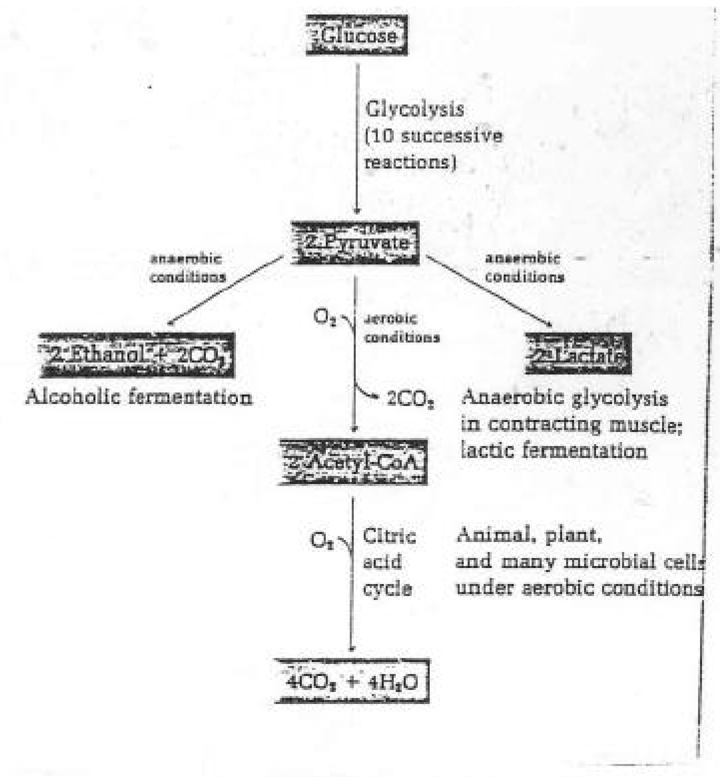
Glycolysis
Embden-Meyerhoff pathway

- Introduction to Glycolysis
- Glycolysis
- Entry of glucose into the cell
- Preparatory phase of glycolysis
- Energy production



Glycolysis

- Ancient Pathway
- In cytoplasm
- No oxygen required
- Used for energy production
- Production of intermediates for other pathways
- Found in tissues with limited blood supply

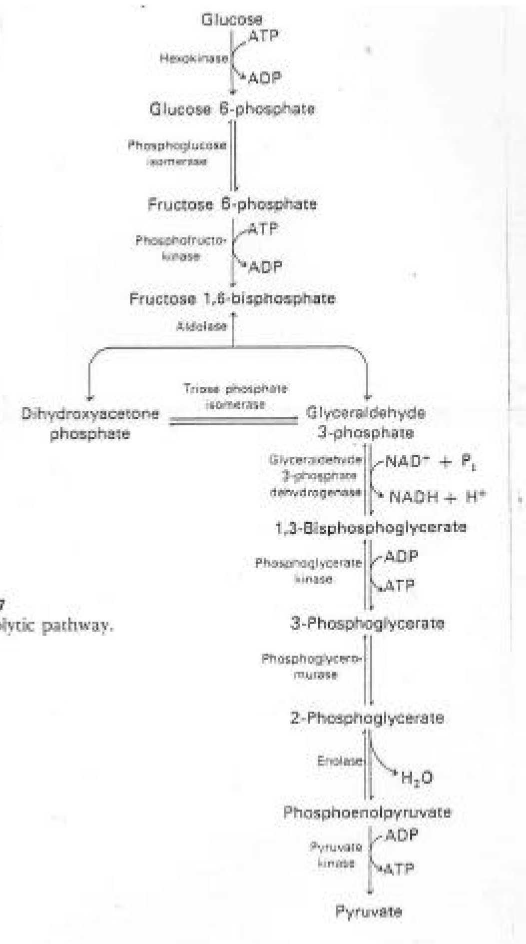
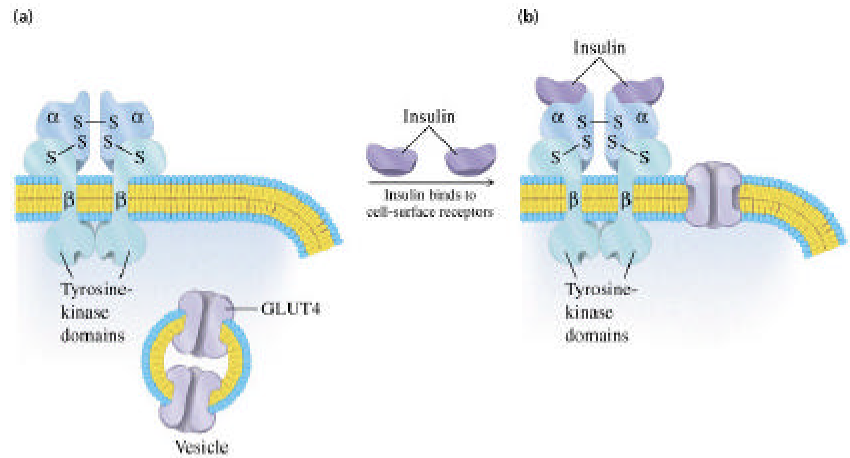
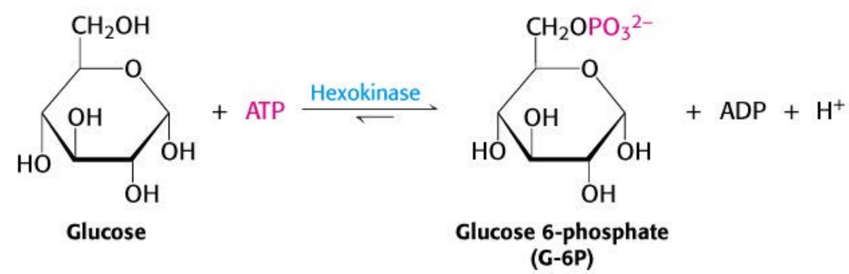


