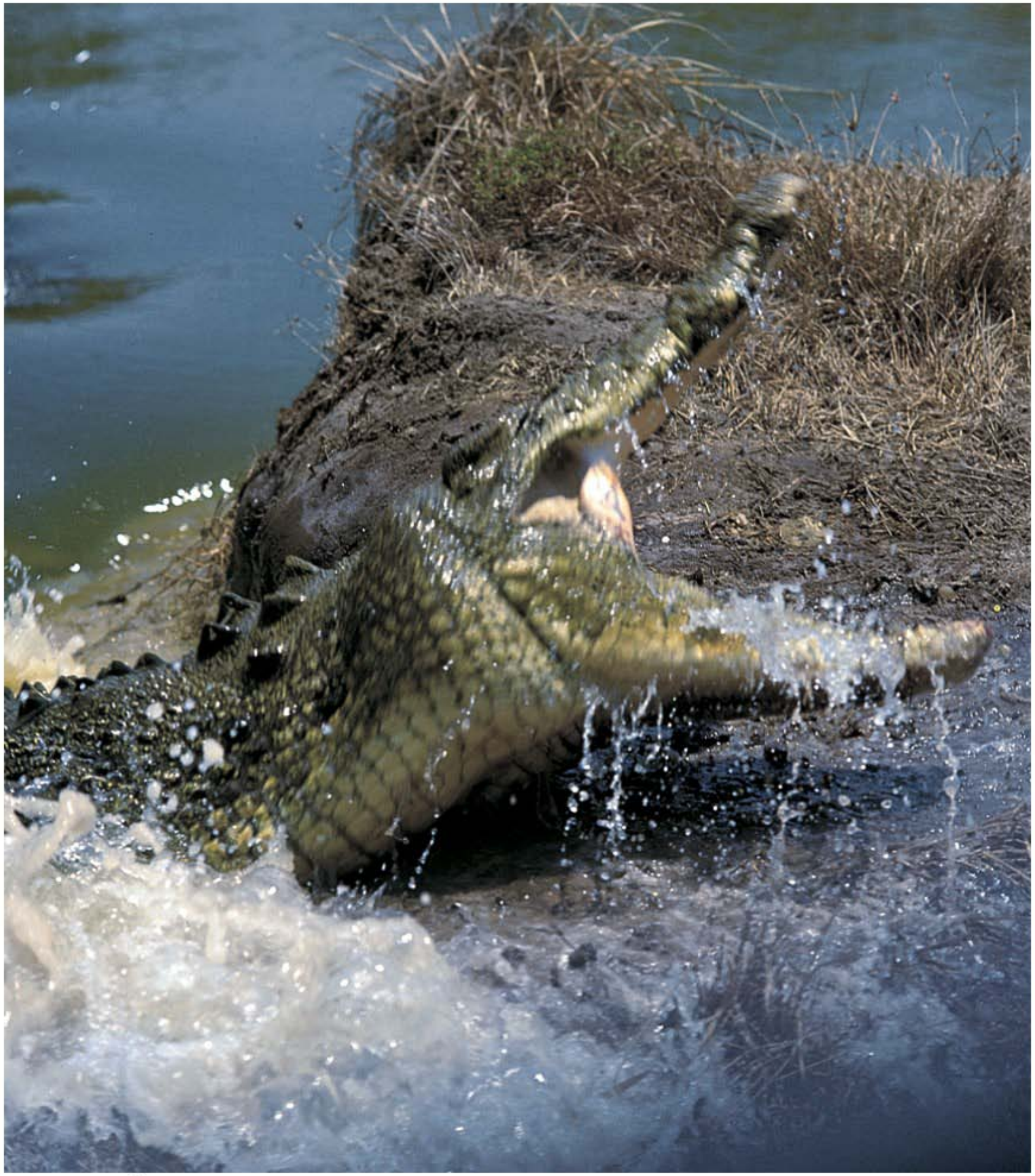
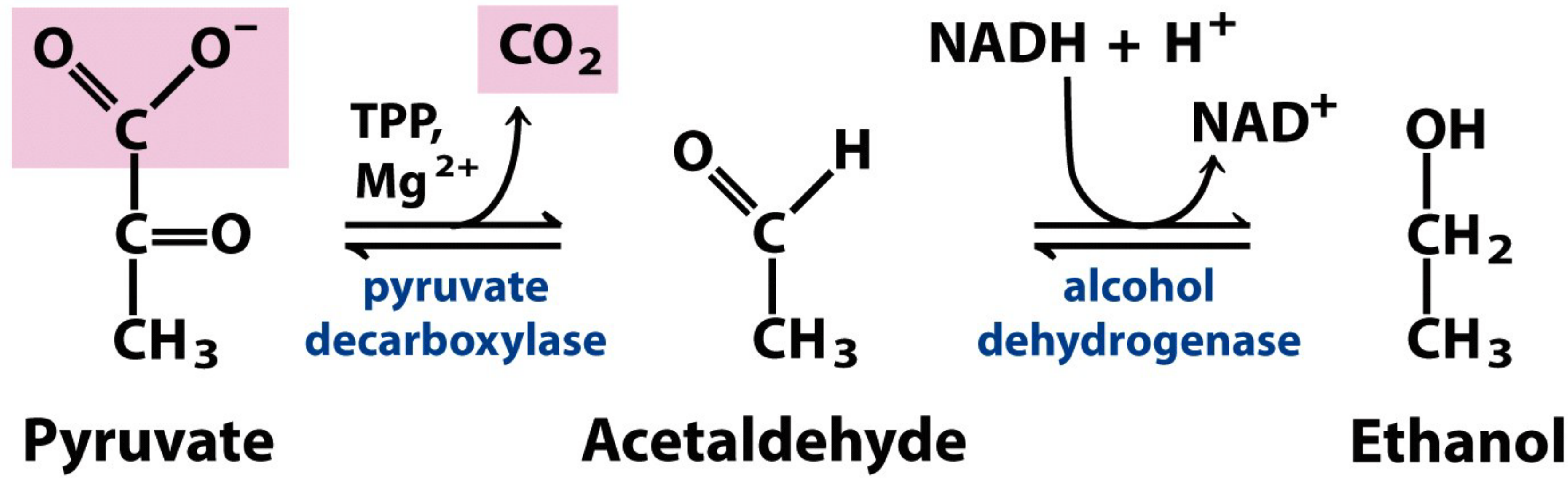


Pyruvate is the terminal electron acceptor in lactic acid fermentation



Box 14-2 figure 1



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Ethanol is the reduced product in ethanol fermentation

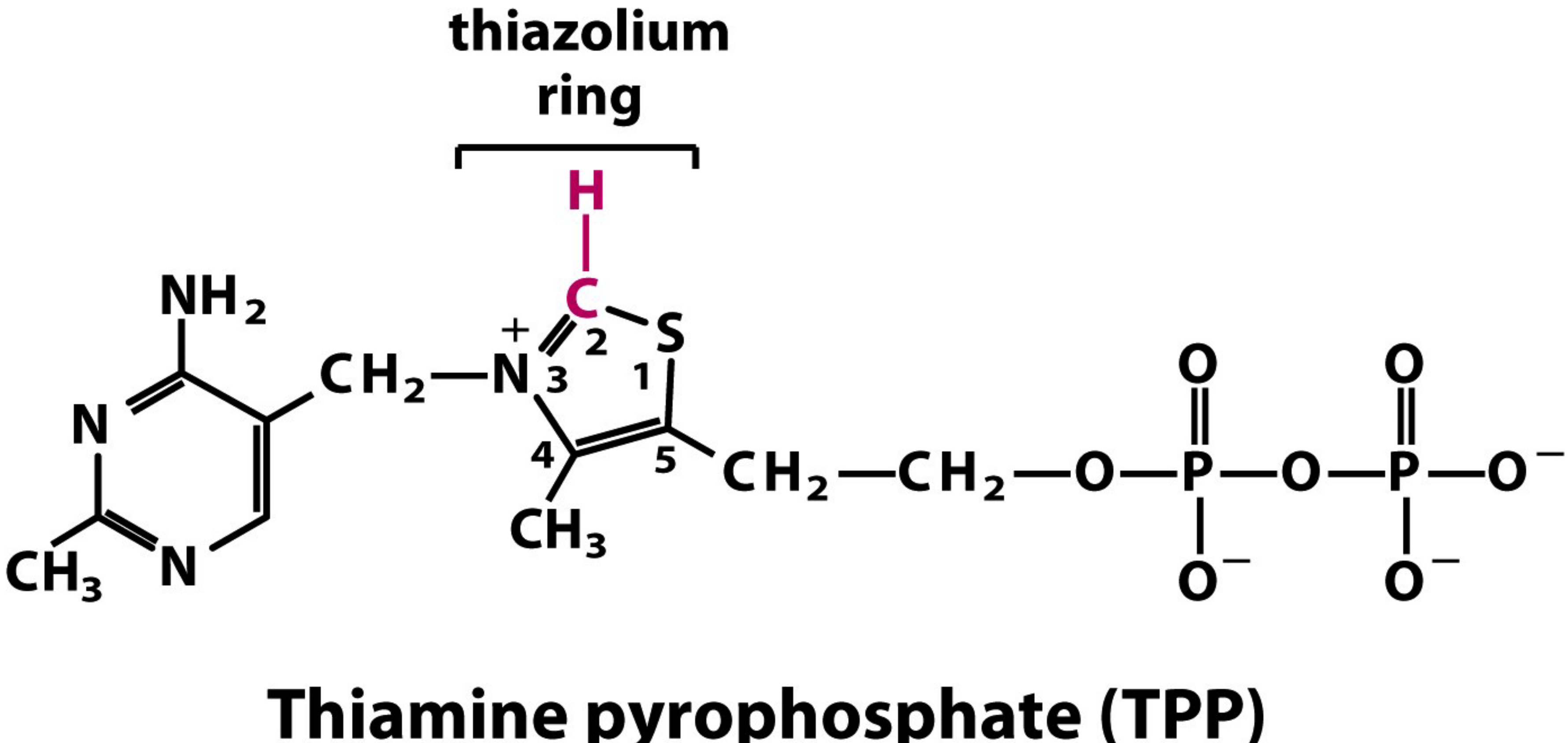
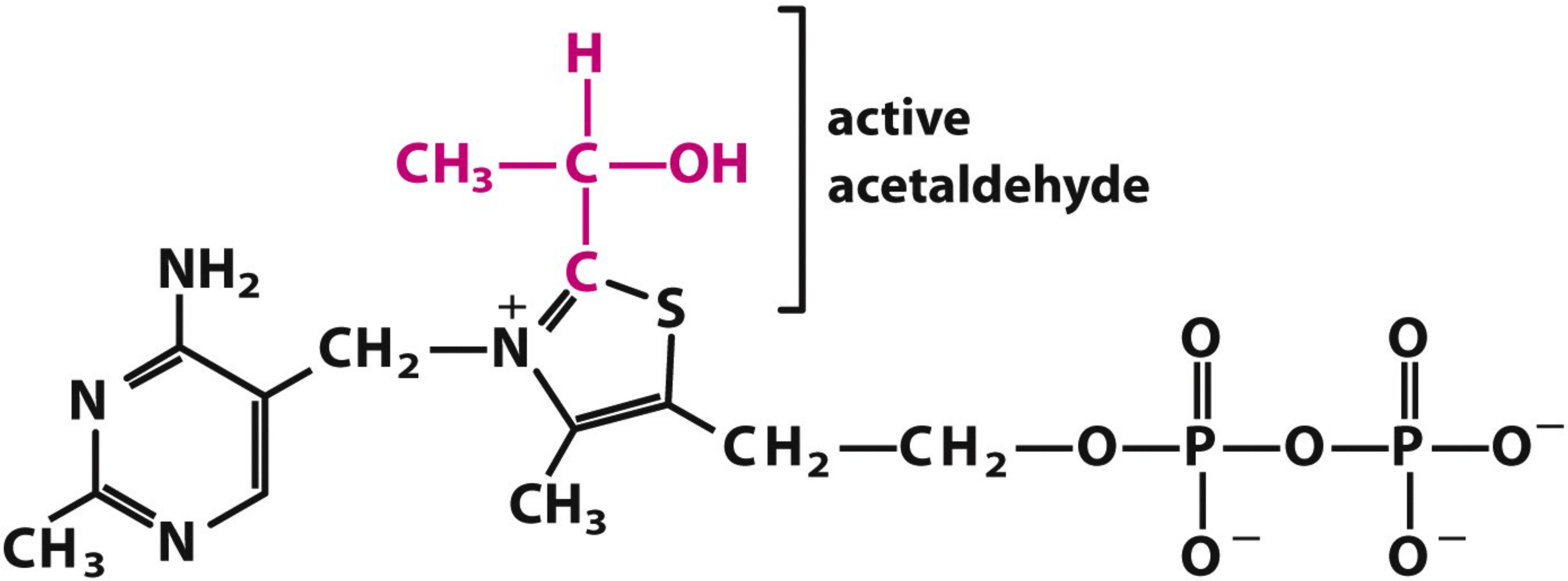


Figure 14-14a

Thiamine pyrophosphate (TPP) and its role in pyruvate decarboxylation



Hydroxyethyl thiamine pyrophosphate

Figure 14-14b
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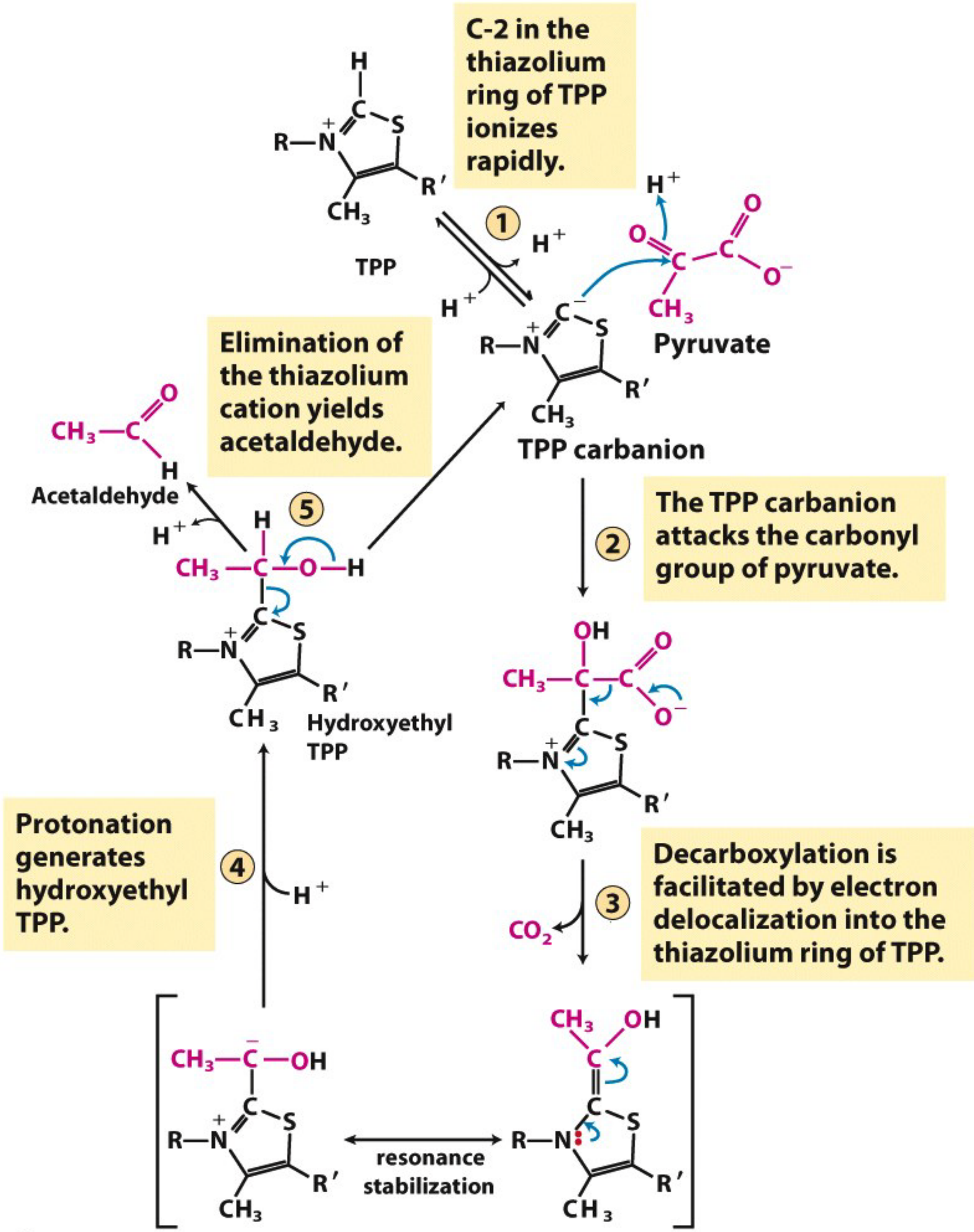


Figure 14-14c

TPP carries "active acetaldehyde" groups

TABLE 14–1 Some TPP-Dependent Reactions

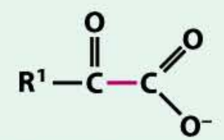
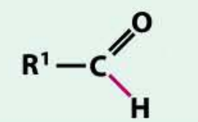
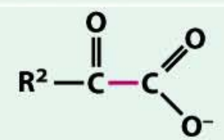
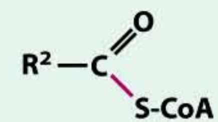
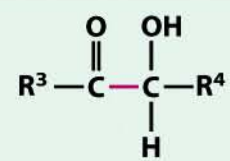
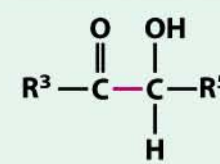
Enzyme	Pathway(s)	Bond cleaved	Bond formed
Pyruvate decarboxylase	Ethanol fermentation		
Pyruvate dehydrogenase α-Ketoglutarate dehydrogenase	Synthesis of acetyl-CoA Citric acid cycle		
Transketolase	Carbon-assimilation reactions Pentose phosphate pathway		

