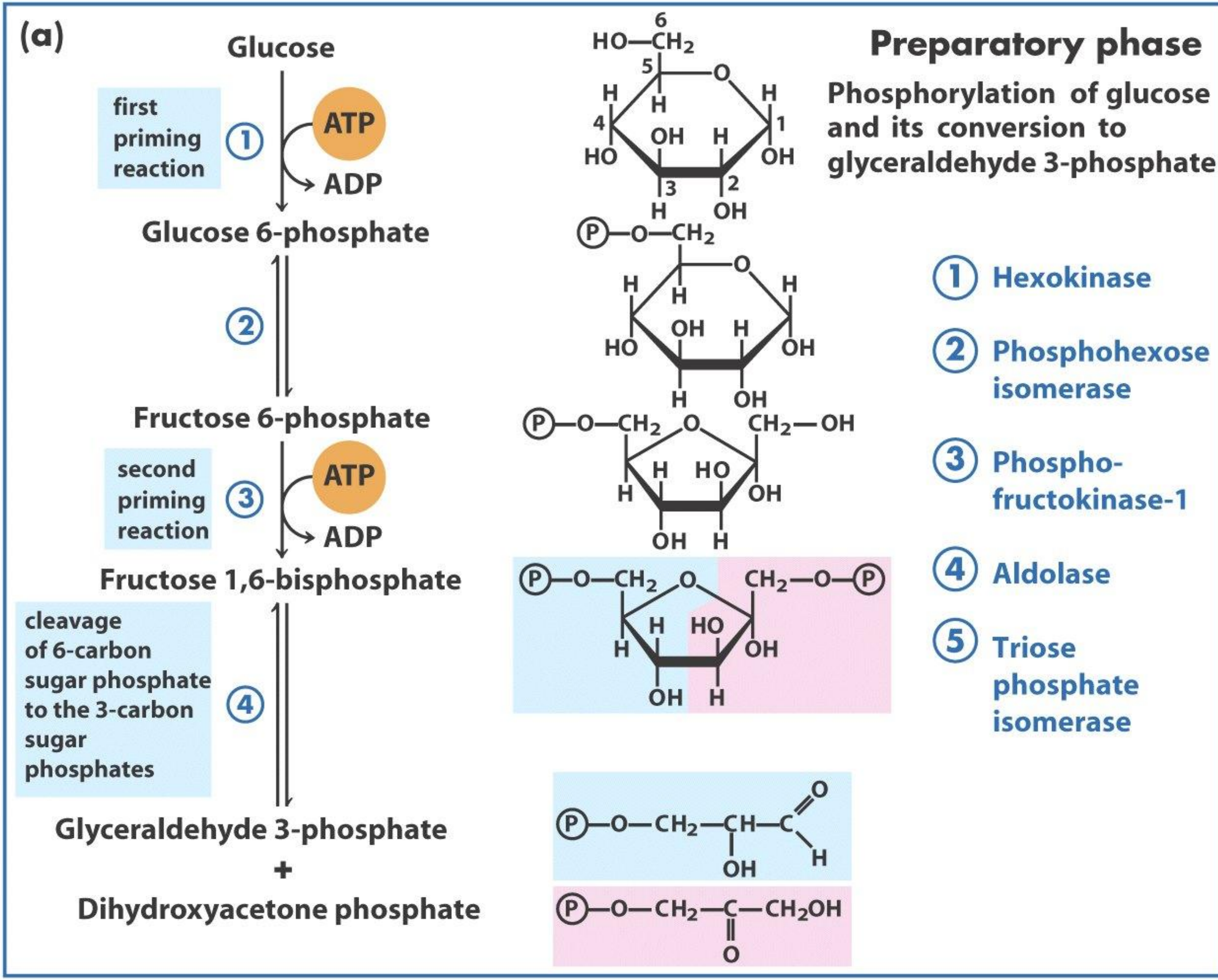
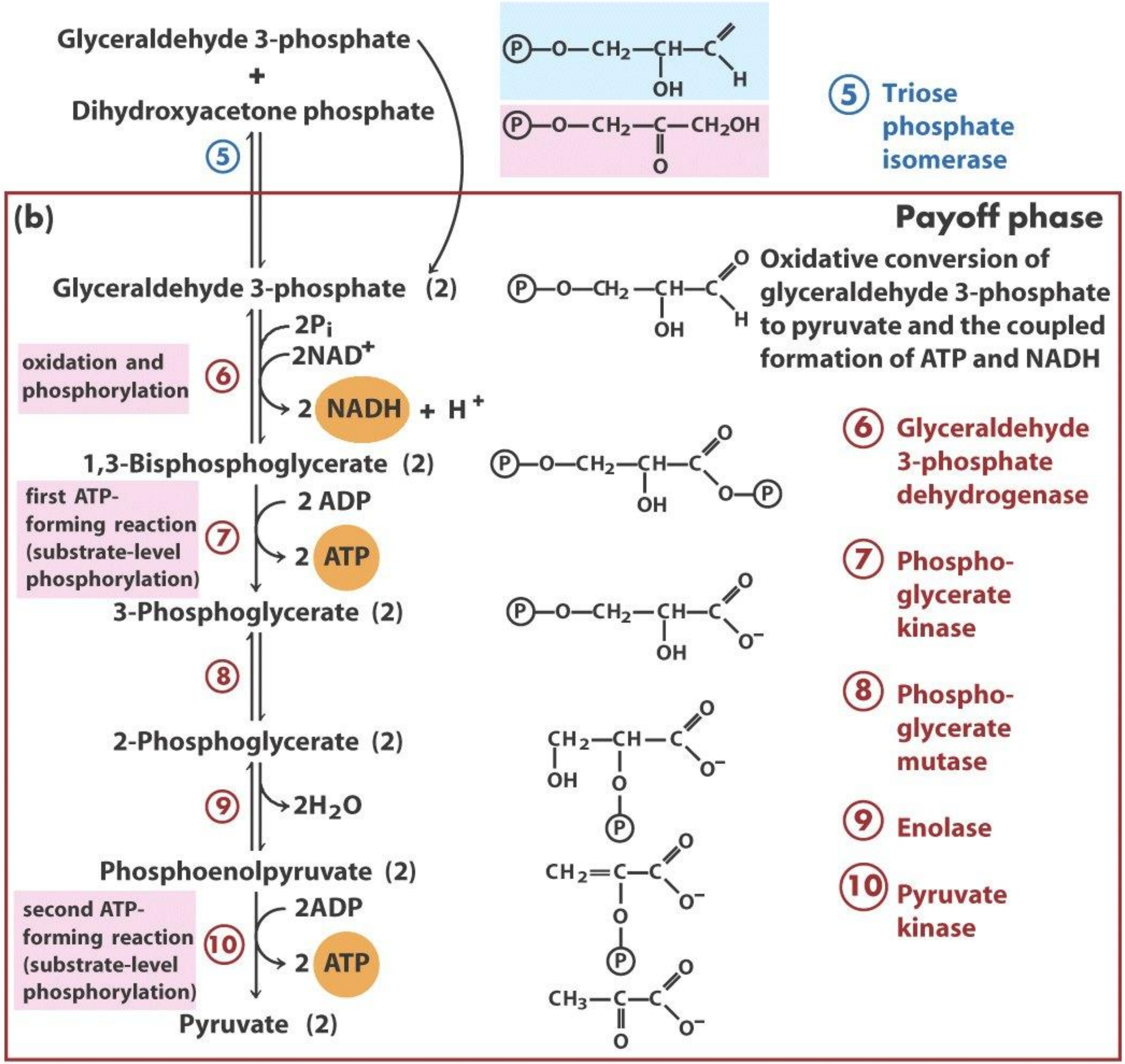
Feeder pathways , Alternative Pathways of Pyruvate & Glucose

Dr.Sulieman Al-Khalil



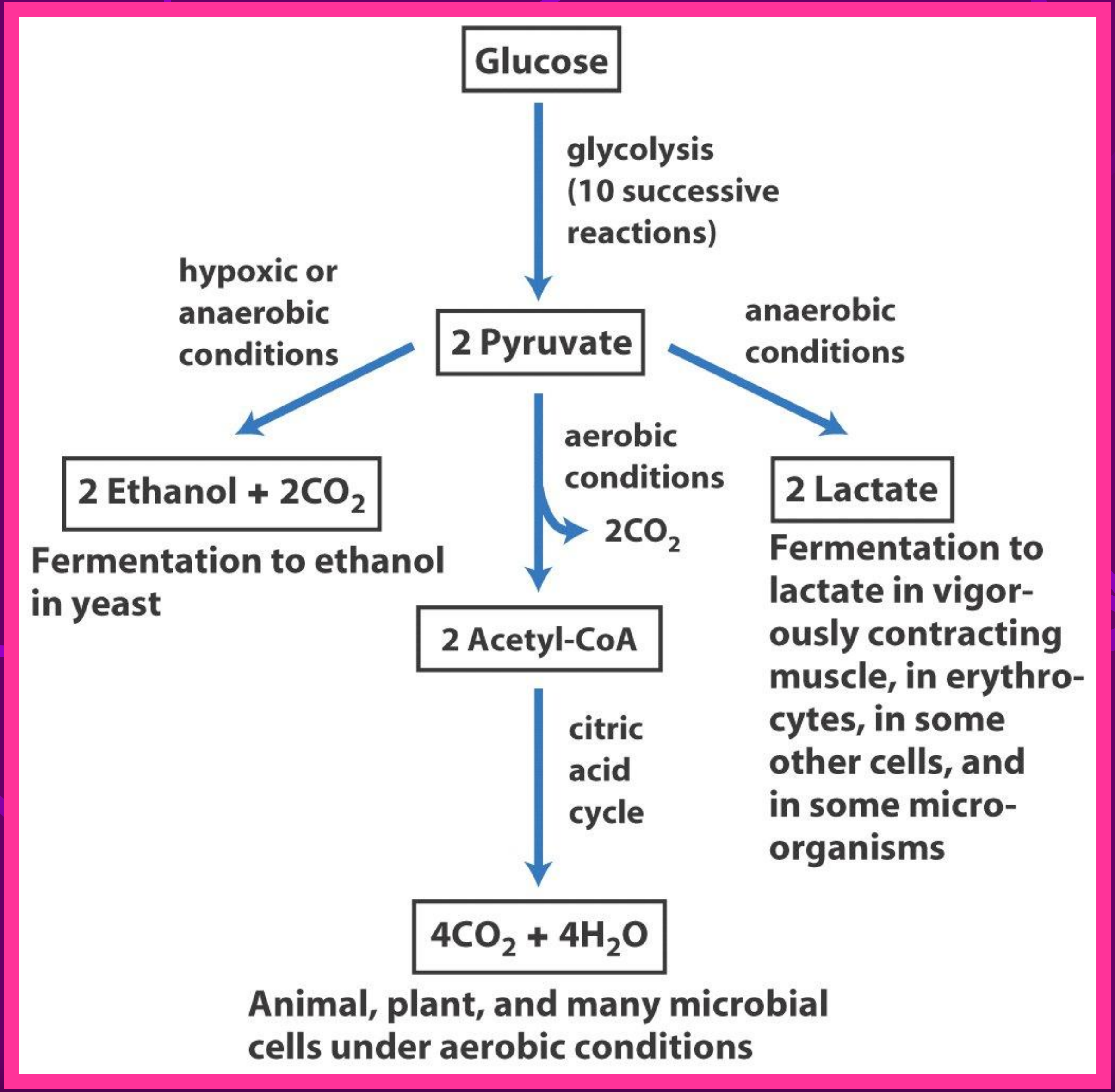
(a)
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to the 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase



Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
5 Triose phosphate isomerase
(b)
Payoff phase
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
Glyceraldehyde 3-phosphate (2)
2Pi
2NAD+
oxidation and phosphorylation
6
2 NADH + H+
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
2 ADP
7
2 ATP
3-Phosphoglycerate (2)
8
2-Phosphoglycerate (2)
9
2H2O
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
2ADP
10
2 ATP
Pyruvate (2)
6 Glyceraldehyde 3-phosphate dehydrogenase
7 Phospho-glycerate kinase
8 Phospho-glycerate mutase
9 Enolase
10 Pyruvate kinase

