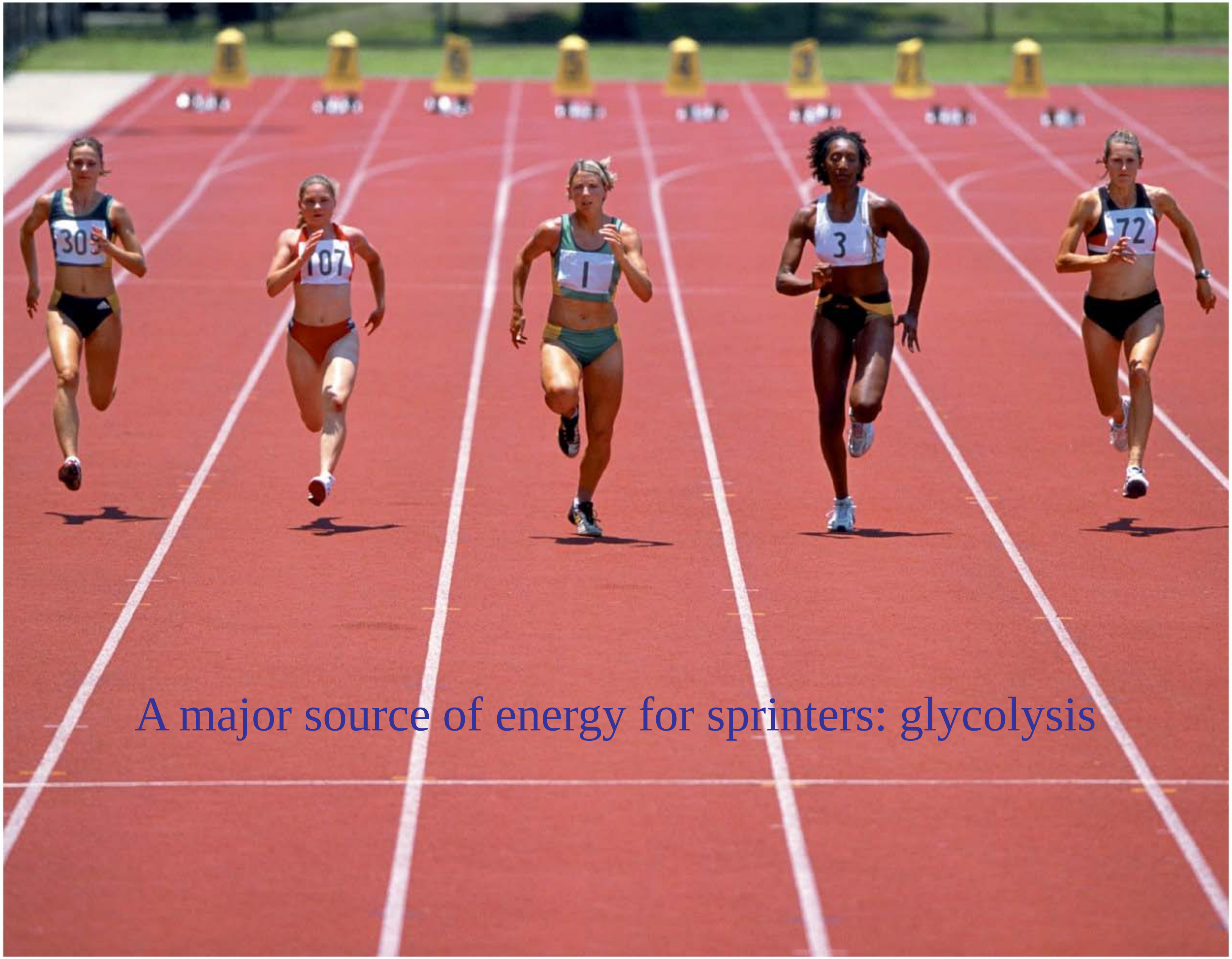
Chapter 2-I:

Glucose Catabolism



A major source of energy for sprinters: glycolysis

Chapter 14 Opener Fundamentals of Biochemistry, 2/e

Glycolysis
Embden-Meyerhof-Parnas pathway

Generation of
- two pyruvate molecules
- 2 ATP
- 2 NADH

10 enzymatic reactions to
generate high-E compounds

stage I: two glyceraldehyde-3-P
two ADP
stage II: two pyruvate
four ATP

Bypass to pentose phosphate pathway

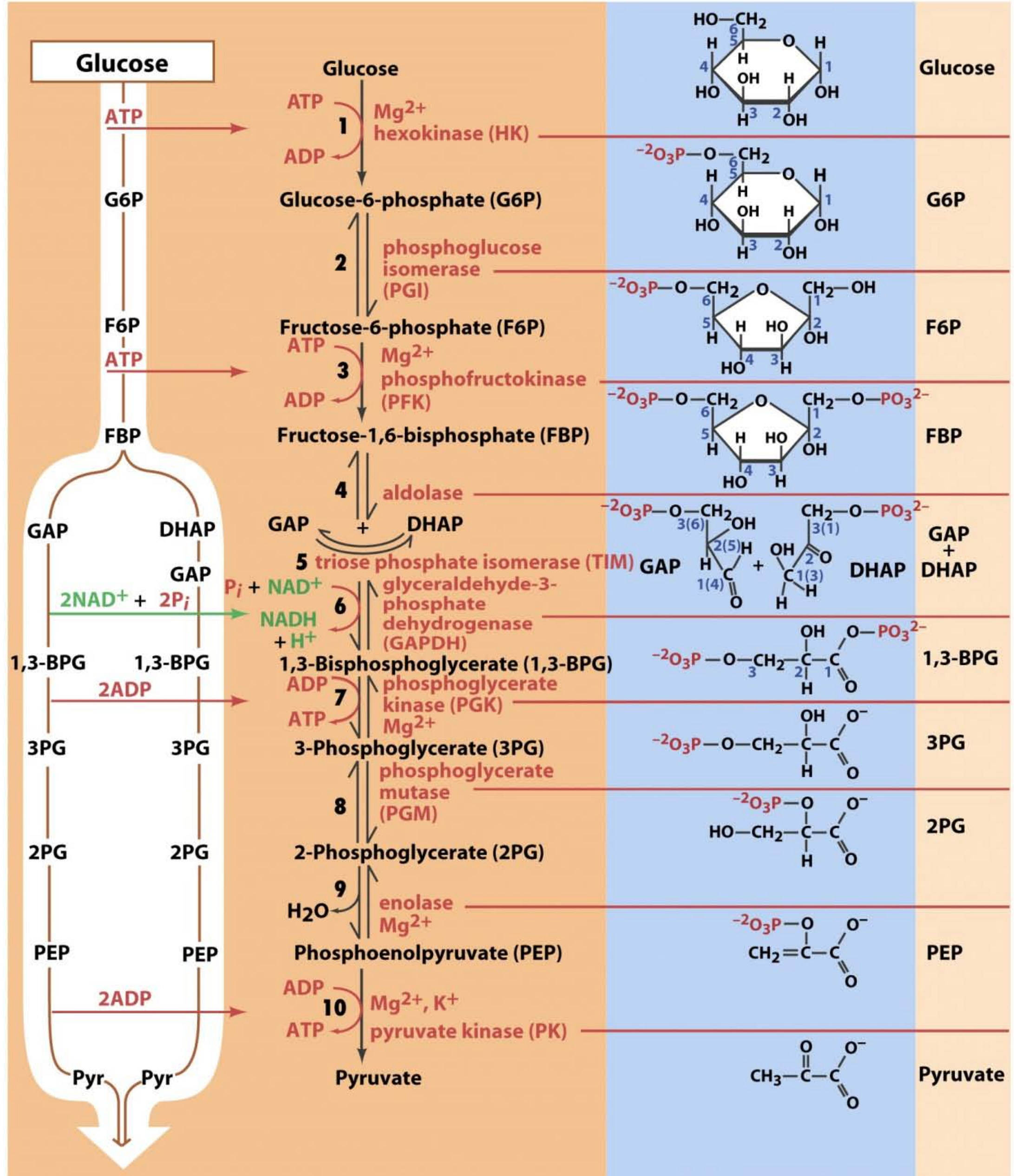


Figure 14-1 Fundamentals of Biochemistry, 2/e

Stage I

Hexokinase: glucose to G6P (ATP to ADP)
Phosphoglucose isomerase (PGI): G6P to F6P
Phosphofructokinase (PFK): F6P to FBP (ATP to ADP)
Aldolase: FBP to DHAP & GAP
Triose phosphate isomerase (TIM): DHAP to GAP

Net: glucose to 2 GAP (2ATP to 2ADP)

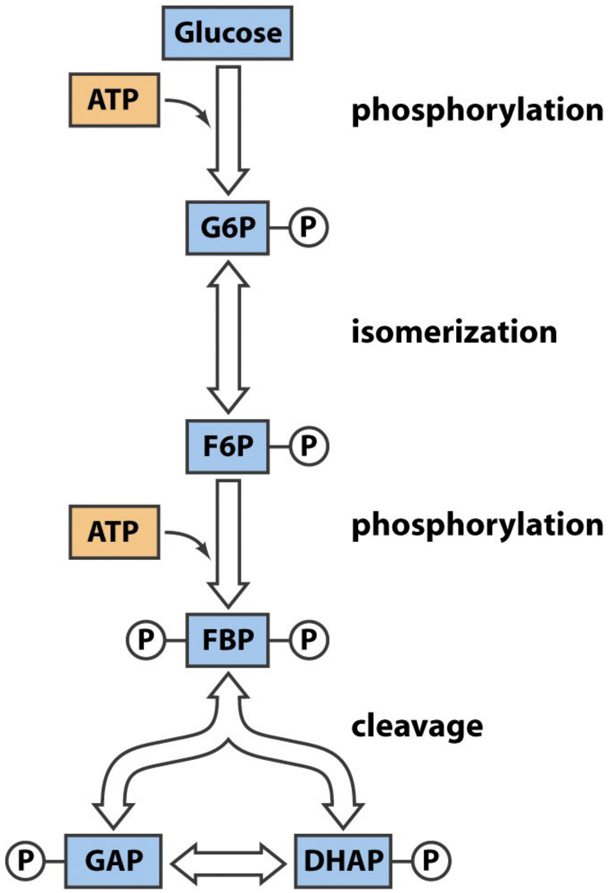
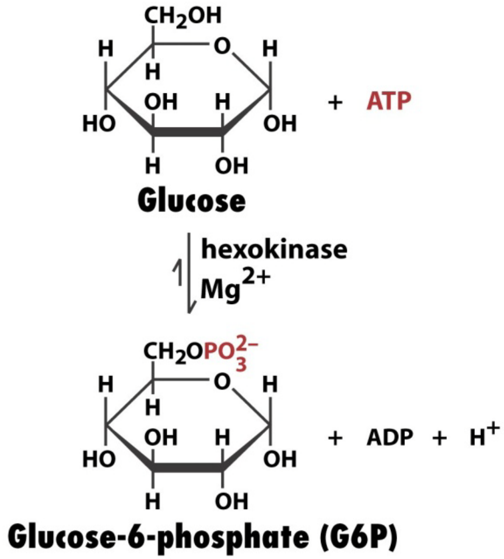