Table 14-1
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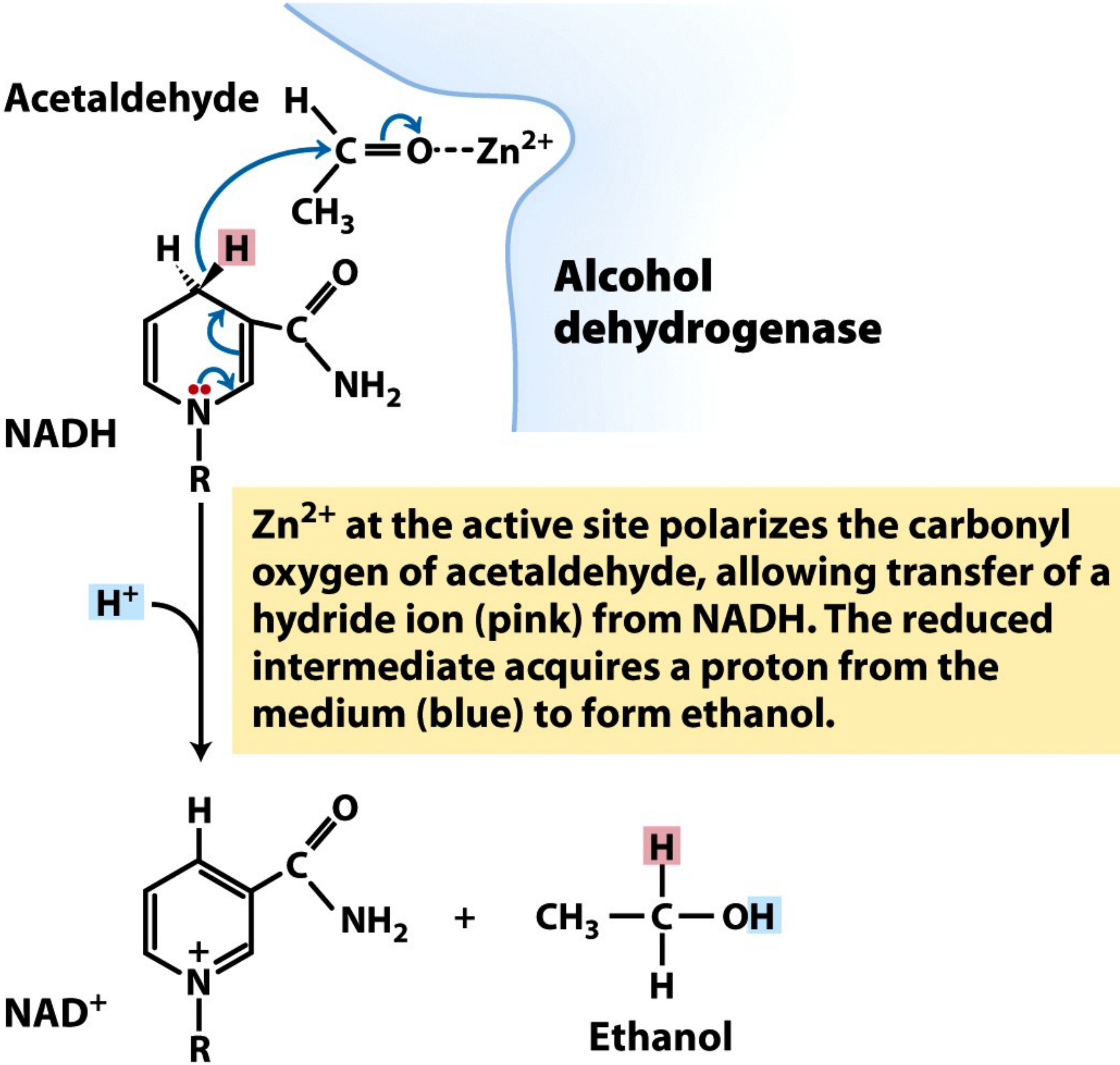

Figure 14-13
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Box 14-3 figure 1

Fermentations are used to produce some common foods and industrial chemicals

14.4 Gluconeogenesis

Generation (genesis) of new (neo) glucose

The biosynthesis of carbohydrates (especially glucose) from simpler, nocarbohydrate precursors such as lactate or pyruvate.

Precursors include:

1. lactate or pyruvate
2. glycerol and all the TCA cycle intermediates
3. most of the amino acids（except lysine and leucine）

glucogenic amino acids

Necessity

- Human metabolism consume 160±20 g glucose per day, 70% in brain
- Body fluids carry only about 20g free glucose
- Glycogen stores can provide only 180-200 g glucose
- In vigorous exercise, muscle cells become anaerobic and pyruvate is converted to lactate. Gluconeogenesis salvages this pyruvate and lactate.

organs, subcellular structures

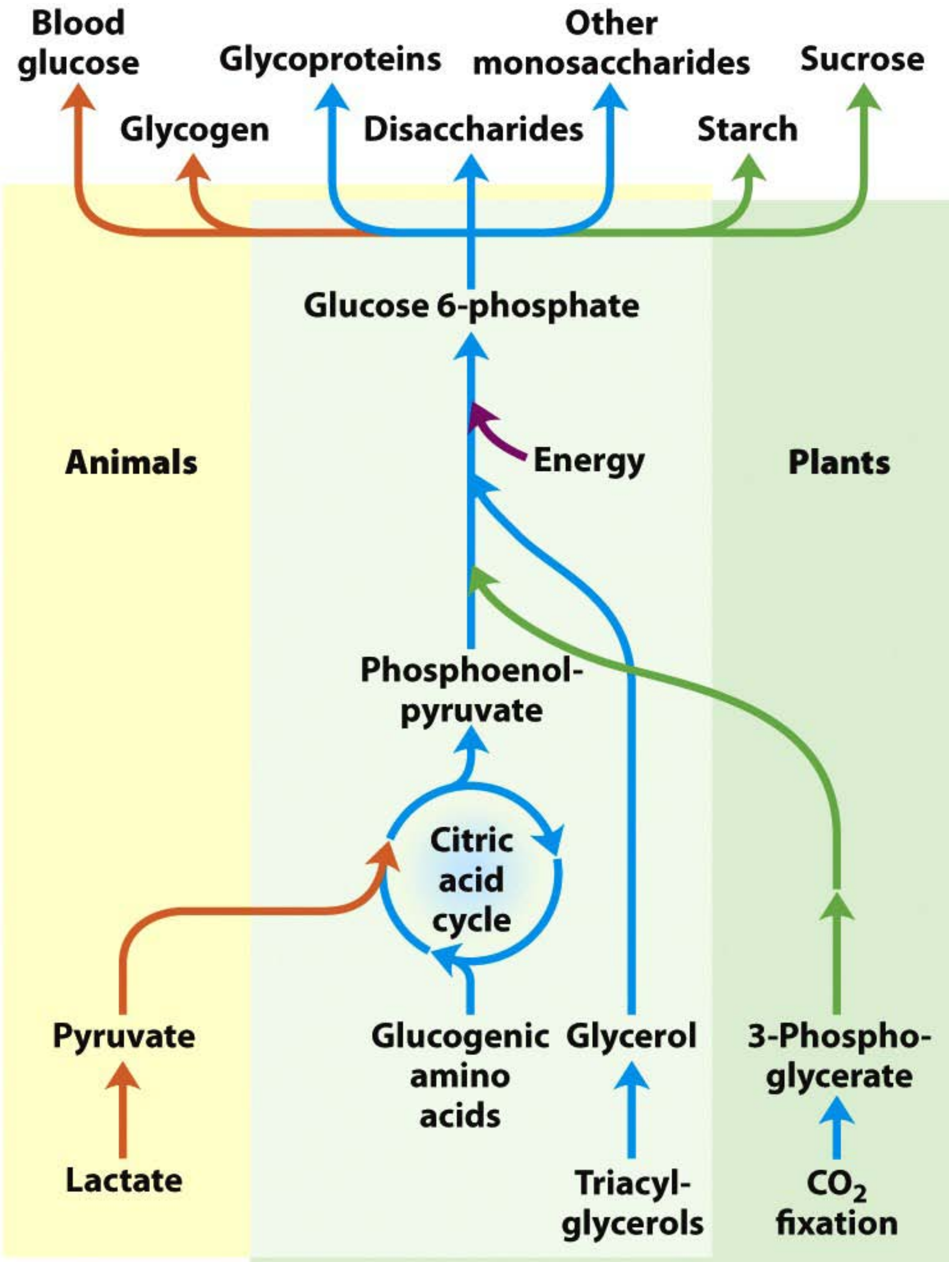

Figure 14-15

Carbohydrate synthesis from simple precursors

TABLE 14–2 Free-Energy Changes of Glycolytic Reactions in Erythrocytes

Glycolytic reaction step	$\Delta G'^{\circ}$ (kJ/mol)	ΔG (kJ/mol)
1 Glucose + ATP $\longrightarrow$ glucose 6-phosphate + ADP	−16.7	−33.4
2 Glucose 6-phosphate $\rightleftharpoons$ fructose 6-phosphate	1.7	0 to 25
3 Fructose 6-phosphate + ATP $\longrightarrow$ fructose 1,6-bisphosphate + ADP	−14.2	−22.2
4 Fructose 1,6-bisphosphate $\rightleftharpoons$ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate	23.8	−6 to 0
5 Dihydroxyacetone phosphate $\rightleftharpoons$ glyceraldehyde 3-phosphate	7.5	0 to 4
6 Glyceraldehyde 3-phosphate + P_i + NAD^+ $\rightleftharpoons$ 1,3-bisphosphoglycerate + NADH + H^+	6.3	−2 to 2
7 1,3-Bisphosphoglycerate + ADP $\rightleftharpoons$ 3-phosphoglycerate + ATP	−18.8	0 to 2
8 3-Phosphoglycerate $\rightleftharpoons$ 2-phosphoglycerate	4.4	0 to 0.8
9 2-Phosphoglycerate $\rightleftharpoons$ phosphoenolpyruvate + H_2O	7.5	0 to 3.3
10 Phosphoenolpyruvate + ADP $\longrightarrow$ pyruvate + ATP	−31.4	−16.7

Note: $\Delta G'^{\circ}$ is the standard free-energy change, as defined in Chapter 13 (pp. 491–492). ΔG is the free-energy change calculated from the actual concentrations of glycolytic intermediates present under physiological conditions in erythrocytes, at pH 7. The glycolytic reactions bypassed in gluconeogenesis are shown in red. Biochemical equations are not necessarily balanced for H or charge (p. 501).

Table 14-2

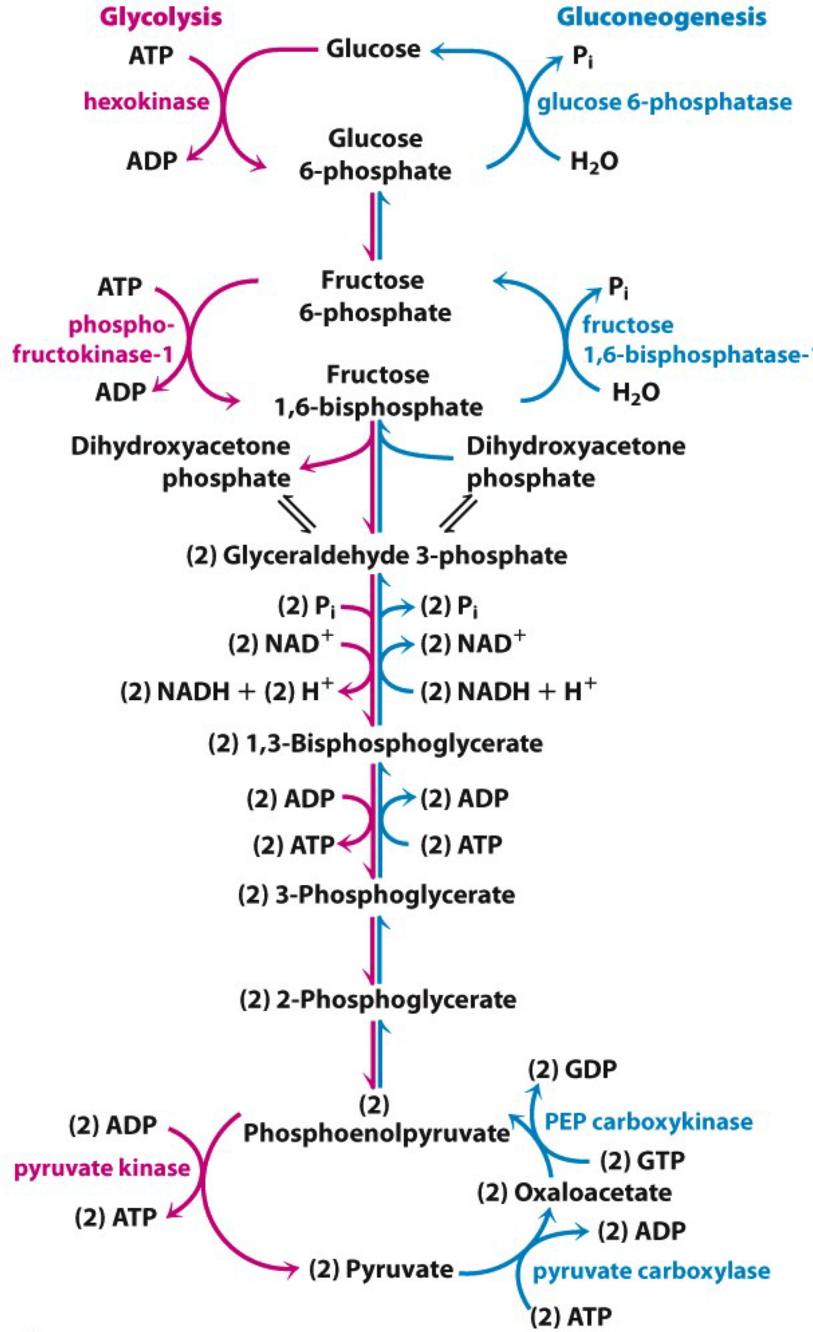

Figure 14-16

Opposing pathways of glycolysis and gluconeogenesis in rat liver

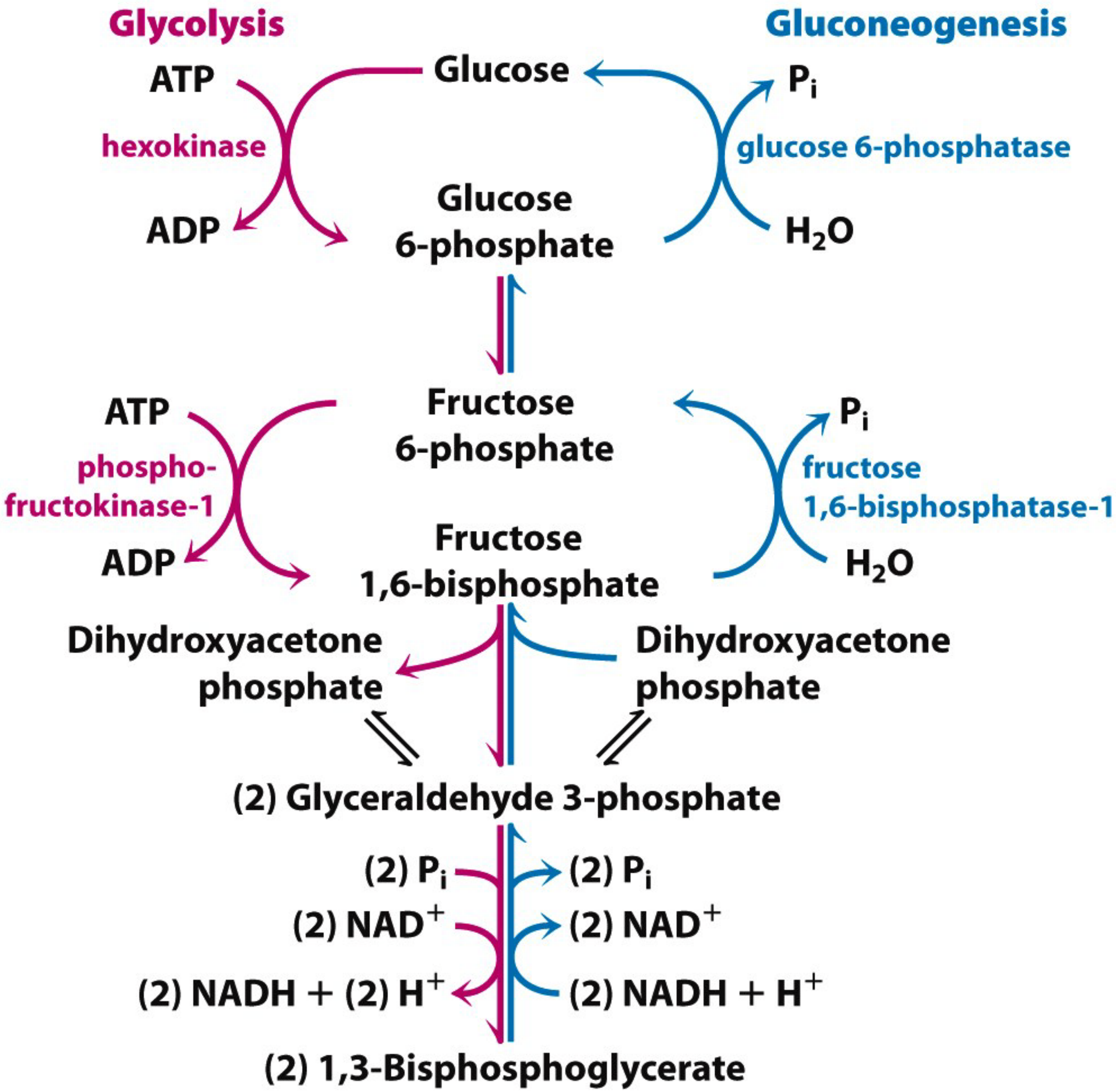

Figure 14-16 part 1

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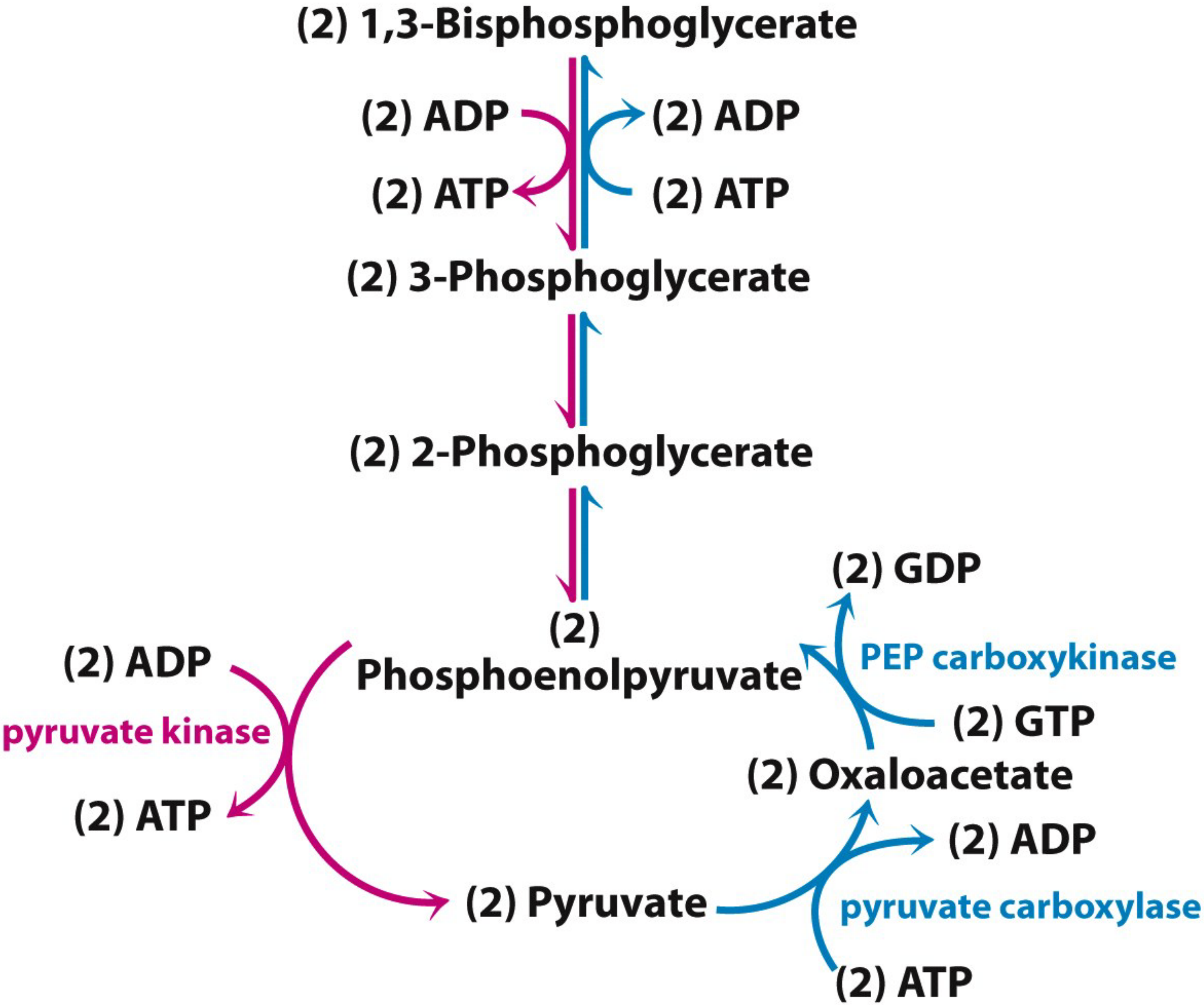