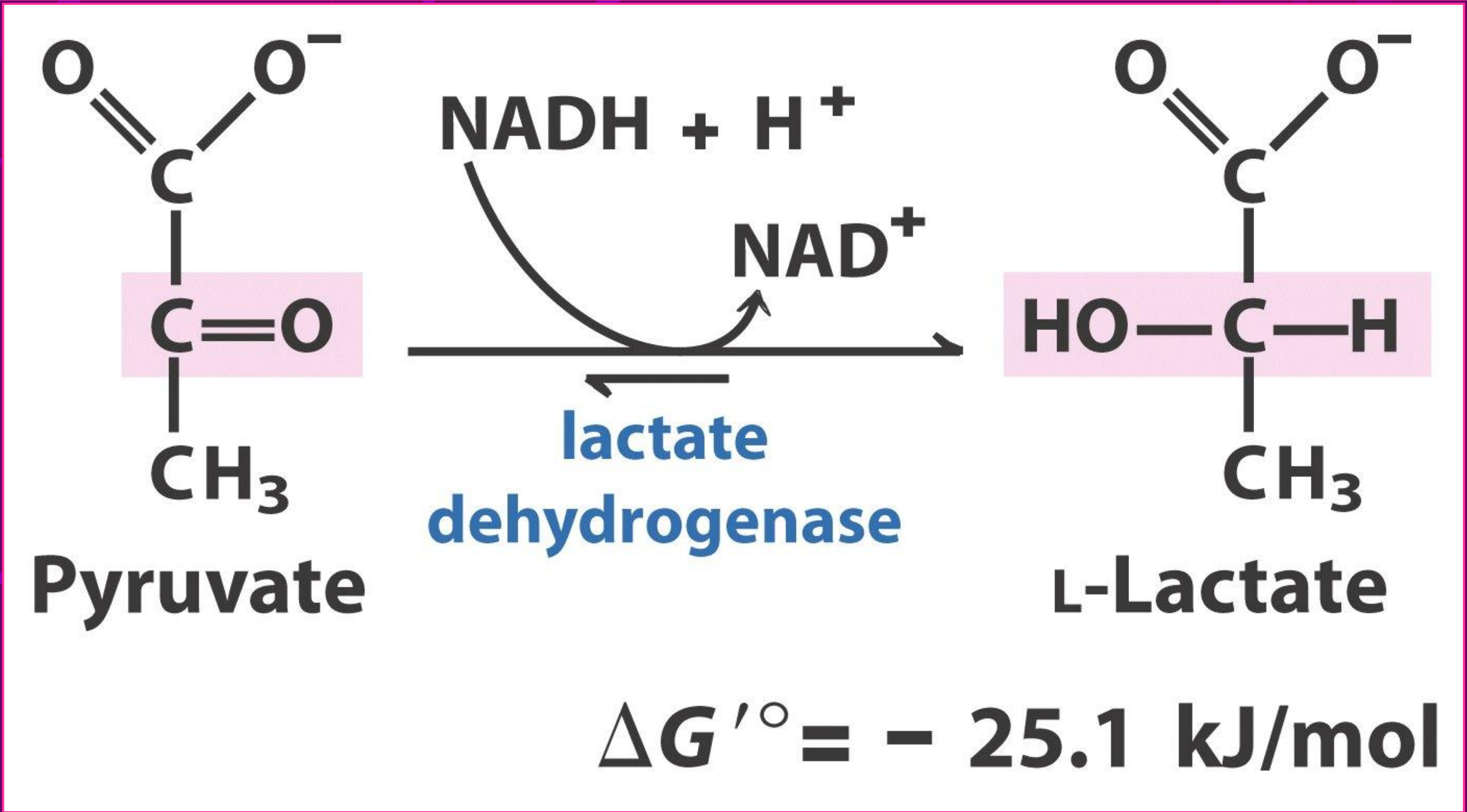
- Pyruvate produced from glycolysis can be converted to lactate or ethanol in anaerobic fermentation. No net oxidation of sugars occurs in fermentation.
- Many different sugar molecules can enter the glycolysis pathway, and they do so by a variety of pathways to enter at various points in the pathway.
- Glucose 6-phosphate can enter the pentose phosphate pathway instead of the glycolytic pathway. The pentose phosphate pathway provides a means of generating the reducing agent NADPH and of generating ribose sugars.

Fates of Pyruvate



- Pyruvate is an important junction in carbohydrate catabolism .
- Under aerobic conditions it is oxidized to acetate, which enters the citric acid cycle and is ultimately oxidized to CO_2 and H_2O.
- On the other hand, if oxygen is not available further oxidation of pyruvate is not possible and the cell must be content with the 2 molecules of ATP generated during glycolysis.
- There are two different main fermentation pathways, which convert pyruvate to different end products; which of these pathways is taken depends on the cell type and the organism.

Fermentation to Produce Lactose

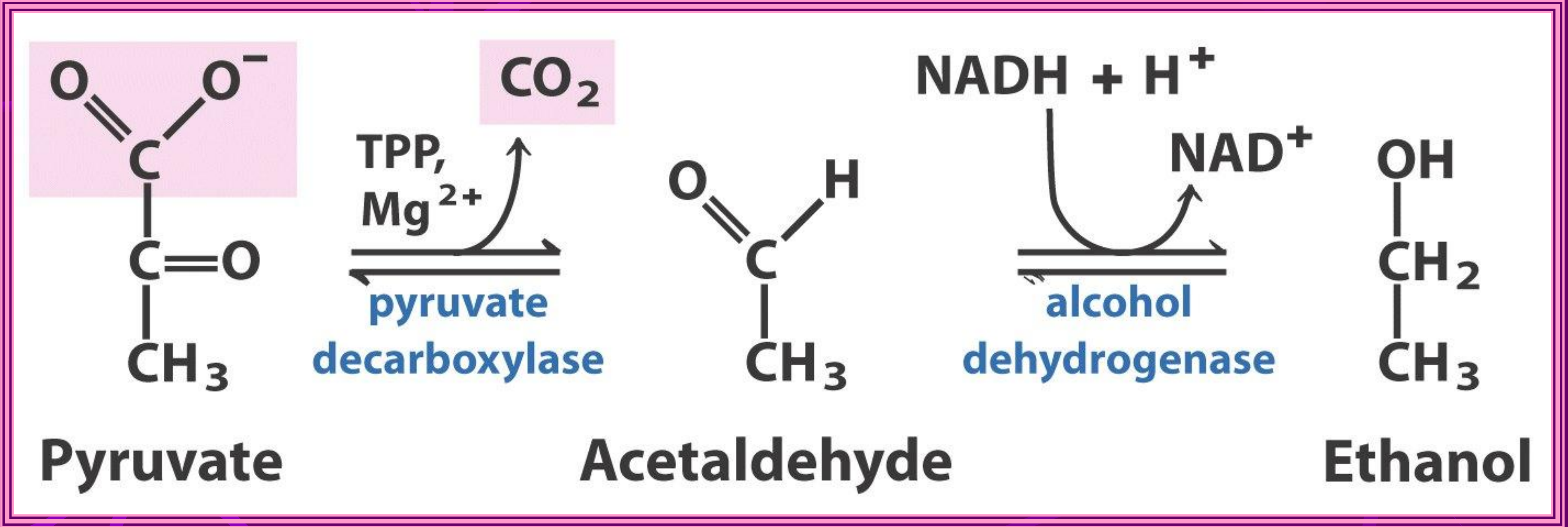


Lactic acid fermentation

- Animal tissues reduce pyruvate to lactate under anaerobic conditions, concomitantly oxidizing NADH back to NAD+, which is needed for continued glycolysis.
- Reaction is catalyzed by **lactate dehydrogenase** (operating in reverse, DG'° = –25.1 kJ/mol).
- Lactate can be recycled; it is carried in blood to the liver where it is converted back to glucose (in a process requiring the input of energy).

- There is no net redox change in the overall glycolytic process of converting glucose to lactate (the oxidation reaction in step 6 of glycolysis is balanced by the reduction of pyruvate to lactate).
- On the other hand, the reaction does generate one net H+, which is released to solution.
- This acidification is important in vigorous exercise, when rapid metabolism uses all available oxygen and begins producing lactate, acidifying muscle and ultimately limiting the duration of vigorous exercise.
- Many microorganisms also ferment glucose and other hexoses to lactate.
- The acidification produced by this process as certain bacteria ferment lactose in milk is the basis for the curdling process that produces cheese and yogurt.

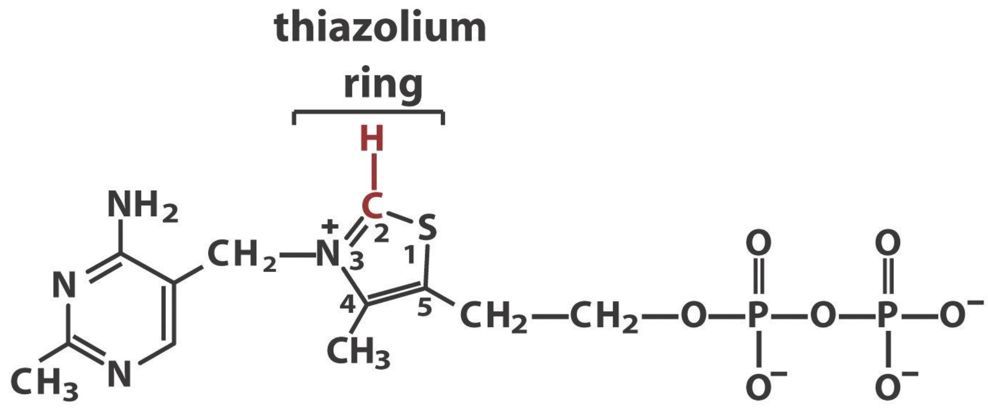
Fermentation to Ethanol



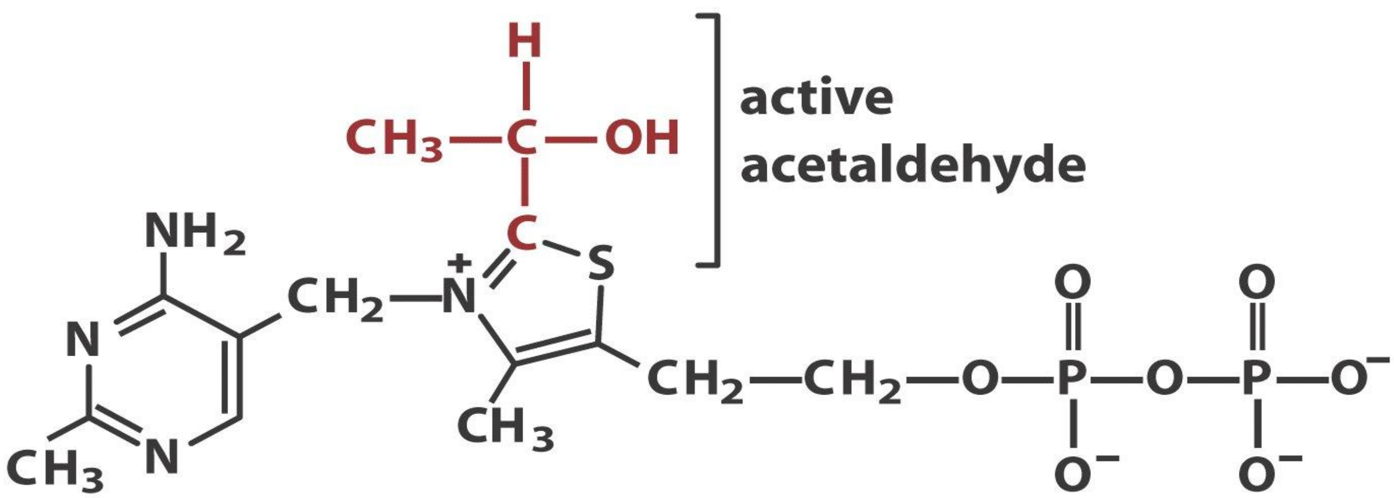
Ethanol fermentation

- Yeast and other microorganisms ferment glucose to ethanol and CO2 rather than to lactate.
- Pyruvate is converted to ethanol in two steps. First pyruvate is decarboxylated to acetaldehyde, then acetaldehyde is reduced to ethanol.

