CHEM 539

Molecular Metabolism: Pathways and Regulation

Spring 2015

PPT Set 2b

Glucose transport; glycolysis; degradation of other monosaccharides; alternatives to glycolysis

Mechanism of the PGK reaction

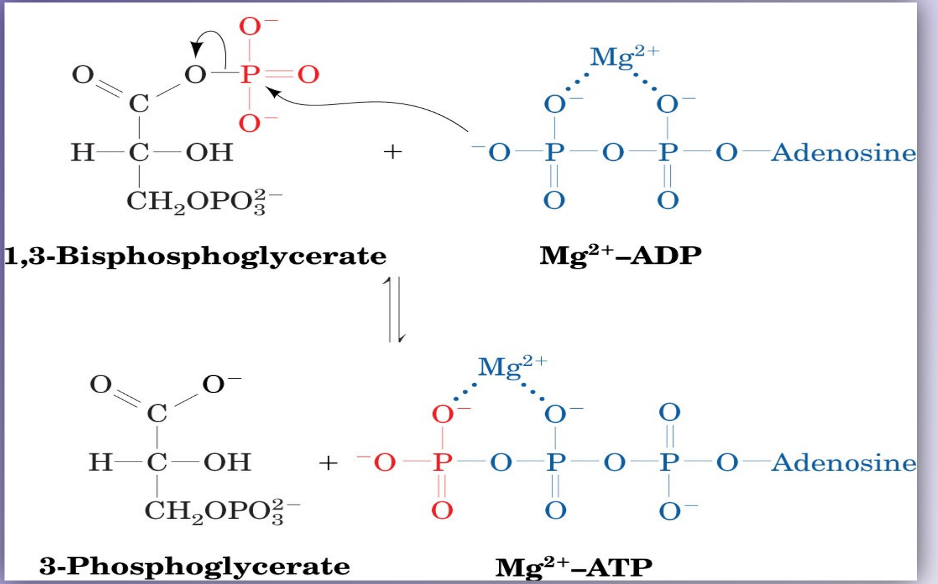
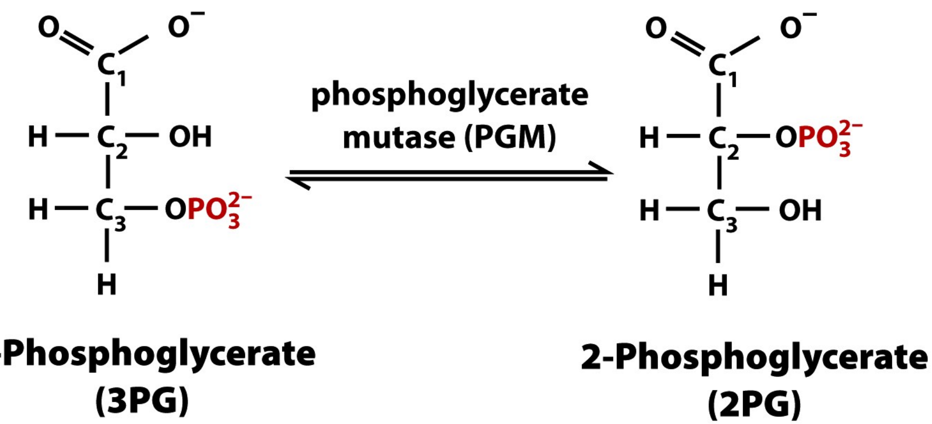
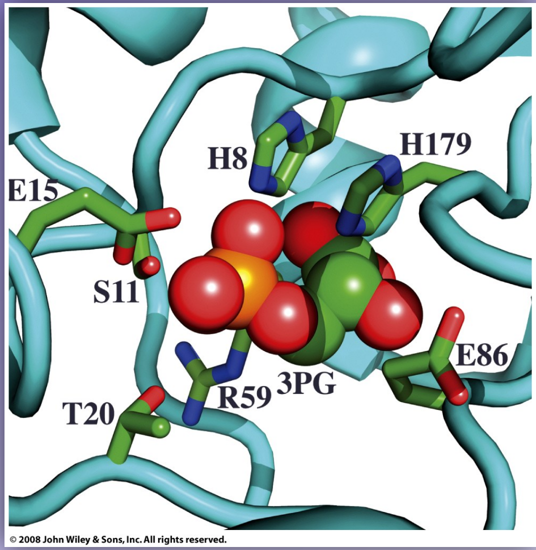


Table 15-1	$\Delta G^{\circ\prime}$ and ΔG for the Reactions of Glycolysis in Heart Muscle[a]		
Reaction	**Enzyme**	**$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)**	**ΔG ($kJ \cdot mol^{-1}$)**
1	Hexokinase	−20.9	−27.2
2	PGI	+2.2	−1.4
3	PFK	−17.2	−25.9
4	Aldolase	+22.8	−5.9
5	TIM	+7.9	~0
6 + 7	GAPDH + 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).