Figure 15-7
The glycolytic pathway.

Entry of glucose into the cell

- Transport
- hexokinase
- glucokinase in liver
- hexokinase vs glucokinase
- forms anion to keep in cell





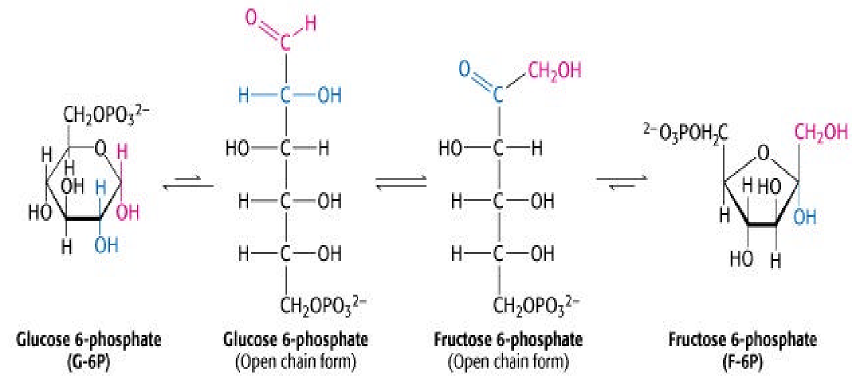
Glucose Transporters

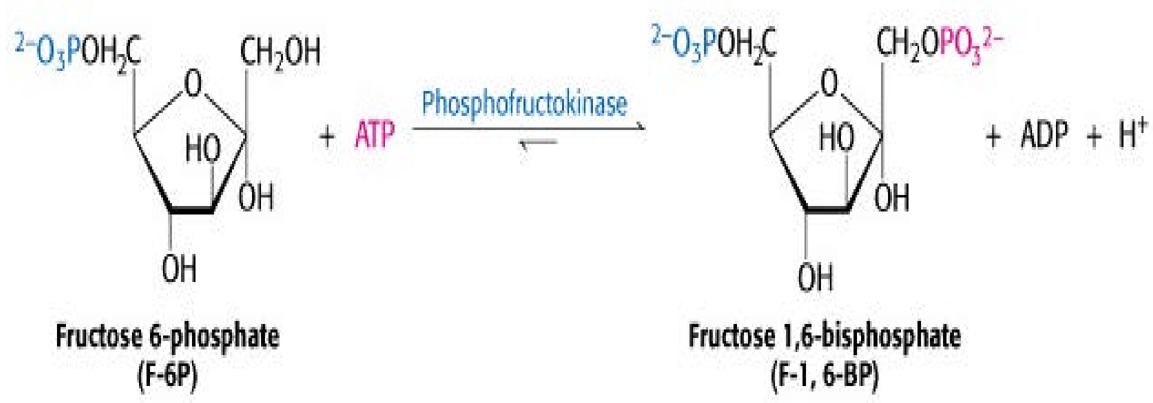
TABLE 16.4 Family of glucose transporters

