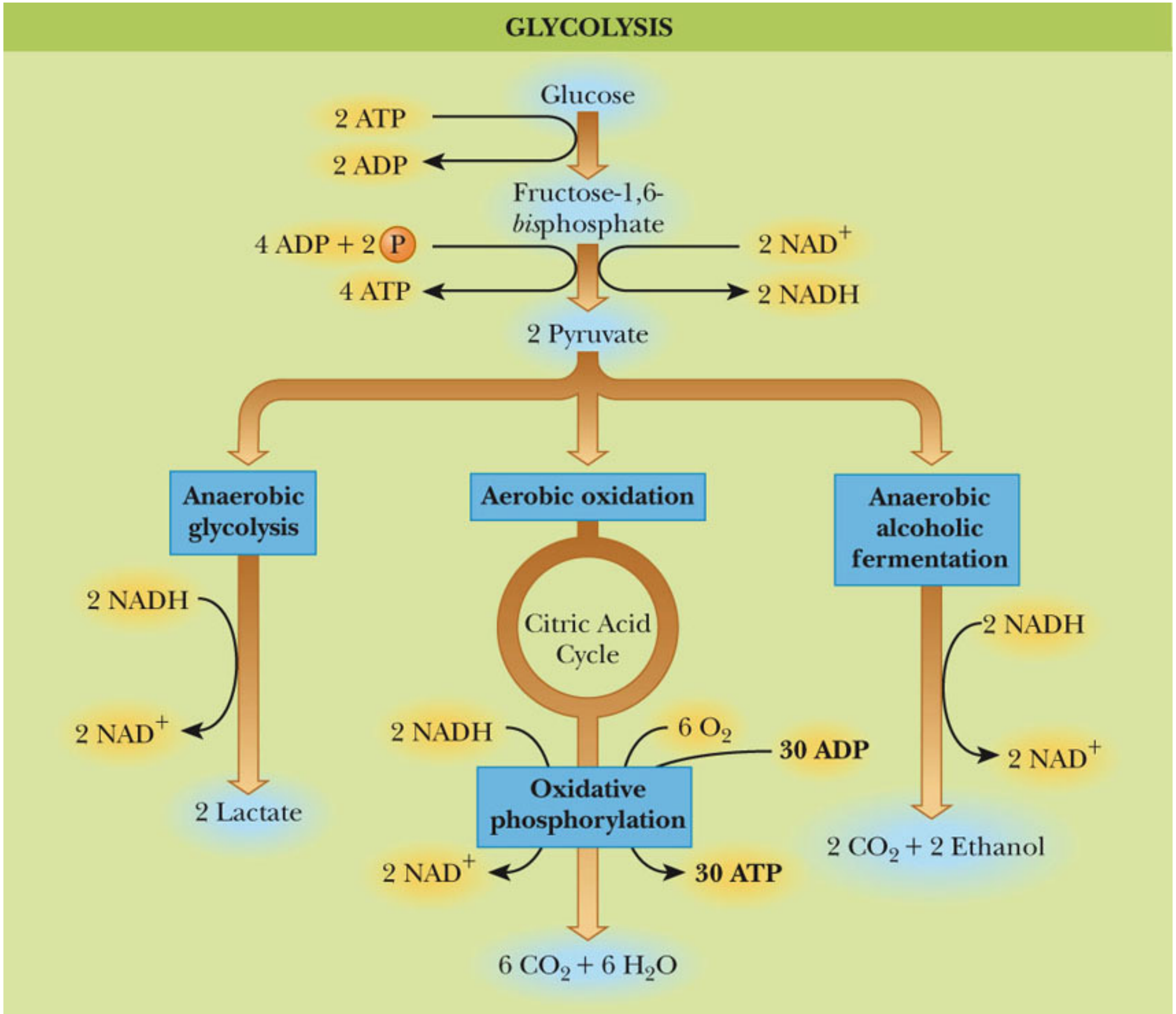
Glycolysis

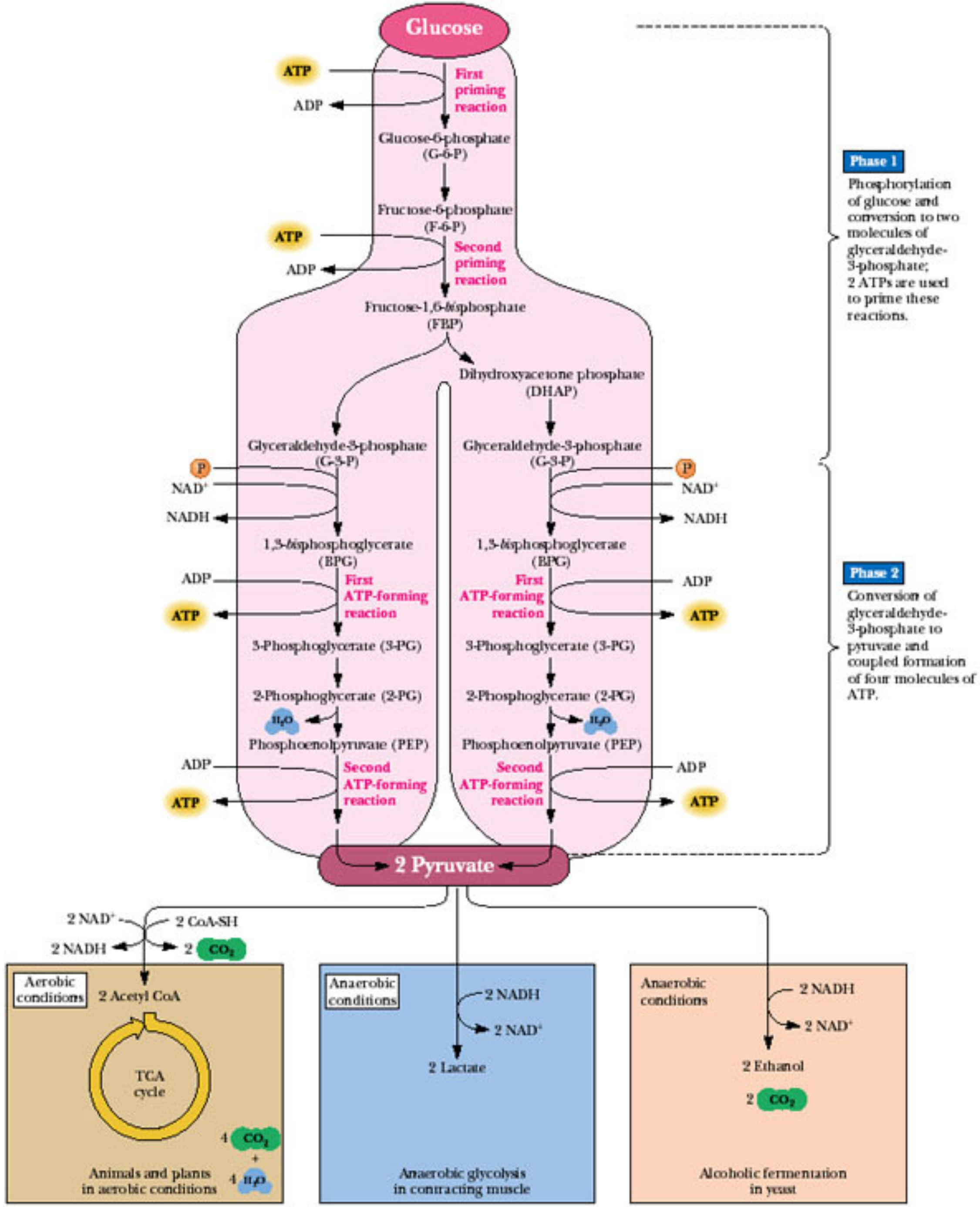
Chapter 17

The Overall Pathway of Glycolysis

- Glycolysis is the first stage of glucose metabolism
- One molecule of glucose is converted to pyruvate which gives rise to 2 molecules of ATP via substrate level phosphorylation.
- Note that all of the steps of glycolysis are enzymatically catalyzed.
- It plays a key role in the way organisms extract energy from nutrients
- Once Pyruvate is formed, it has one of several fates

Fates of Pyruvate From Glycolysis





Glucose
ATP
ADP
First priming reaction
Glucose-6-phosphate (G-6-P)
Fructose-6-phosphate (F-6-P)
ATP
ADP
Second priming reaction
Fructose-1,6-*bis*phosphate (FBP)
Dihydroxyacetone phosphate (DHAP)
Glyceraldehyde-3-phosphate (G-3-P)
Glyceraldehyde-3-phosphate (G-3-P)
P
NAD^+
NADH
P
NAD^+
NADH
1,3-*bis*phosphoglycerate (BPG)
1,3-*bis*phosphoglycerate (BPG)
ADP
First ATP-forming reaction
ATP
ADP
First ATP-forming reaction
ATP
3-Phosphoglycerate (3-PG)
3-Phosphoglycerate (3-PG)
2-Phosphoglycerate (2-PG)
2-Phosphoglycerate (2-PG)
H_2O
H_2O
Phosphoenolpyruvate (PEP)
Phosphoenolpyruvate (PEP)
ADP
Second ATP-forming reaction
ATP
ADP
Second ATP-forming reaction
ATP
2 Pyruvate
Phase 1
Phosphorylation of glucose and conversion to two molecules of glyceraldehyde-3-phosphate; 2 ATPs are used to prime these reactions.
Phase 2
Conversion of glyceraldehyde-3-phosphate to pyruvate and coupled formation of four molecules of ATP.
2 NAD^+
2 CoA-SH
2 NADH
2 CO_2
Aerobic conditions
2 Acetyl CoA
TCA cycle
4 CO_2
+
4 H_2O