3-Phosphoglycerate mutase




H8
H179
E15
S11
T20
R59
3PG
E86
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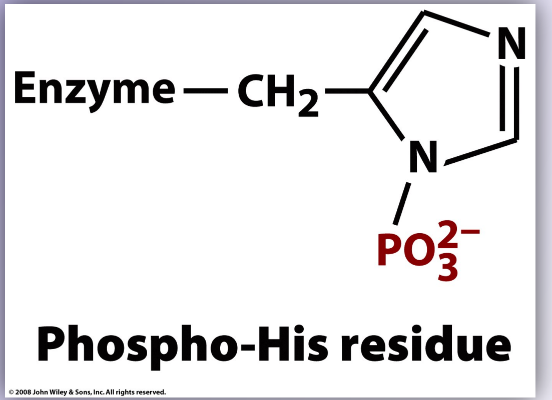
Enzyme — CH2
N
N
PO3 2−
Phospho-His residue
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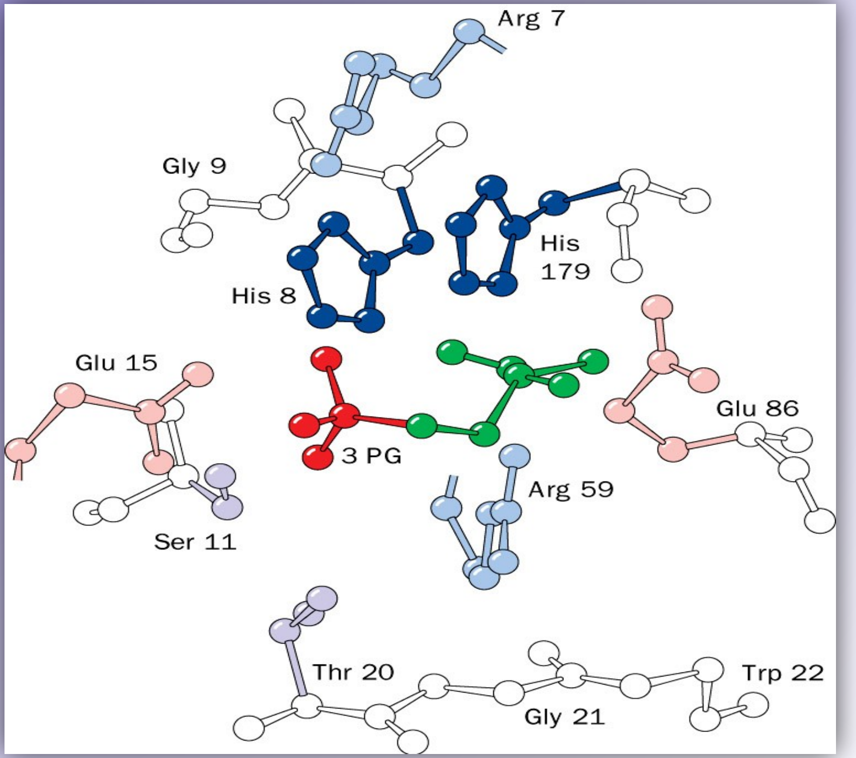
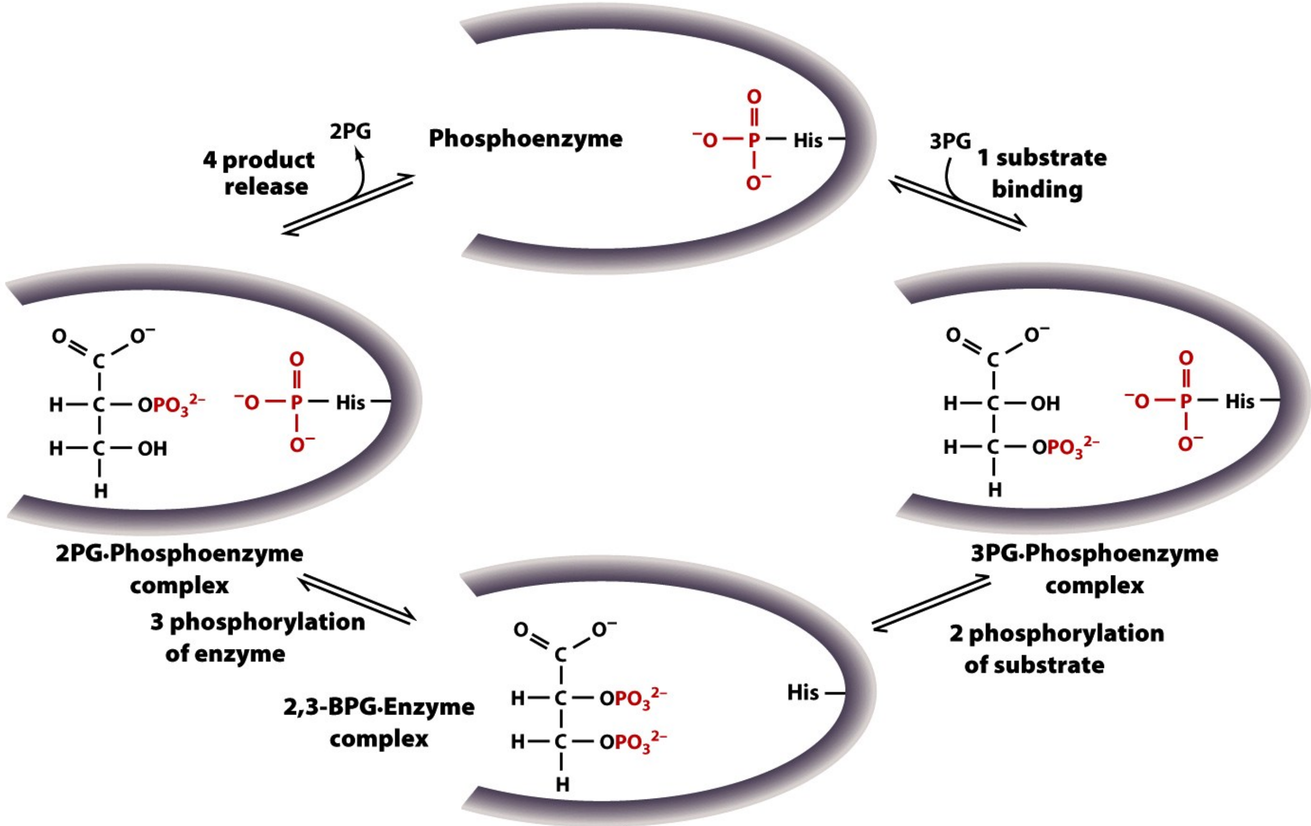
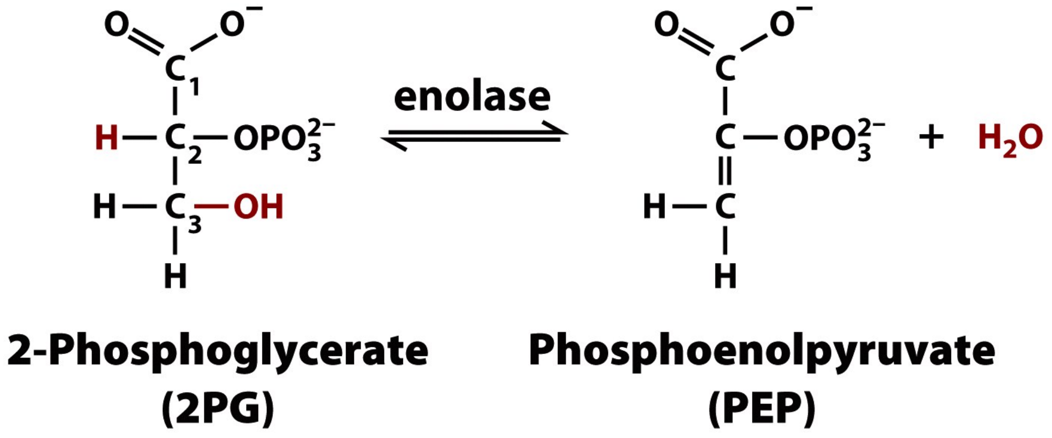
The active site region of yeast phosphoglycerate mutase (dephospho form) showing the substrate, 3-phosphoglycerate, and some of the side chains that approach it