Name	Tissue location	K_m	Comments
GLUT1	All mammalian tissues	1 mM	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15–20 mM	In the pancreas, plays a role in regulation of insulin In the liver, removes excess glucose from the blood
GLUT3	All mammalian tissues	1 mM	Basal glucose uptake
GLUT4	Muscle and fat cells	5 mM	Amount in muscle plasma membrane increases with endurance training
GLUT5	Small intestine	—	Primarily a fructose transporter

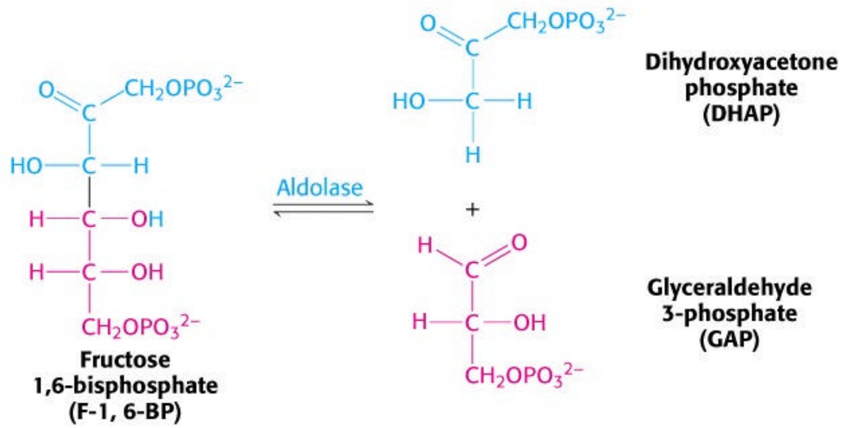
Preparatory phase of glycolysis

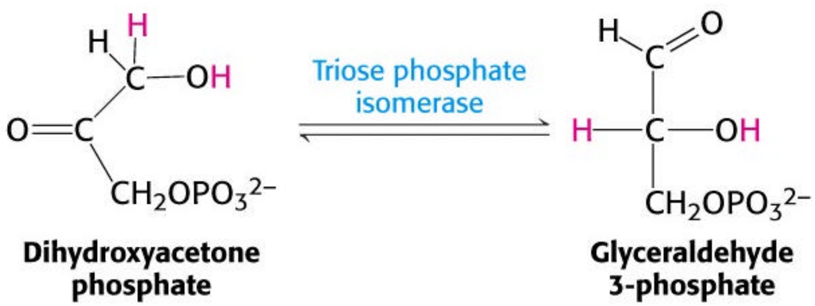
- 2 ATP
- Phosphofructokinase (PFK-1)
- regulated
- allosterically