Thiamine pyrophosphate (TPP) and pyruvate decarboxylation

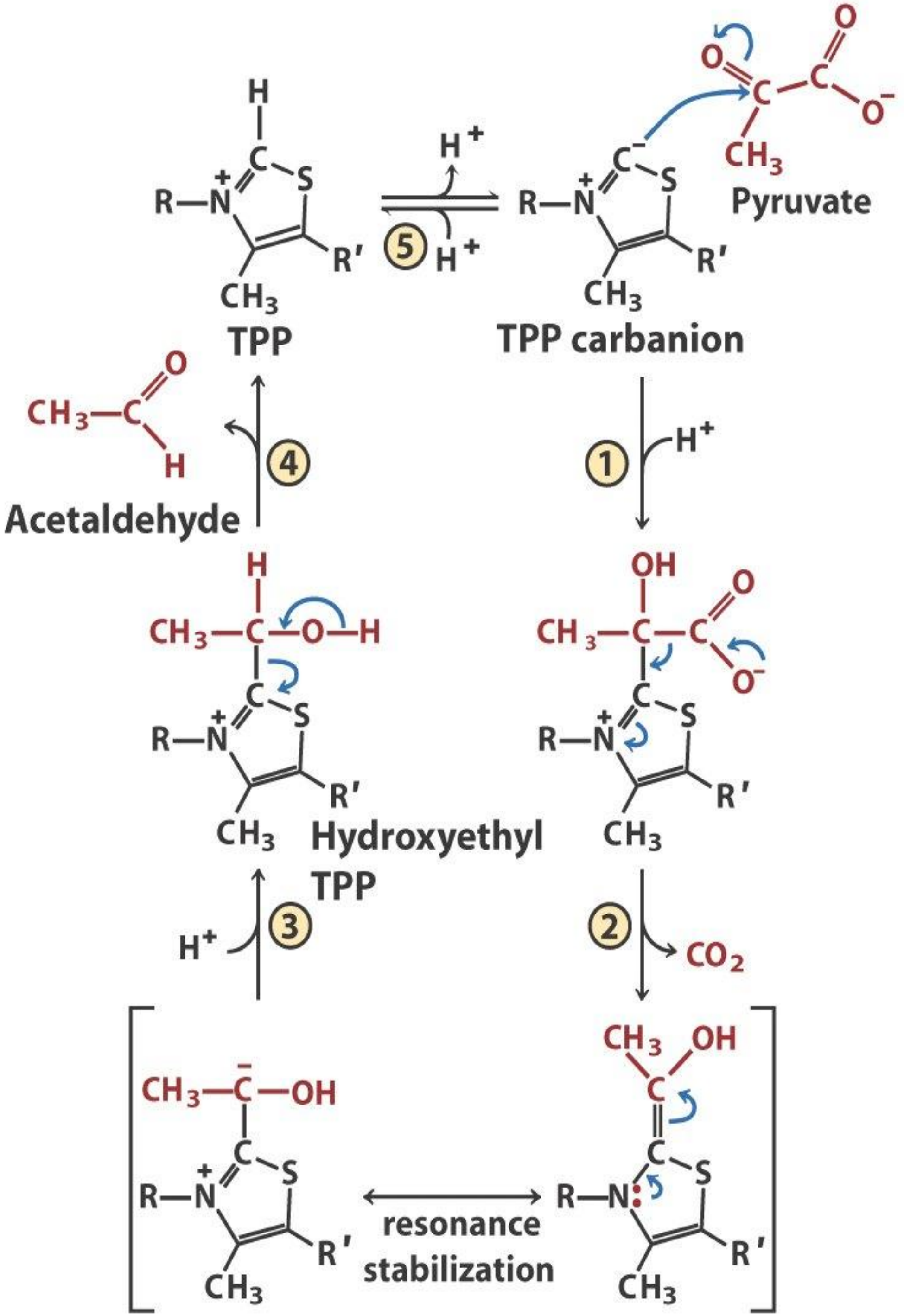


Thiamine pyrophosphate (TPP)



Hydroxyethyl thiamine pyrophosphate

Thiamine pyrophosphate (TPP) and pyruvate decarboxylation



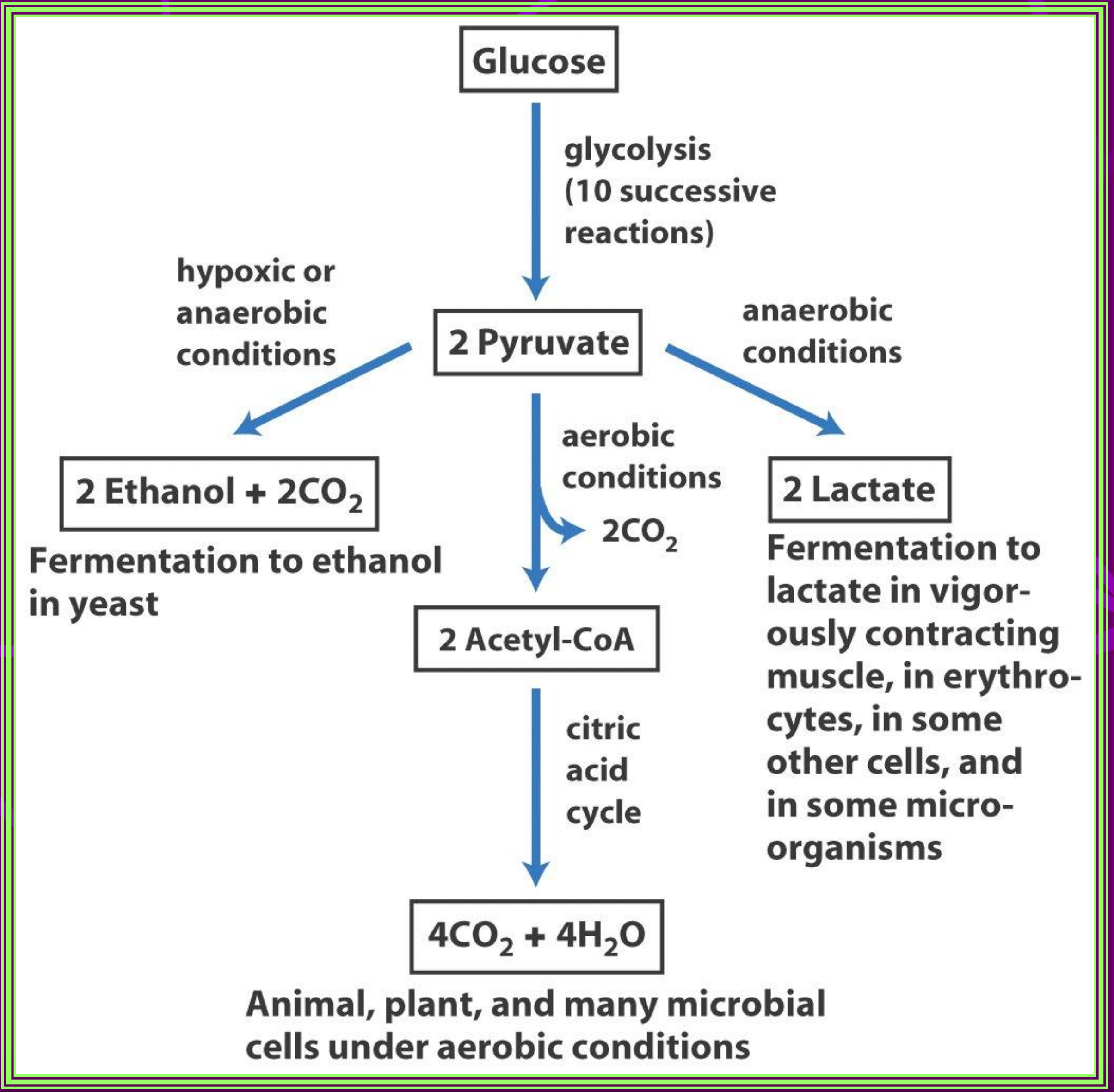
1) **Decarboxylation of pyruvate**

- Catalyzed by **pyruvate decarboxylase**. This enzyme uses an important coenzyme, thiamine pyrophosphate, which is derived from vitamin B1

2) **Reduction of acetaldehyde to ethanol**

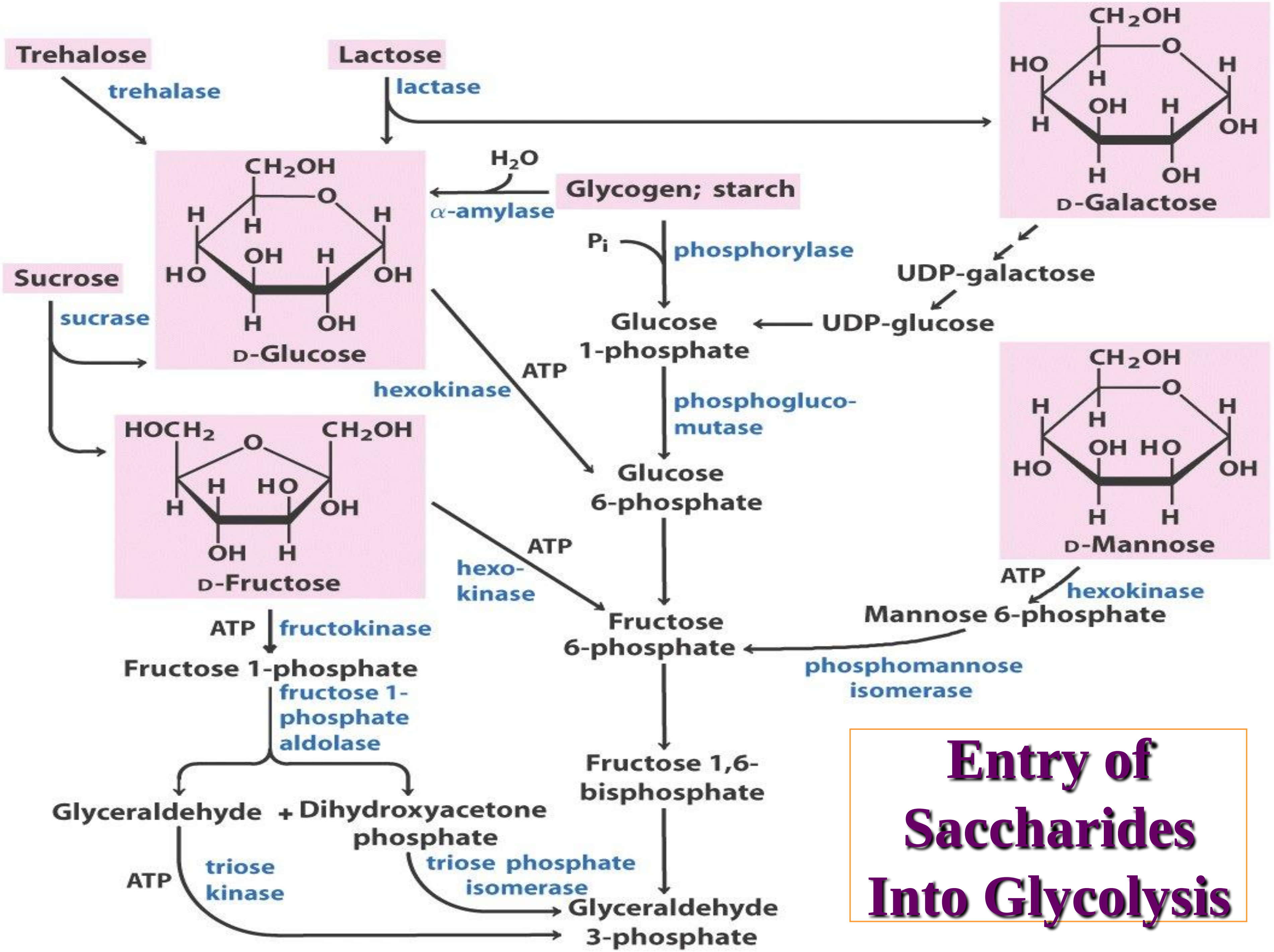
- Catalyzed by **alcohol dehydrogenase** (again performing the reverse reaction of the one implied by its name).
- Net reaction of glycolysis is:
- Glucose + 2ADP + 2Pi → 2 ethanol + 2CO2 + 2ATP + 2H2O
- In this and other fermentation reactions, the ratio of carbons :hydrogens in the substrates and products is the same: 1:2 (here both carbon products, ethanol and CO2, must be included in the calculation).