Animals and plants in aerobic conditions
Anaerobic conditions
2 NADH
2 NAD^+
2 Lactate
Anaerobic glycolysis in contracting muscle
Anaerobic conditions
2 NADH
2 NAD^+
2 Ethanol
2 CO_2
Alcoholic fermentation in yeast

Fig. 17-2, p.465

The Reactions of Glycolysis

- **Phosphorylation** of glucose to give glucose-6-phosphate
- **Isomerization** of glucose-6-phosphate to give **fructose-6-phosphate**
- **Phosphorylation** of fructose-6-phosphate to yield fructose-1,6-bisphosphate
- **Cleavage** of fructose-1,6,-bisphosphate to give **glyceraldehyde-3-phosphate** and **dihydrooxyacetone phosphate**
- **Isomerization** of dihyroxyacetone phosphate to give **glyceraldehyde-3-phosphate**

The Reactions of Glycolysis (Cont'd)

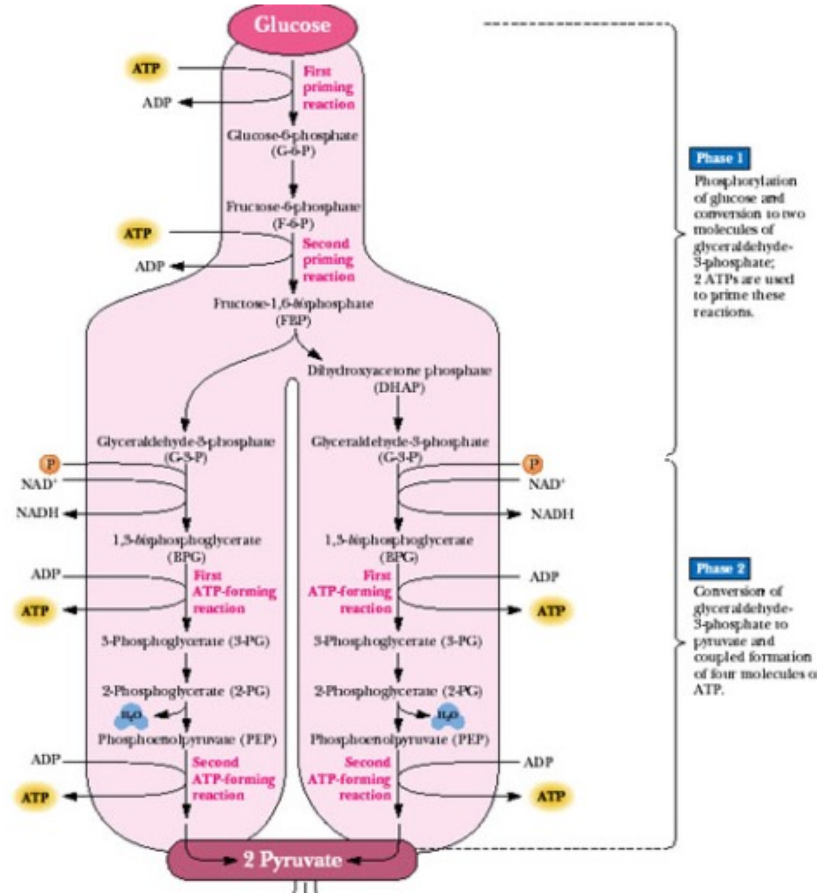
- **Oxidation** of glyceraldehyde-3-phosphate to give I,3-bisphosphoglycerate
- **Transfer of a phosphate group** from 1,3-bisphosphoglycerate to ADP to give ATP
- **Isomerization** of 3-phosphoglycerate to give **2-phosphoglycerate**
- **Dehydration** of 2-phosphoglycerate to give **phosphoenolpyruvate**
- **Transfer of a phosphate group** from phosphoenolpyruvate to ADP to give pyruvate

Glycolysis phases

- The pathway of glycolysis can be seen as consisting of 2 separate phases:

1. **The chemical priming phase requiring energy in the form of ATP:**
   - 2 equivalents of ATP are used to convert glucose to fructose 1,6-bisphosphate (F1,6BP).

2. **The energy-yielding phase:**
   - F1,6BP is degraded to pyruvate, with the production of
   - 4 equivalents of ATP and 2 equivalents of NADH.