Proposed mechanism of 3-phosphoglycerate mutase

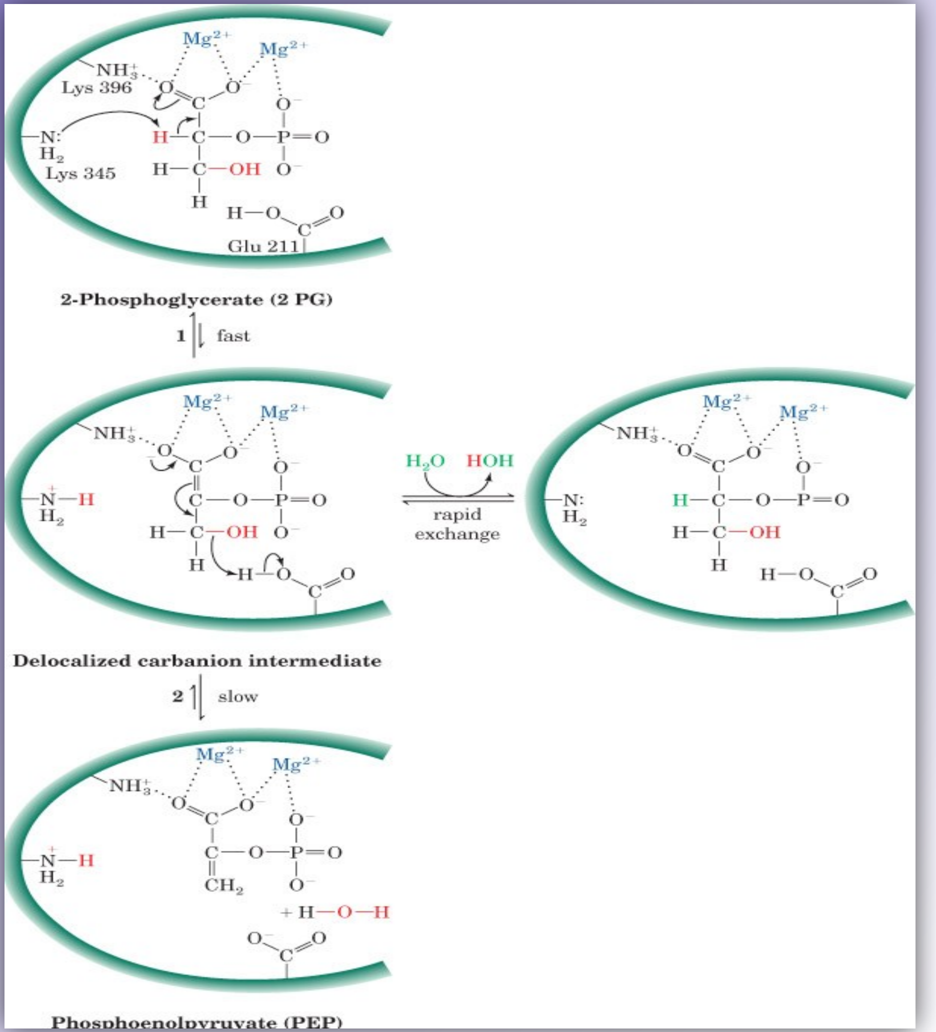


Enolase

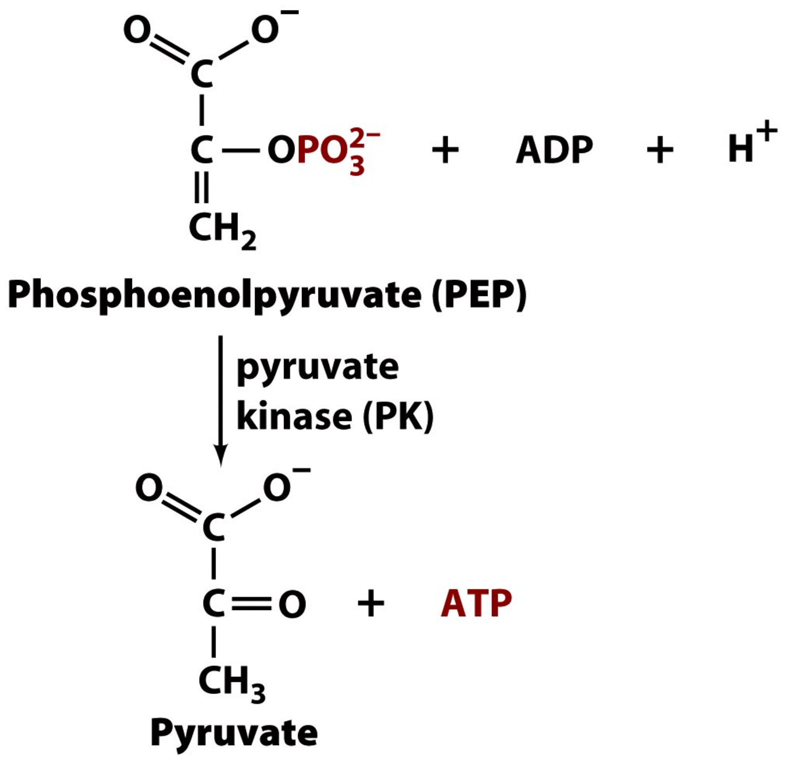


O
O⁻
C1
H — C2 — OPO3 2−
H — C3 — OH
H
enolase
C
C — OPO3 2−
H — C
H
+ H2O
2-Phosphoglycerate
(2PG)
Phosphoenolpyruvate
(PEP)

Proposed reaction mechanism of enolase

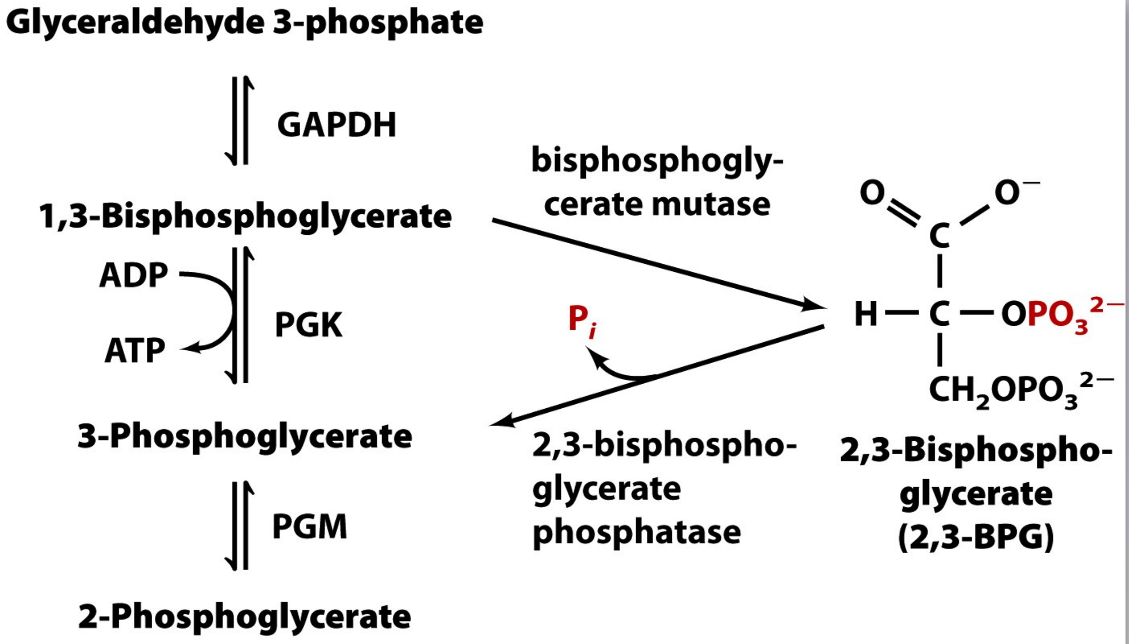


Pyruvate kinase

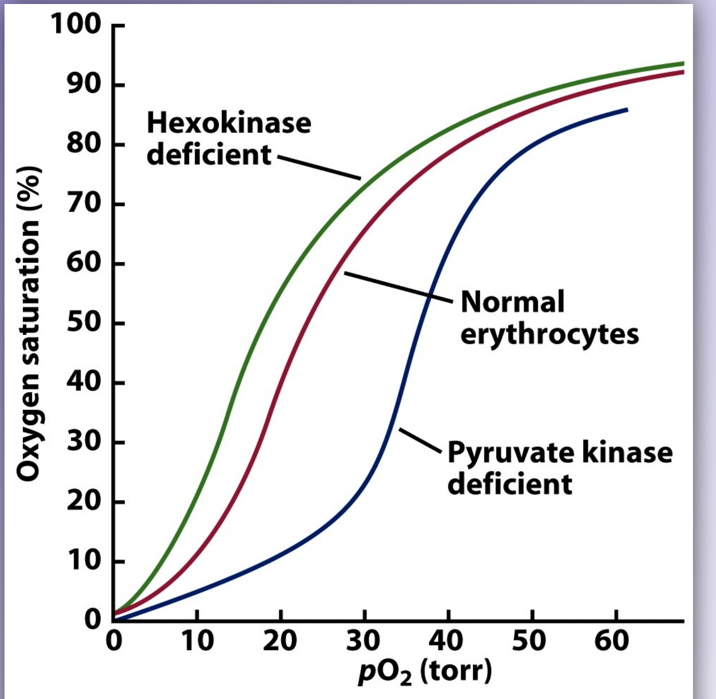


Second substrate-level phosphorylation reaction of glycolysis

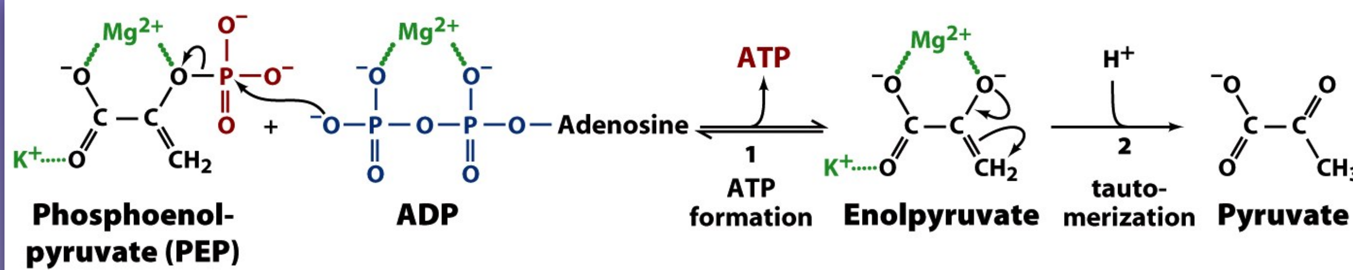
Glycolytic detour: 2,3-BPG biosynthesis in erythrocytes