Fates of Pyruvate



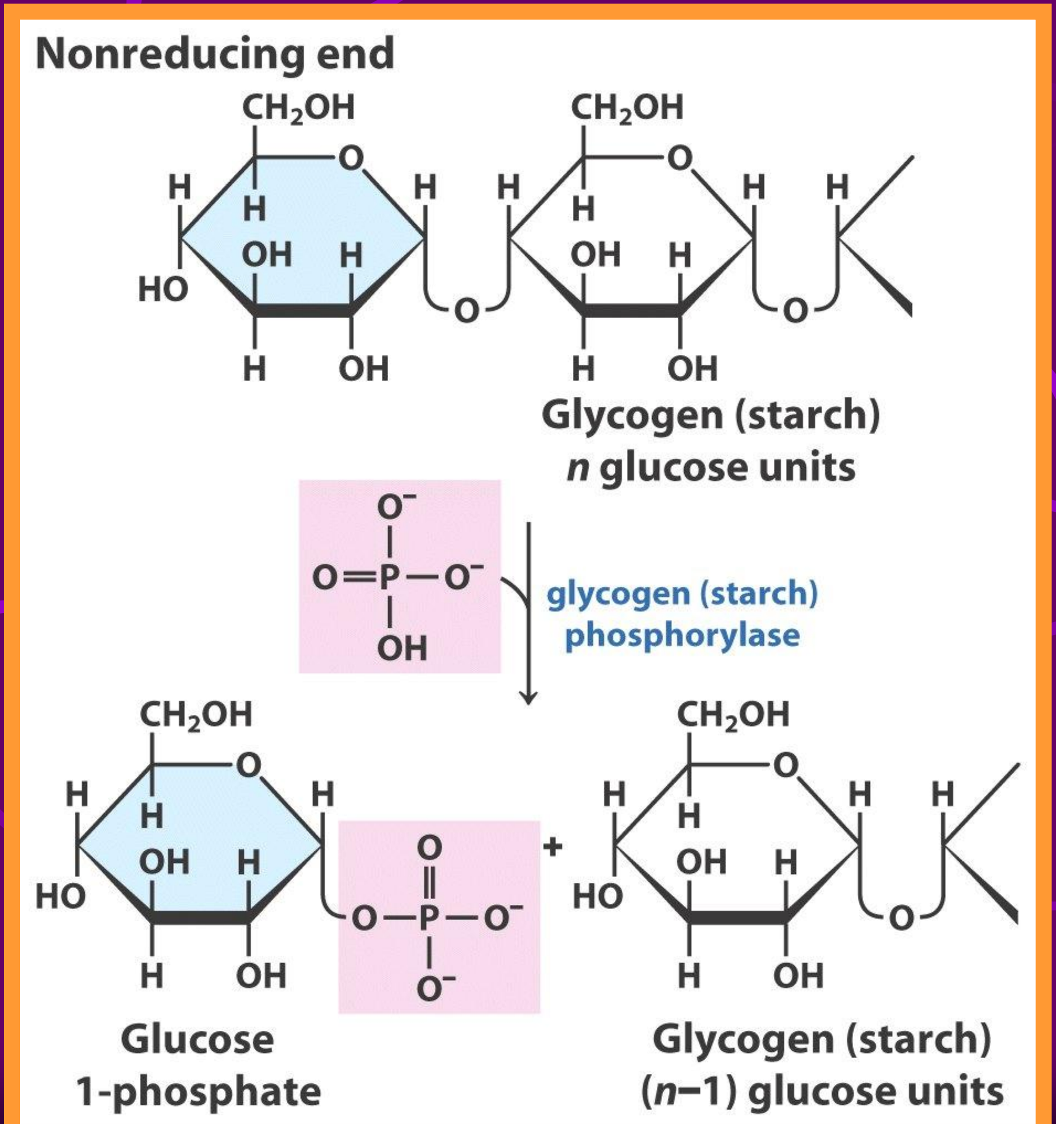
Feeder pathways for glycolysis

- Glucose is not the only saccharide used in glycolysis.
- Most significant are the storage polysaccharides glycogen and starch (which, remember, are polymers of glucose), disaccharides maltose, lactose, trehalose, and sucrose, and the monosaccharides fructose, mannose, and galactose.
- All of these are funneled into the glycolysis pathway



Entry of Saccharides Into Glycolysis

Generation of glucose monomer from glycogen



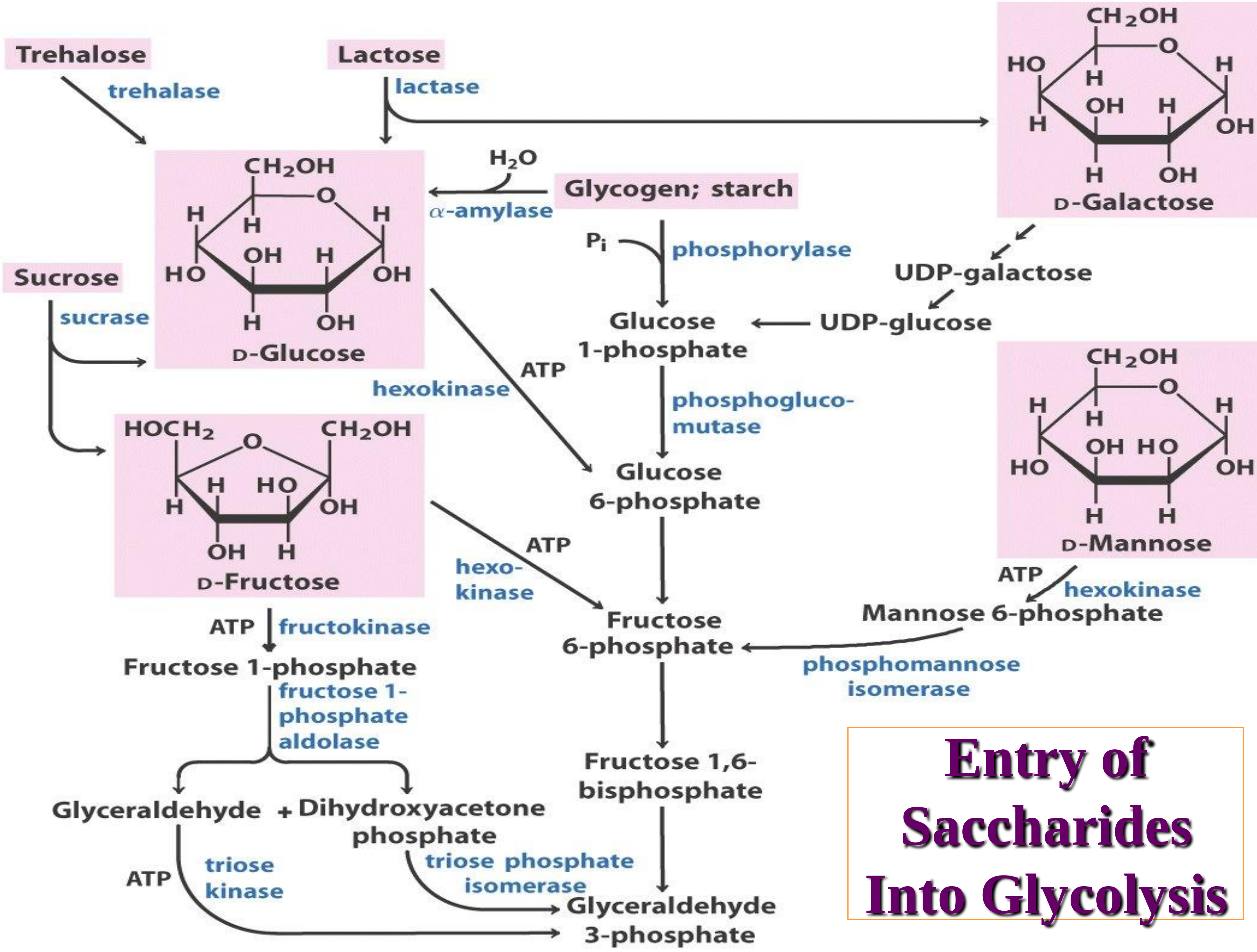
Entry of glycogen and starch

- Two-step pathway:

1. first the polymers are broken down to monomers via phosphorolysis to give glucose 1-phosphate.

   This reaction is catalyzed by the enzyme **glycogen phosphorylase** (starch phosphorylase for starch).
2. Then glucose 1-phosphate is converted to glucose 6-phosphate by **phosphoglucomutase**.

Entry of Saccharides Into Glycolysis



Breakdown of disaccharides

- Disaccharides are first converted enzymatically to their constituent monosaccharides
  - maltose → 2 glucose, catalyzed by **maltase**
  - sucrose → glucose + fructose, catalyzed by **sucrase**
  - lactose → galactose + glucose, catalyzed by **lactase**
- All of these disaccharides are hydrolyzed to their corresponding monosaccharides by enzymes attached to the outer surface of the intestinal epithelial cells.
- Only the monosaccharides are transported into the epithelial cells. They then are transported to the blood and carried throughout the body.

Entry of fructose into glycolysis

- In muscle and kidney

  Fructose + ATP --> fructose 6-phophate + ADP

  (**hexokinase**)

- In liver

  Fructose + ATP --> fructose 1-phophate + ADP

  (**fructokinase**)