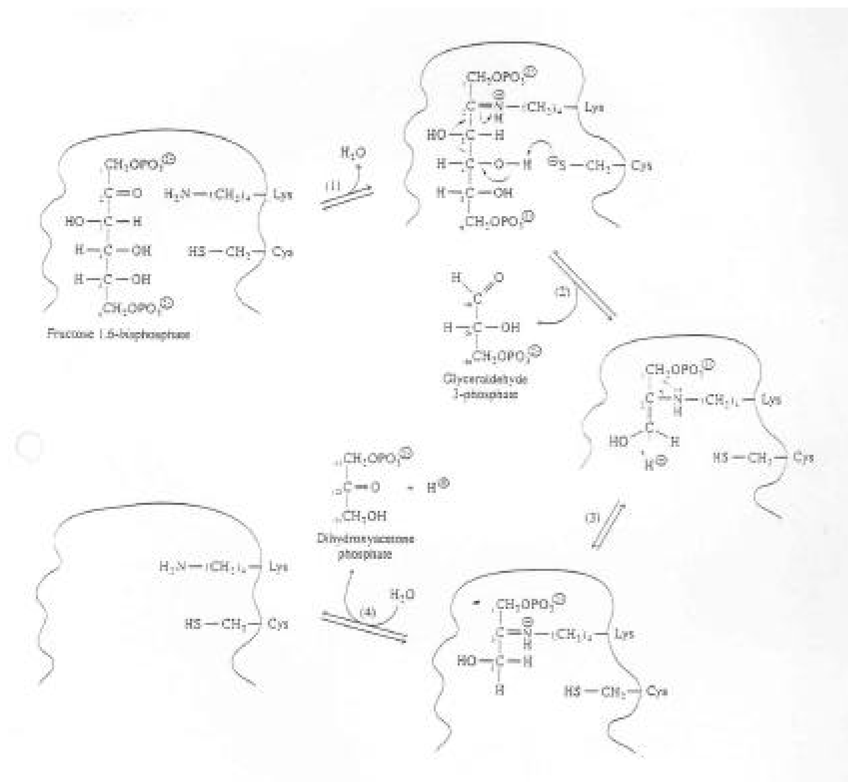




Mechanism: Aldolase

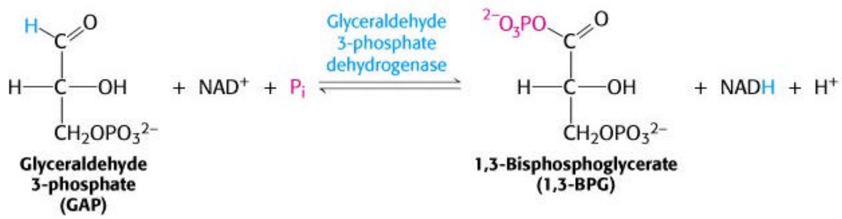


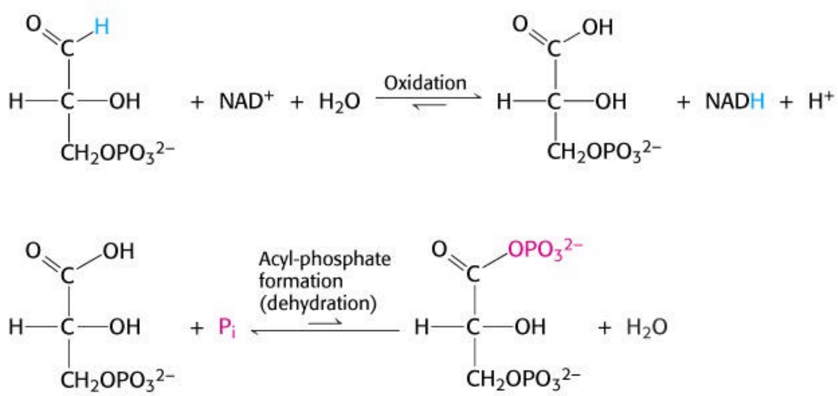




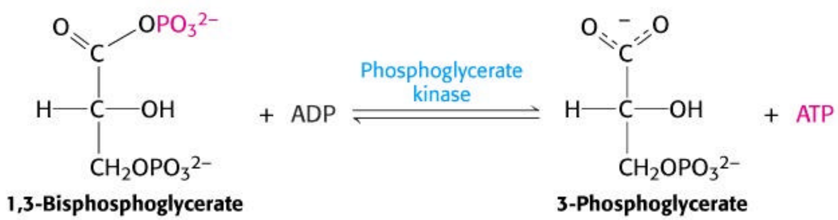
Energy production

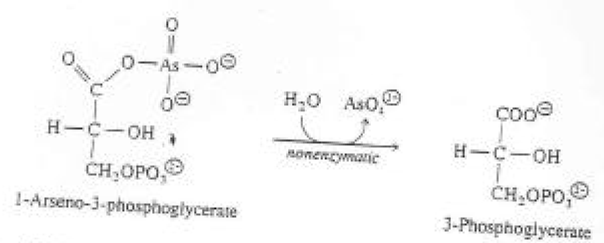
- 1,3 BPGA
- PEP
- 4 ATP & 2 NADH
- Pyruvate end product
- effect of aresenate