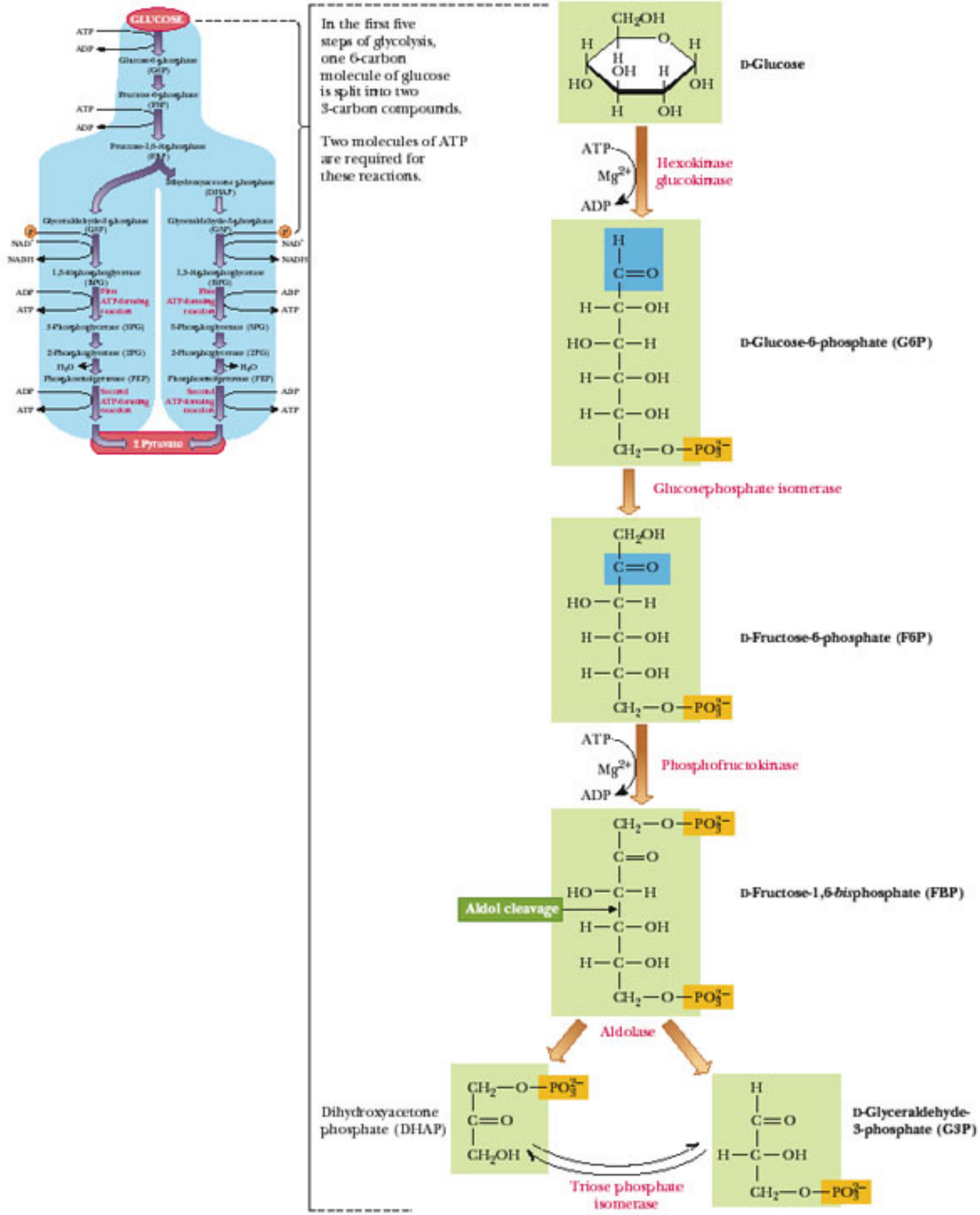

GLUCOSE
2 Pyruvate
In the first five steps of glycolysis, one 6-carbon molecule of glucose is split into two 3-carbon compounds.
Two molecules of ATP are required for these reactions.
D-Glucose
ATP
Mg2+
ADP
Hexokinase
glucokinase
D-Glucose-6-phosphate (G6P)
Glucosephosphate isomerase
D-Fructose-6-phosphate (F6P)
Phosphofructokinase
D-Fructose-1,6-bisphosphate (FBP)
Aldol cleavage
Aldolase
Dihydroxyacetone phosphate (DHAP)
D-Glyceraldehyde-3-phosphate (G3P)
Triose phosphate isomerase

Fig. 17-3, p.468

Phosphofructokinase is a key regulatory enzyme

- **Phosphofructokinase (PFK):**

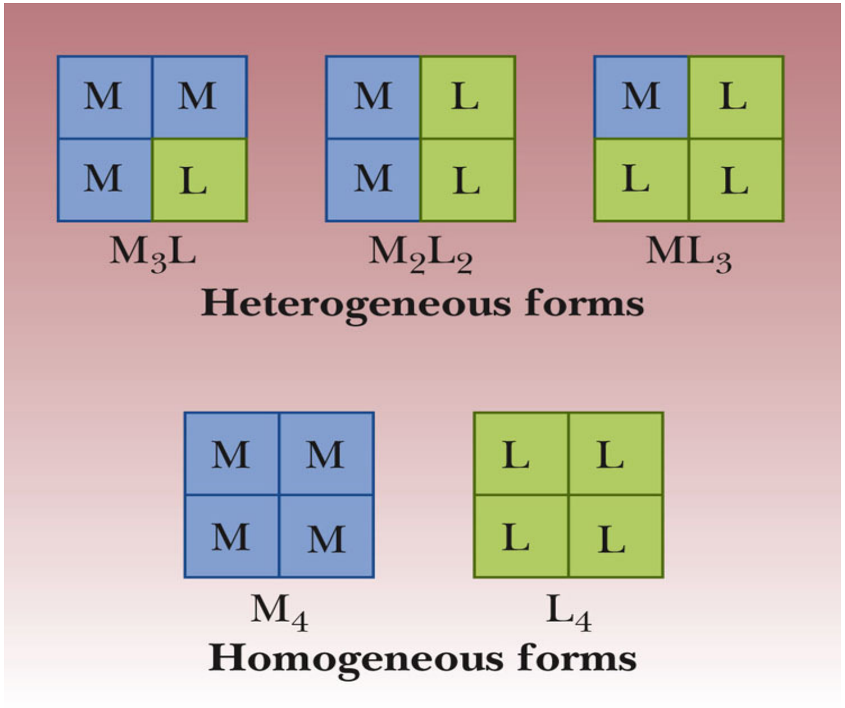
- Exists as a tetramer and subject to allosteric feedback regulation