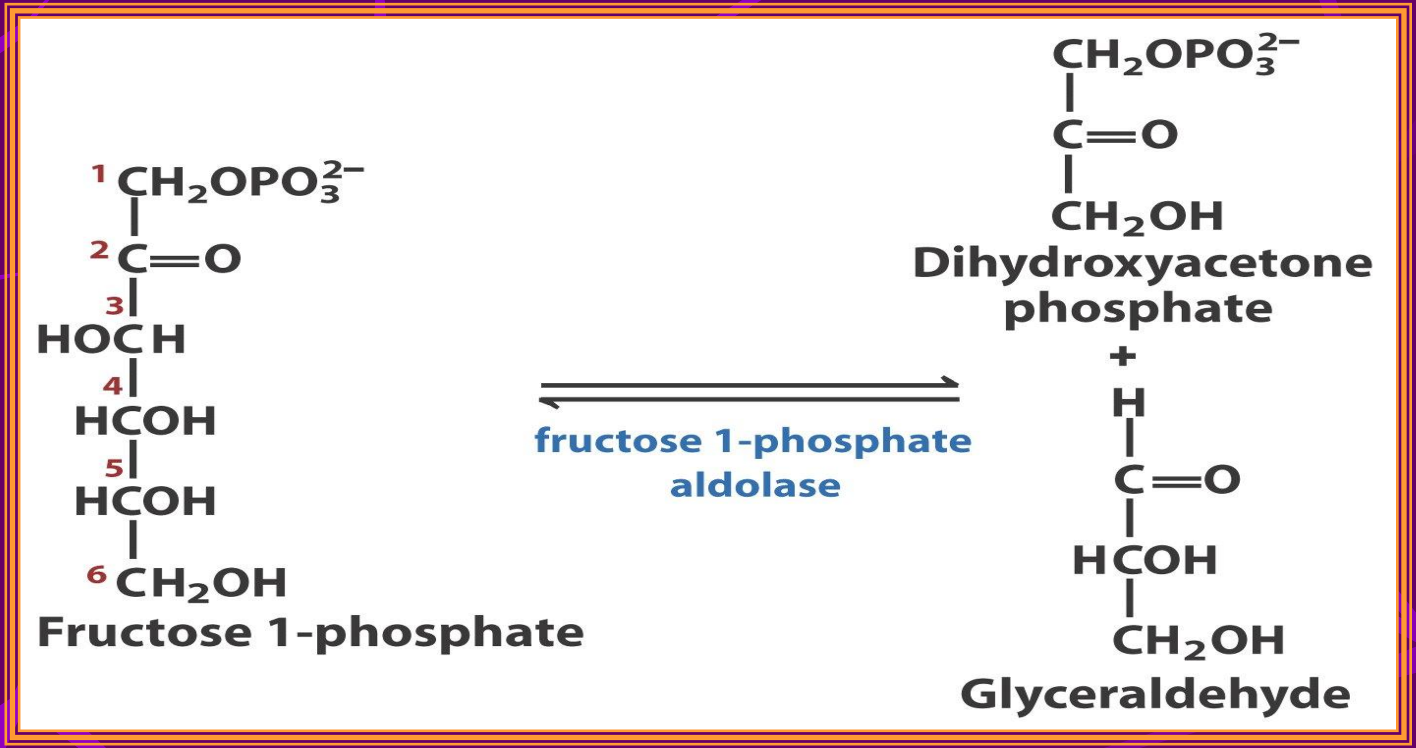
  Fructose 1-P --> glyceraldehyde + DHAP

  (**fructose 1-phosphate aldolase**)

  Glyceraldehyde --> glyceraldehyde 3-phosphate

  (**triose kinase**)

Cleavage of fructose 1-phosphate

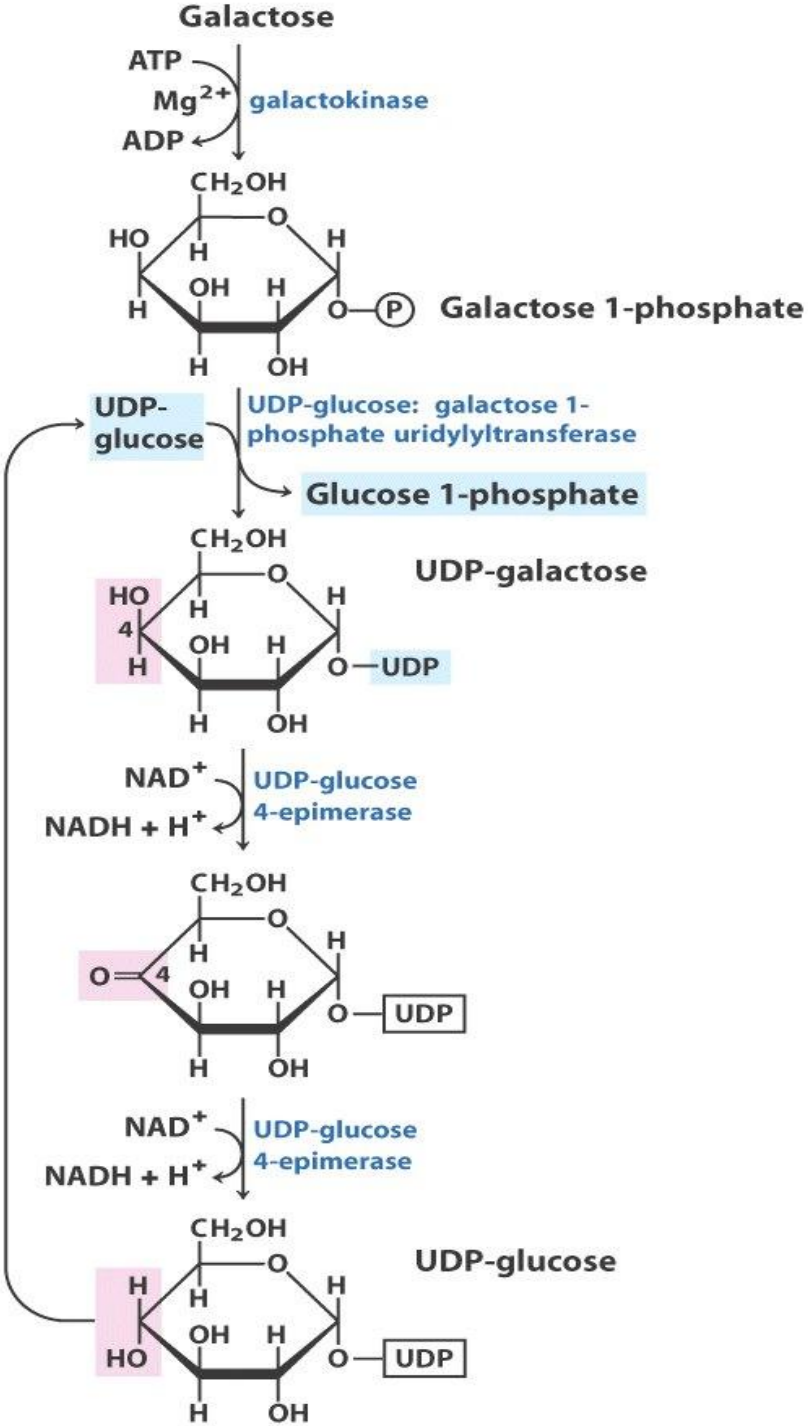


- 2 ATPs used to activate fructose in each pathway
- The overall process from hexose to 2 triose phosphates requires 2 ATP for either pathway, just as for glucose.
- However, the phosphorylations occur at different steps for each of the two fructose pathways.

Galactose:

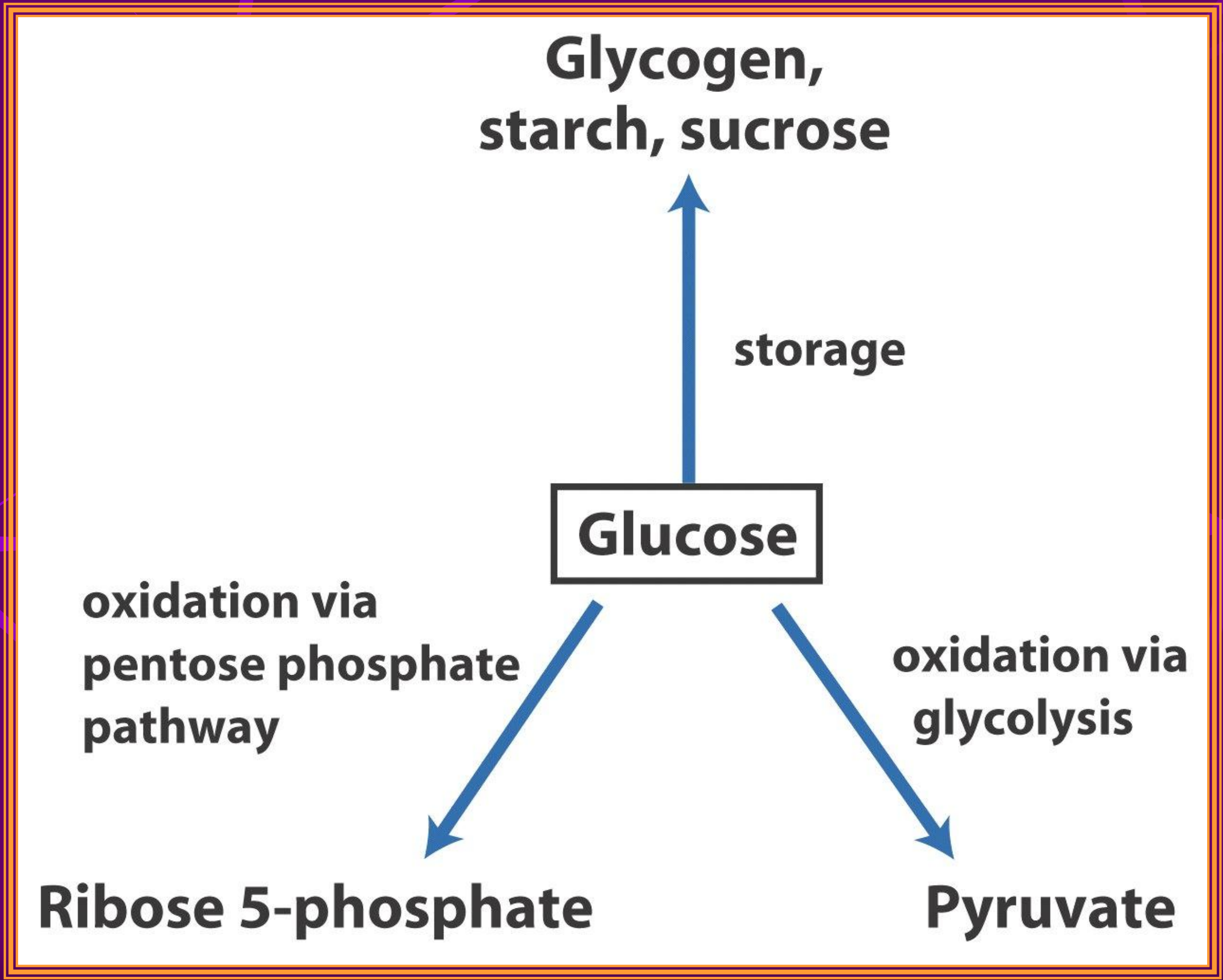
- Converted to glucose 1-phosphate by a set of reactions in which uridine diphosphate (UDP) functions as a coenzyme-like carrier of hexose groups
- Galactose + ATP → galactose 1-phosphate + ADP (galactokinase)
- Galactose 1-phosphate + UDP-glucose → UDP galactose + glucose 1-phosphate (hexose 1-phosphate uridylyltransferase)
- UDP-galactose → UDP-glucose (UDP-galactose-4-epimerase)

D-galactose: UDP-galactose intermediate



- Net reaction: galactose + ATP → glucose-1-phosphate + ADP
- Several human genetic diseases result from problems with galactose metabolism. In **galactosemia**, the enzyme that transfers UDP from glucose to galactose is defective, preventing the overall conversion of galactose to glucose.