Figure 14-7 Fundamentals of Biochemistry, 2/e

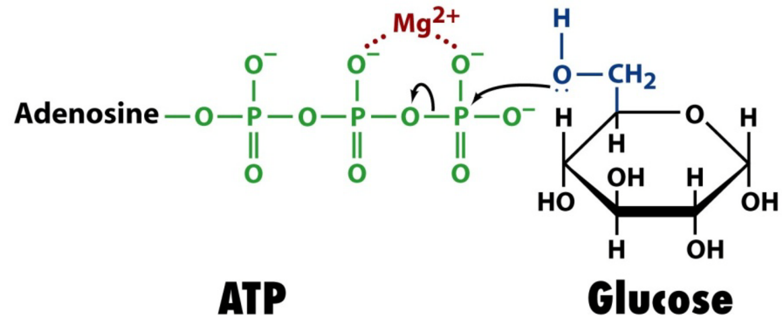
Hexokinase

Nonspecific enzyme
  low Km

Glucokinase
  Liver enzyme
  high Km
  blood glucose control



Unnumbered figure pg 431a Fundamentals of Biochemistry, 2/e



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Substrate induced conformational change
prevent ATP hydrolysis

glucose

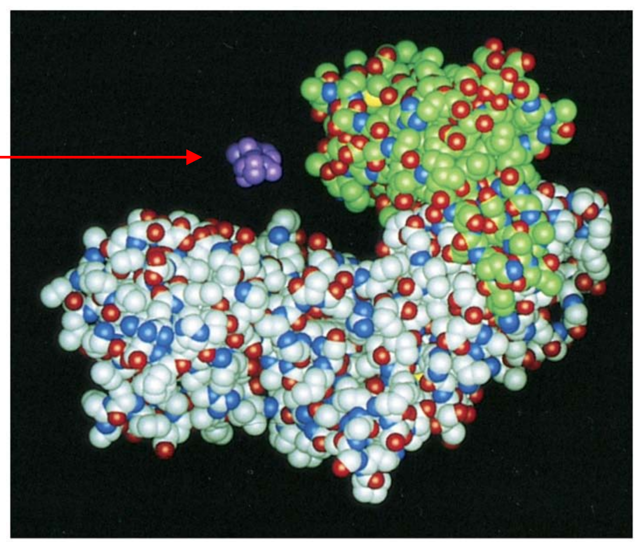


Figure 14-2a Fundamentals of Biochemistry, 2/e

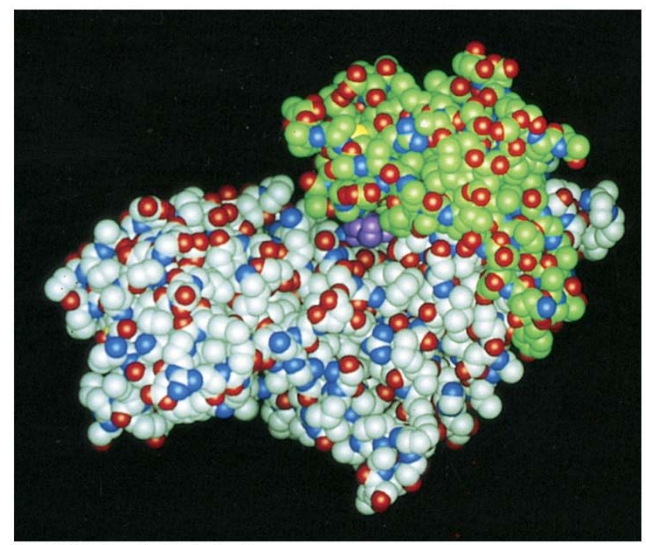
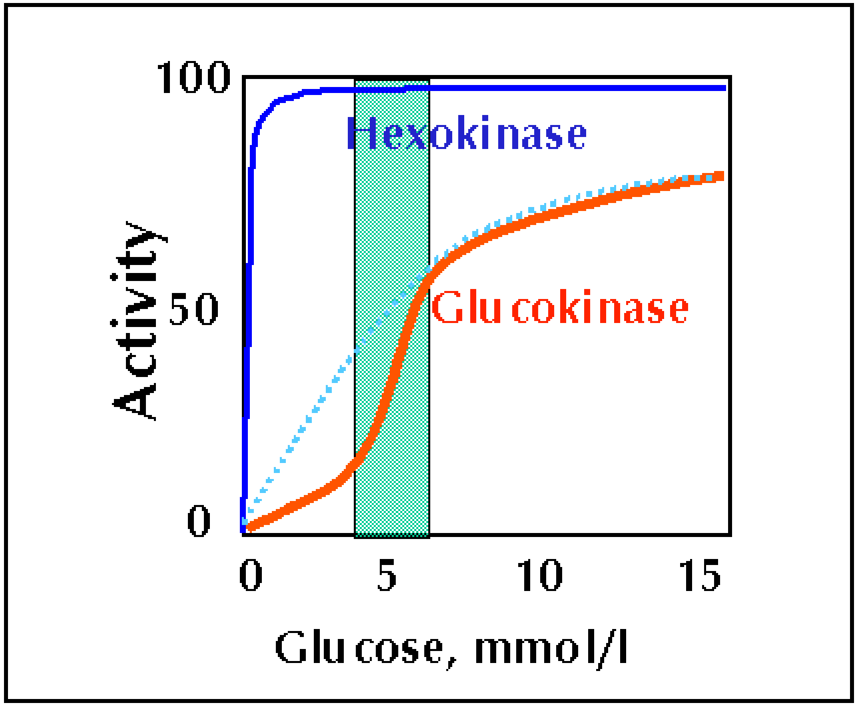
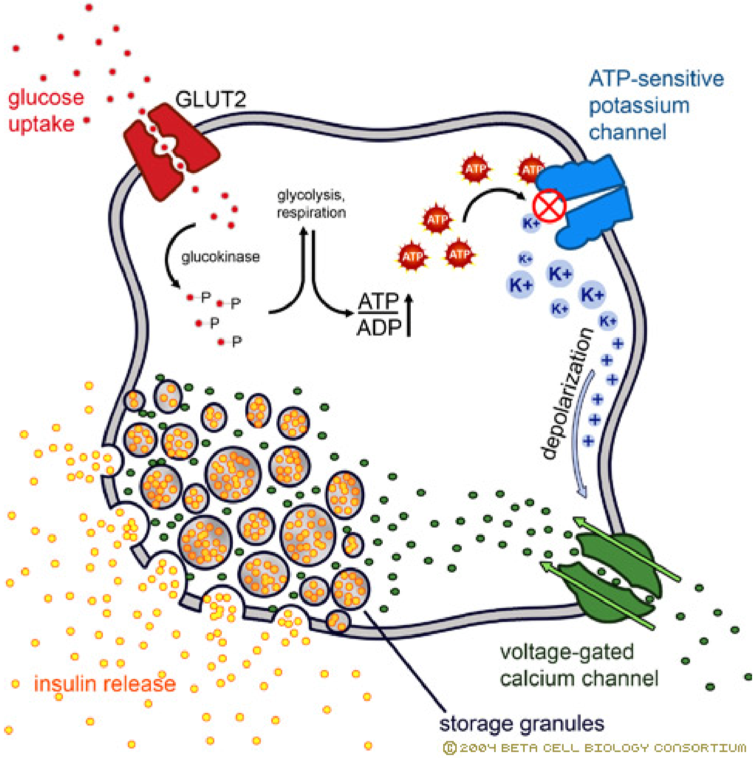