Figure 14-16 part 2
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(1) Synthesis of PEP from pyruvate

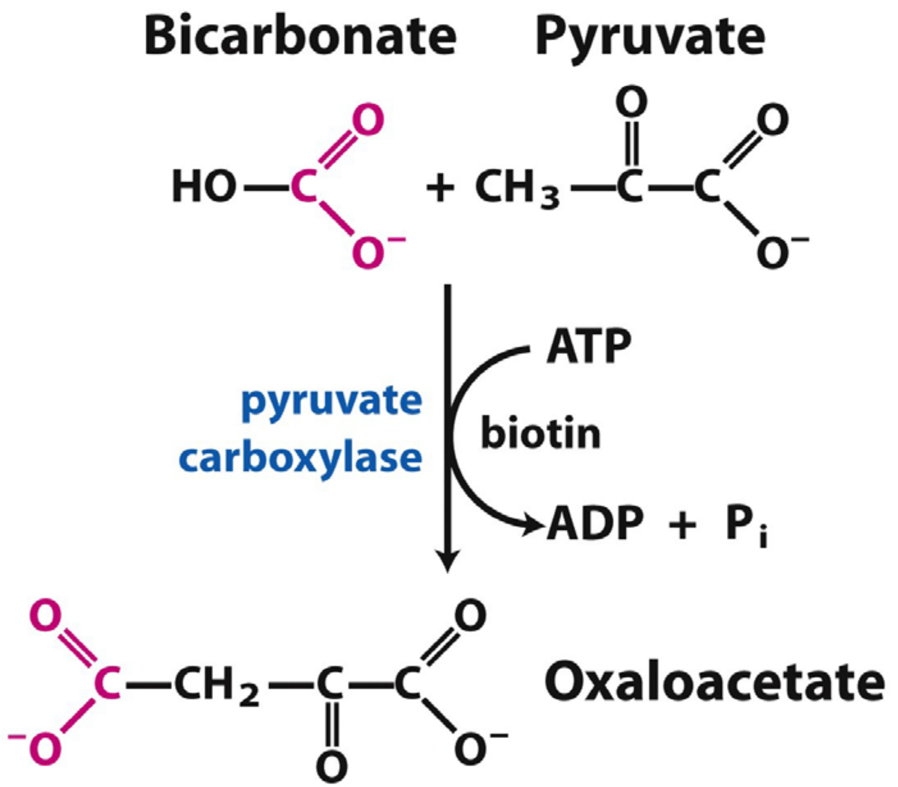
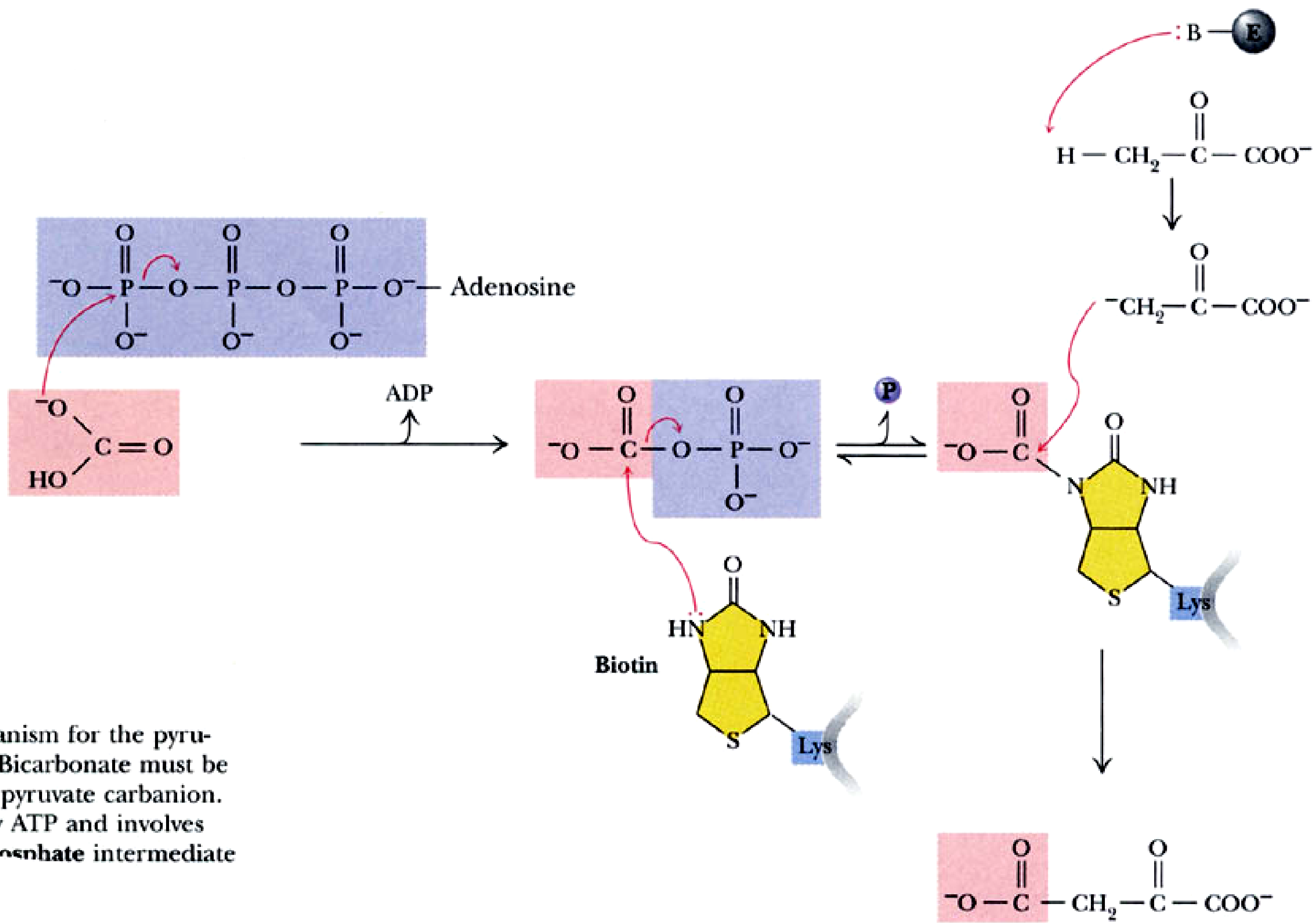
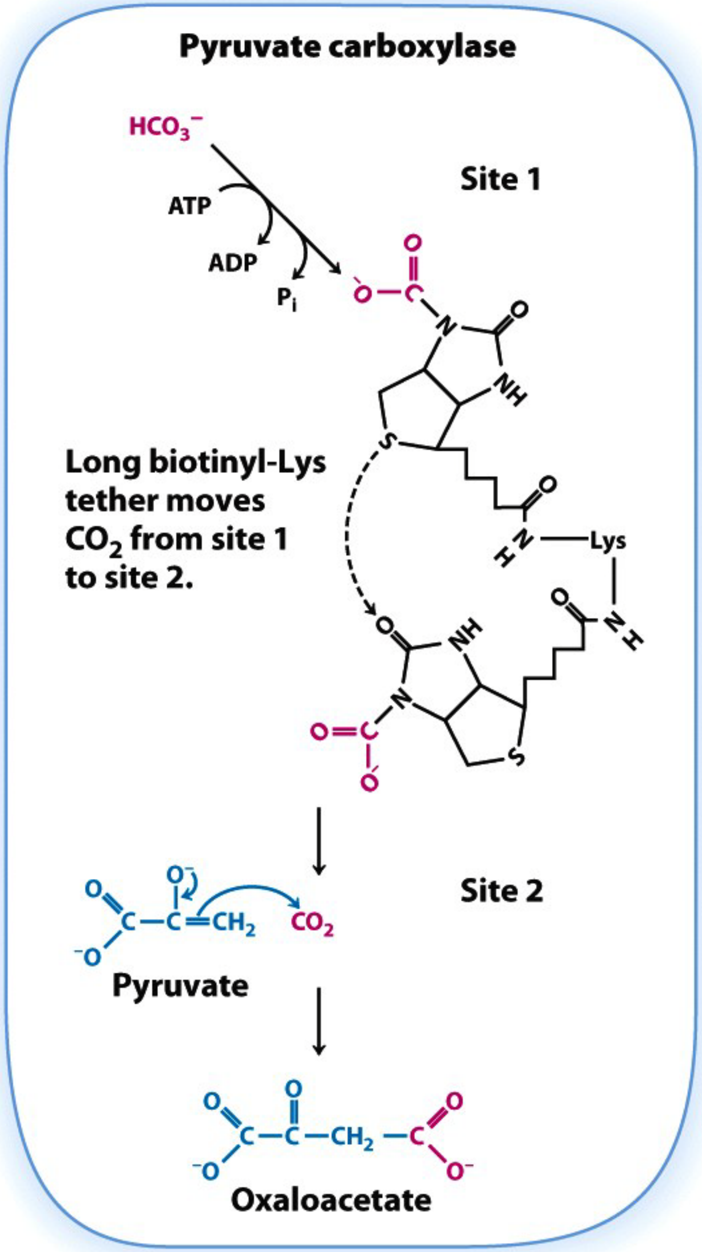


Figure 14-17a



ıanism for the pyru-
. Bicarbonate must be
: pyruvate carbanion.
ɔy ATP and involves
hosphate intermediate



Pyruvate carboxylase
HCO_3^-
ATP
ADP
P_i
Site 1
Long biotinyl-Lys tether moves CO_2 from site 1 to site 2.
Lys
Site 2
CO_2
Pyruvate
Oxaloacetate

Figure 14-18

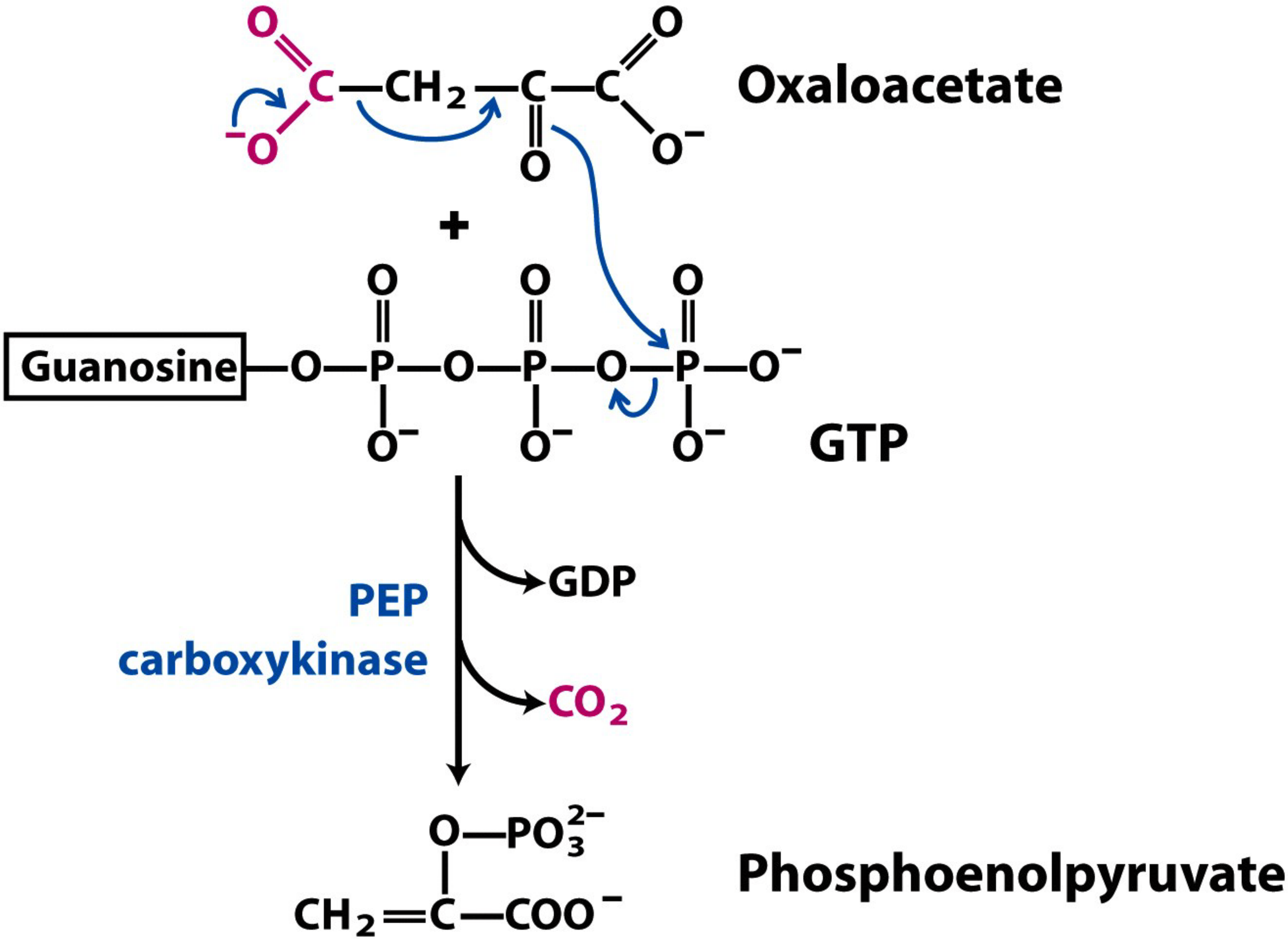


Figure 14-17b
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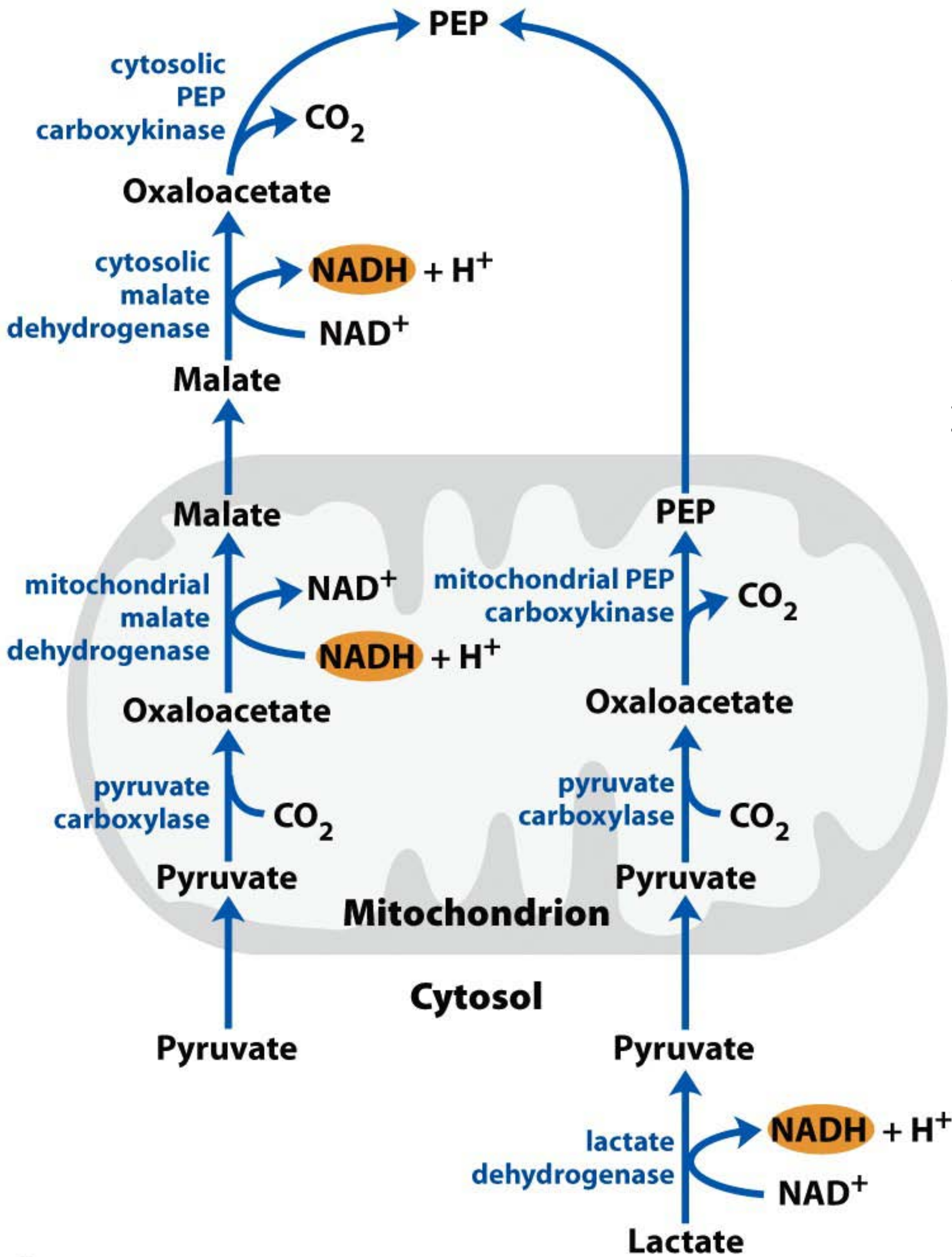
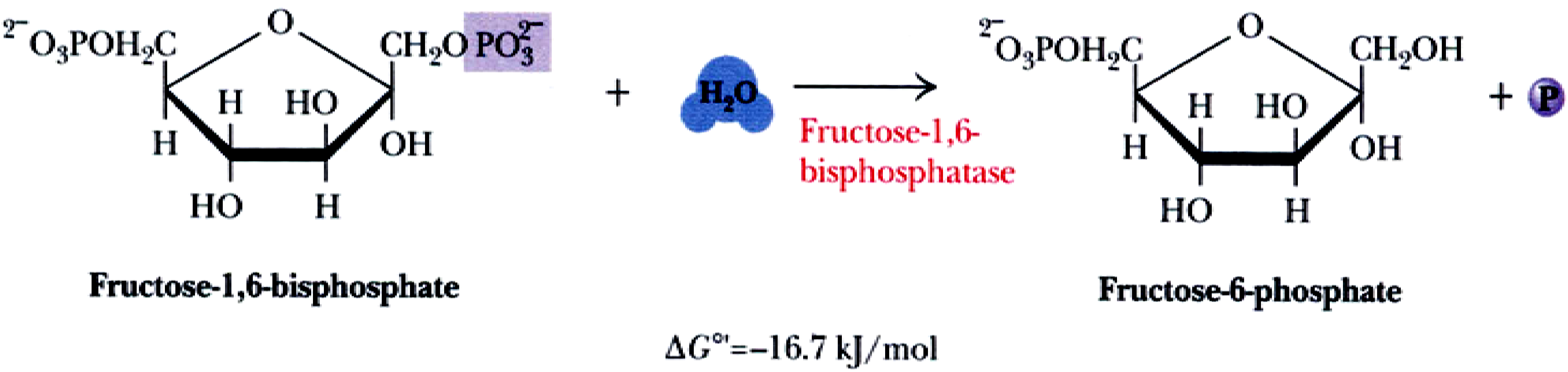