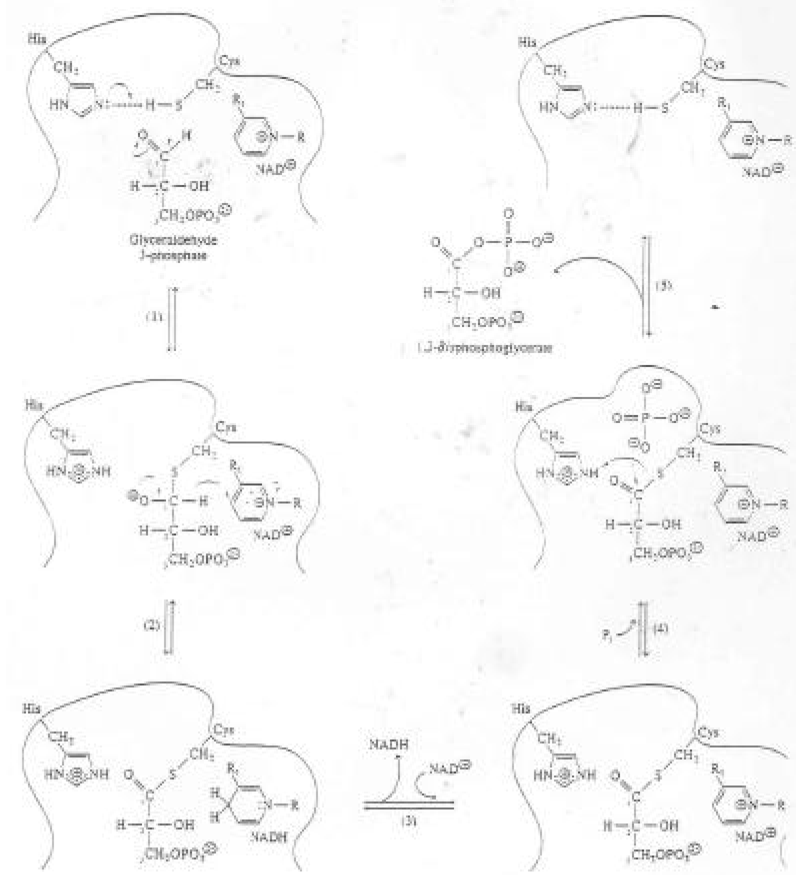


Mechanism: dehydrogenase





(Figure 12·14). This nonenzymatic hydrolysis produces 3-phosphoglycerate and regenerates inorganic arsenate, which can again react with a thioacyl-enzyme intermediate. Glycolysis can proceed from 3-phosphoglycerate, but the ATP-producing reaction involving 1,3-*bis*phosphoglycerate is bypassed. As a result, there is no net formation of ATP from glycolysis, with potentially lethal consequences.



PEP to Pyruvate

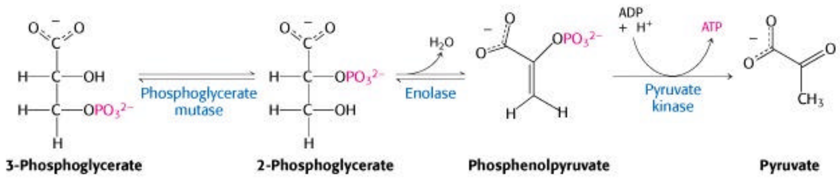
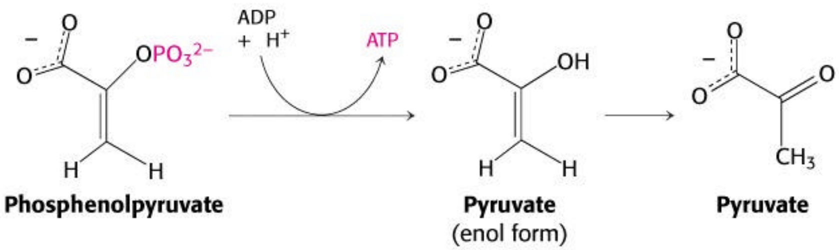


Table 15-1
Consumption and generation of ATP in glycolysis

Reaction	ATP change per glucose
Glucose ⟶ glucose 6-phosphate	−1
Fructose 6-phosphate ⟶ fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate ⟶ 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate ⟶ 2 pyruvate	+2
Net	+2



ENERGY YIELD IN THE CONVERSION OF GLUCOSE INTO PYRUVATE

The net reaction in the transformation of glucose into pyruvate is

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

Biological Systems

- Net 2 ATP
- 2 NADH
- Most reactions at equilibrium can be reversed

Table 15-3
Typical concentrations of glycolytic intermediates in erythrocytes

Intermediate	μM
Glucose	5000
Glucose 6-phosphate	83
Fructose 6-phosphate	14
Fructose 1,6-bisphosphate	31
Dihydroxyacetone phosphate	138
Glyceraldehyde 3-phosphate	19
1,3-Bisphosphoglycerate	1
2,3-Bisphosphoglycerate	4000
3-Phosphoglycerate	118
2-Phosphoglycerate	30
Phosphoenolpyruvate	23
Pyruvate	51
Lactate	2900
ATP	1850
ADP	138
P_i	1000

After S. Minakami and H. Yoshikawa, *Biochem. Biophys. Res. Comm.* 18(1965):345.