Figure 14-2b Fundamentals of Biochemistry, 2/e

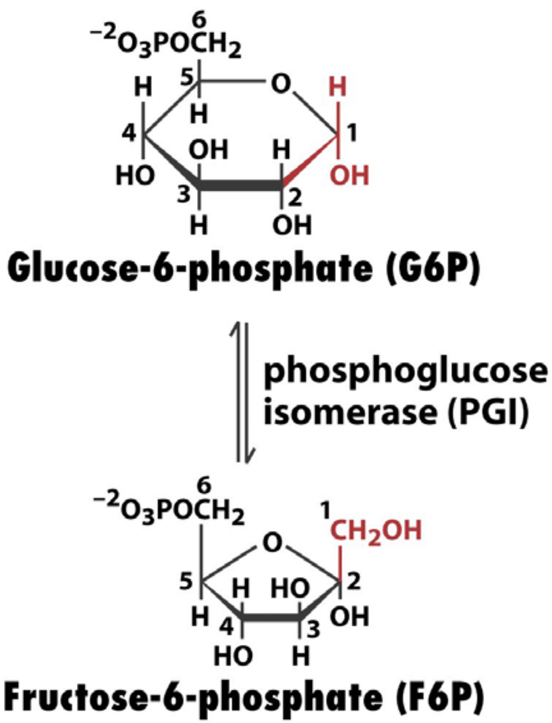
A glucose sensor in beta cells





http://en.wikipedia.org/wiki/Glucokinase

Phosphoglucose isomerase (PGI)



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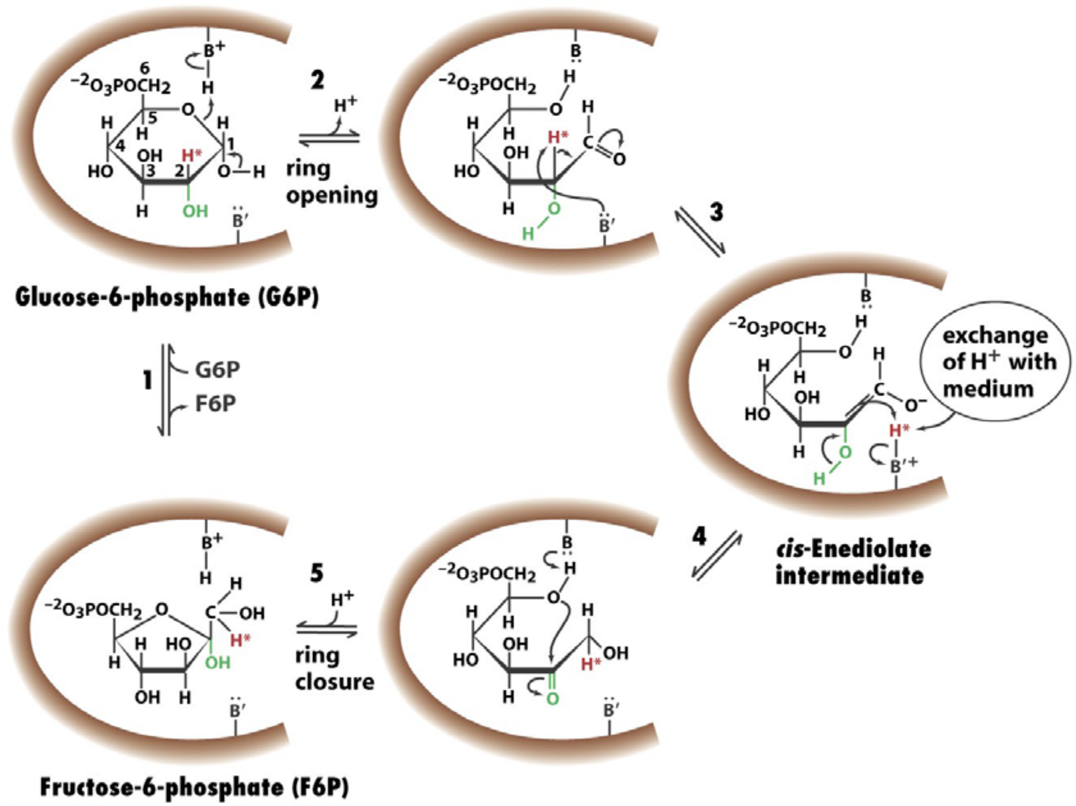
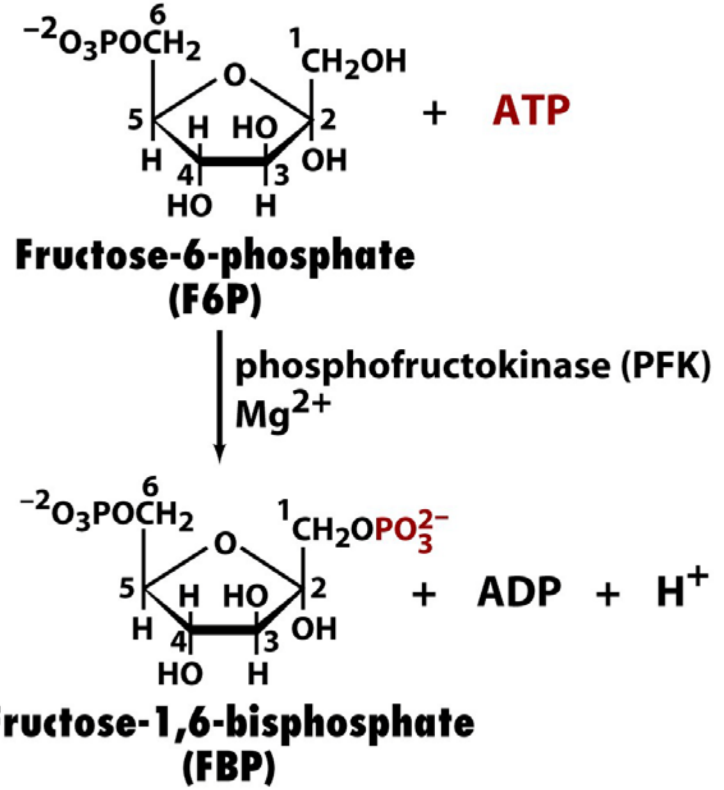