Figure 14-19

[NADH]/[NAD^+] ratio in the cytosol is about 10^5 times lower than in mitochondria

Alternative paths from pyruvate to phosphoenolpyruvate

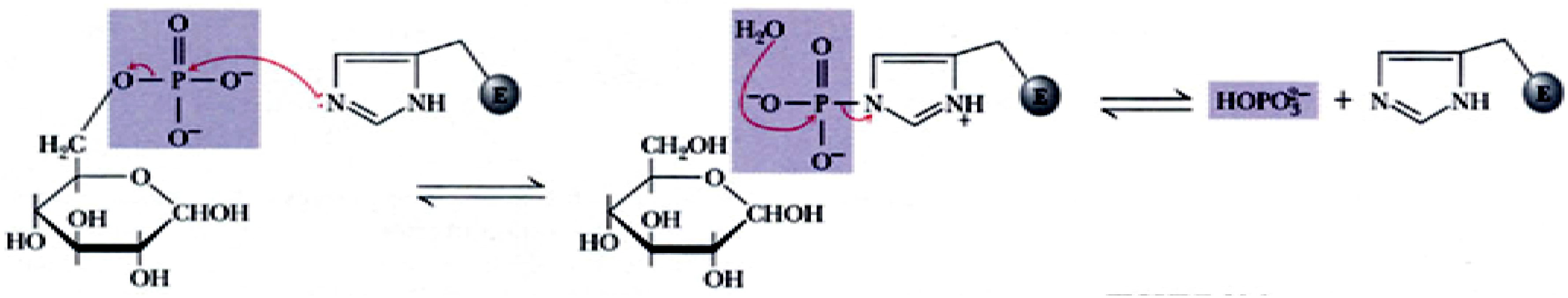
(2) Conversion of FBP to fructose-6-phosphate



Citrate is an allosteric activator, but AMP and fructose-2,6-bisphosphate is an allosteric inhibitor for this enzyme.

(3) Conversion of G-6-p to glucose

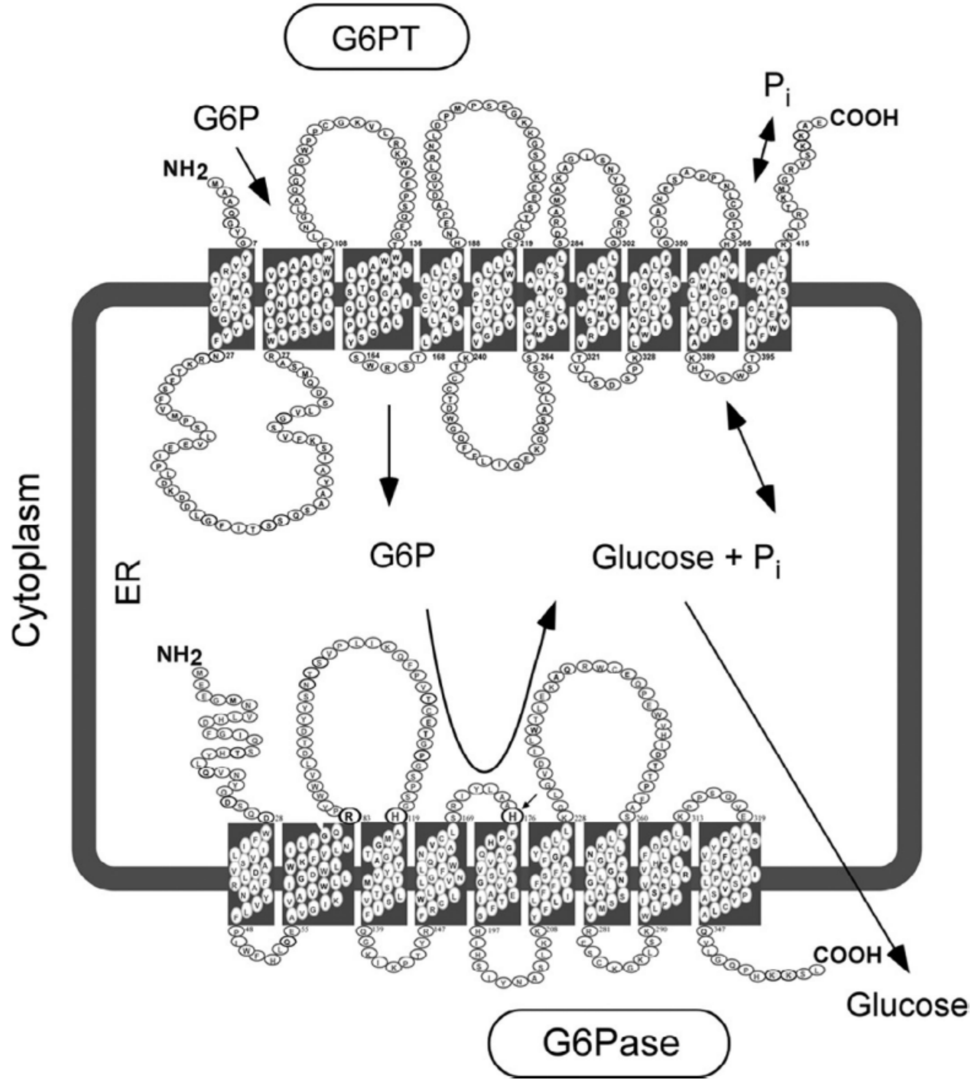
Glucose-6-phosphatase



This enzyme is present in the membranes of the endoplasmic reticulum of liver and kidney cell, absent in muscle and brain

Von Gieke's disease (type I glycogen storage disease)

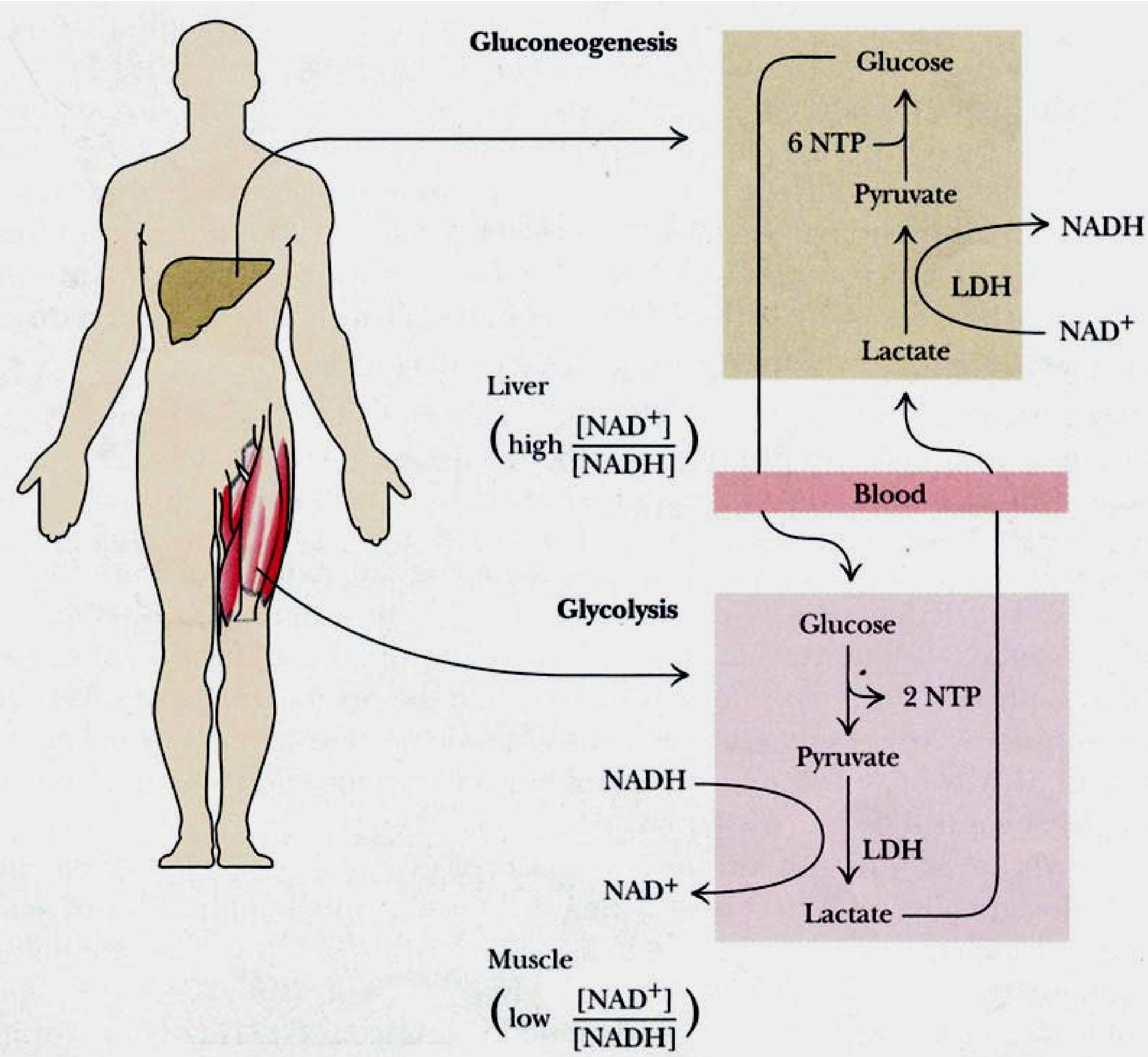
Carl and Gerty cori 1947 Nobel



The G6PT(G-6-P transporter)/G6Pase complex. The diagram shows a cross-section of the ER

Curr Top Membr. 2014;73:357-82.
The SLC37 family of sugar-phosphate/phosphate exchangers

Dr. **Gerty Theresa Cori**, née **Radnitz**, (August 15, 1896 – October 26, 1957) was an American biochemist born in Prague (Austrian Empire, now Czech Republic) who, together with her husband Carl Ferdinand Cori and Argentine physiologist Bernardo Houssay, received a Nobel Prize in Physiology or Medicine in 1947 for their discovery of how glycogen (animal starch) — a derivative of glucose — is broken down and resynthesized in the body, for use as a store and source of energy.



The Cori cycle

The cycle of reactions that includes glucose conversion to lactate in muscle and lactate conversion to glucose in liver

Gluconeogenesis is energitically expensive, but essential

TABLE 14–3	Sequential Reactions in Gluconeogenesis Starting from Pyruvate
Pyruvate + HCO_3^- + ATP ⟶ oxaloacetate + ADP + P_i	×2
Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO_2 + GDP	×2
Phosphoenolpyruvate + H_2O ⇌ 2-phosphoglycerate	×2
2-Phosphoglycerate ⇌ 3-phosphoglycerate	×2
3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP	×2
1,3-Bisphosphoglycerate + NADH + H^+ ⇌ glyceraldehyde 3-phosphate + NAD^+ + P_i	×2
Glyceraldehyde 3-phosphate ⇌ dihydroxyacetone phosphate	
Glyceraldehyde 3-phosphate + dihydroxyacetone phosphate ⇌ fructose 1,6-bisphosphate	
Fructose 1,6-bisphosphate ⟶ fructose 6-phosphate + P_i	
Fructose 6-phosphate ⇌ glucose 6-phosphate	
Glucose 6-phosphate + H_2O ⟶ glucose + P_i	
Sum: 2 Pyruvate + 4ATP + 2GTP + 2NADH + $2H^+$ + $4H_2O$ ⟶ glucose + 4ADP + 2GDP + $6P_i$ + $2NAD^+$	

Note: The bypass reactions are in red; all other reactions are reversible steps of glycolysis. The figures at the right indicate that the reaction is to be counted twice, because two three-carbon precursors are required to make a molecule of glucose. The reactions required to replace the cytosolic NADH consumed in the glyceraldehyde 3-phosphate dehydrogenase reaction (the conversion of lactate to pyruvate in the cytosol or the transport of reducing equivalents from mitochondria to the cytosol in the form of malate) are not considered in this summary. Biochemical equations are not necessarily balanced for H and charge (p. 501).

Table 14-3

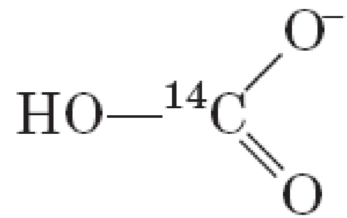
TABLE 14–4	Glucogenic Amino Acids, Grouped by Site of Entry
Pyruvate	**Succinyl-CoA**
Alanine	Isoleucine*
Cysteine	Methionine
Glycine	Threonine
Serine	Valine
Threonine	**Fumarate**
Tryptophan*	Phenylalanine*
α-Ketoglutarate	Tyrosine*
Arginine	**Oxaloacetate**
Glutamate	Asparagine
Glutamine	Aspartate
Histidine	
Proline	

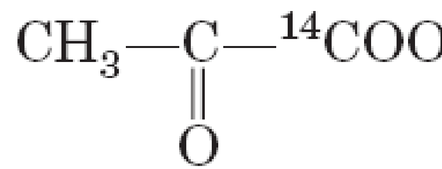
Note: All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis.

*These amino acids are also ketogenic (see Fig. 18–21).

Table 14-4

16. Pathway of Atoms in Gluconeogenesis A liver extract capable of carrying out all the normal metabolic reactions of the liver is briefly incubated in separate experiments with the following ^{14}C-labeled precursors:

(a) [^{14}C]Bicarbonate, 

(b) [1-^{14}C]Pyruvate, 

Trace the pathway of each precursor through gluconeogenesis. Indicate the location of ^{14}C in all intermediates and in the product, glucose.

14.5 Pentose phosphate pathway of glucose oxidation

A pathway that serves to interconvert hexoses and pentoses and is a source of reducing equivalents and pentoses for biosynthetic processes, present in most organisms.

hexose monophosphate pathway

phosphogluconate pathway.