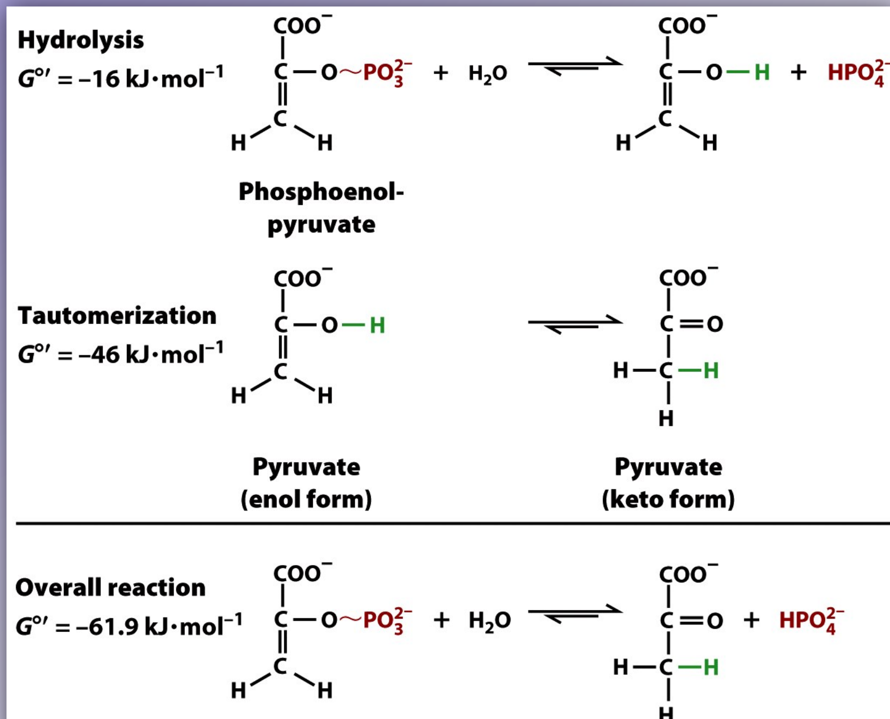


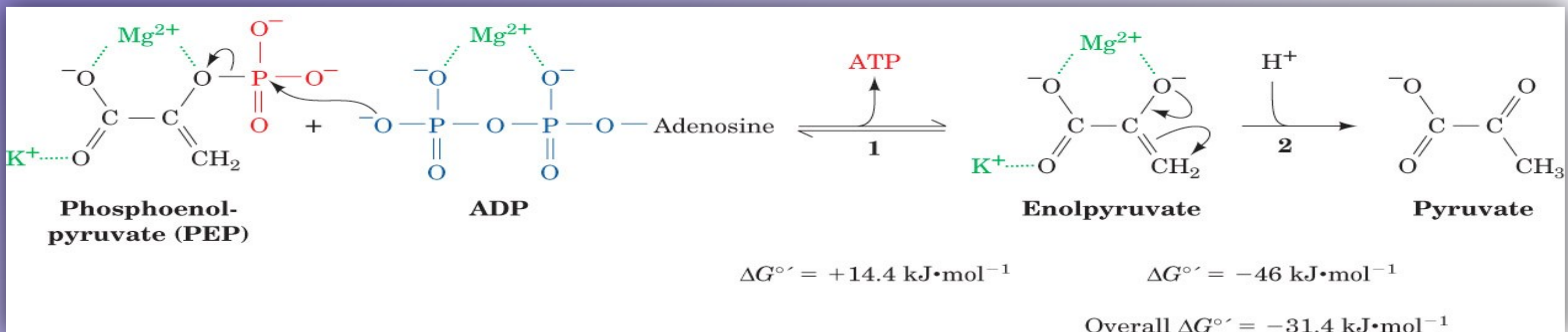
Impact of 2,3-BPG on O_2-hemoglobin binding affinity: hexokinase and PK deficiencies



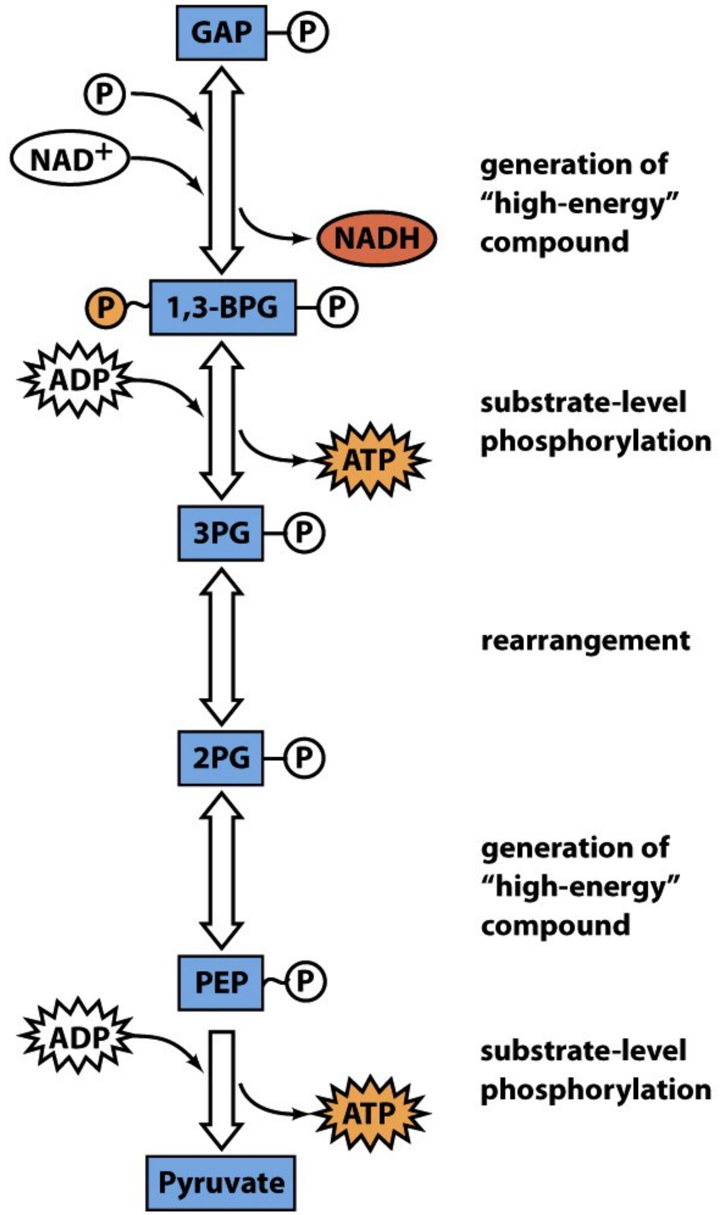
Explanation of the very (-) change in free energy associated with the PK reaction



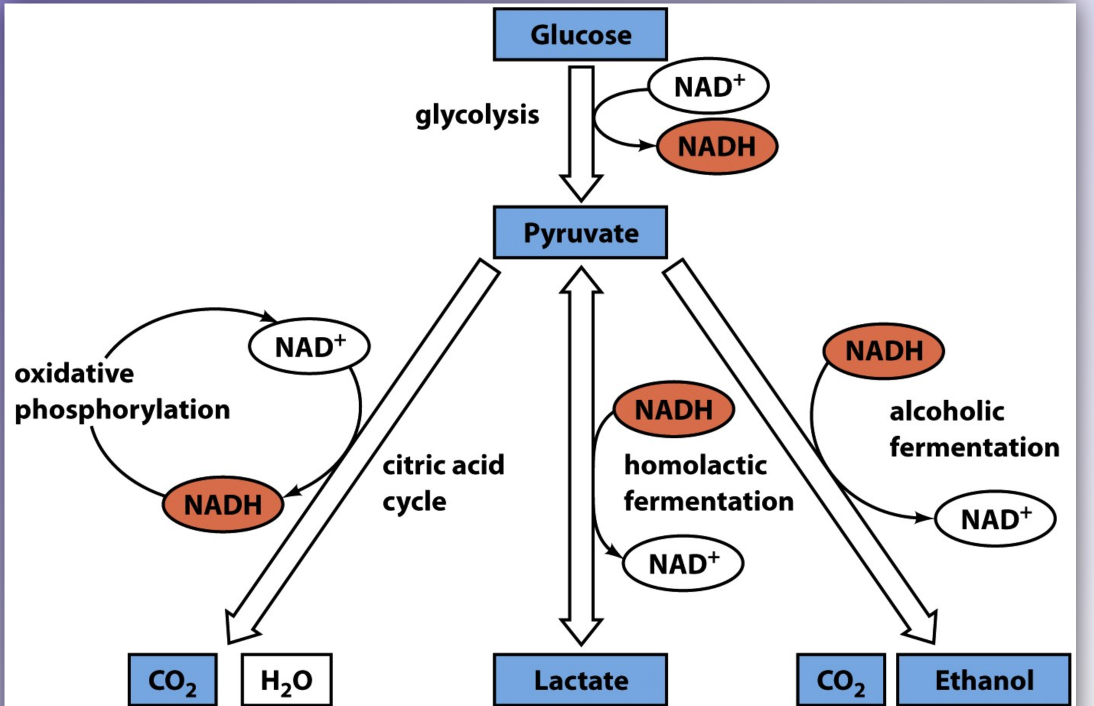



Mg2+
Mg2+
ATP
Mg2+
H+
K+
Adenosine
1
2
K+
Phosphoenol-pyruvate (PEP)
ADP
Enolpyruvate
Pyruvate
ΔG°′ = +14.4 kJ•mol−1
ΔG°′ = −46 kJ•mol−1
Overall ΔG°′ = −31.4 kJ•mol−1