Overall reactions of glycolysis

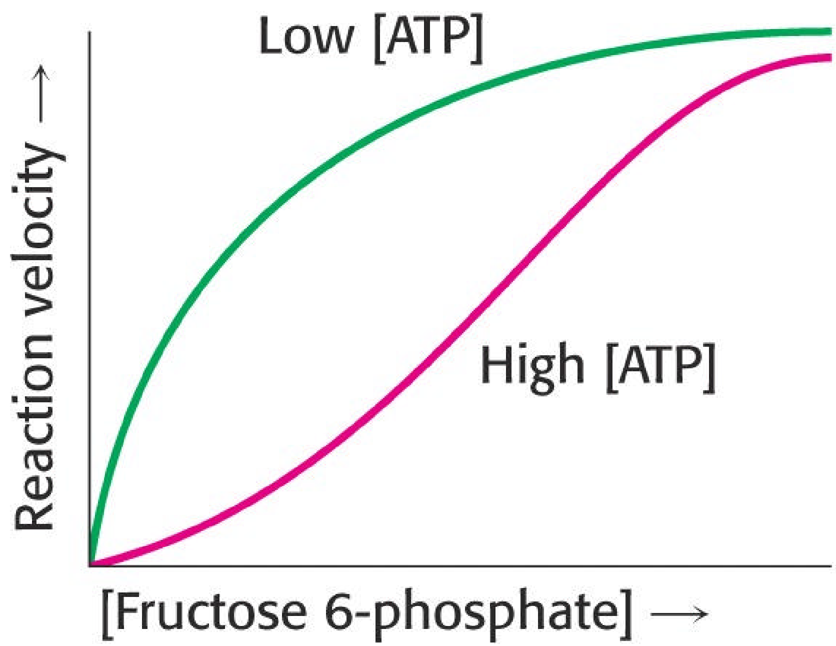
TABLE 16.3 Reactions of glycolysis

Step	Reaction	Enzyme	Reaction type	$\Delta G^{\circ\prime}$ in kcal mol^{-1} (kJ mol^{-1})	ΔG in kcal mol^{-1} (kJ mol^{-1})
1	Glucose + ATP $\longrightarrow$ glucose 6-phosphate + ADP + H^+	Hexokinase	Phosphoryl transfer	−4.0 (−16.7)	−8.0 (−33.5)
2	Glucose 6-phosphate $\rightleftharpoons$ fructose 6-phosphate	Phosphoglucose isomerase	Isomerization	+0.4 (+1.7)	−0.6 (−2.5)
3	Fructose 6-phosphate + ATP $\longrightarrow$ fructose 1,6-bisphosphate + ADP + H^+	Phosphofructokinase	Phosphoryl transfer	−3.4 (−14.2)	−5.3 (−22.2)
4	Fructose 1,6-bisphosphate $\rightleftharpoons$ dihydroxyacetonephosphate + glyceraldehyde 3-phosphate	Aldolase	Aldol cleavage	+5.7 (+23.8)	−0.3 (−1.3)
5	Dihydroxyacetone phosphate $\rightleftharpoons$ glyceraldehyde 3-phosphate	Triose phosphate isomerase	Isomerization	+1.8 (+7.5)	+0.6 (+2.5)
6	Glyceraldehyde 3-phosphate + P_i + NAD^+ $\rightleftharpoons$ 1,3-bisphosphoglycerate + NADH + H^+	Glyceraldehyde 3-phosphate dehydrogenase	Phosphorylation coupled to oxidation	+1.5 (+6.3)	+0.6 (+2.5)
7	1,3-Bisphosphoglycerate + ADP $\rightleftharpoons$ 3-phosphoglycerate + ATP	Phosphoglycerate kinase	Phosphoryl transfer	−4.5 (−18.8)	+0.3 (+1.3)
8	3-Phosphoglycerate $\rightleftharpoons$ 2-phosphoglycerate	Phosphoglycerate mutase	Phosphoryl shift	+1.1 (+4.6)	+0.2 (+0.8)
9	2-Phosphoglycerate $\rightleftharpoons$ phosphoenolpyruvate + H_2O	Enolase	Dehydration	+0.4 (+1.7)	−0.8 (−3.3)
10	Phosphoenolpyruvate + ADP + H^+ $\longrightarrow$ pyruvate + ATP	Pyruvate kinase	Phosphoryl transfer	−7.5 (−31.4)	−4.0 (−16.7)

Note: ΔG, the actual free-energy change, has been calculated from $\Delta G^{\circ\prime}$ and known concentrations of reactants under typical physiologic conditions. Glycolysis can proceed only if the ΔG values of all reactions are negative. The small positive ΔG values of three of the above reactions indicate that the concentrations of metabolites in vivo in cells undergoing glycolysis are not precisely known.