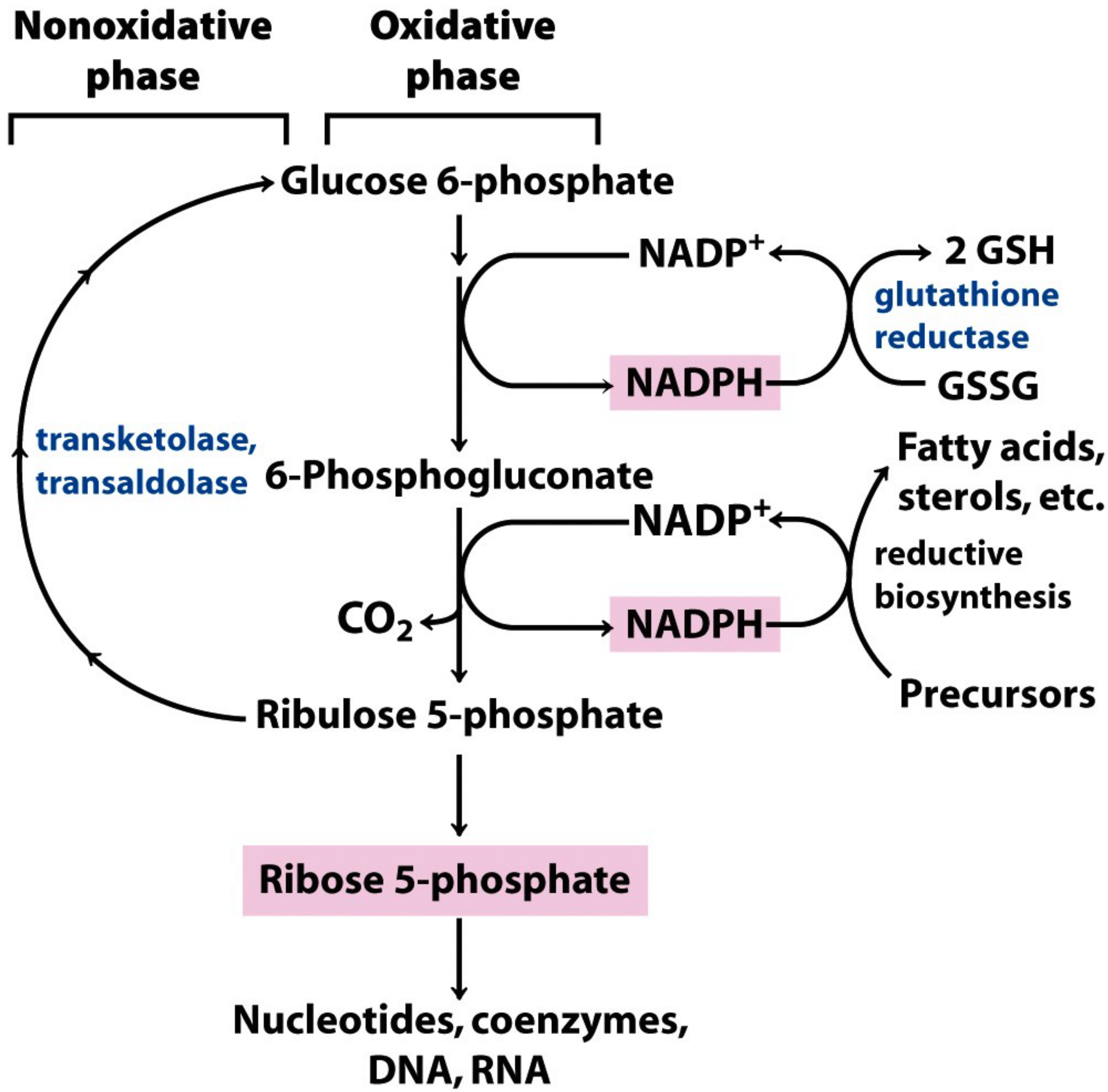
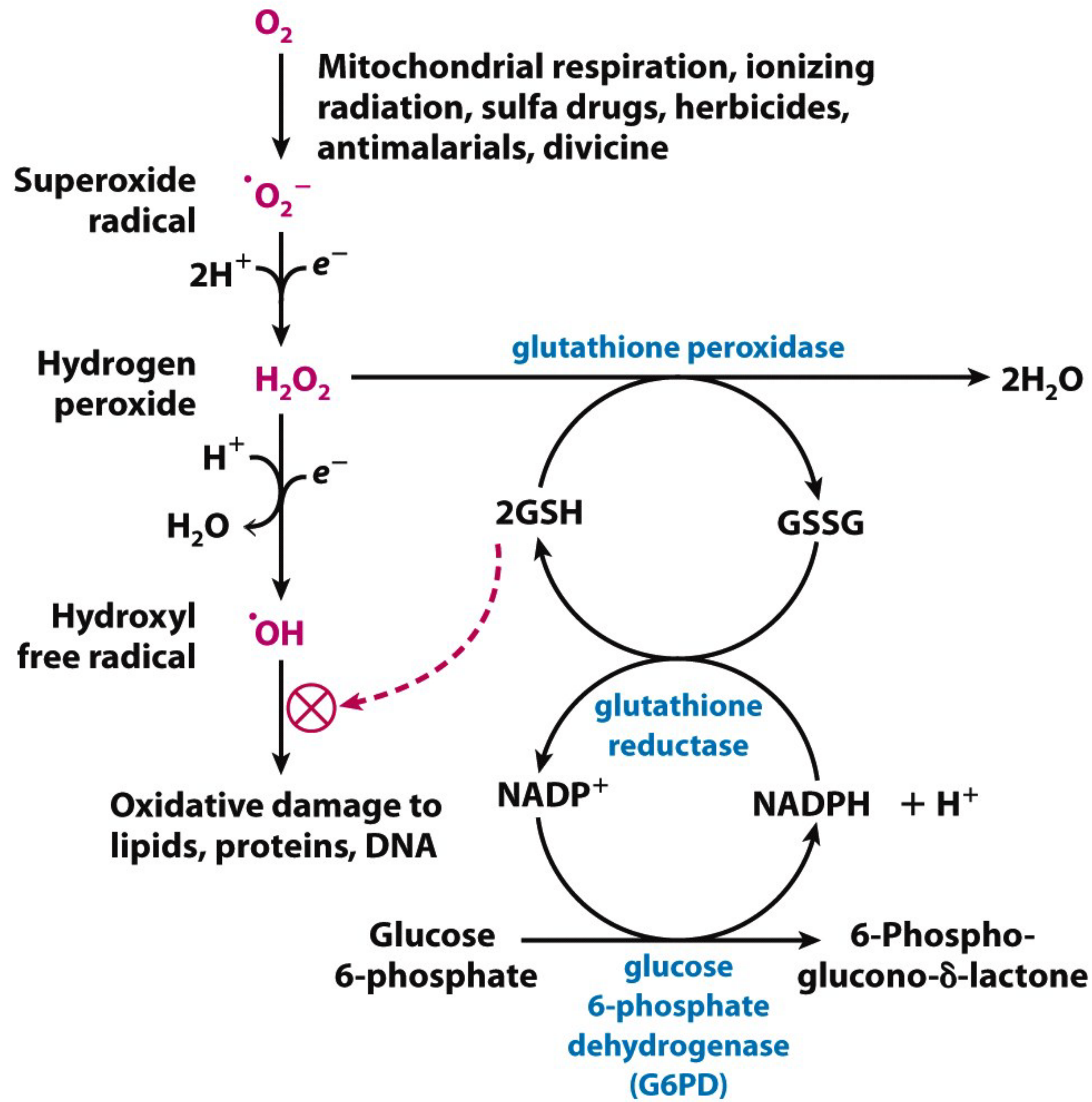

Nonoxidative phase
Oxidative phase
Glucose 6-phosphate
$NADP^+$
2 GSH
glutathione reductase
NADPH
GSSG
transketolase, transaldolase
6-Phosphogluconate
Fatty acids, sterols, etc.
$NADP^+$
reductive biosynthesis
CO_2
NADPH
Precursors
Ribulose 5-phosphate
Ribose 5-phosphate
Nucleotides, coenzymes, DNA, RNA

Figure 14-20



Box 14-4 figure 1

Role of NADPH and glutathione in protecting cells against ROS

Superoxide dismutases (SOD)

- $Cu^{2+}-SOD + O_2^- \rightarrow Cu^+-SOD + O_2$
- $Cu^+-SOD + O_2^- + 2H^+ \rightarrow Cu^{2+}-SOD + H_2O_2$