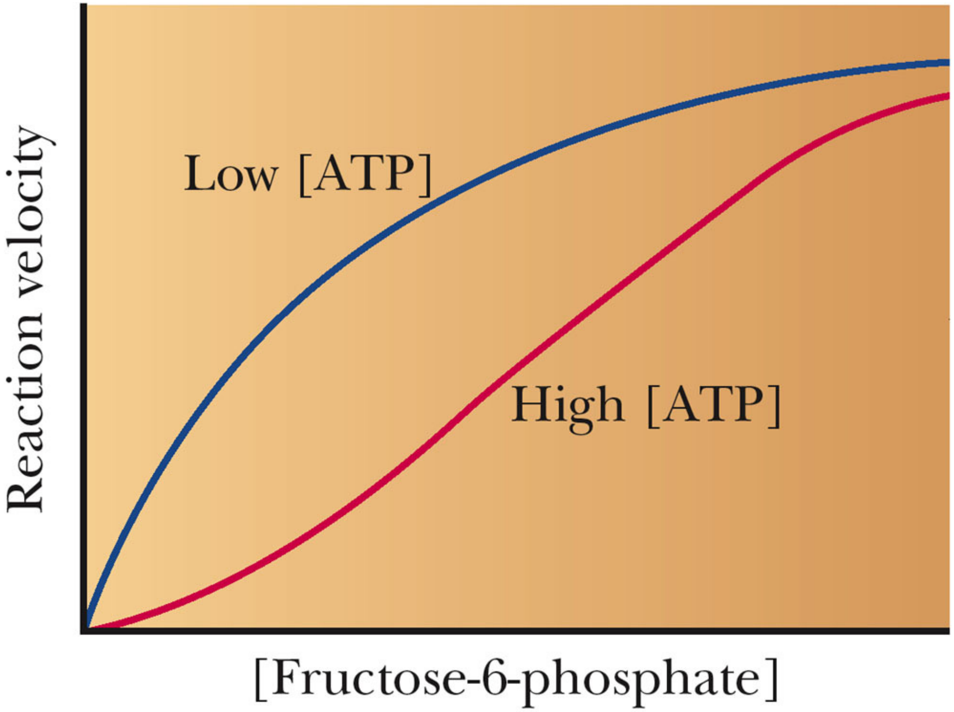
- The tetramer is composed of L and M subunits
  - M_4, M_3L, M_2L_2, ML_3, and L_4 all exist. Combinations of these subunits are called Isozyme
  - Muscles are rich in M_4; the liver is rich in L_4

- ATP is an allosteric effector;
  - high levels inhibit the enzyme
  - low levels activate it

- Fructose-1,6-bisphosphate is also an allosteric effector

Phosphofructokinase is a key regulatory enzyme





Summary

- In the first stages of glycolysis, glucose is converted to two molecules of glyceraldehyde-3-phosphate
- The key intermediate in this series of reactions is fructose-1,6-bisphosphate.
- The enzyme that catalyzes this reaction, phosphofructokinase, is subject to allosteric control