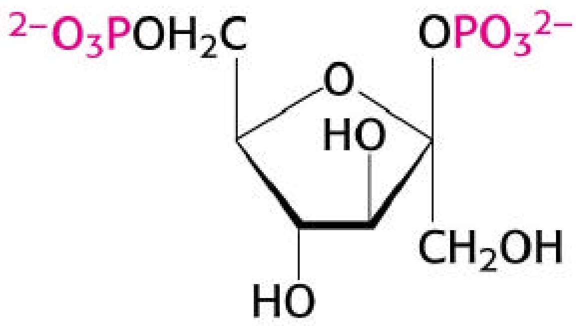
Regulation of glycolysis

- ATP/ADP ratios are important
- Two roles: energy production and building blocks for biosynthesis

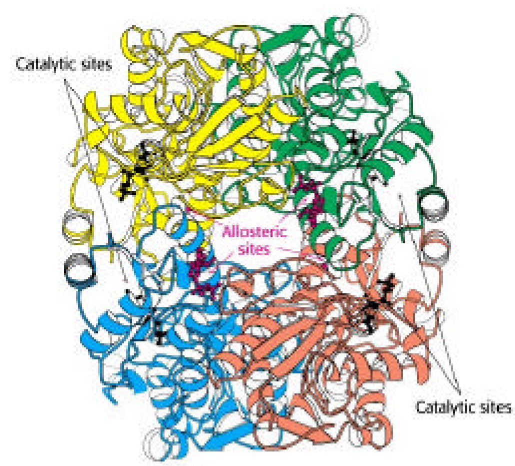


Phosphofructokinase: Highly regulated

- Allosteric enzyme:
- Activated by ADP and AMP
- Inhibited by ATP and Citrate (from TCA cycle)
- Fructose 2,6 bisphosphate regulation

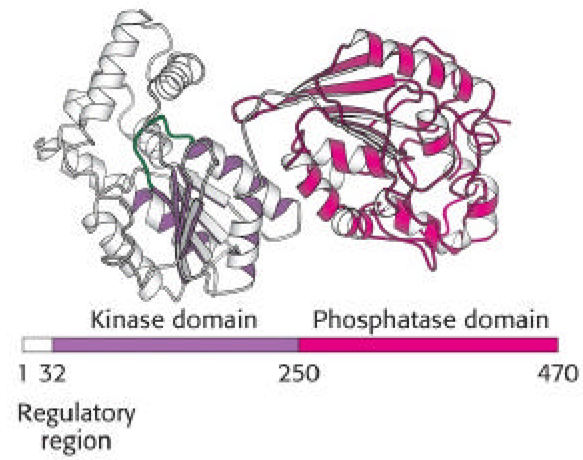


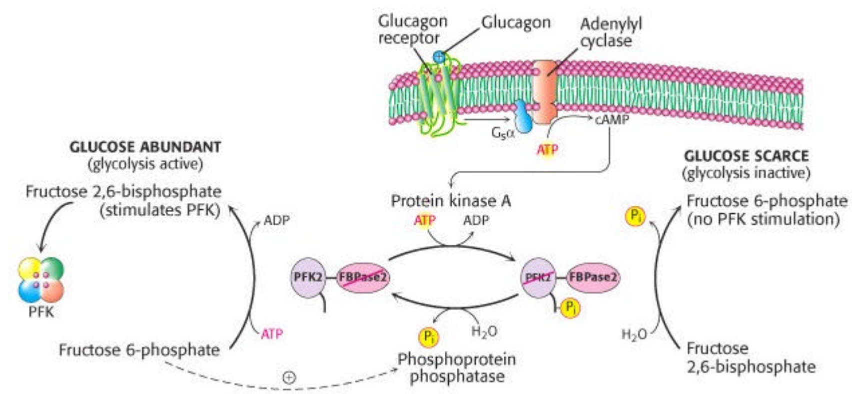
Fructose 2,6-bisphosphate (F-2,6-BP)