Pentose phosphate pathway

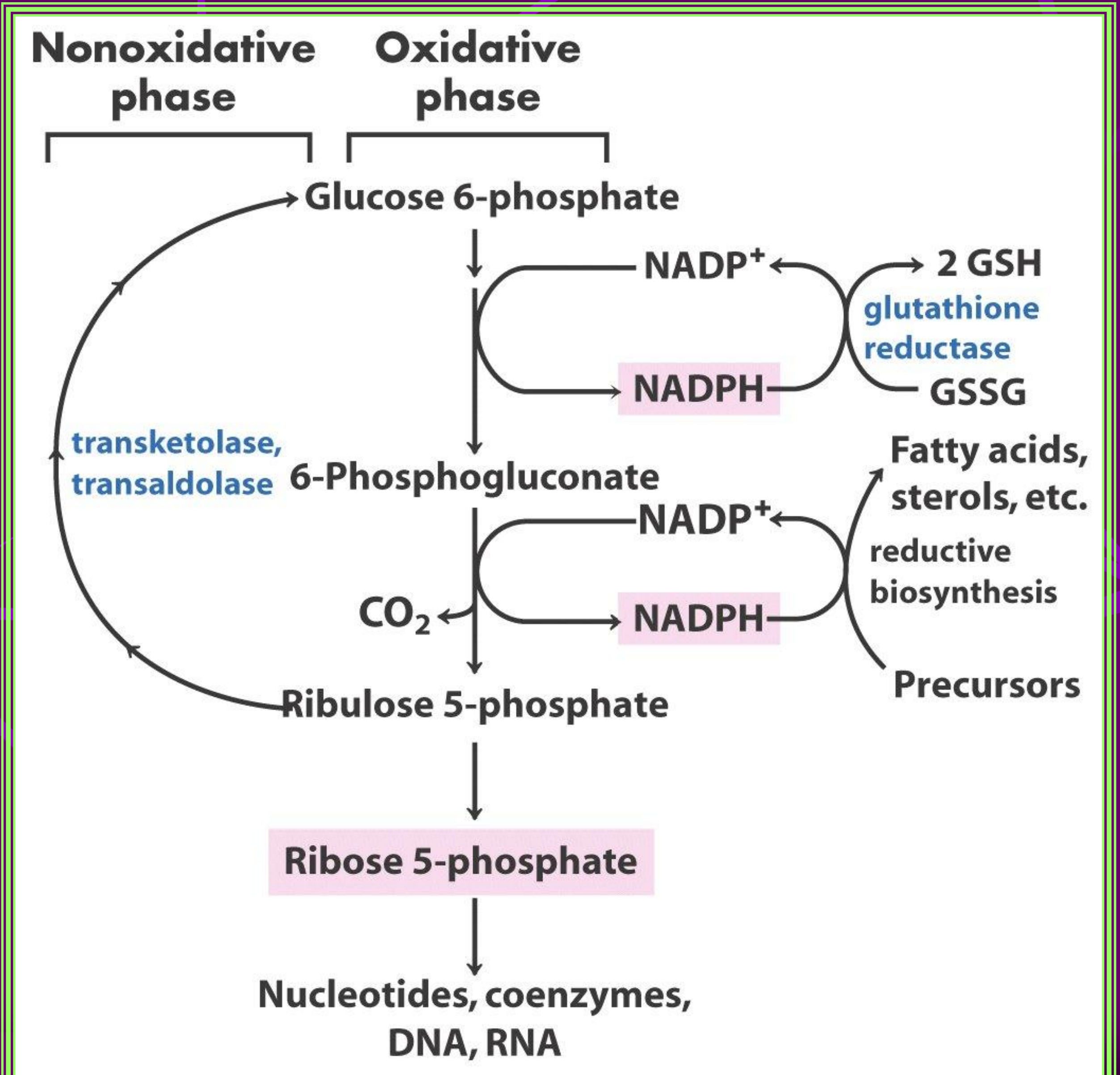


Pentose phosphate pathway

1. Generates reduced NADPH, used in anabolic metabolism.

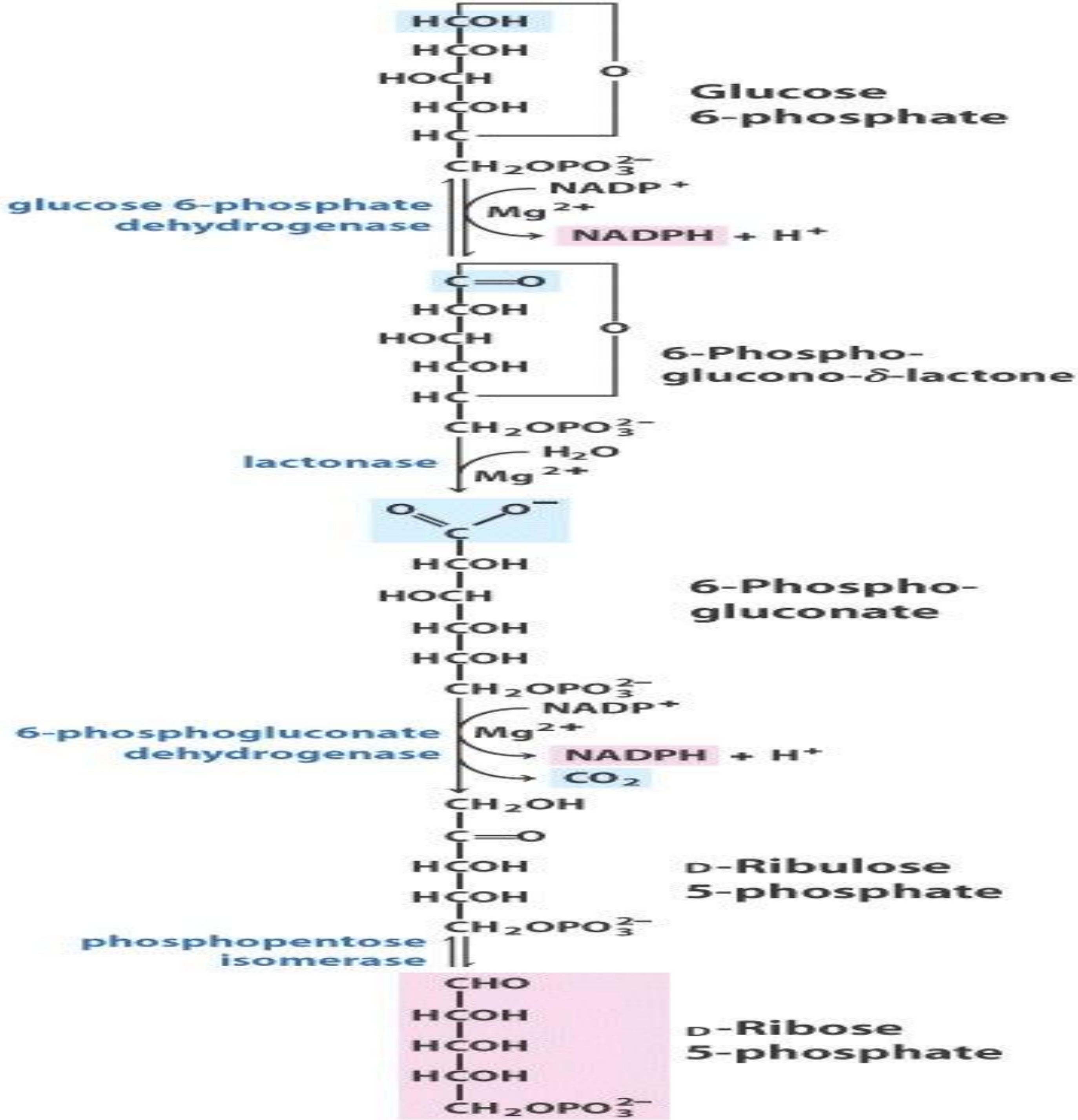
2. Produces ribose, used in nucleic acid synthesis.

Pentose phosphate pathway

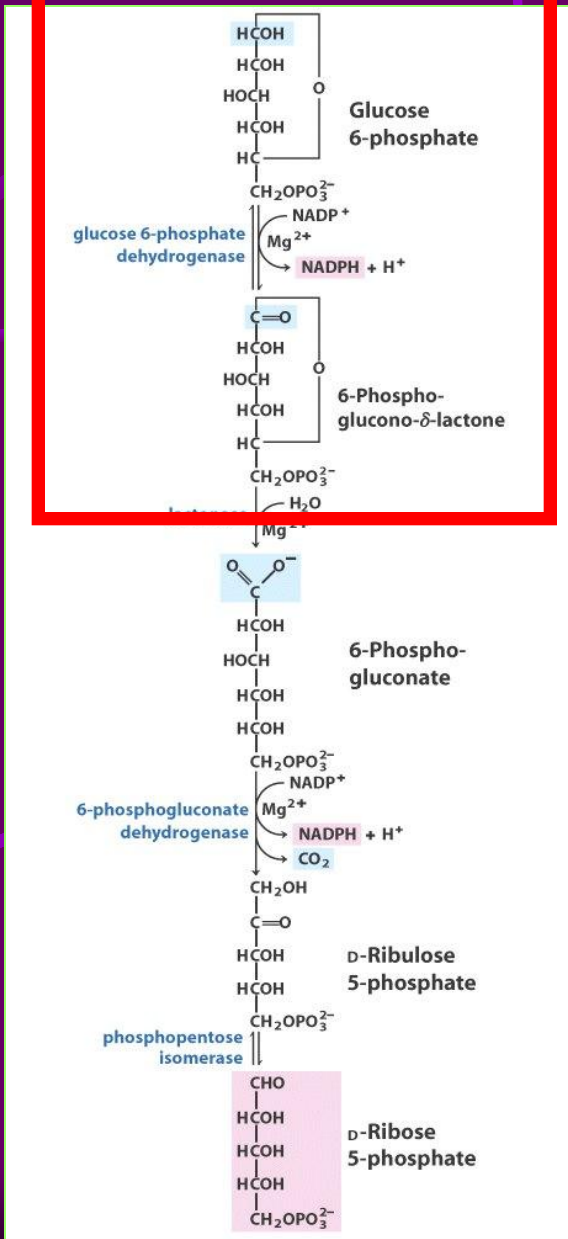


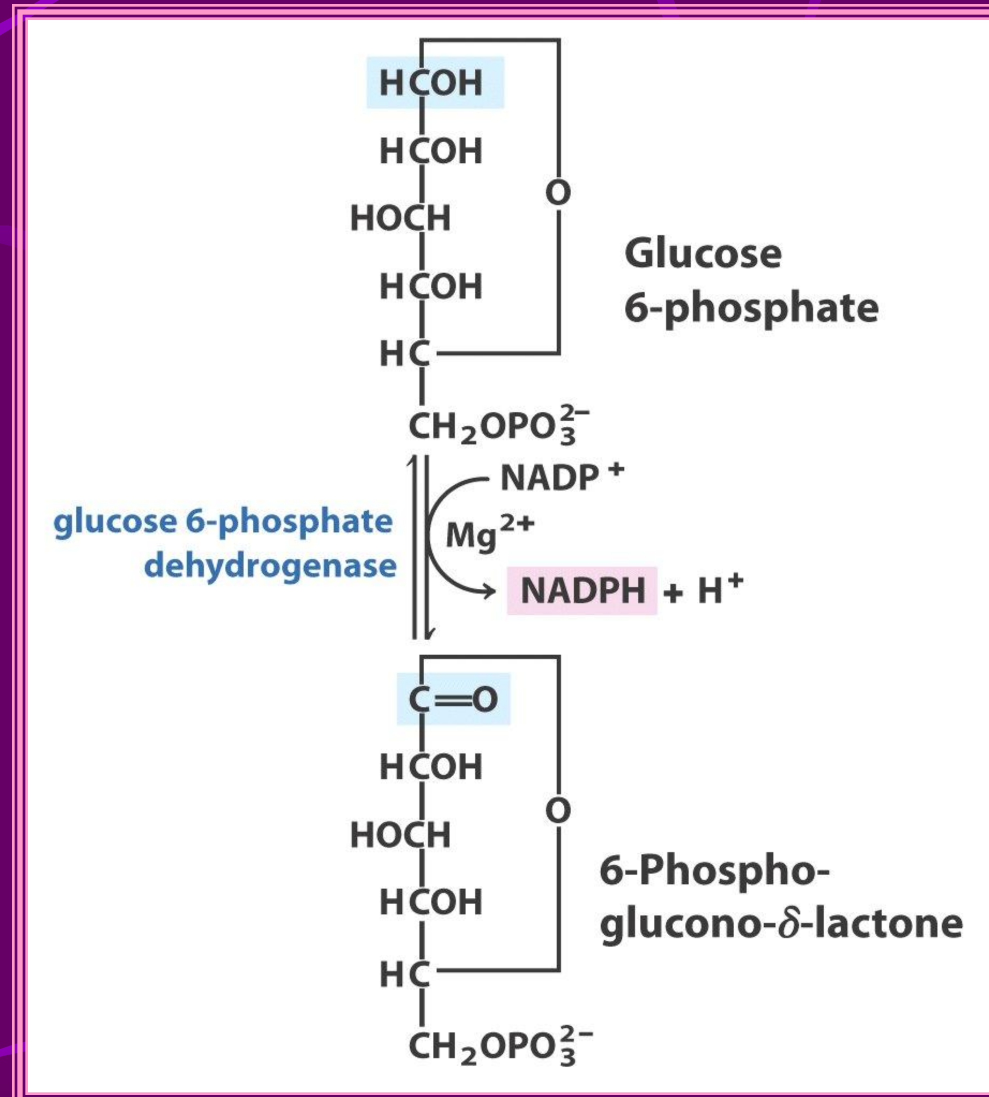
The Pentose phosphate pathway

- The pentose phosphate pathway, also called the phosphogluconate pathway, produces NADPH and ribose 5-phosphate.
- Glucose 6-phosphate can enter this pathway instead of the glycolytic pathway.
- Two functions of the pentose phosphate pathway.
  - First, NADPH is used almost universally as the reducing agent in anabolic (biosynthetic) pathways.
  - Second, the pathway generates D-ribose for synthesis of nucleic acids.