Figure 14-3 Fundamentals of Biochemistry, 2/e

Phosphofructokinase (PFK)

- Central role in control of glycolysis as a rate-determining step
- Allosteric regulation



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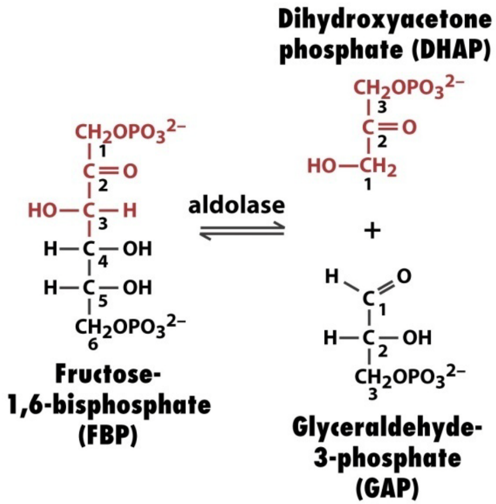
Aldolase



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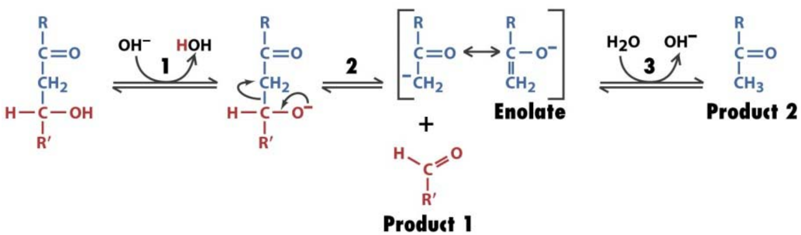


Figure 14-4 Fundamentals of Biochemistry, 2/e

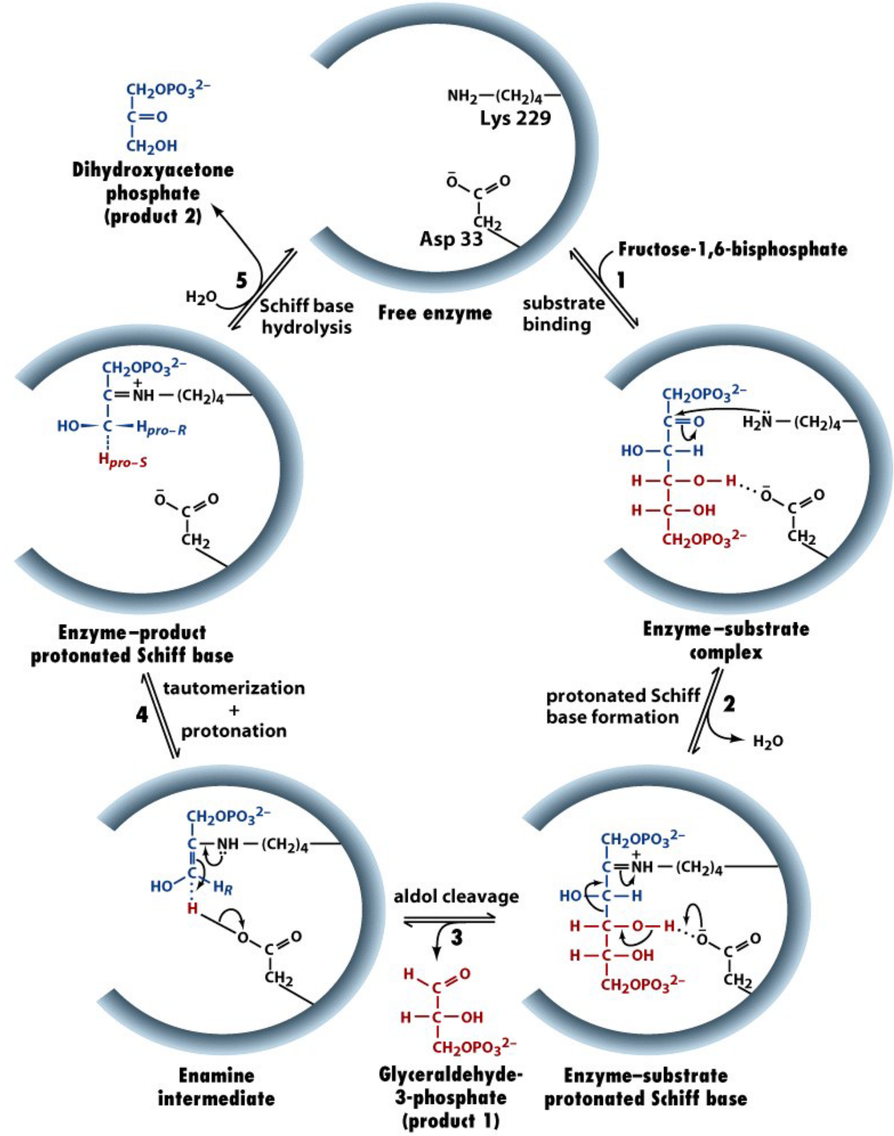
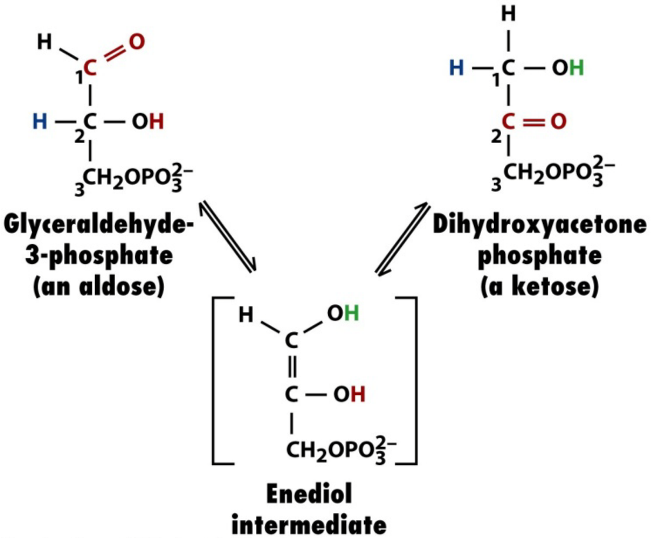