$$2\,O_2^- + 2H^+ \longrightarrow O_2 + H_2O_2$$

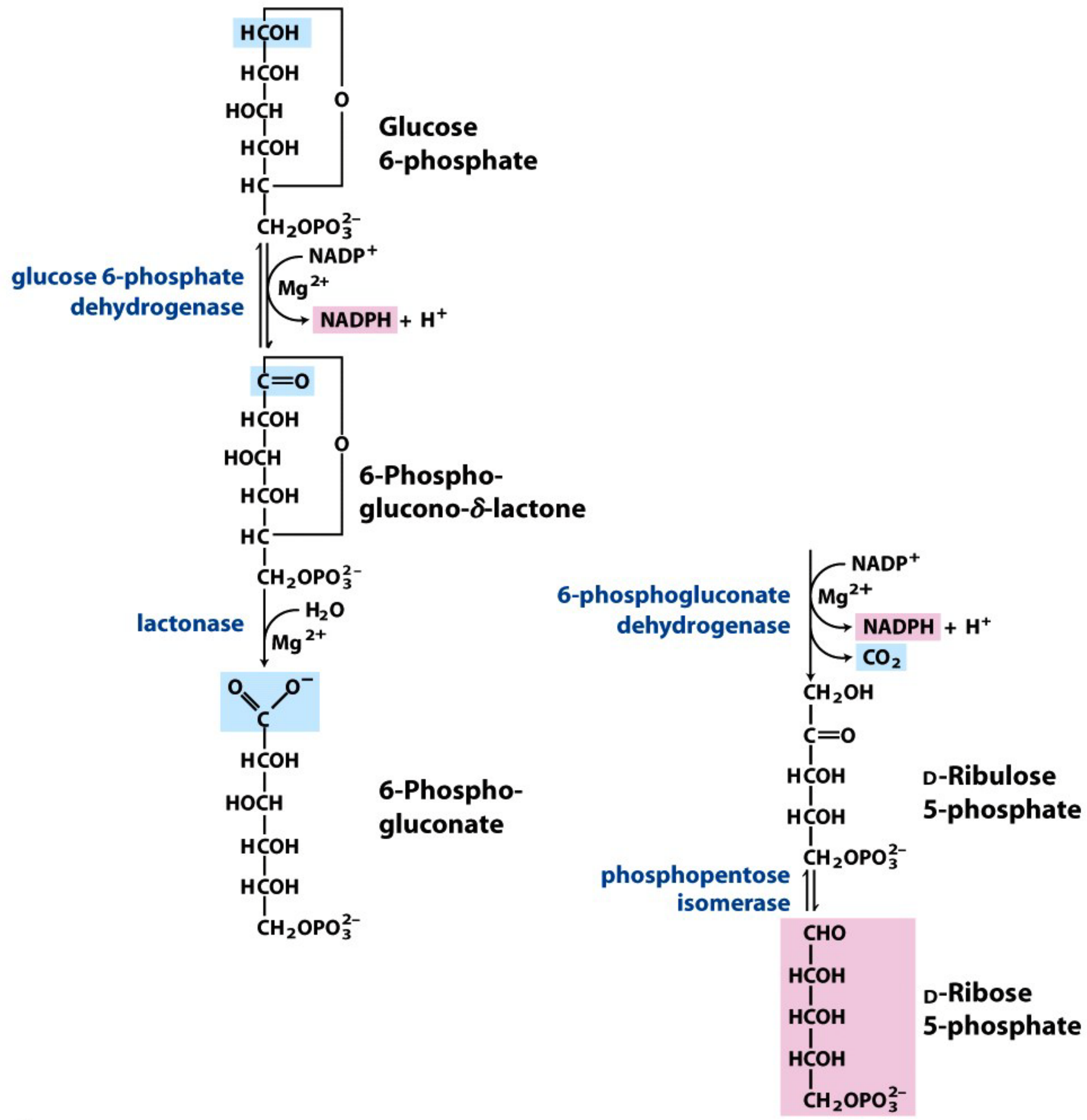


Figure 14-21

The oxidative phase produces pentose phosphates and NADPH

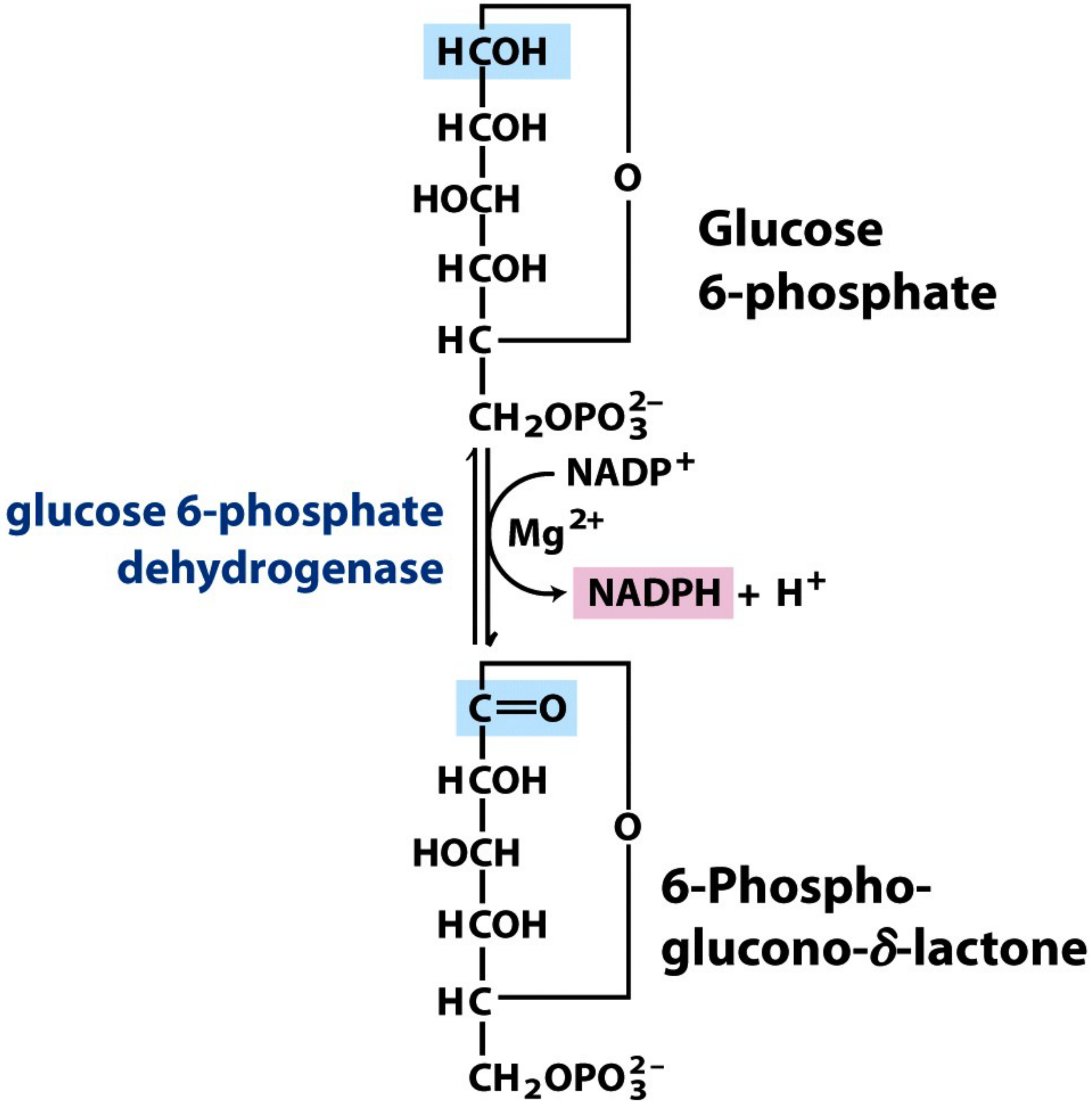


Figure 14-21 part 1

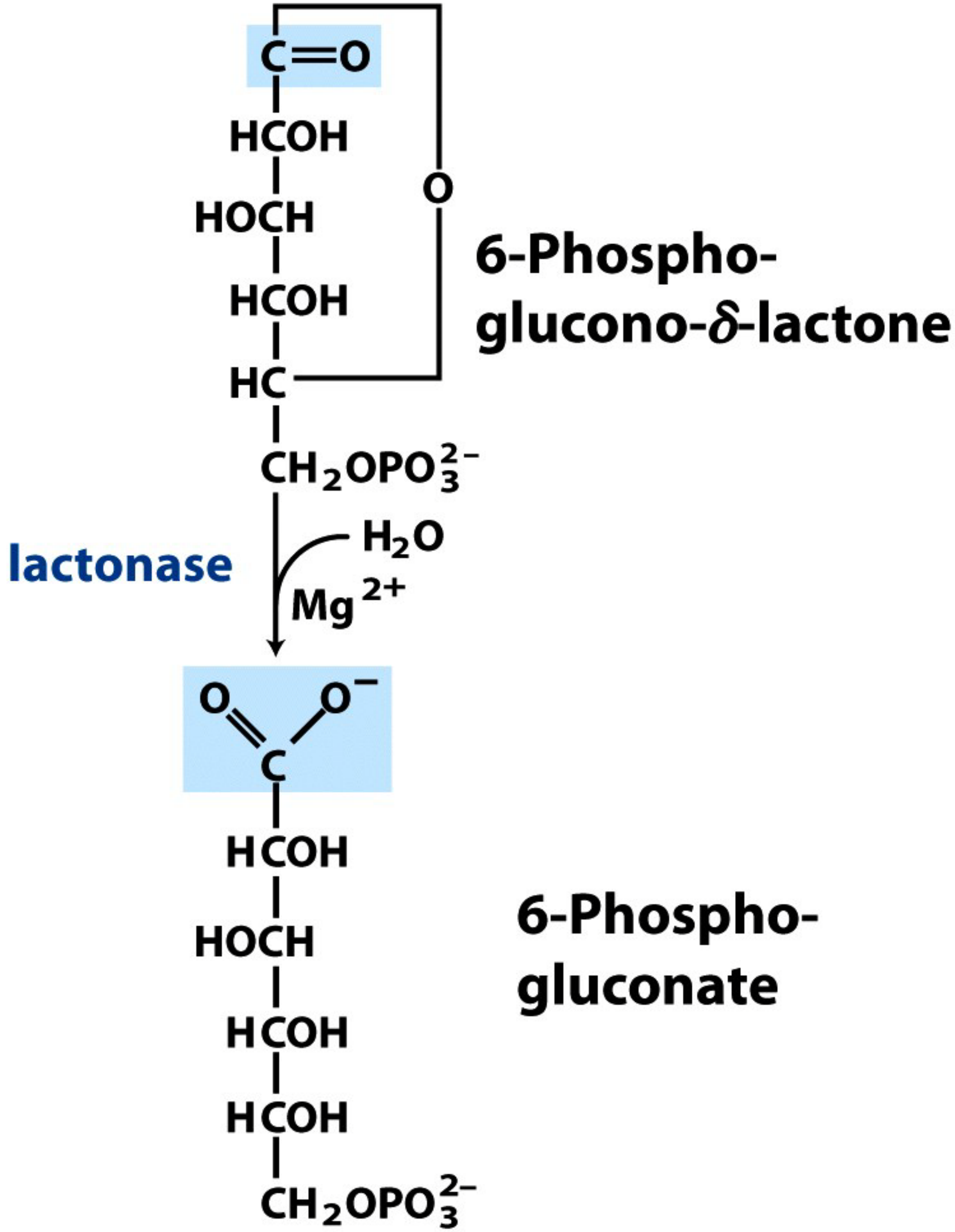


Figure 14-21 part 2

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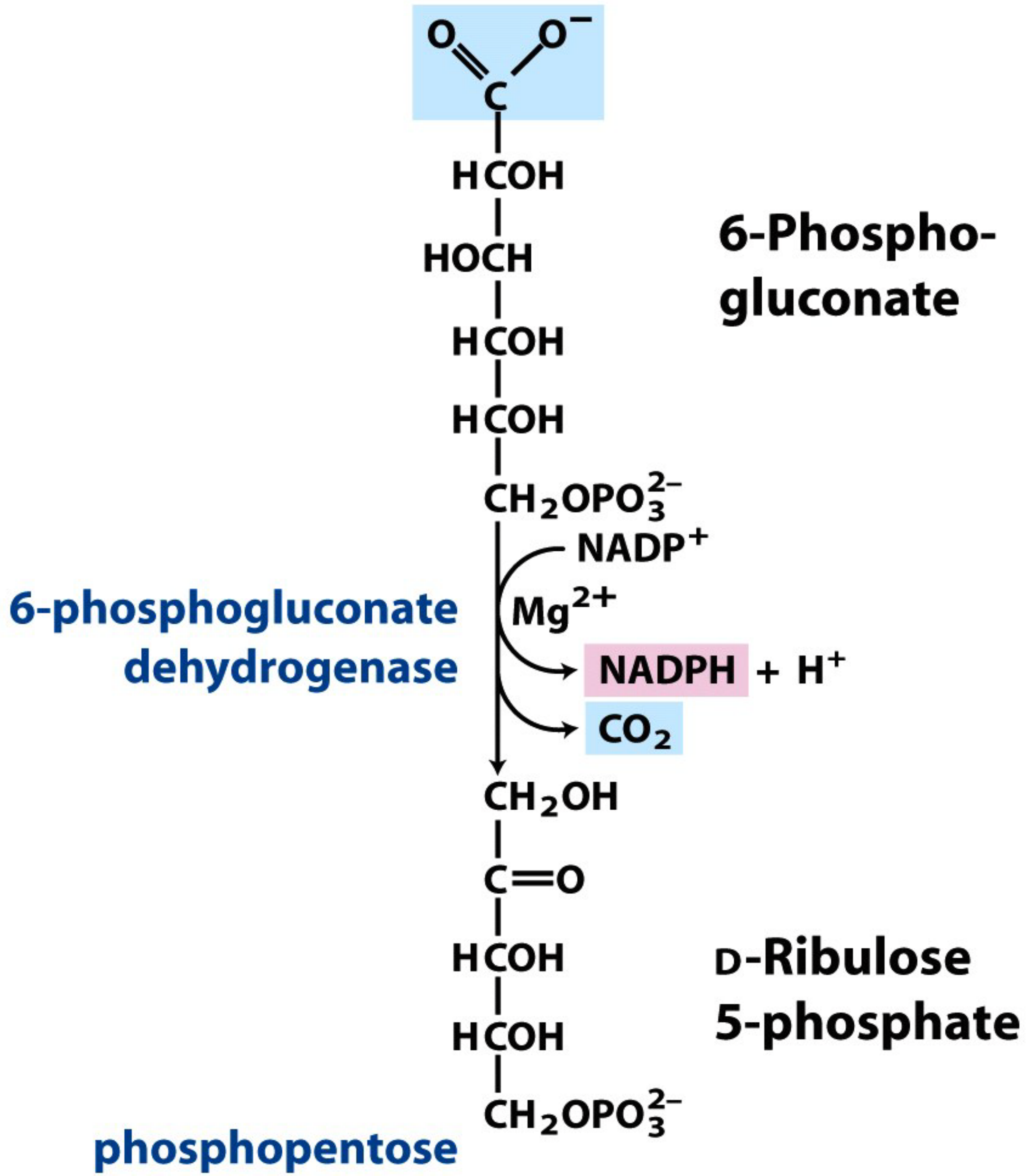

Figure 14-21 part 3
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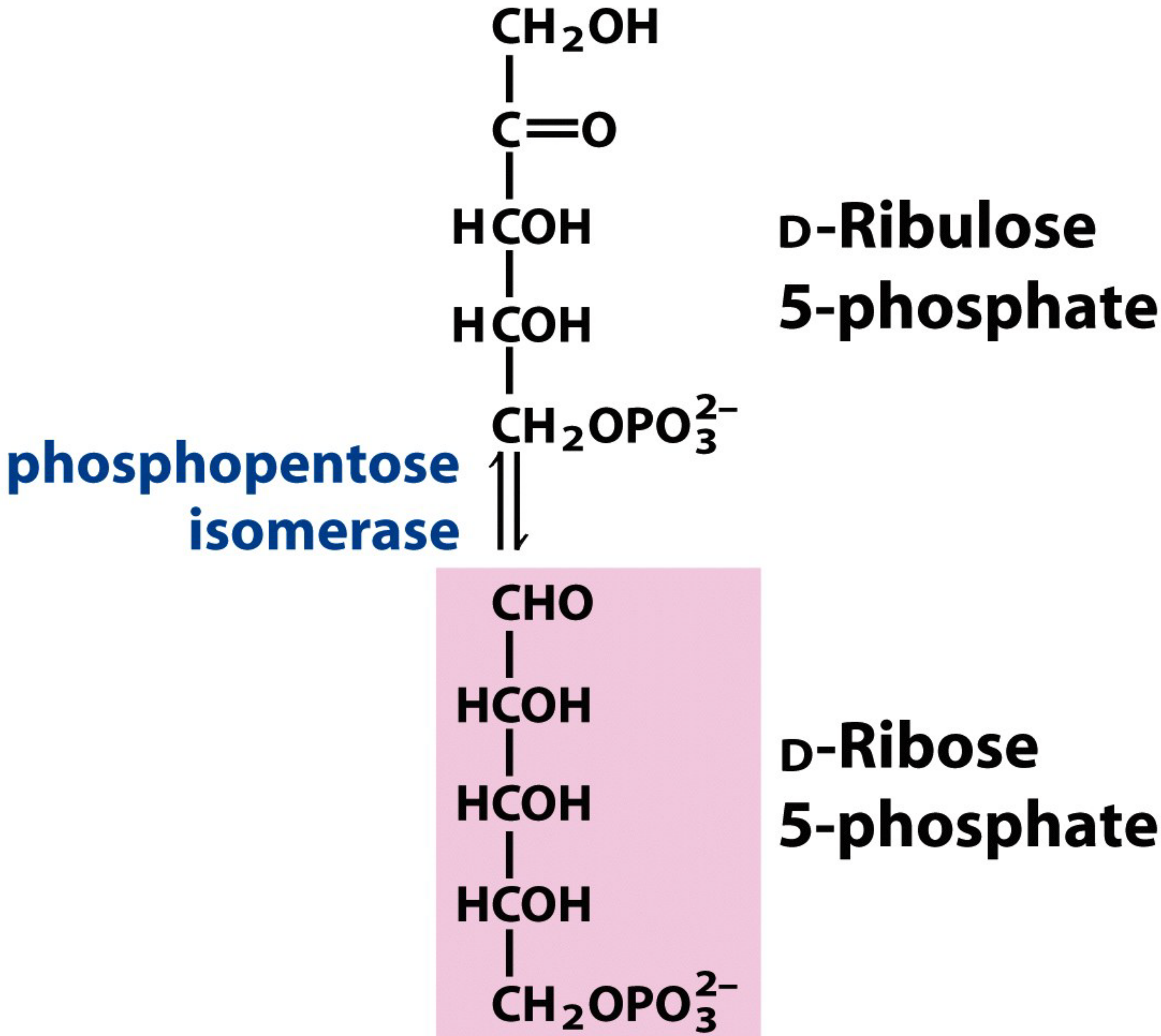

Figure 14-21 part 4
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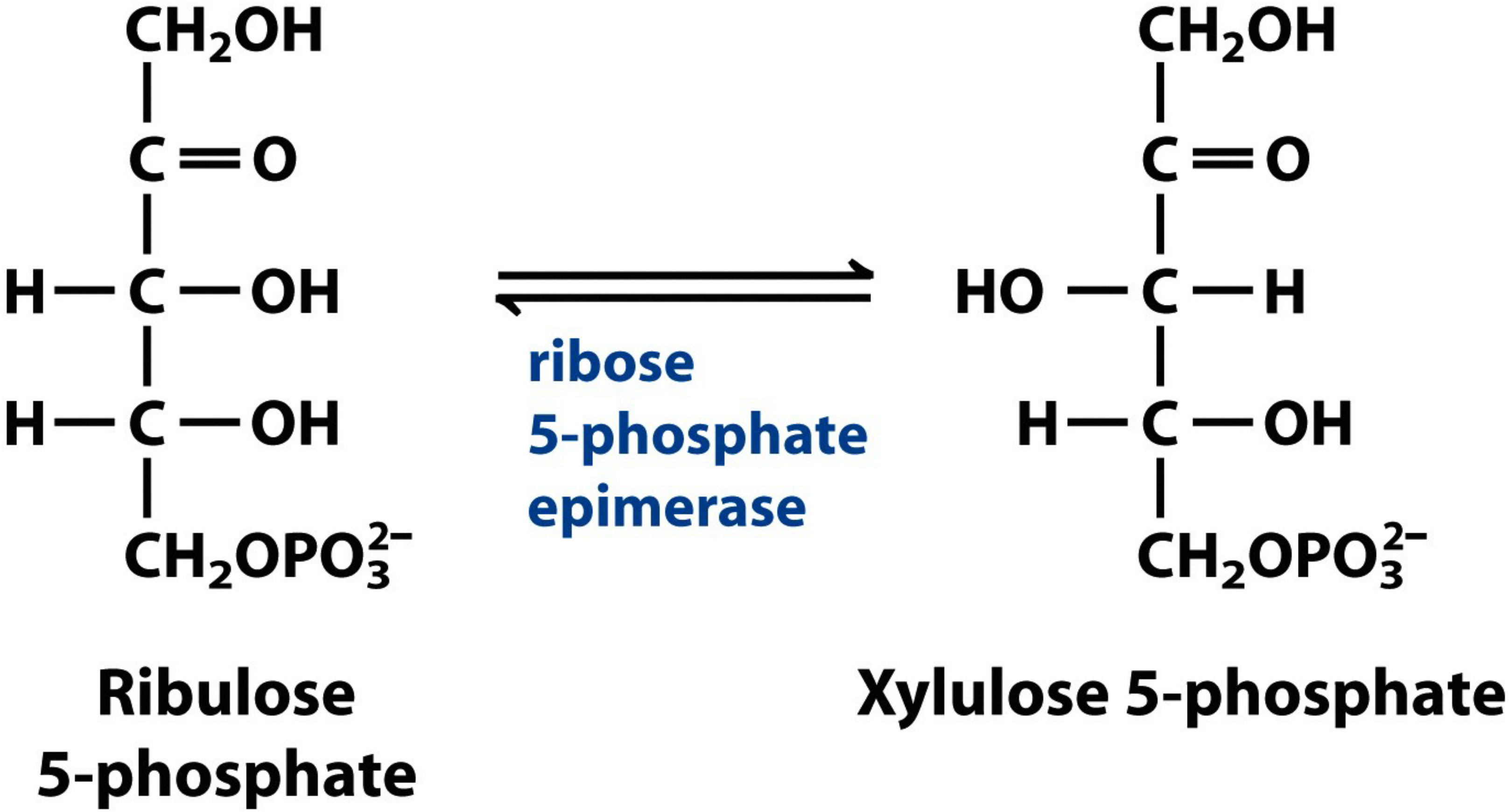

Unnumbered 14 p560

The nonoxidative phase recycles pentose phosphates to G-6-p

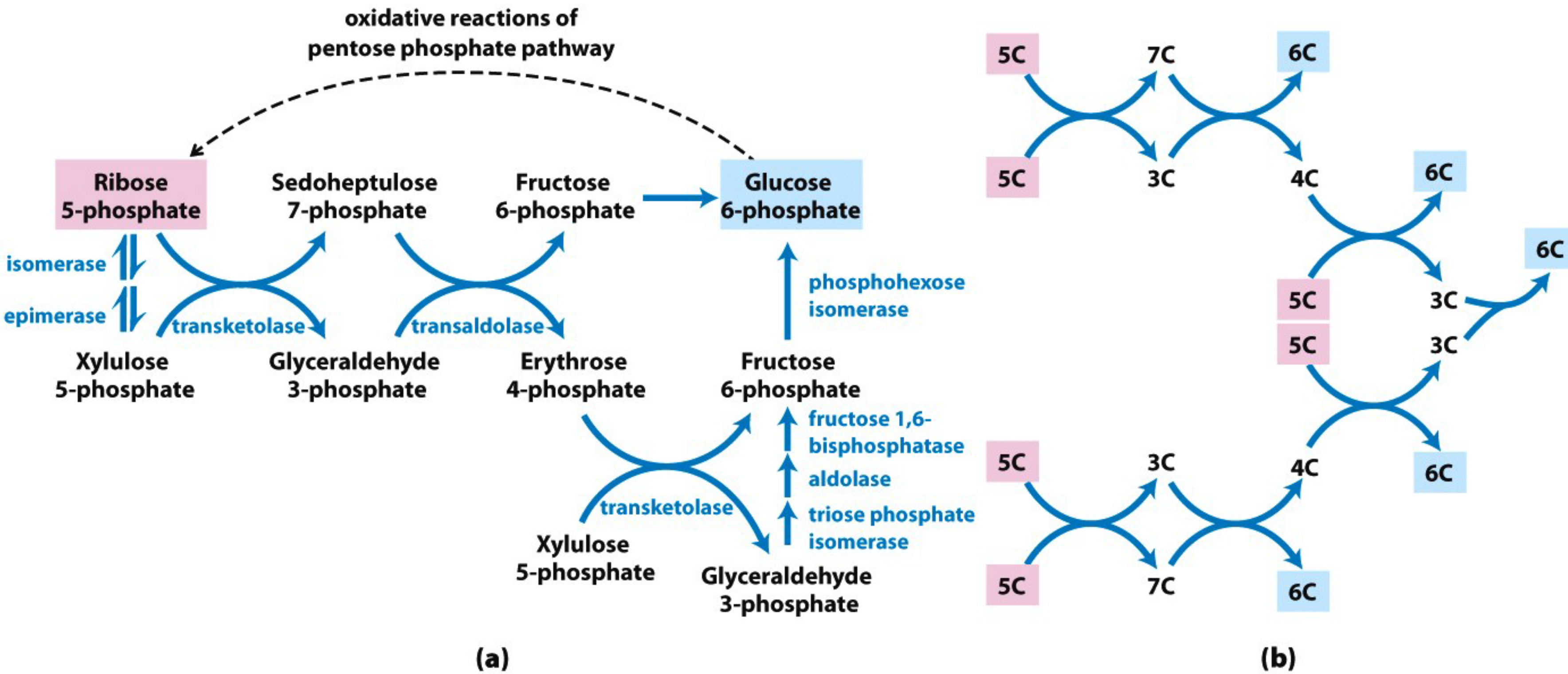

Figure 14-22

Nonoxidative reactions of the pentose phosphate pathway

(a) Pentose phosphates are converted to hexose phosphates

(b) six pentoses (5C) are converted to five hexoses (6C)