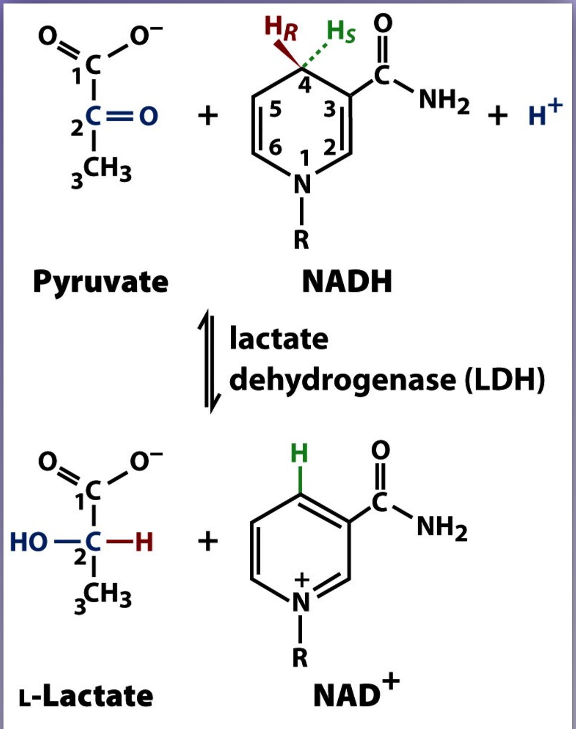
Second half of glycolysis: ATP-yielding phase