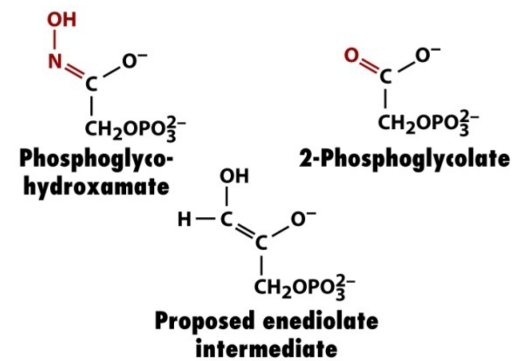
Figure 14-5 Fundamentals of Biochemistry, 2/e

Stabilization of enolate intermediate through increased electron delocalization

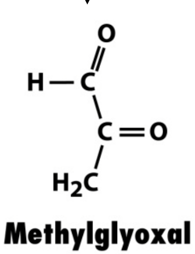
Triose phosphate isomerase (TIM)

- DHAP-GAP: ketose-aldose isomers
- Isomerization via enediol intermediate
- General acid-base catalysis
- Catalytically perfect enzyme: diffusion controlled reaction rate
- Keq = [GAP]/[DHAP] = 4.73×10^{-2}





in solution



prevent dephosphorylation

flexible loop

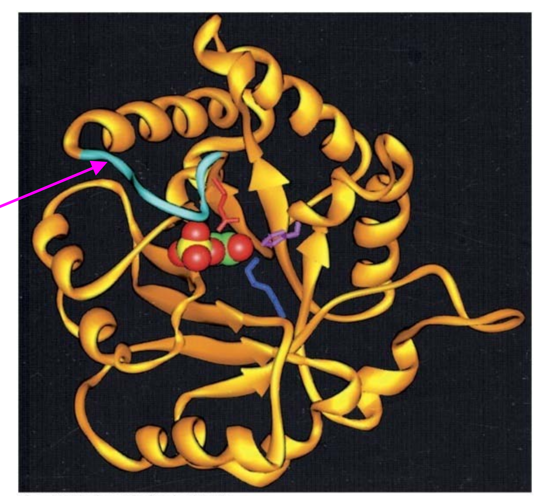


Figure 14-6 Fundamentals of Biochemistry, 2/e

Stage II

GAP dehydrogenase (GAPDH): GAP to 1,3-BPG (NAD to NADH)
Phosphoglycerate kinase (PGK): 1,3-BPG to 3PG (ADP to ATP)
Phosphoglycerate mutase (PGM): 3PG to 2PG
Enolase: 2PG to phosphoenolpyruvate (PEP)
Pyruvate kinase (PK): PEP to pyruvate (ADP to ATP)

Net: 2GAP to 2 pyruvate (4ADP to 4ATP & 2NAD to 2NADH)