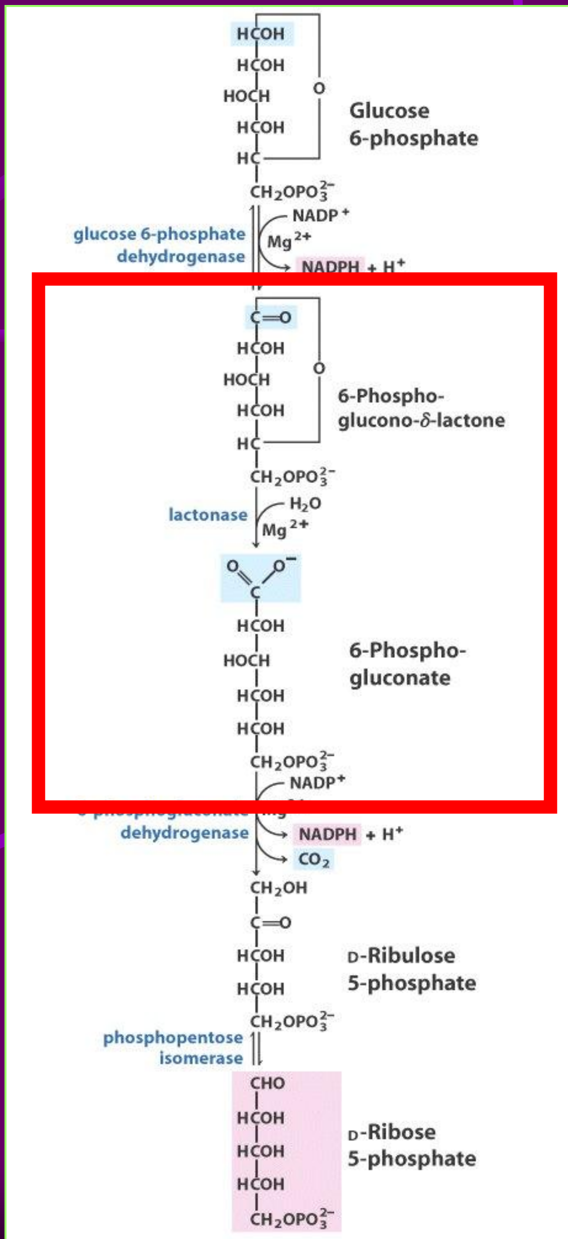

Glucose 6-phosphate
glucose 6-phosphate dehydrogenase
NADP+
Mg2+
NADPH + H+
6-Phospho-glucono-δ-lactone
lactonase
H2O
Mg2+
6-Phospho-gluconate
6-phosphogluconate dehydrogenase
NADP+
Mg2+
NADPH + H+
CO2
D-Ribulose 5-phosphate
phosphopentose isomerase
D-Ribose 5-phosphate