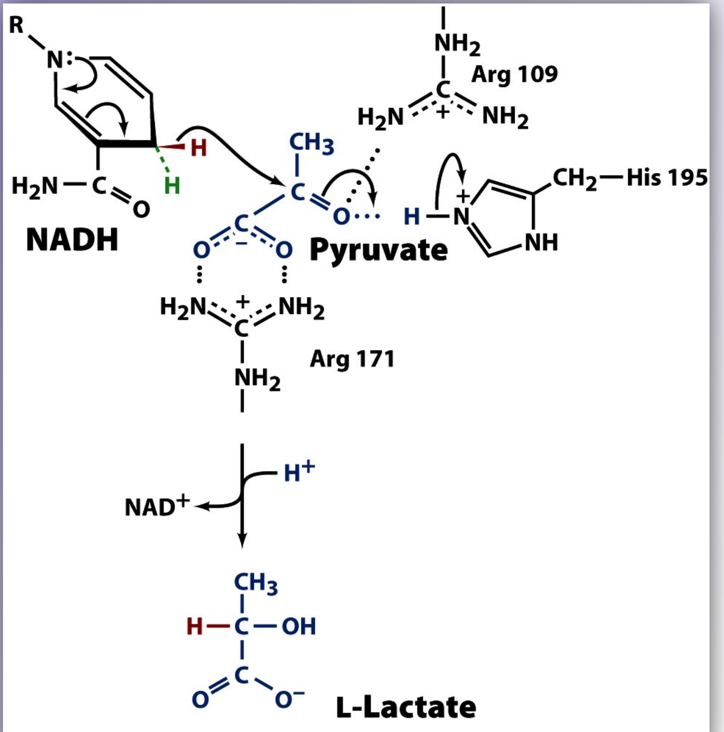


Metabolic fates of pyruvate

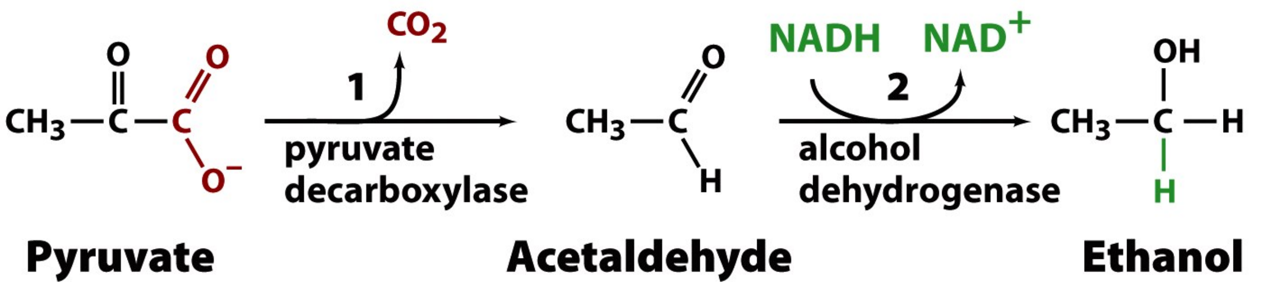


Conversion of pyruvate to lactate: LDH reaction

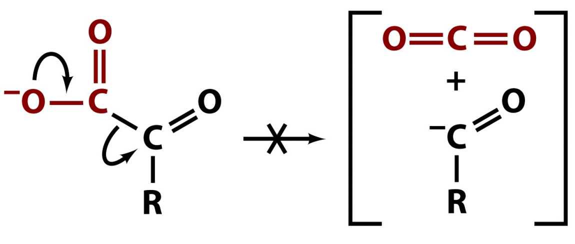


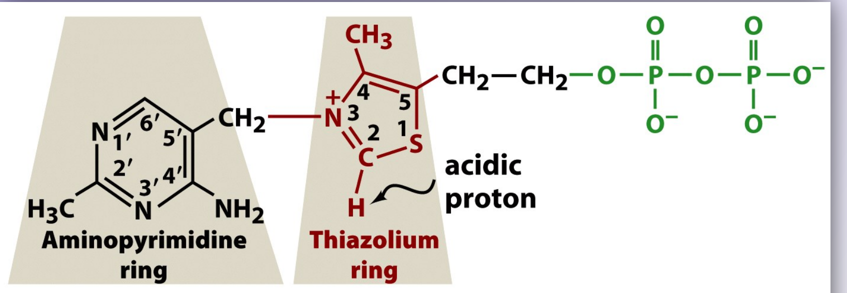


Conversion of pyruvate to ethanol via acetaldehyde



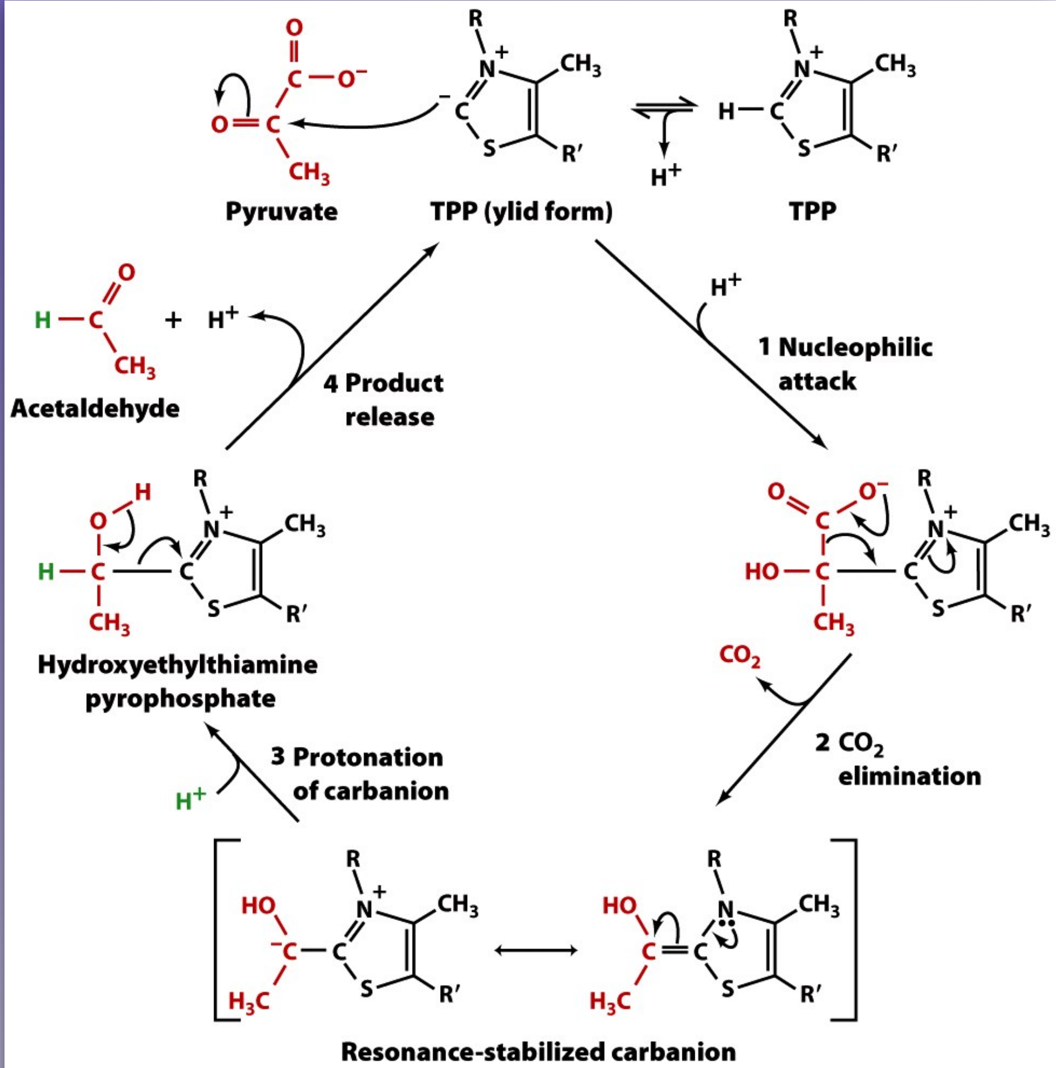
Enzyme-catalyzed decarboxylation of an α-ketoacid (pyruvate): TPP coenzyme is required for charge delocalization



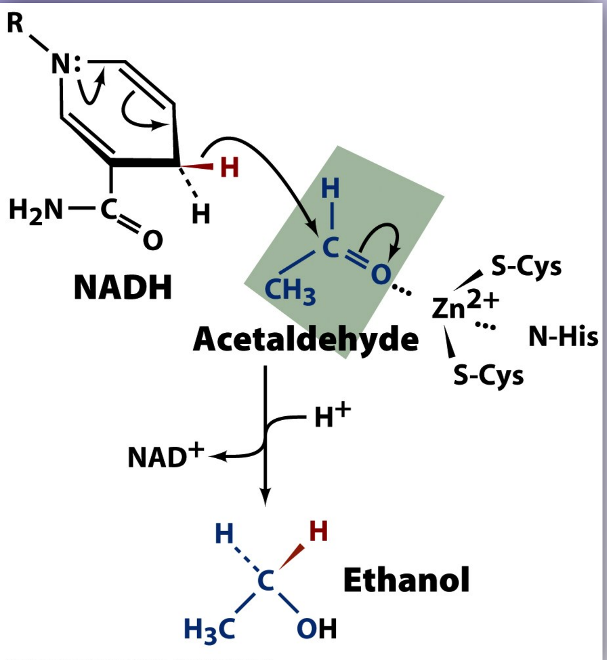


Thiamine pyrophosphate (TPP)

Proposed mechanism of pyruvate decarboxylase



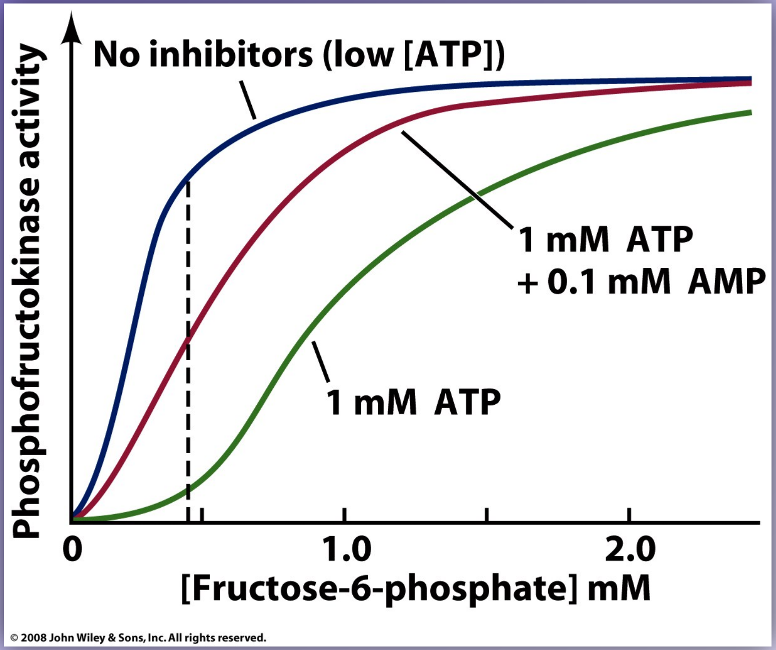
Alcohol dehydrogenase: Stereospecfic transfer of hydride from NADH to acetaldehyde

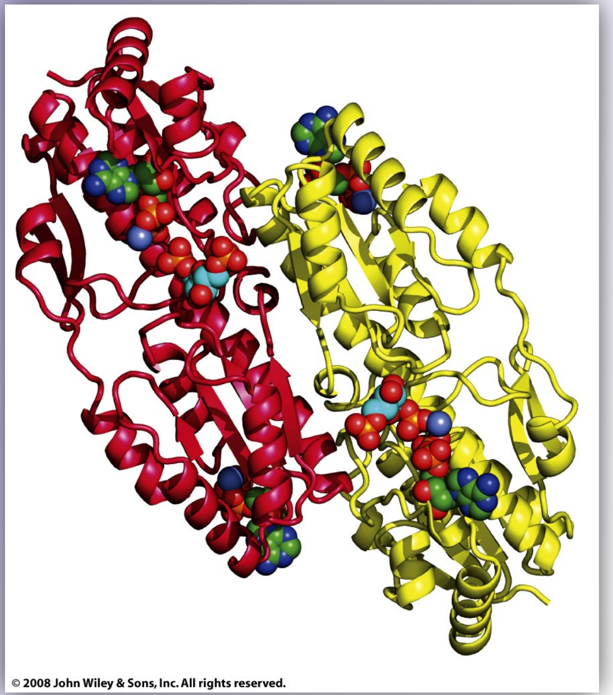


Some effectors of the non-equilibrium enzymes of glycolysis

Enzyme	Inhibitors	Activators[a]
HK	G6P	–
PFK	ATP, citrate, PEP	ADP, AMP, cAMP, FBP, F2,6P, F6P, NH_4^+, P_i
PK (muscle)	ATP	AMP, PEP, FBP