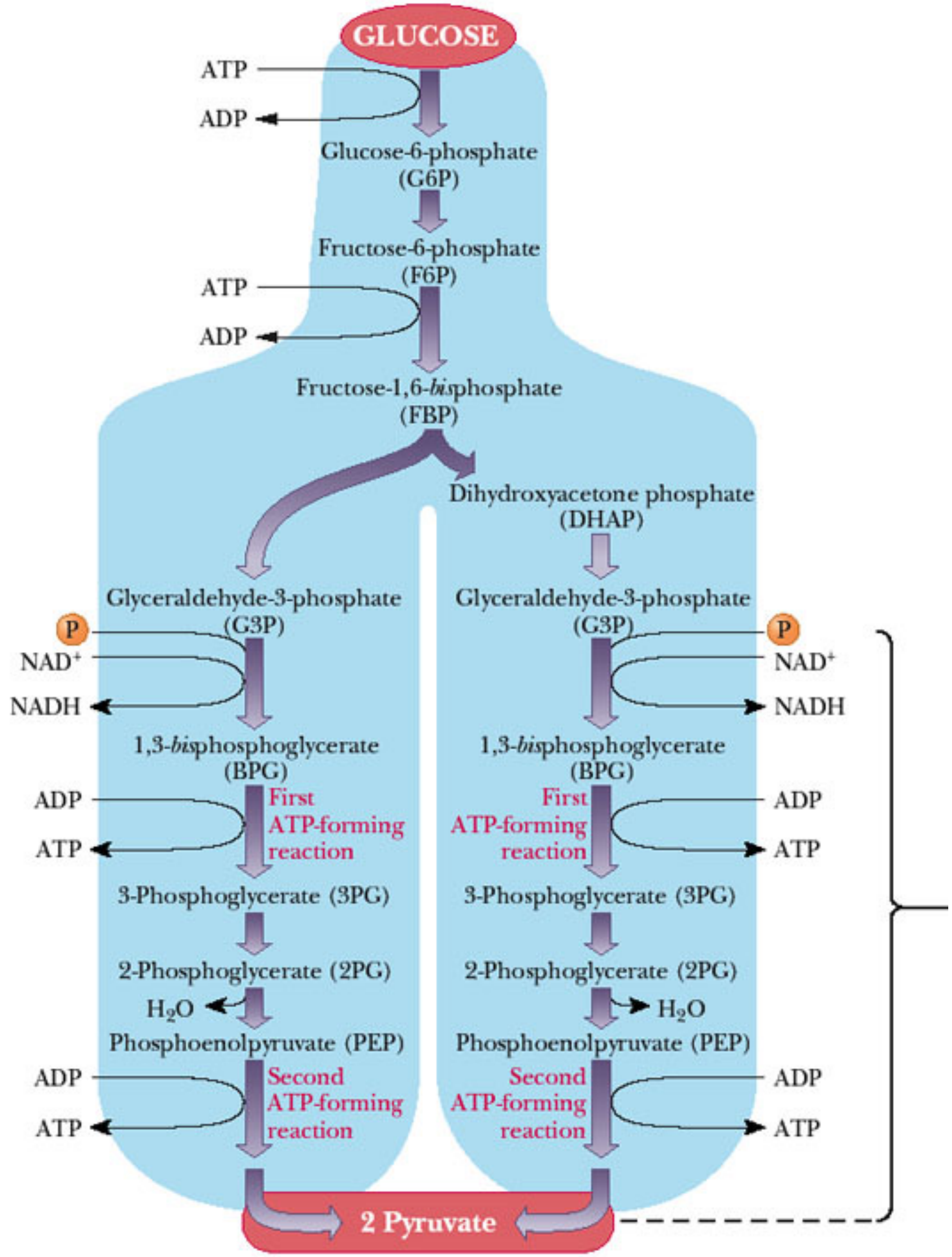


Fig. 17-7a, p.473

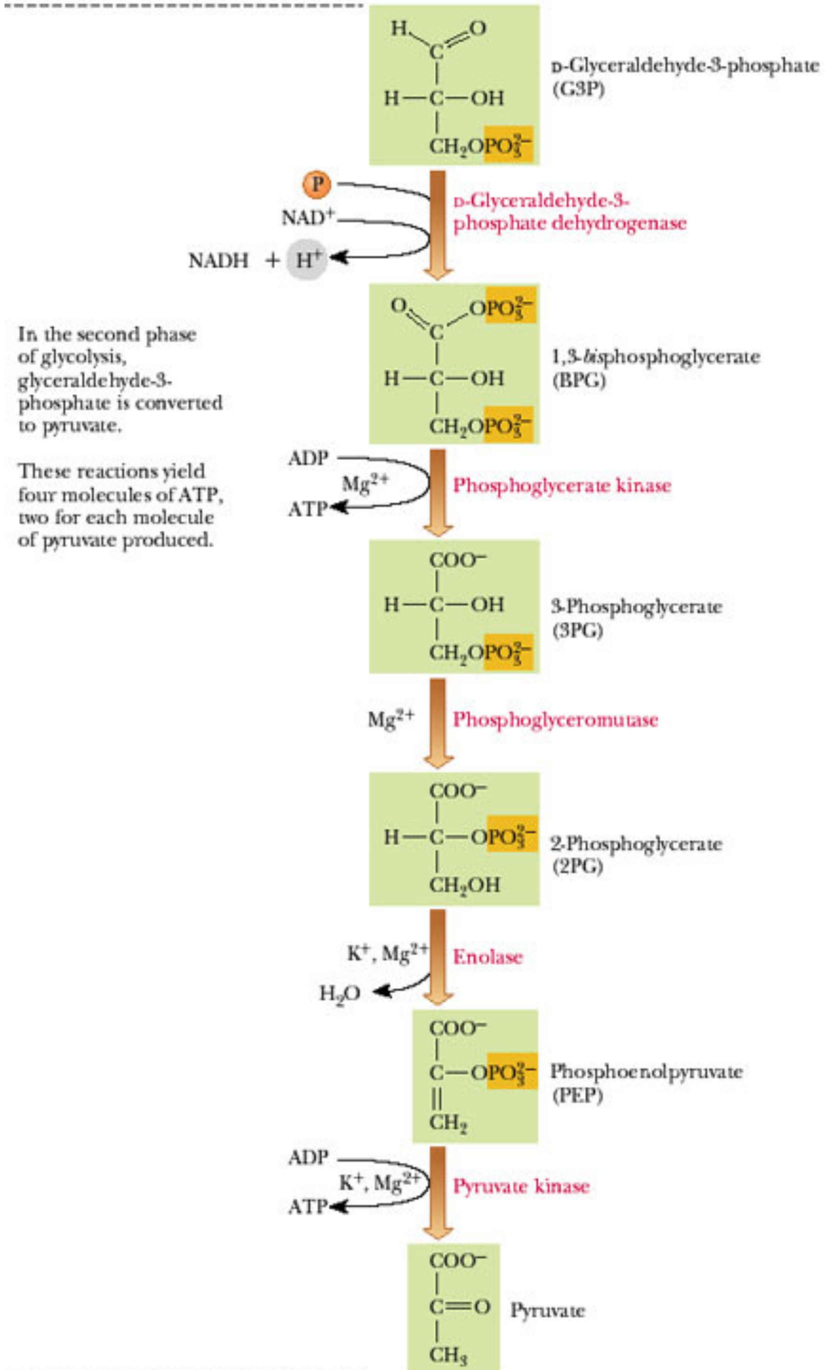


Fig. 17-7b, p.473

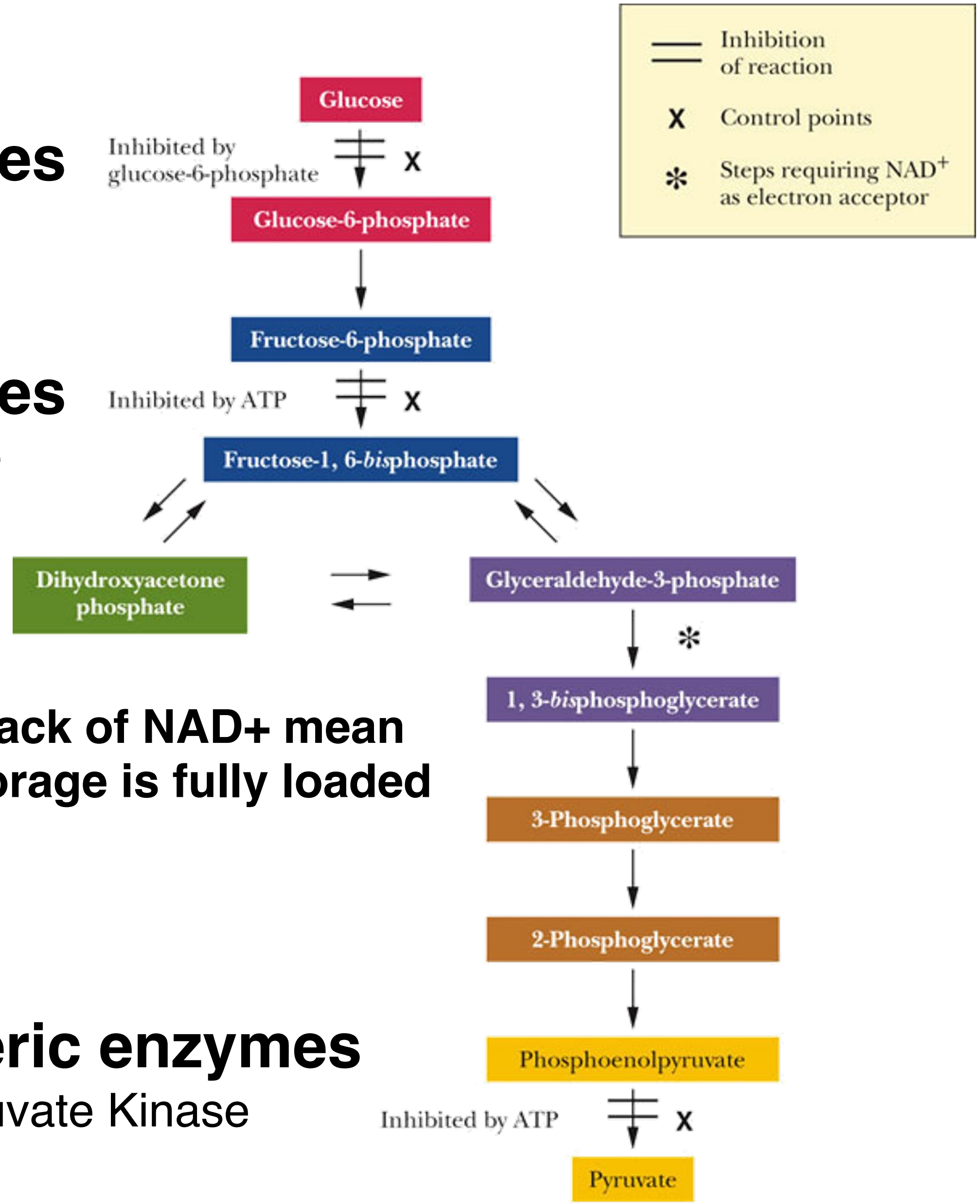
Control Points in Glycolysis

Allosteric enzymes
Hexokinase

Allosteric enzymes
Phosphofrectokinase

Lack of NAD+ mean storage is fully loaded

Allosteric enzymes
Pyruvate Kinase

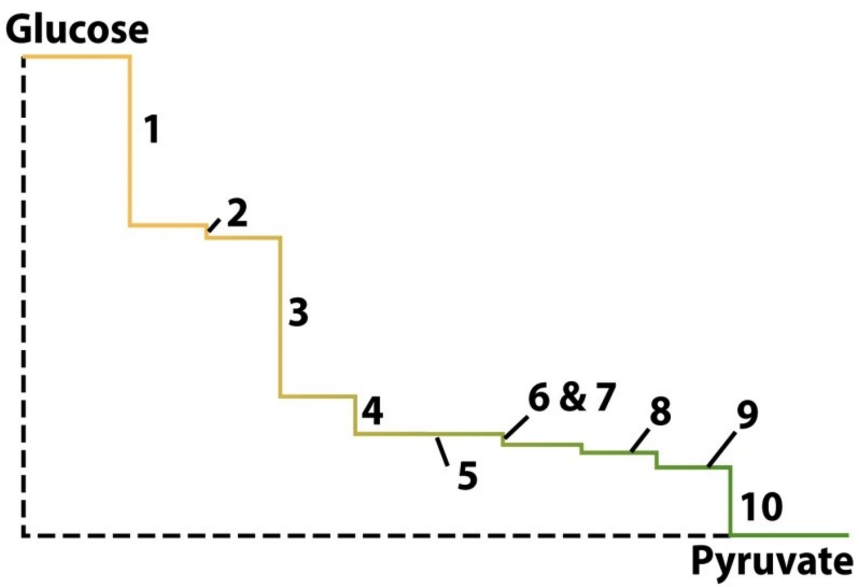


Thermodynamics of Glycolysis

Table 15-1 $\Delta G^{\circ\prime}$ and ΔG for the Reactions of Glycolysis in Heart Muscle[a]

Reaction	Enzyme	$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)	ΔG ($kJ \cdot mol^{-1}$)
1	Hexokinase	−20.9	−27.2
2	PGI	+2.2	−1.4
3	PFK	−17.2	−25.9
4	Aldolase	+22.8	−5.9
5	TIM	+7.9	~0
6 + 7	GAPDH + PGK	−16.7	−1.1
8	PGM	+4.7	−0.6
9	Enolase	−3.2	−2.4
10	PK	−23.0	−13.9