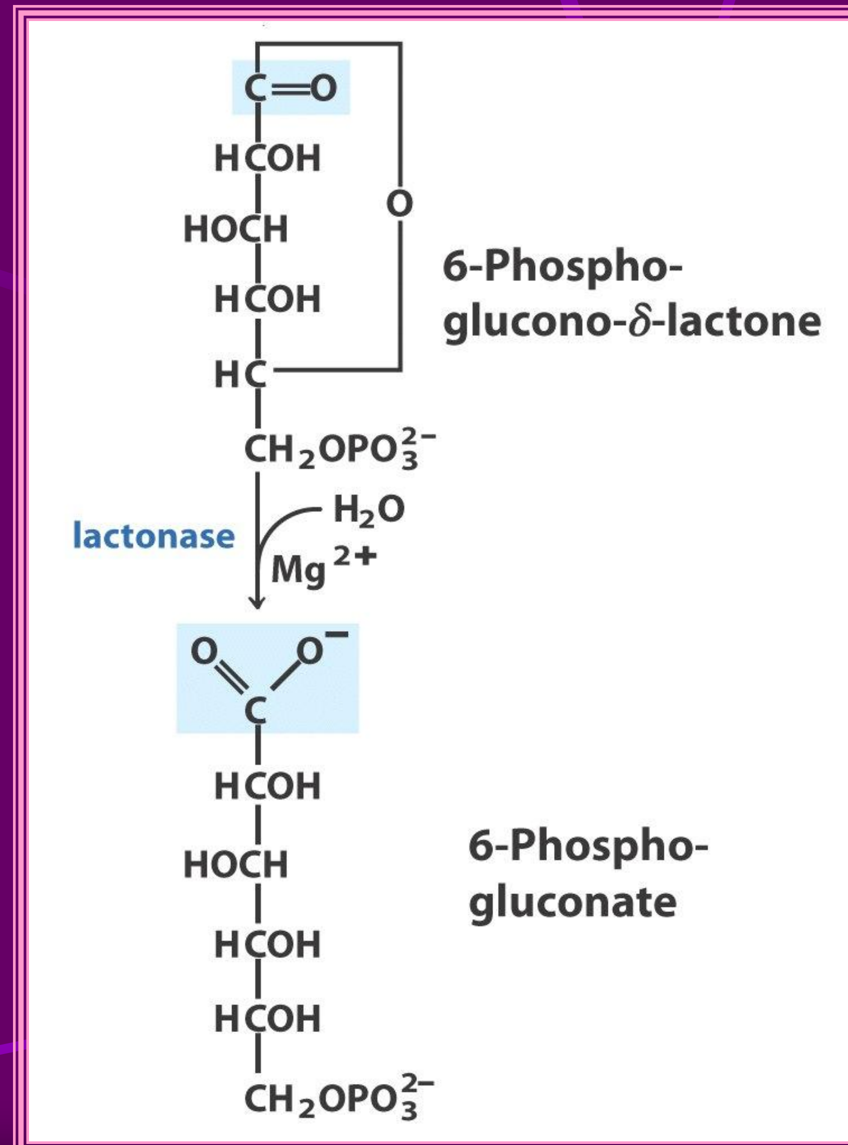
Pentose phosphate pathway



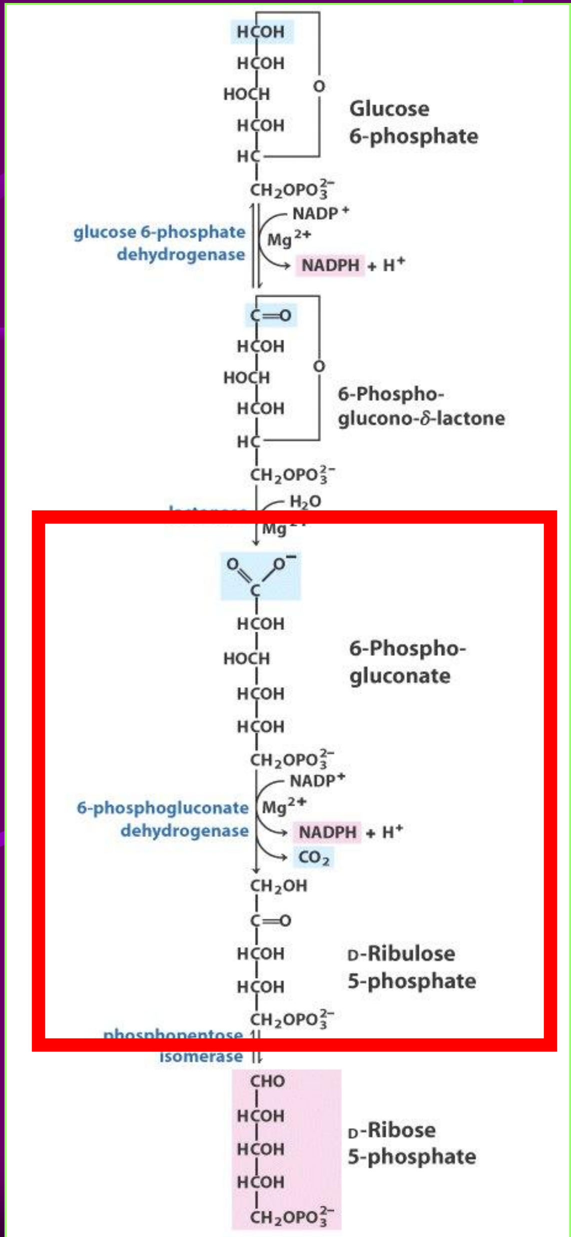


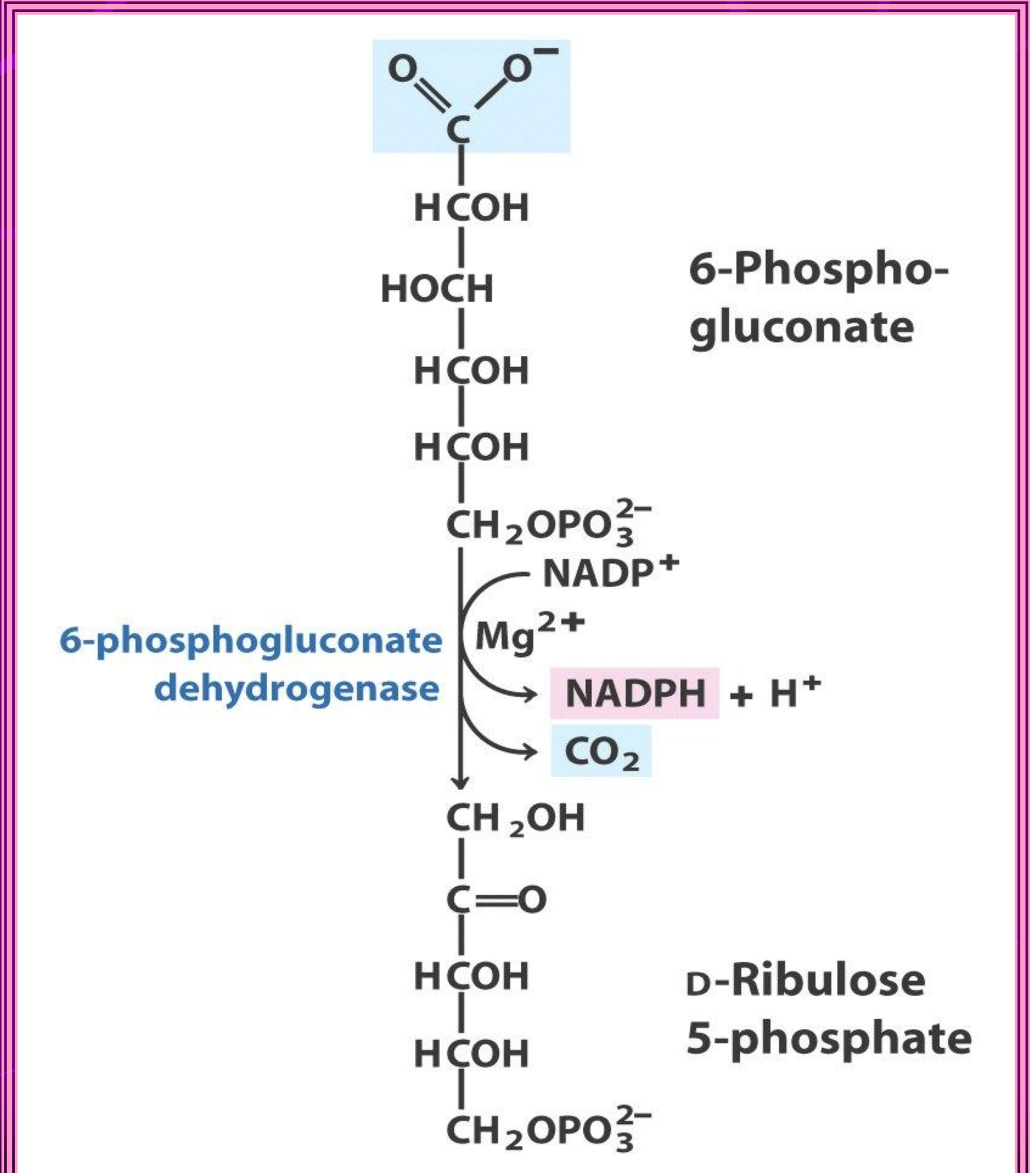
Pentose phosphate pathway





Pentose phosphate pathway

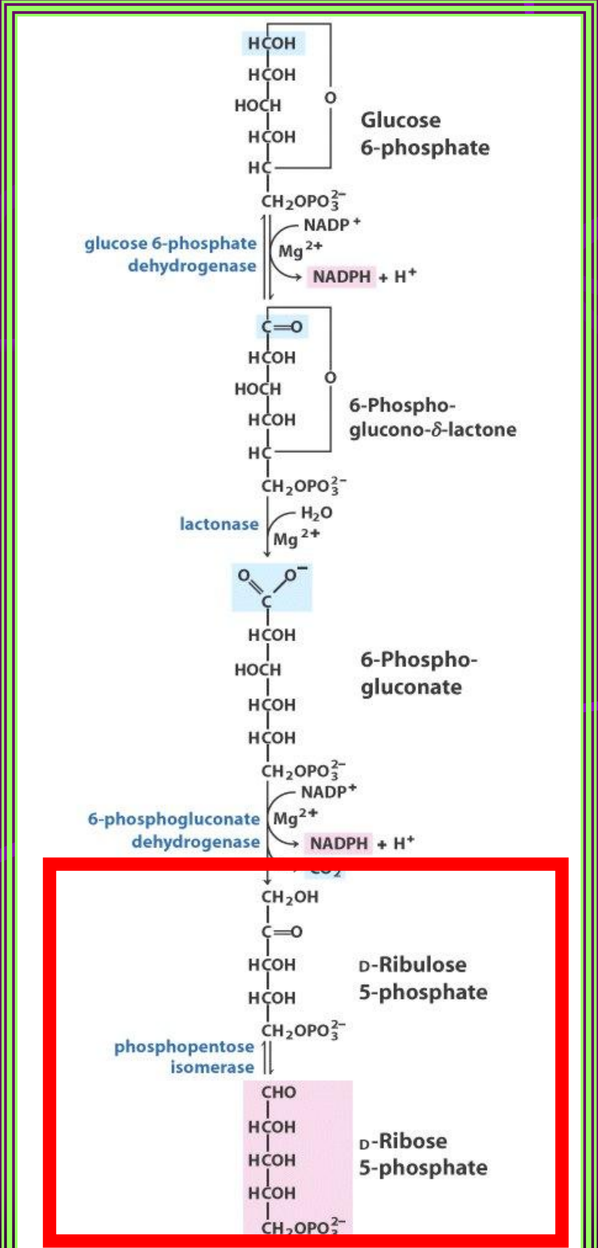


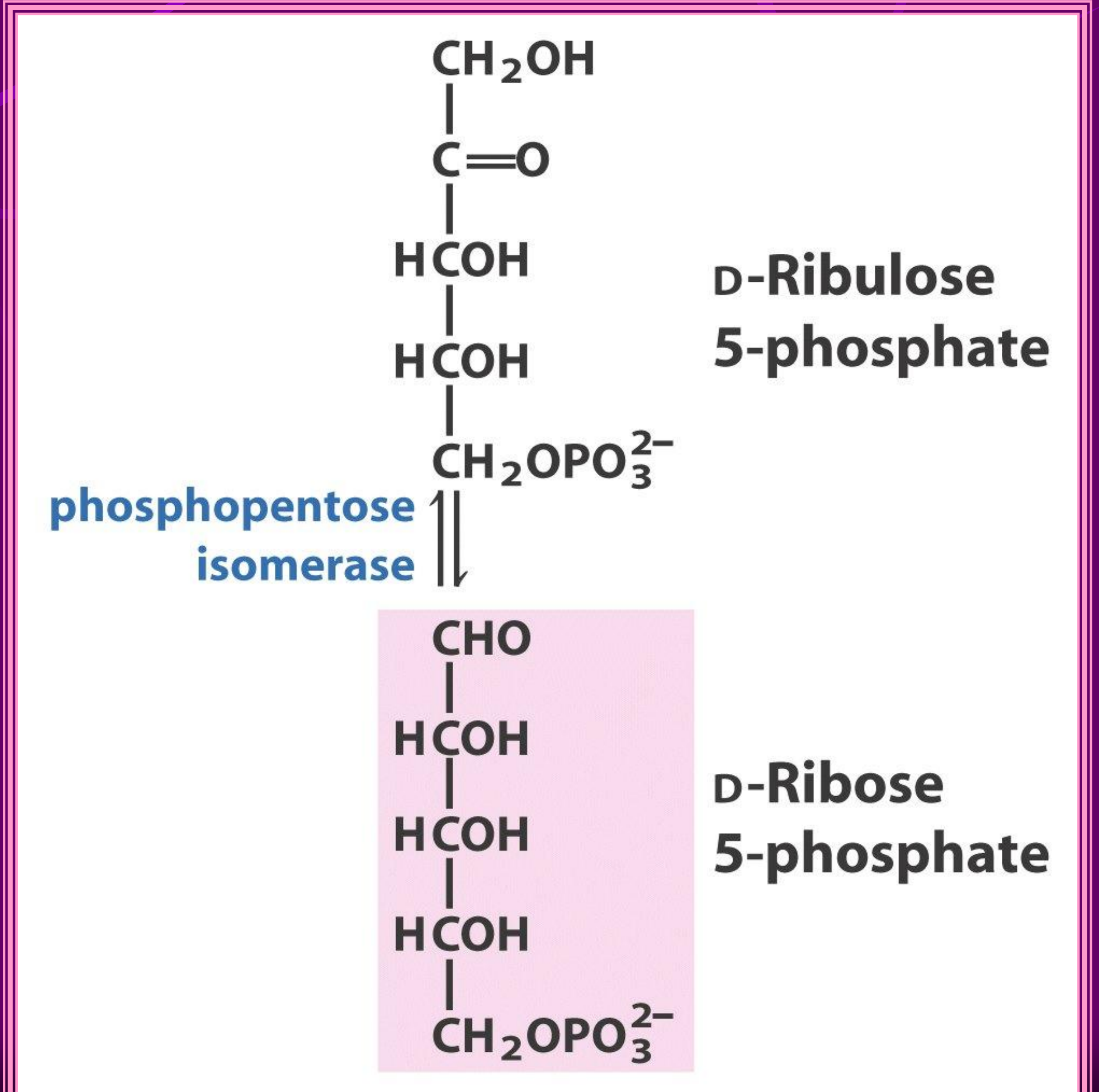


- The overall reaction is:
- glucose 6-phosphate + 2NADP+ + H_2O → ribose 5-phosphate + CO_2 + 2NADPH + 2H+
- The reactions to get there and the enzymes that catalyze them are :

1. Glucose 6-phosphate + NADP+ → 6-phosphoglucono-d-lactone (Glucose 6-phosphate dehydrogenase)
2. 6-phosphoglucono-d-lactone + H_2O → 6-phosphogluconate (Lactonase)
3. 6-phosphogluconate + NADP+ → D-ribulose 5-phosphate + NADPH + CO_2 + H+ (6-phosphogluconate dehydrogenase)

Pentose phosphate pathway

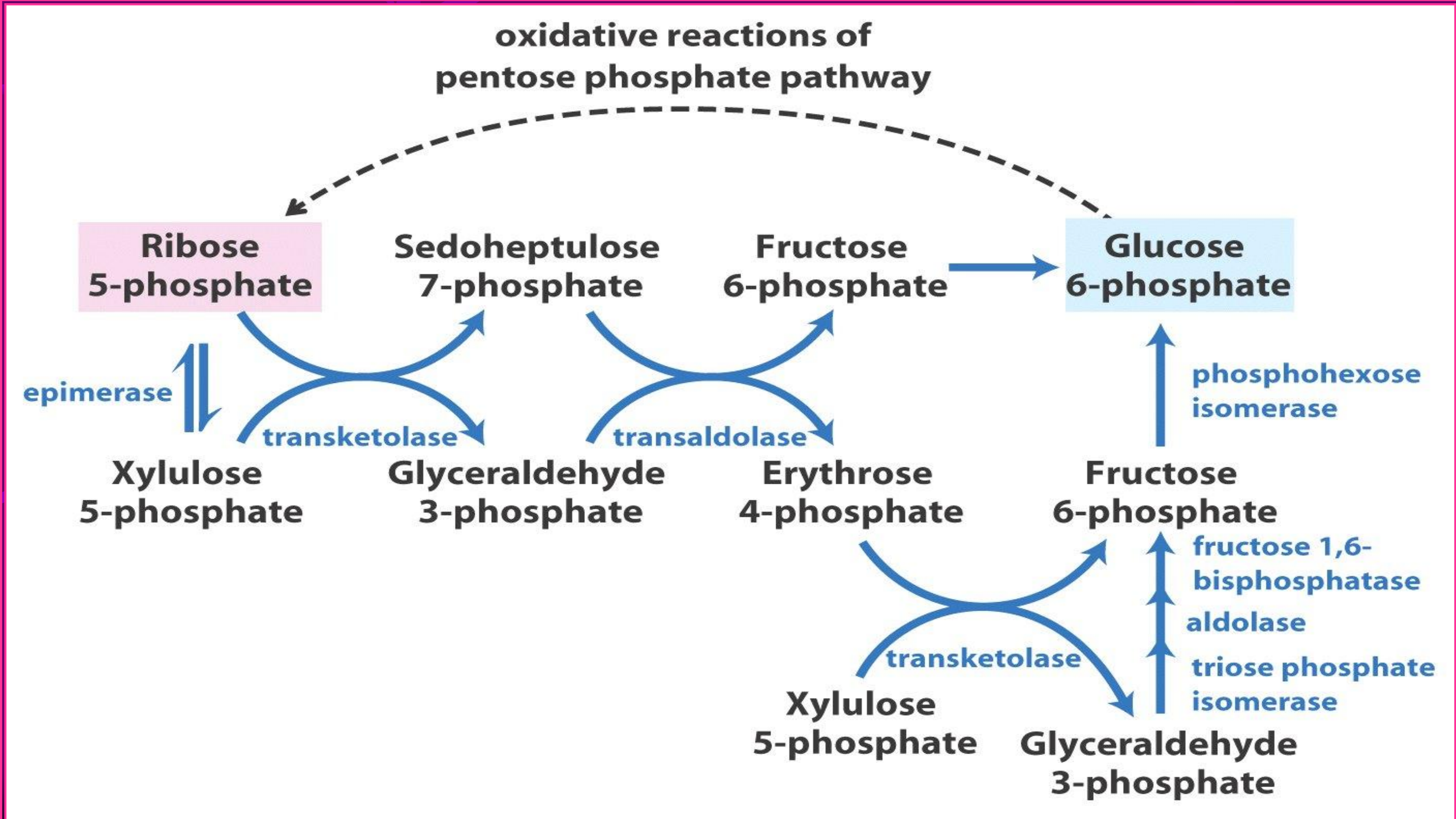




4. D-ribulose 5-phosphate → D-ribose 5-phosphate (phosphopentose isomerase)

- If NADPH is needed but ribose 5-phosphate is not needed, the ribose 5-phosphate is recycled back into glucose 6-phosphate .

Non-oxidative reactions of pentose phosphate pathway



Non-oxidative reactions of pentose phosphate pathway