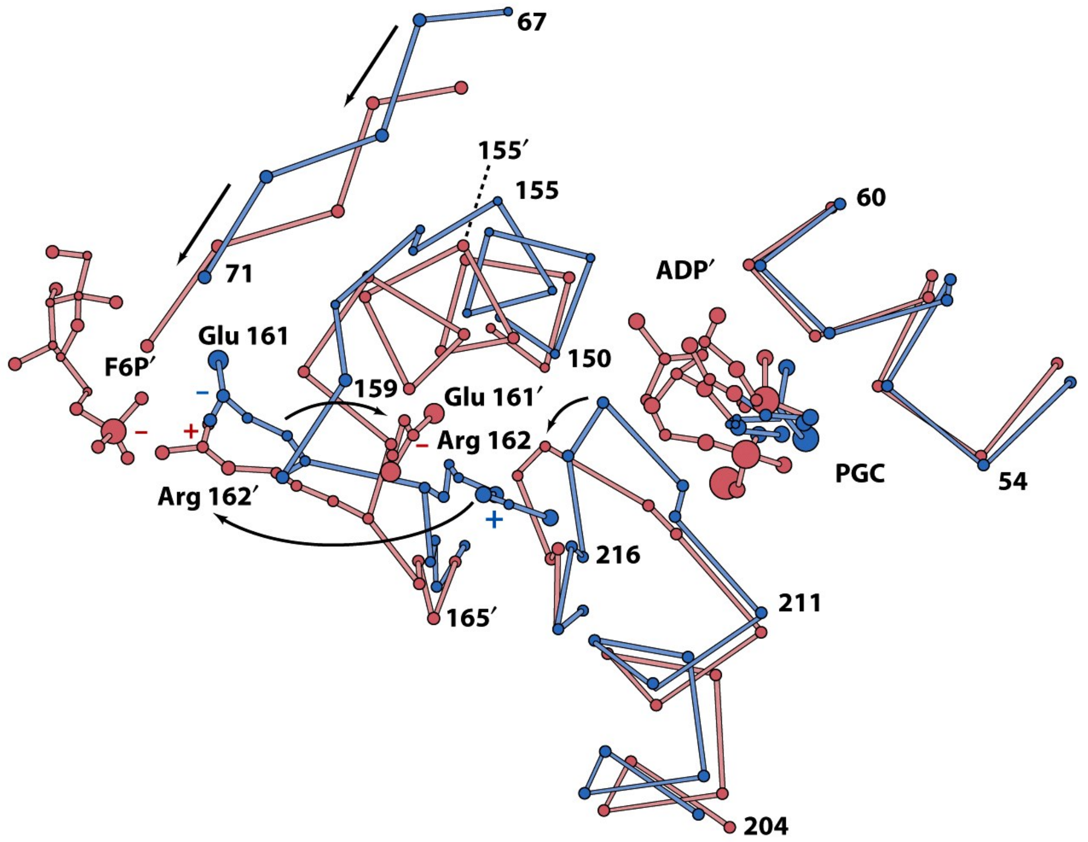
[a]The activators for PFK are better described as deinhibitors of ATP because they reverse the effect of inhibitory concentrations of ATP.



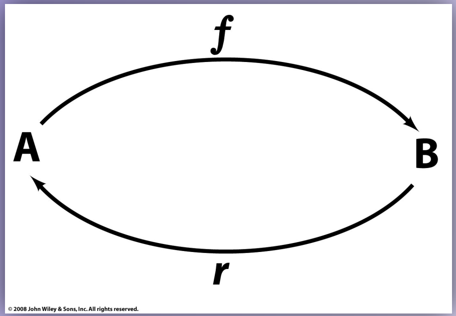


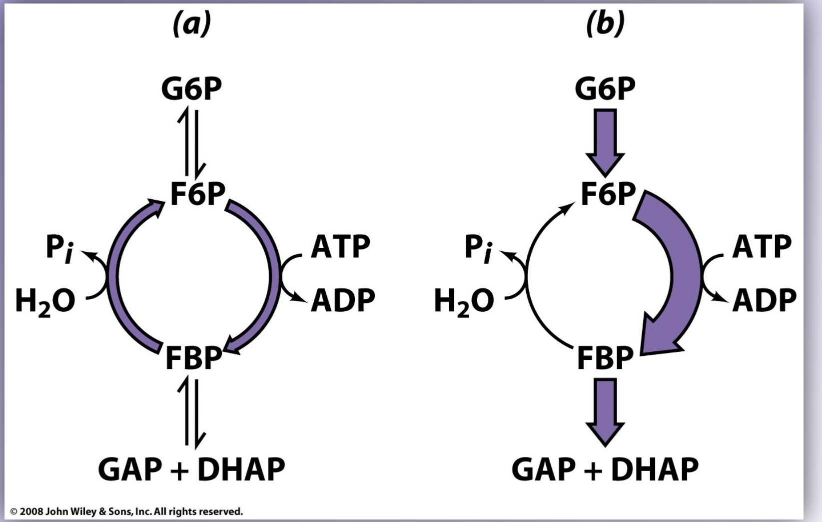
PFK is an allosteric enzyme (tetramer)

T and R states of PFK



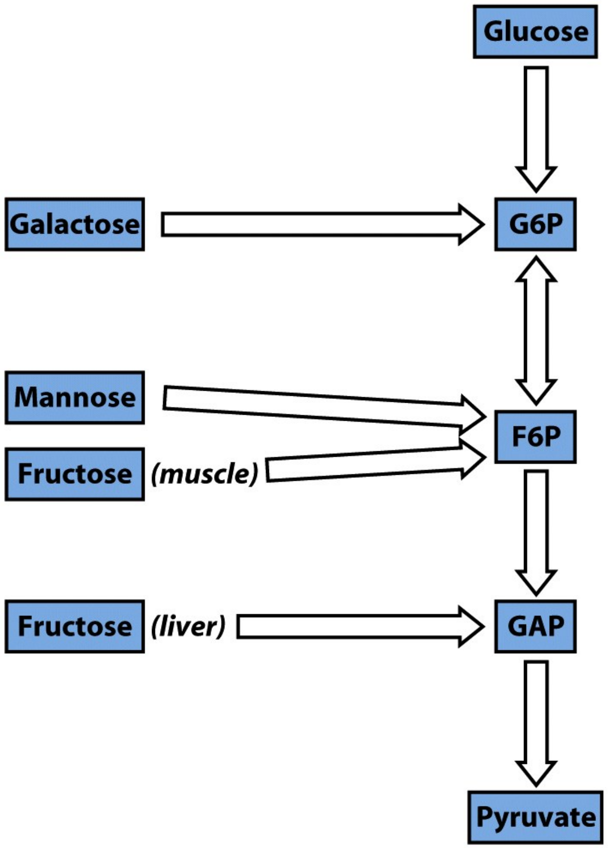
Control of glycolytic flux via substrate cycling