[a]Calculated from data in Newsholme, E.A. and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).



Summary

- In the final stages of glycolysis, two molecules of pyruvate are produced for each molecule of glucose that entered the pathway

- These reactions involve electron transfer, and the net production of two ATP for each glucose

- There are three control points in the glycolytic pathway

The Energy Derived from Glucose Oxidation

- Aerobic glycolysis of glucose to pyruvate, requires two ATP to activate the process, with production of four ATP and two NADH.

$$\text{Glucose} + 2\ \text{ADP} + 2\ \text{NAD}^+ + 2\ \text{Pi}$$

$$\Downarrow$$

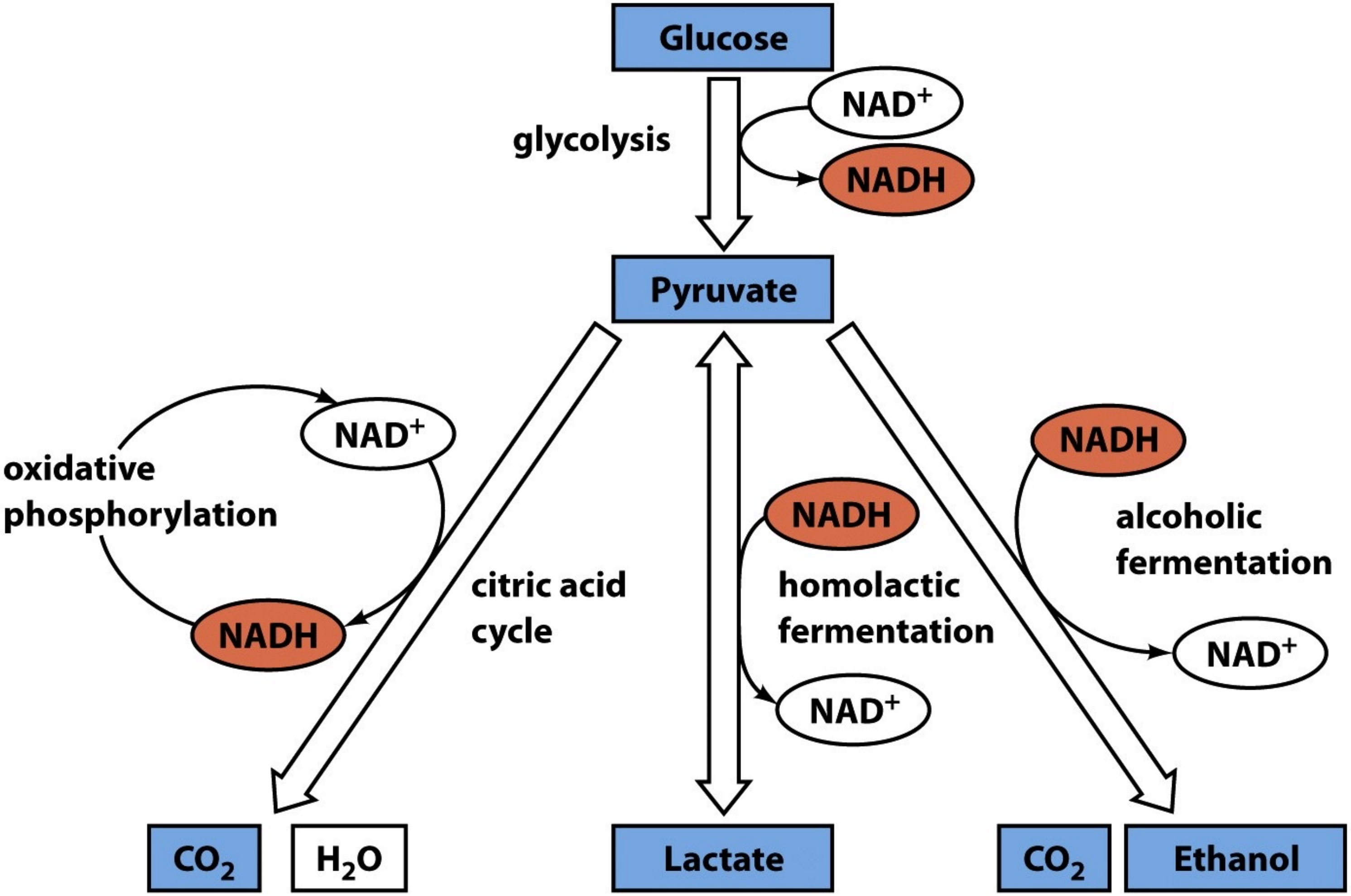
$$2\ \text{Pyruvate} + 2\ \text{ATP} + 2\ \text{NADH} + 2\ \text{H}^+$$