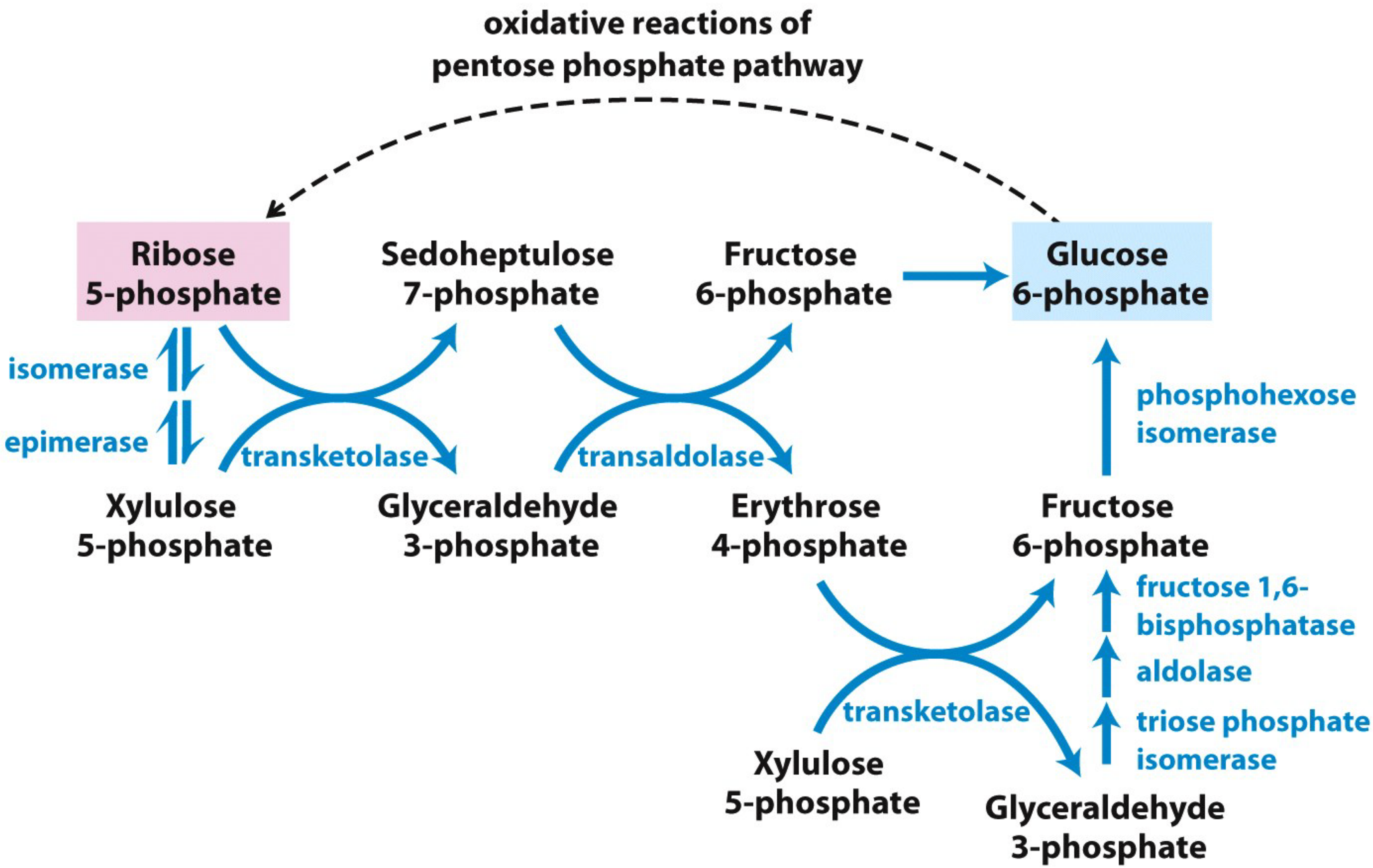

Figure 14-22a
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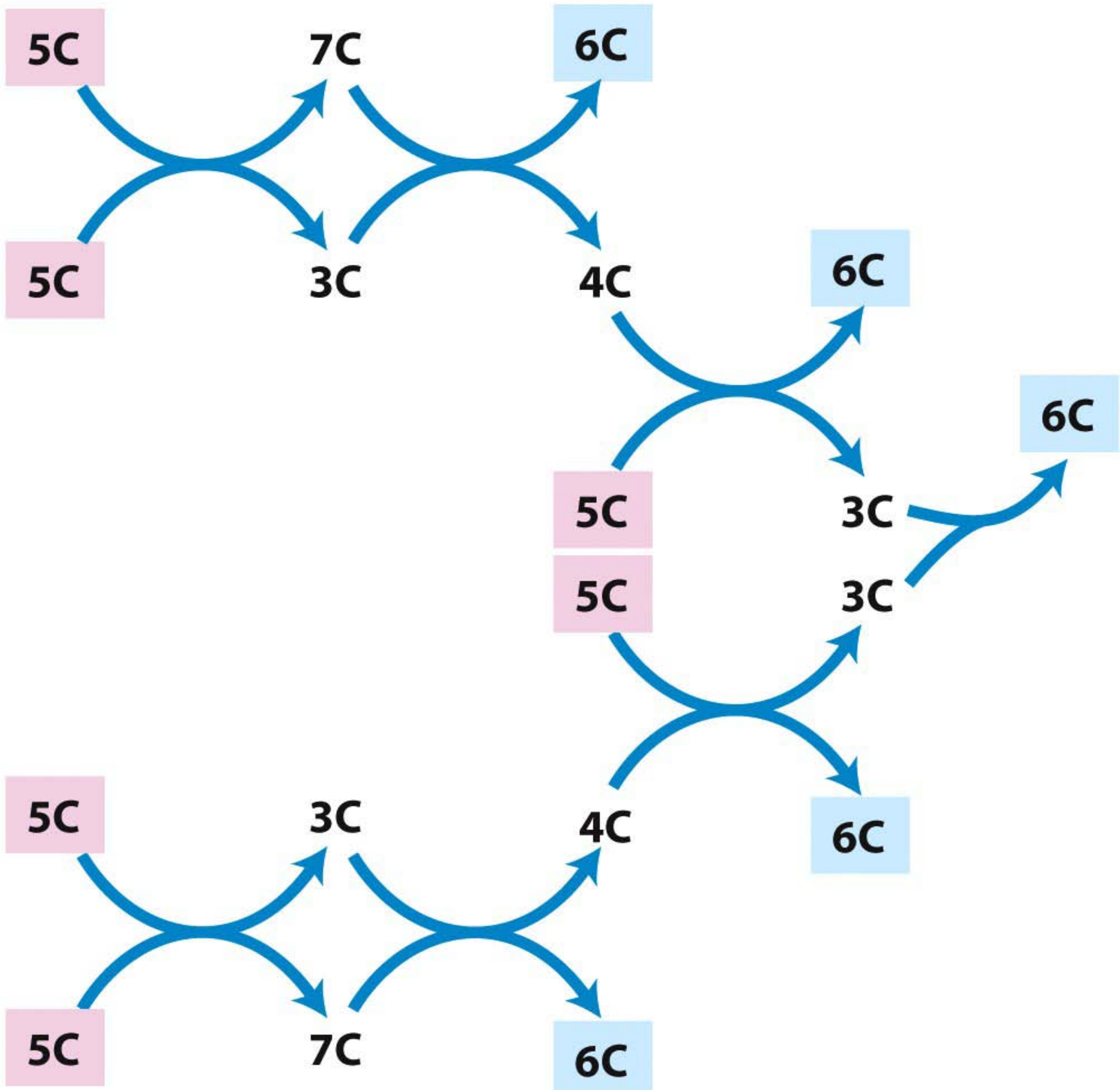

Figure 14-22b
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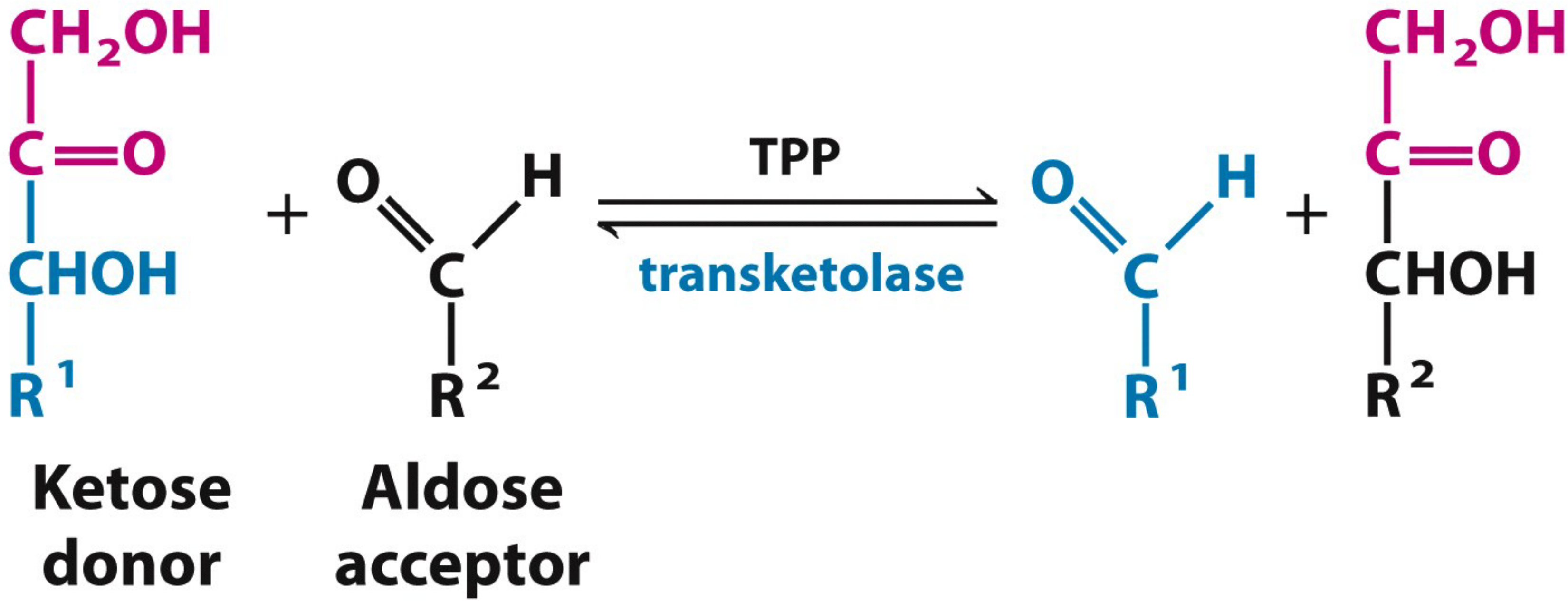

Figure 14-23a
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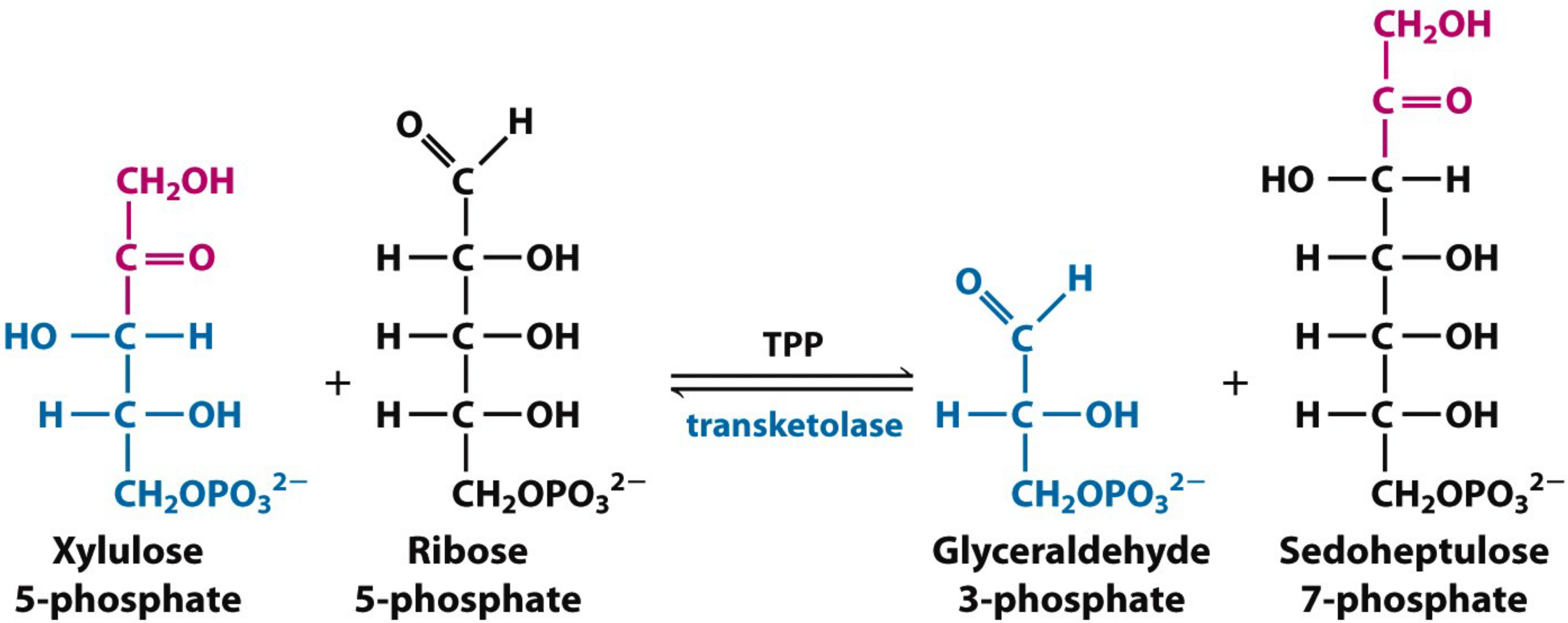

Figure 14-23b

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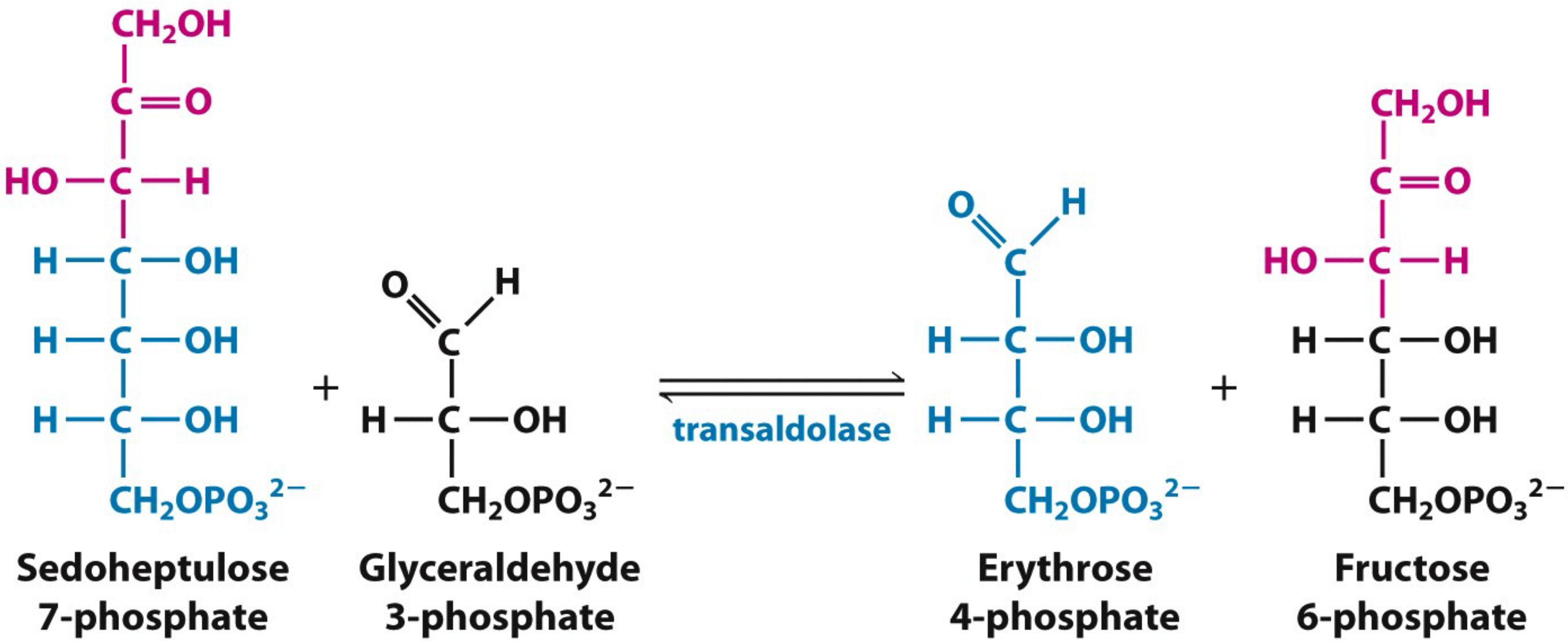

Figure 14-24

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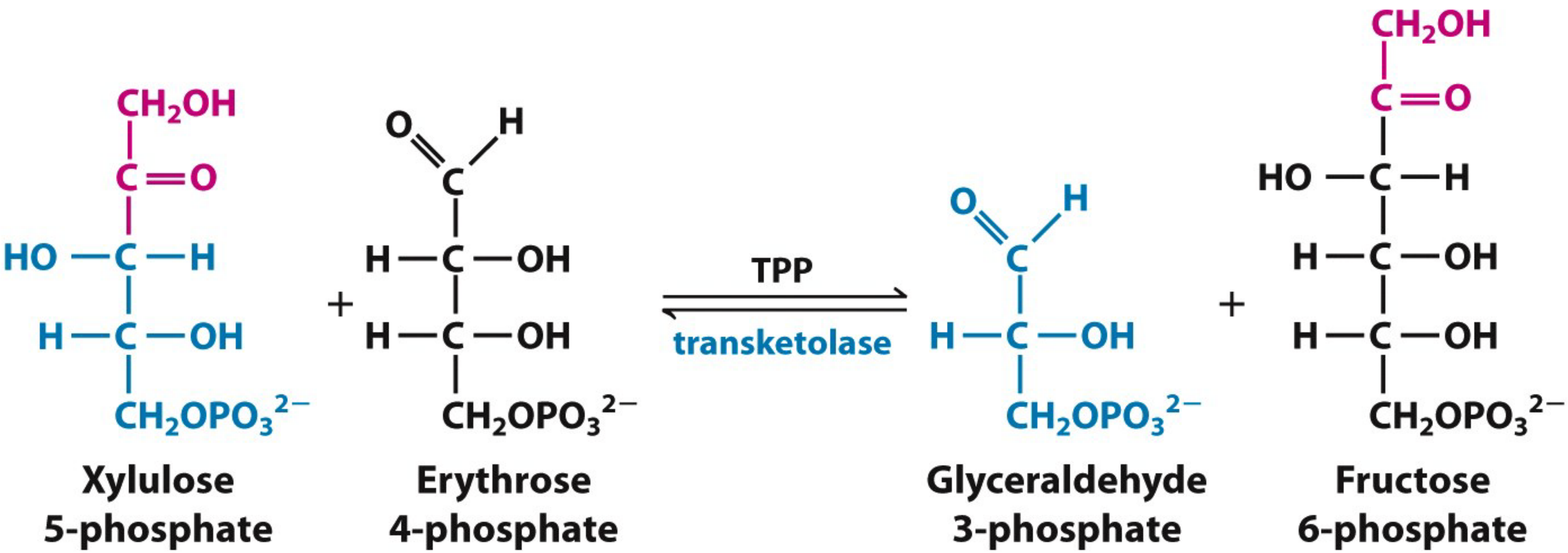

Figure 14-25

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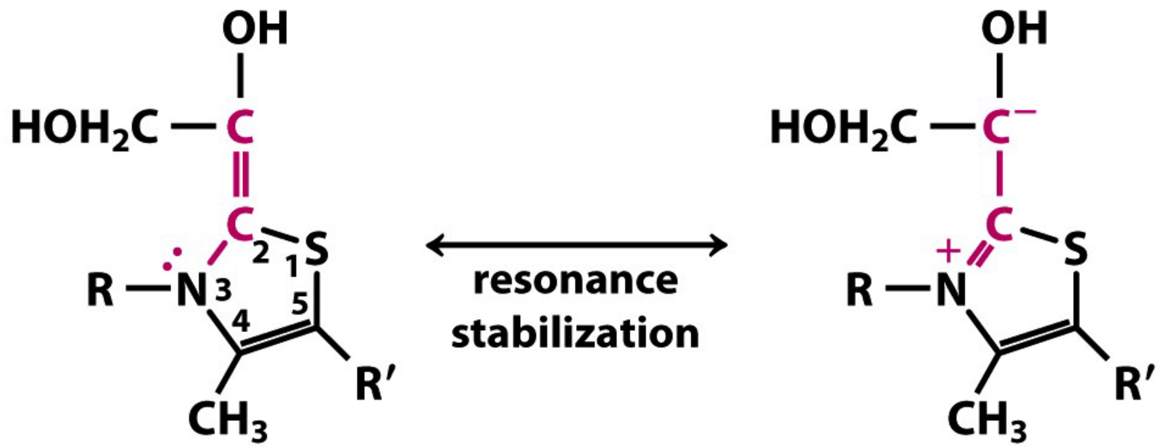
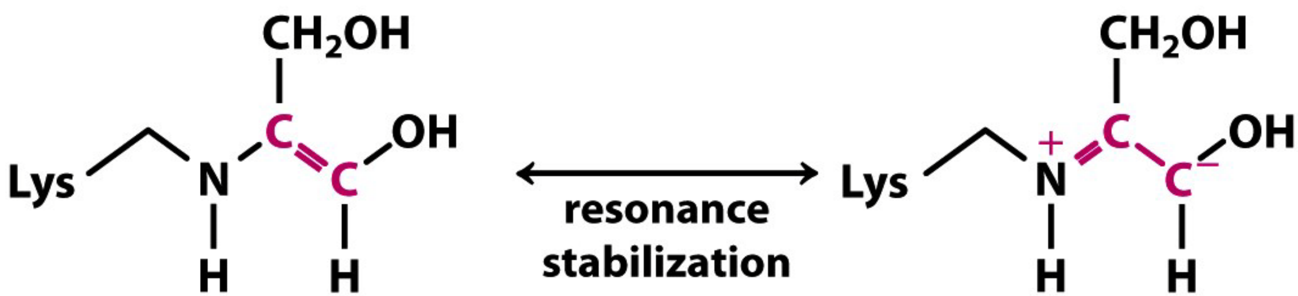
(a) Transketolase