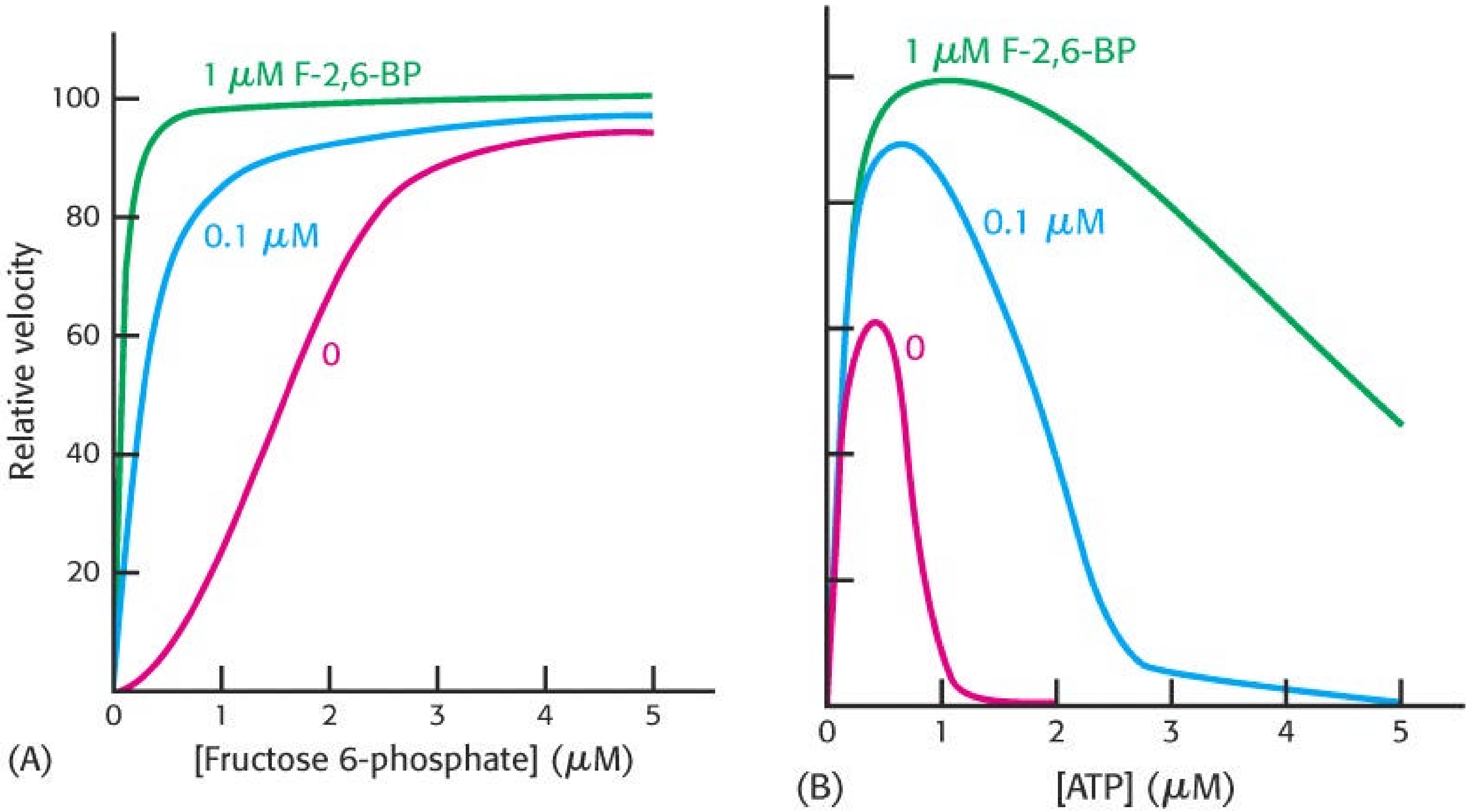
PFK-2

- **Tandem enzyme: PFK-2, both kinase and phsophotase together**
- **Fru 2,6 P potent activator of PFK-1**
- **prevents inhibition of citrate/ATP for fatty acid biosynthesis**
- **Relative velocity curves for PFK-1**
- **Effect of glucagon on PFK-1**





Activation of PFK-1 by Fru 2,6 Bis



Other sites of Regulation

- **Pyruvate kinase**
- **allosteric**
- **stimulated by fructose 1,6P**
- **inhibited by acetyl-CoA, fatty acids**
- **protein kinase inhibits pyruvate kinase**
- **Glyceraldehyde 3-P dehydrogenase**
- **stimulated by NAD+**