Glycolysis NADH

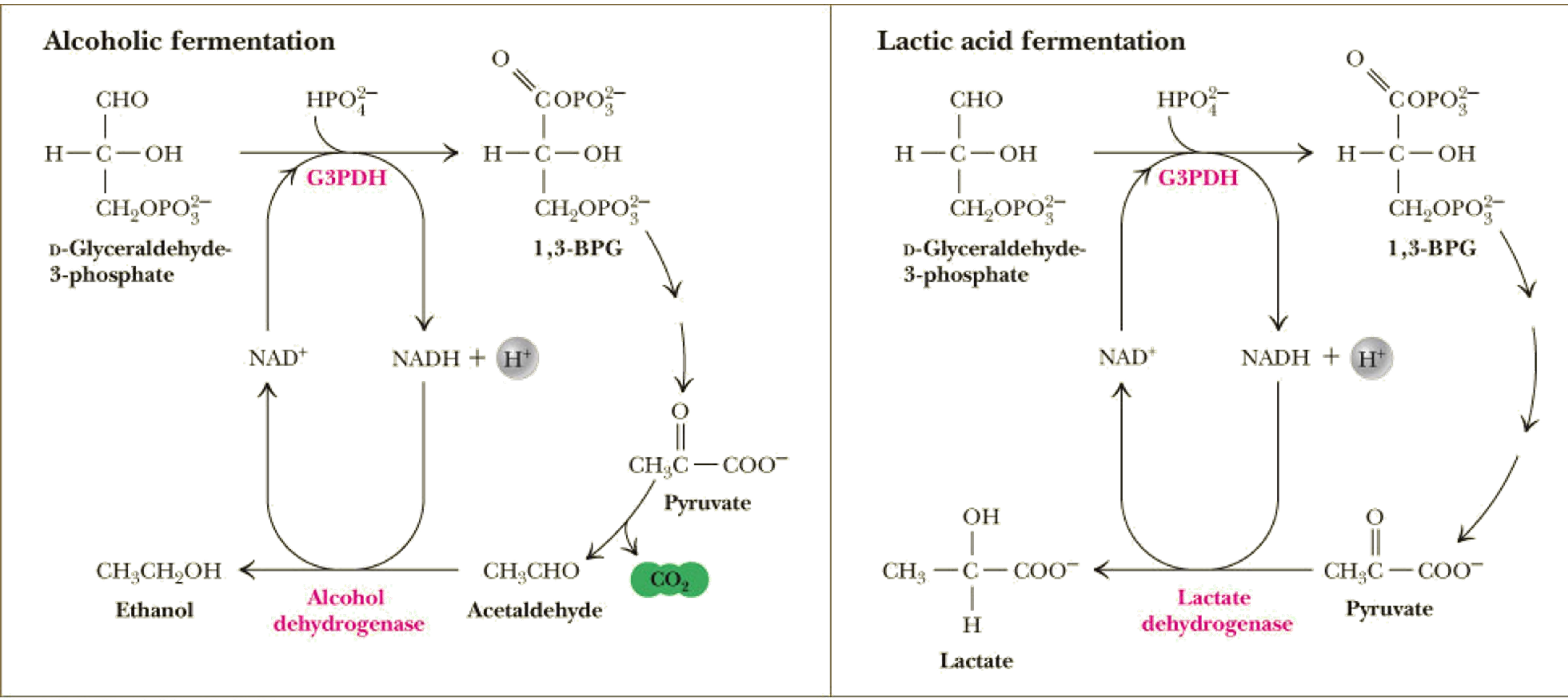
- The NADH generated during glycolysis is used to fuel mitochondrial ATP synthesis via oxidative phosphorylation, producing either two or three equivalents of ATP

- Depending upon whether the glycerol phosphate shuttle or the malate-aspartate shuttle is used to transport the electrons from cytoplasmic NADH into the mitochondria.

Fates of Pyruvate



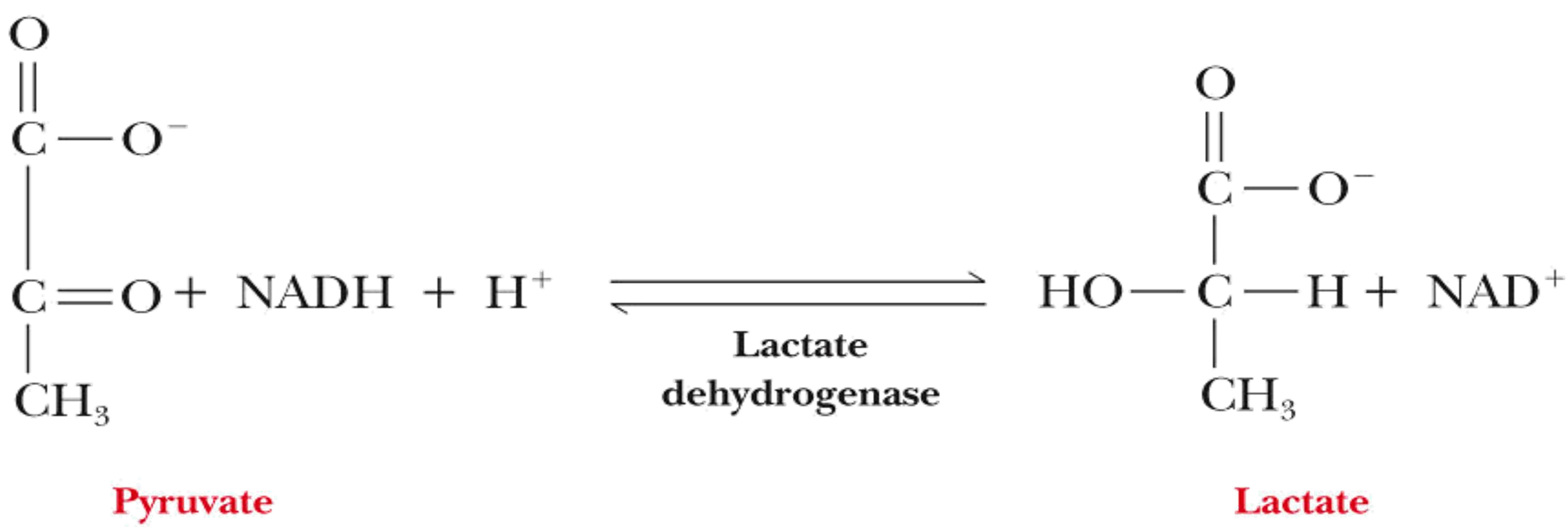
NAD^+ Needs to be Recycled to Prevent Decrease in Oxidation Reactions