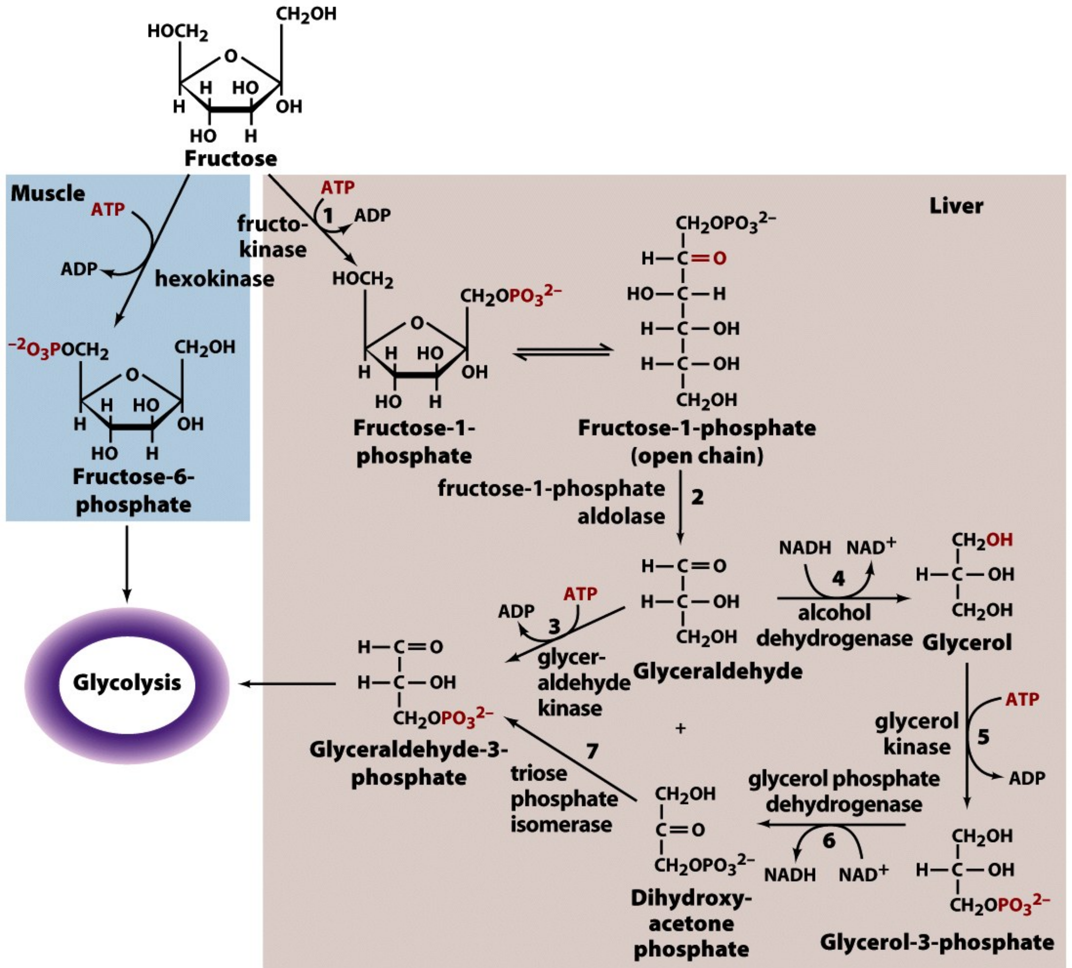


resting muscle active muscle

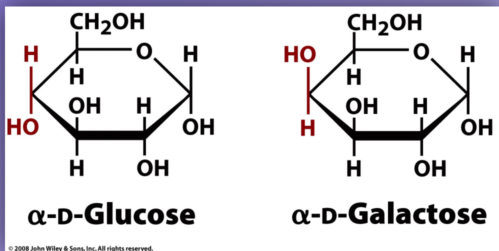
Entry routes of other monosaccharides into glycolysis

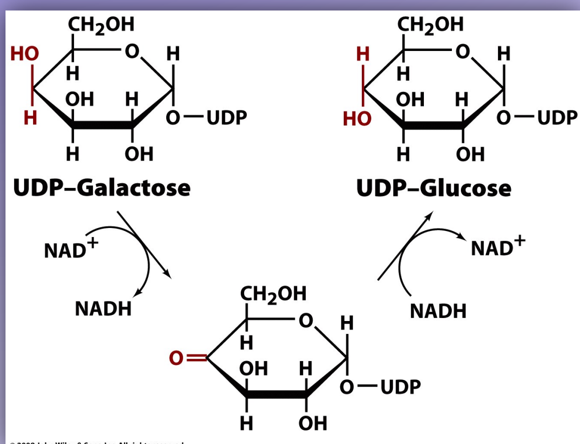


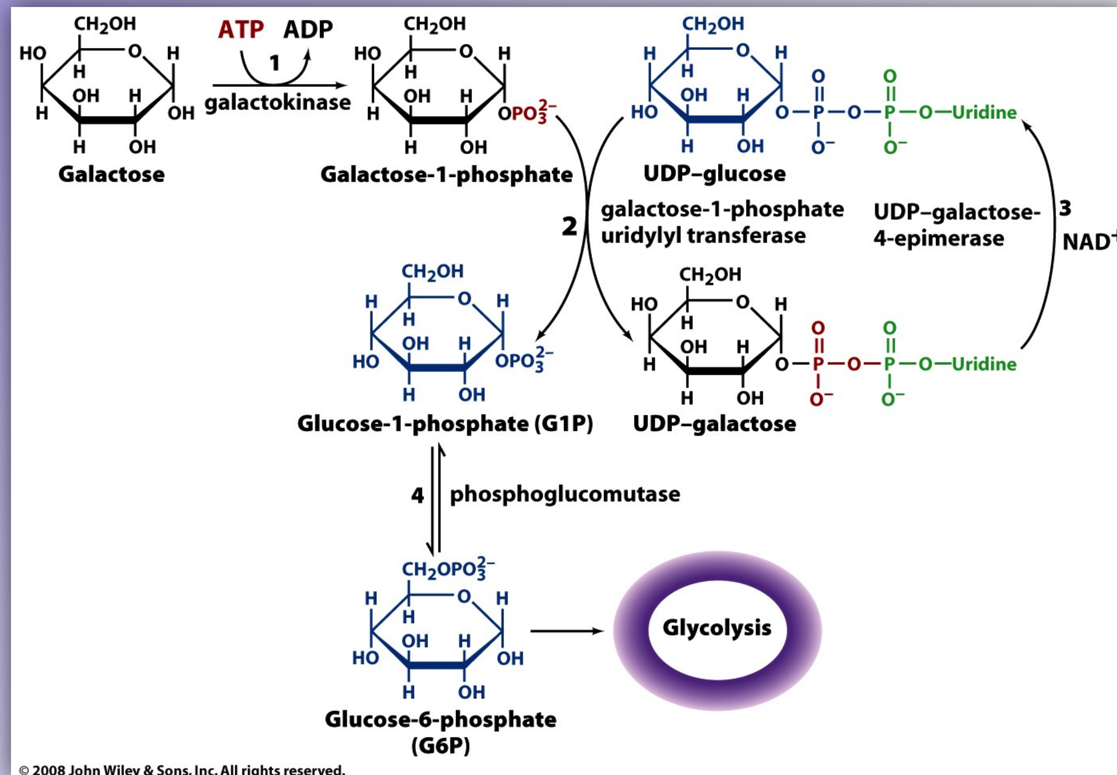
Metabolism of D-fructose is organ-dependent



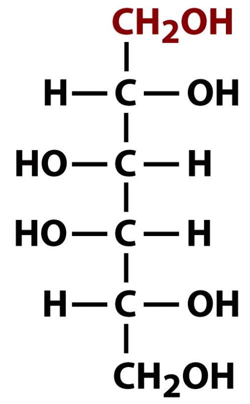
Metabolism of D-galactose (human)





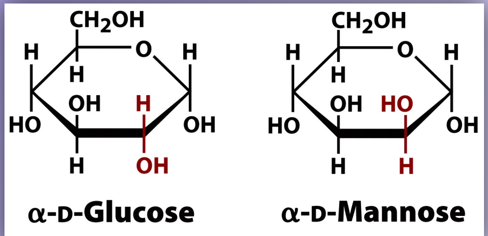


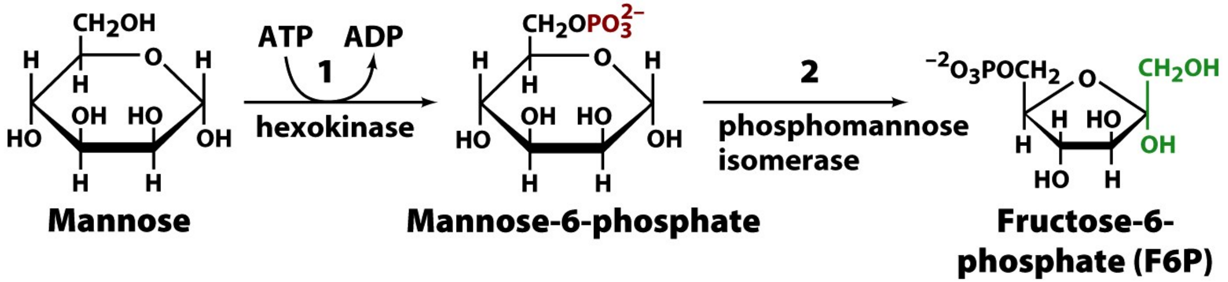
By-product of galactosemia (step 2 deficient)
(buildup in lens of the eye - cataracts)



Galactitol

Metabolism of D-mannose (human)





Entner-Doudoroff pathway for glucose breakdown (bacteria)