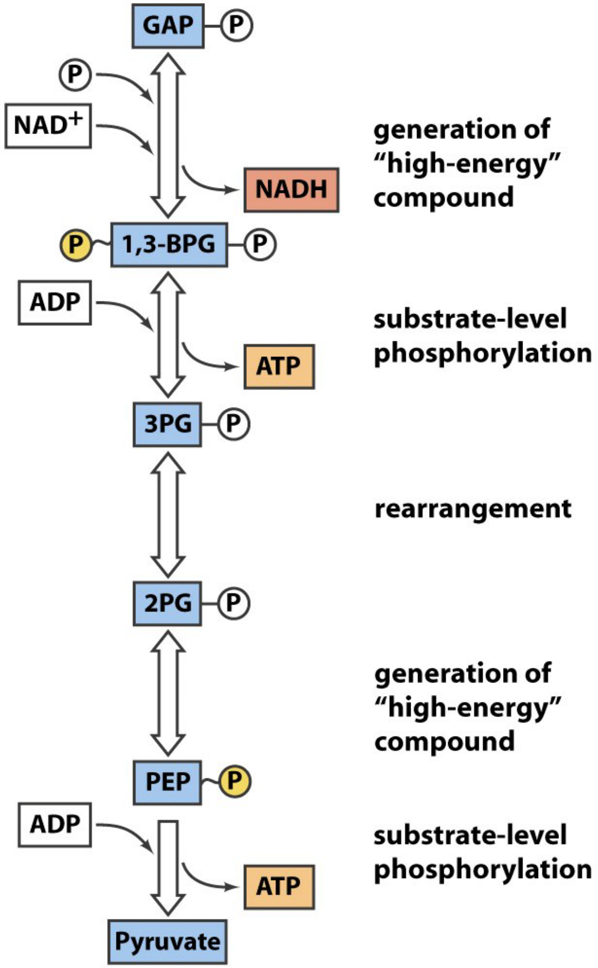
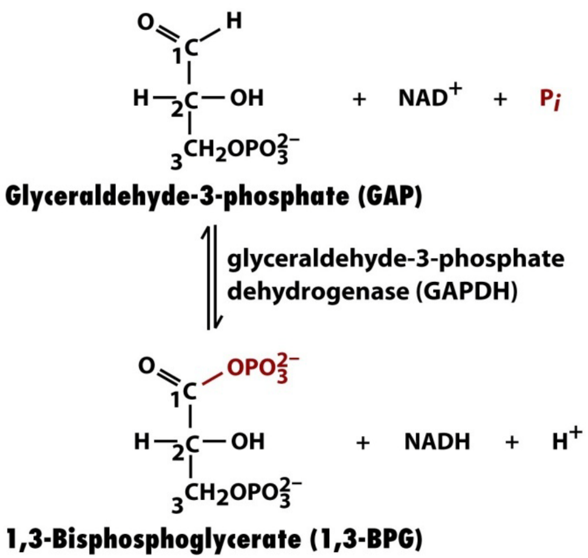


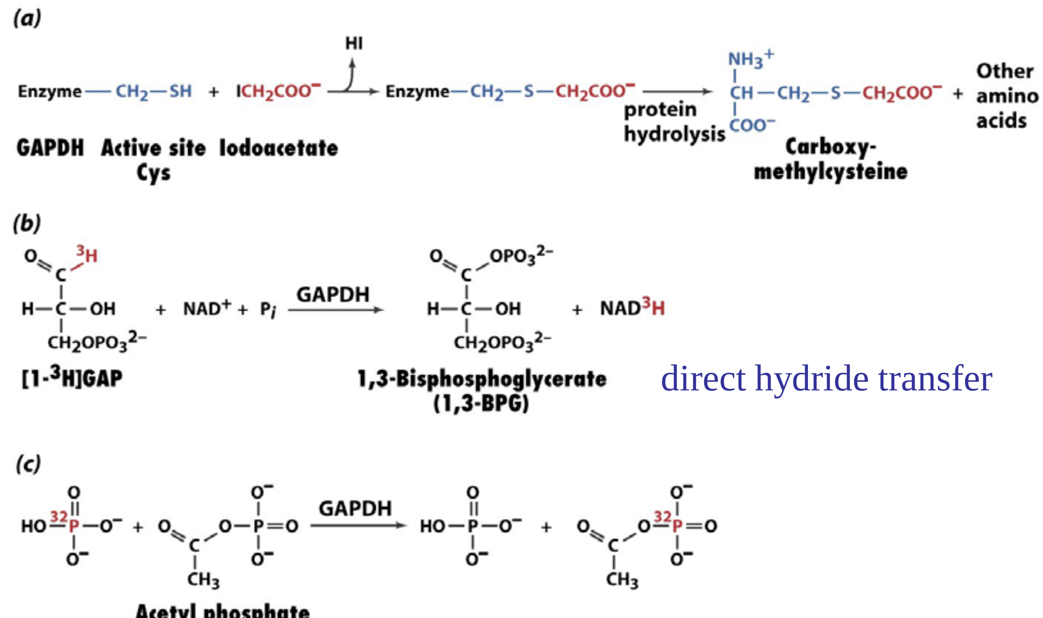
Figure 14-15 Fundamentals of Biochemistry, 2/e

GAP dehydrogenase (GAPDH)

- Generation of high-E compound
- Driven by oxidation of aldehyde
- Generation of NADH
- Slightly unfavorable reaction: $\Delta G^{o\prime} = +6.7$ kJ/mol