TPP

(b) Transaldolase



Protonated
Schiff base

Figure 14-26
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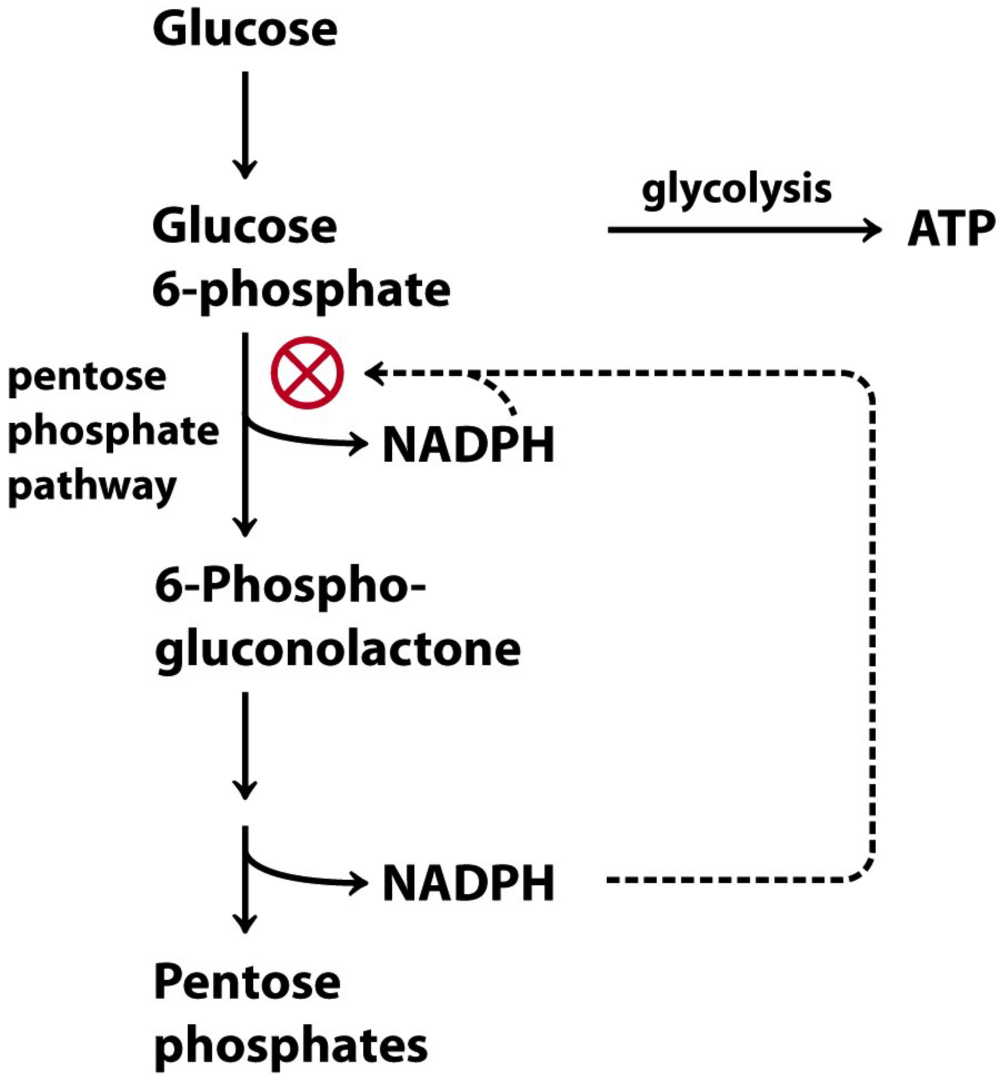
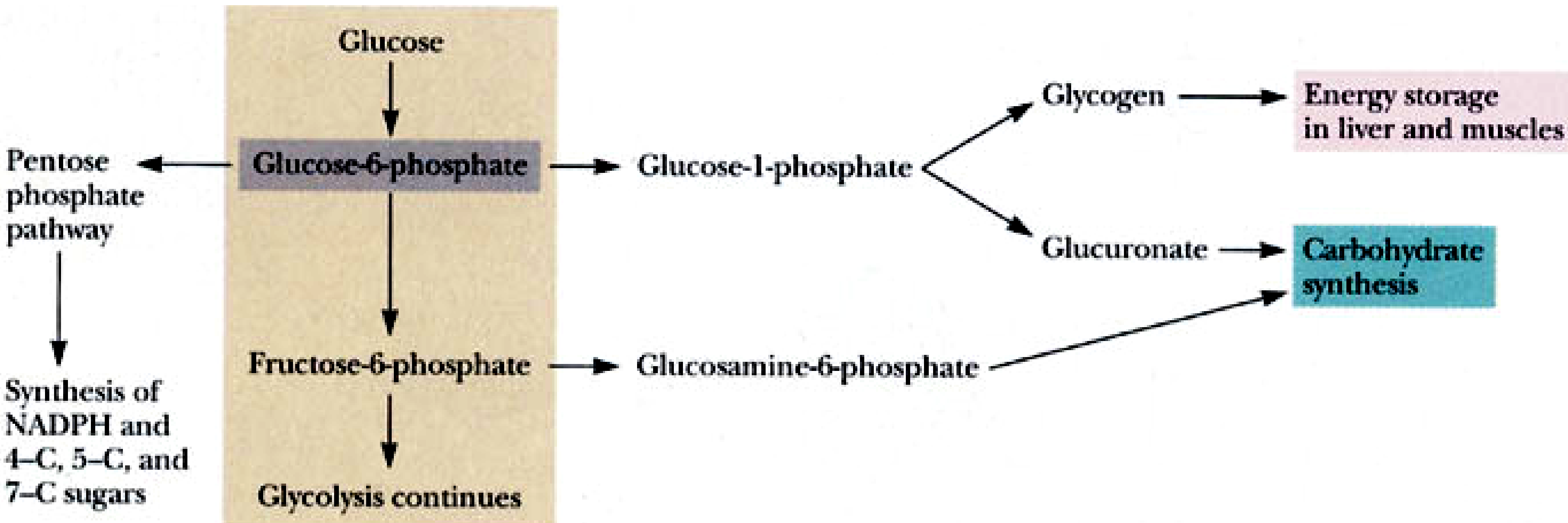


Figure 14-27

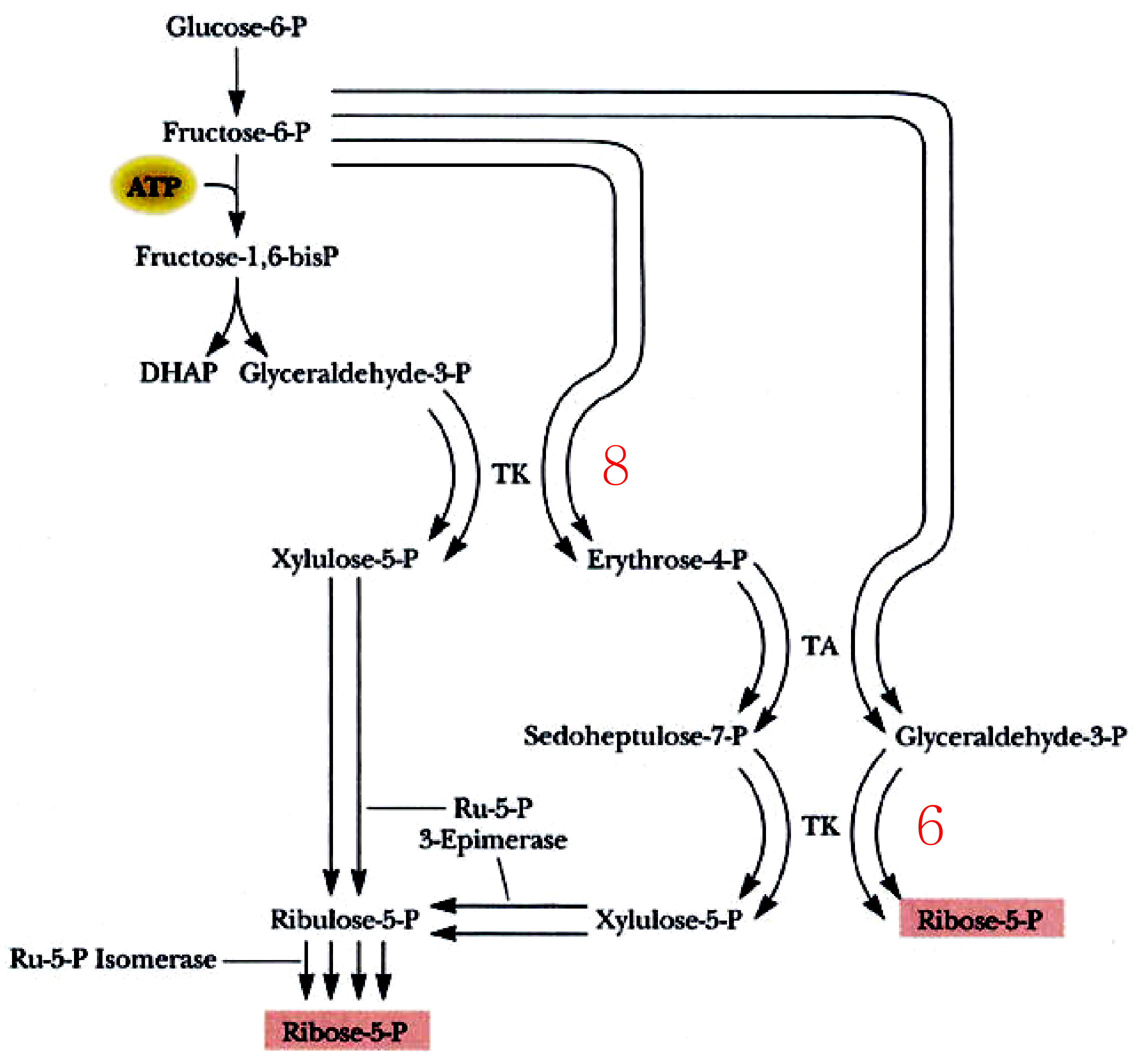
Role of NADPH in regulating the partitioning of G-6-p between glycolysis and the pentose phosphate pathway


Glucose
Glucose-6-phosphate
Pentose phosphate pathway
Synthesis of NADPH and 4–C, 5–C, and 7–C sugars
Fructose-6-phosphate
Glycolysis continues
Glucose-1-phosphate
Glycogen
Energy storage in liver and muscles
Glucuronate
Carbohydrate synthesis
Glucosamine-6-phosphate

(1) both ribose-5-P and NADPH are needed

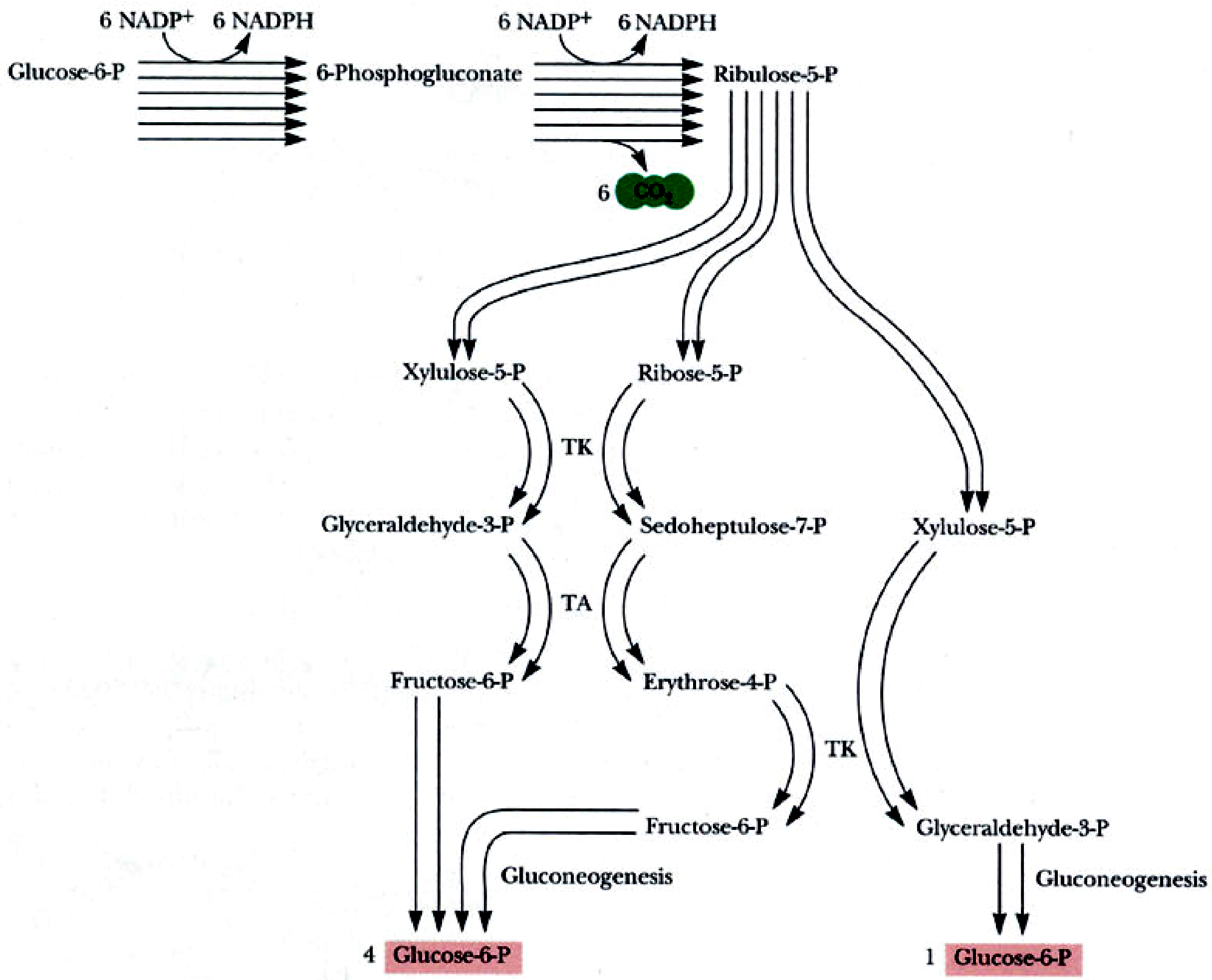
$$\text{G-6-P} + 2\ \text{NADP}^+ \rightarrow \text{ribose-5-P} + 2\ \text{NADPH} + 2\text{H}^+ + \text{CO}_2$$

(2) more ribose-5-P than NADPH is needed



$$5\ G\text{-}6\text{-}P + ATP \rightarrow 6\ ribose\text{-}5\text{-}P + ADP + H^+$$

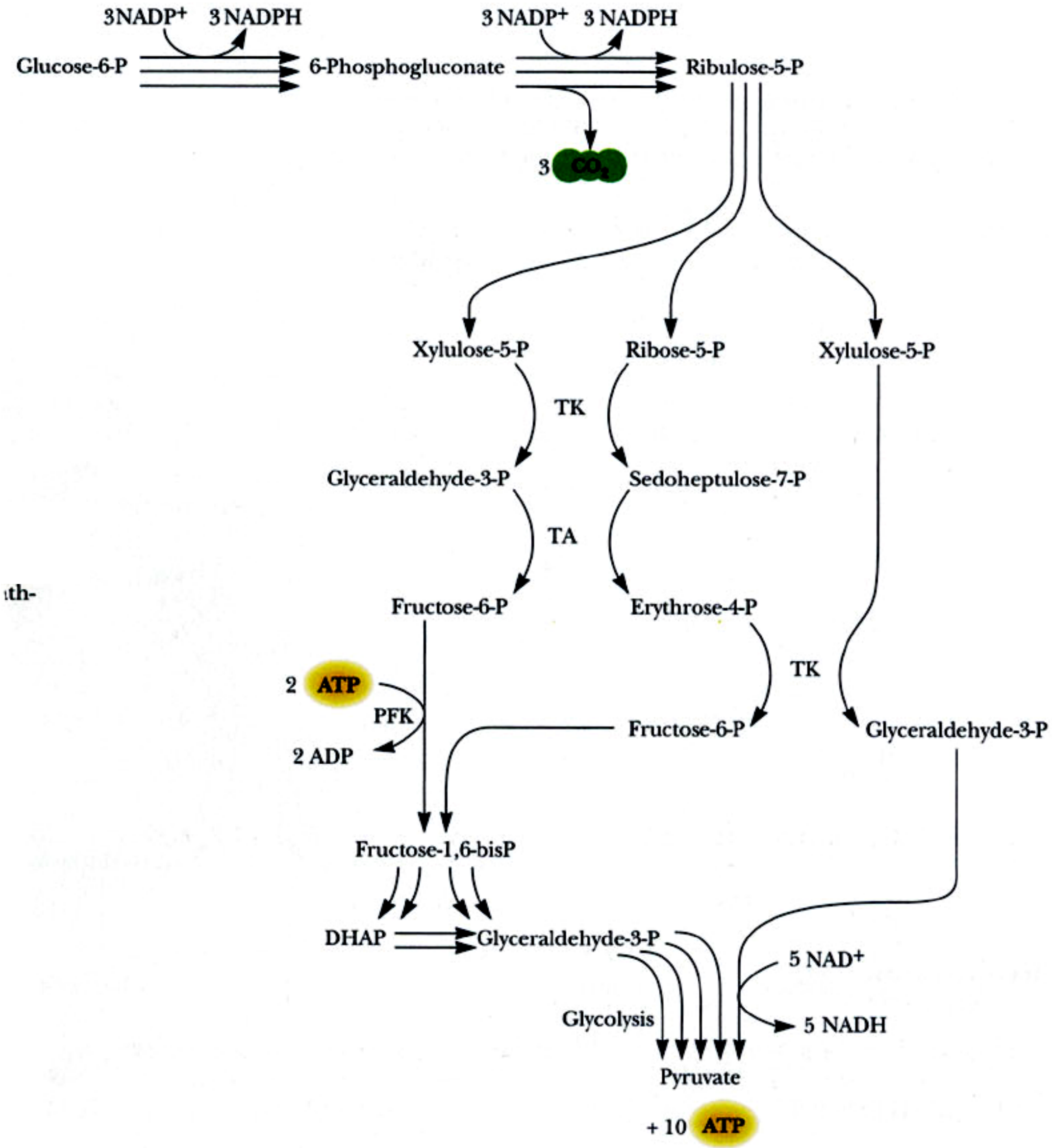
(3) more NADPH than ribose-5-P is needed



$$6G-6-P + 12NADP^+ + 6H_2O \rightarrow 6ribulose-5-P + 6CO_2 + 12NADPH + 12H^+$$

$$6ribulose-5-P \rightarrow 5\ G-6-P + Pi$$

(4) both NADPH and ATP are needed



Both ATP and NADPH can be produced by the version of the pentose phosphate and glycolytic pathways.