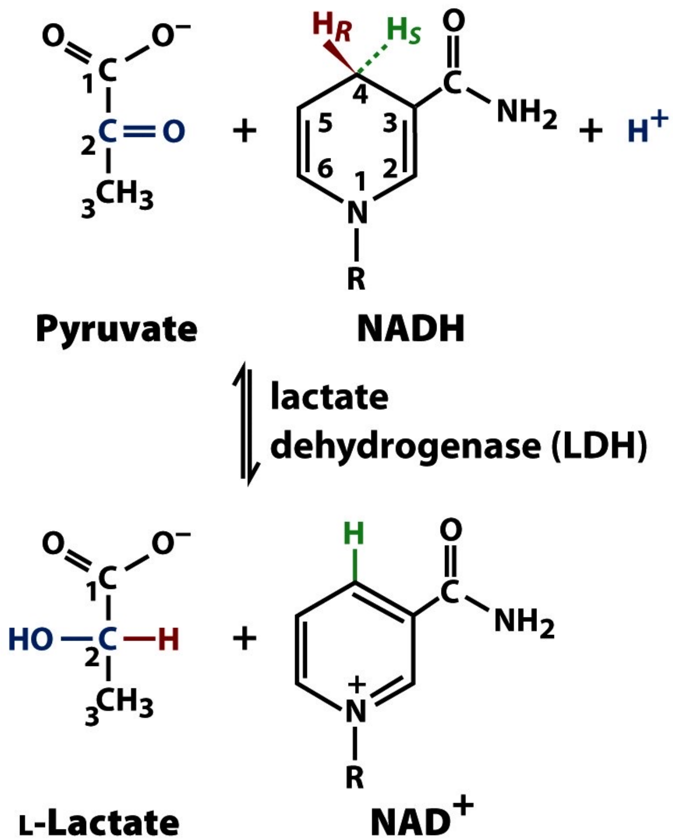
Anaerobic Metabolism of Pyruvate

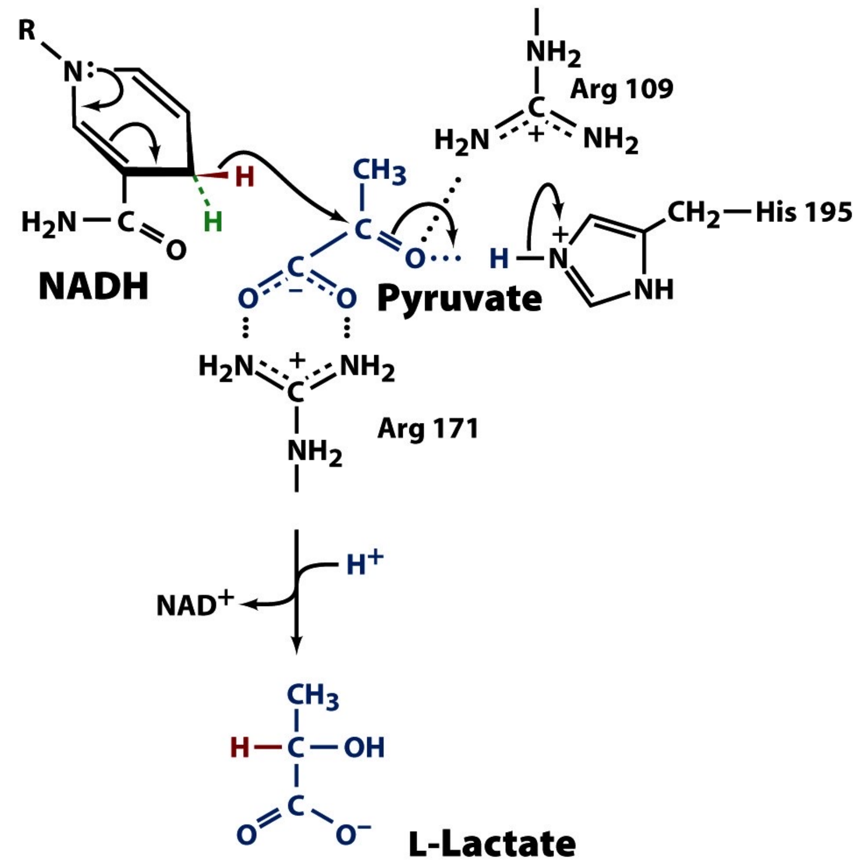
- Under anaerobic conditions, the most important pathway for the regeneration of NAD^+ is reduction of pyruvate to lactic acid

- Lactate dehydrogenase (LDH) is a tetrameric isoenzyme consisting of H and M subunits; H_4 predominates in heart muscle, and M_4 in skeletal muscle



Lactate Dehydrogenase (LDH)



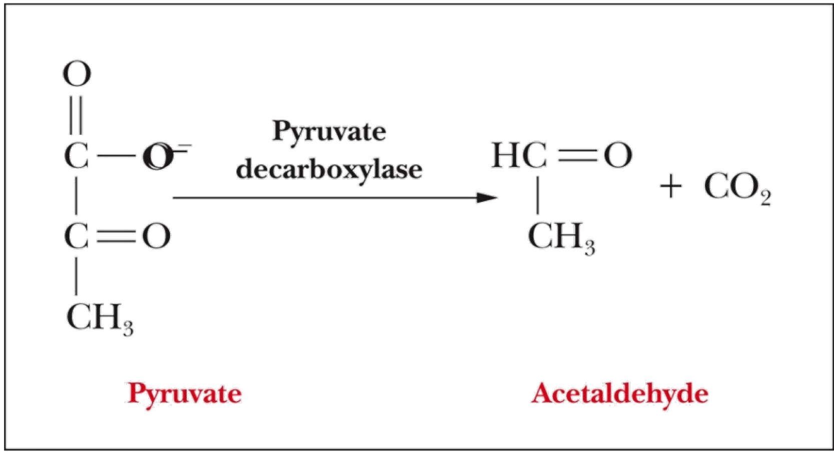


Alcoholic Fermentation

- Two reactions lead to the production of ethanol:
  - Decarboxylation of pyruvate to acetaldehyde
  - Reduction of acetaldehyde to ethanol

- Pyruvate decarboxylase catalyzes the first reaction
  - This enzyme require Mg2+ and the cofactor Thiamine pyrophosphate (TPP)

- Alcohol dehydrogenase catalyzes the conversion of acetaldehyde to ethanol



Energy Efficiency

$$Glu\cos e \rightarrow 2lactate + 2H^{+}$$ ***ΔG°′ = -196 kJ/mol***

$$Glu\cos e \rightarrow 2CO_2 + 2ethanol$$ ***ΔG°′ = -235 kJ/mol***

To make 2 ATP = ΔG°′ = 61 kJ/mol

Therefore, lactate production is 61/196 = 31% efficient
Therefore, ethanol production is 61/235 = 26% efficient
Under biochemical concentrations, the reactions are actually >50% efficient