Reactions to elucidate the enzymatic mechanism



direct hydride transfer

Acyl-enzyme intermediate

Enzymatic mechanism of GAPDH

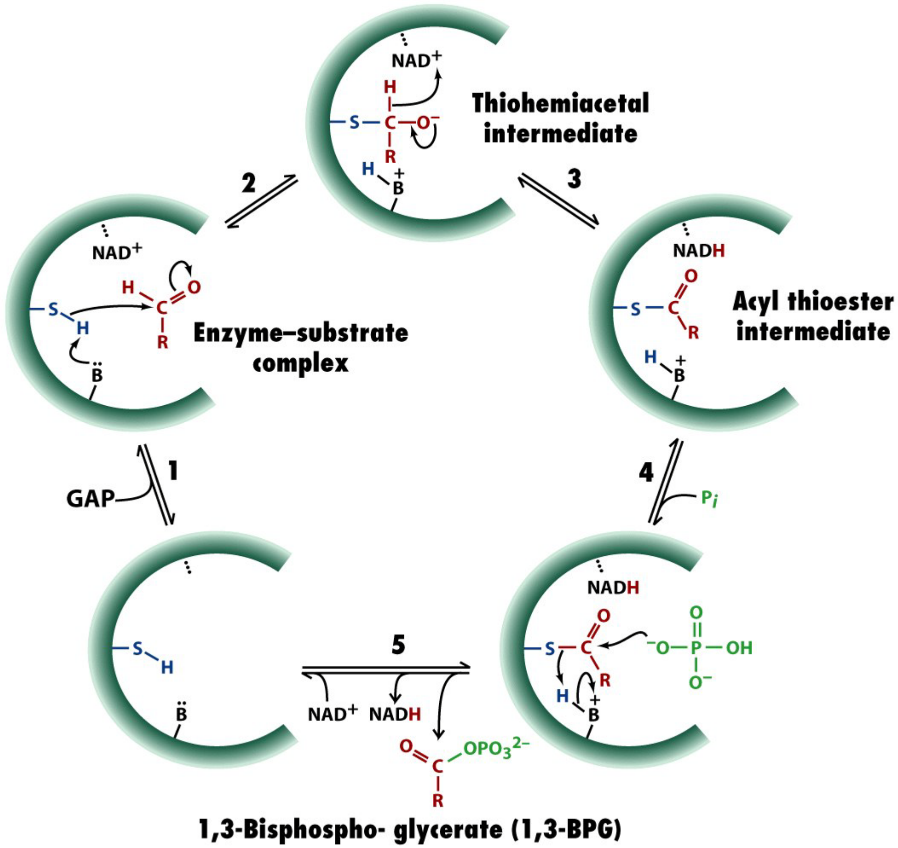


Figure 14-9 Fundamentals of Biochemistry, 2/e

Phosphoglycerate kinase (PKG)

First ATP generation: substrate level phosphorylation

Strong exergonic reaction: coupled to GAPDH rxn to make ATP and NADH

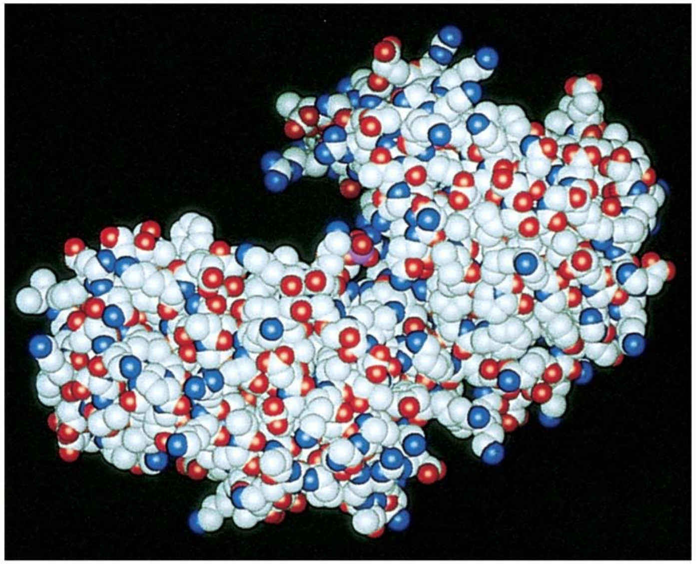
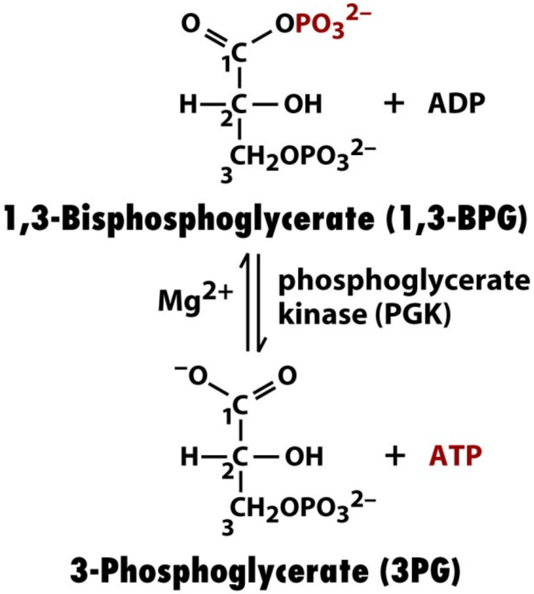


Figure 14-10 Fundamentals of Biochemistry, 2/e

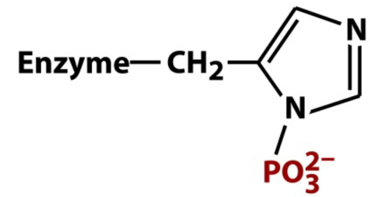


Unnumbered figure pg 441 Fundamentals of Biochemistry, 2/e

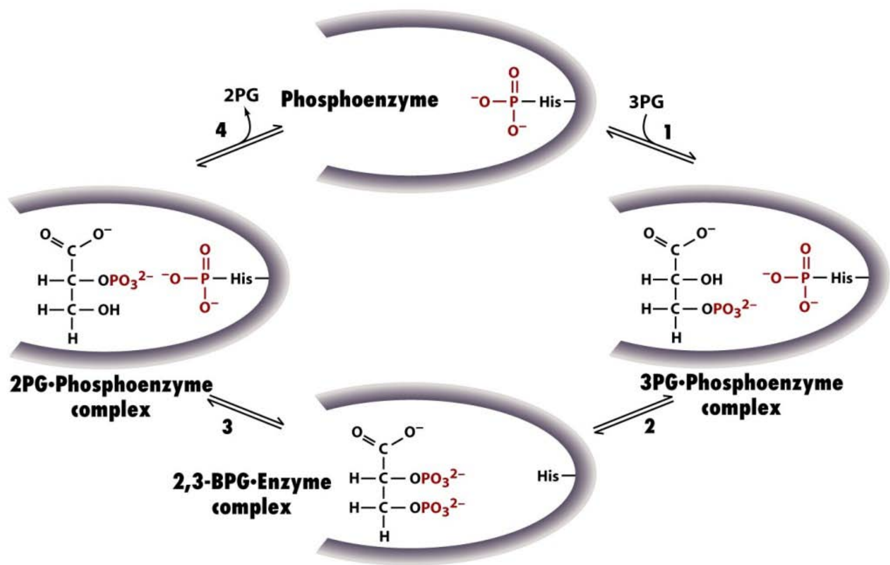
Phosphoglycerate mutase (PGM)

Active site phospho-His group

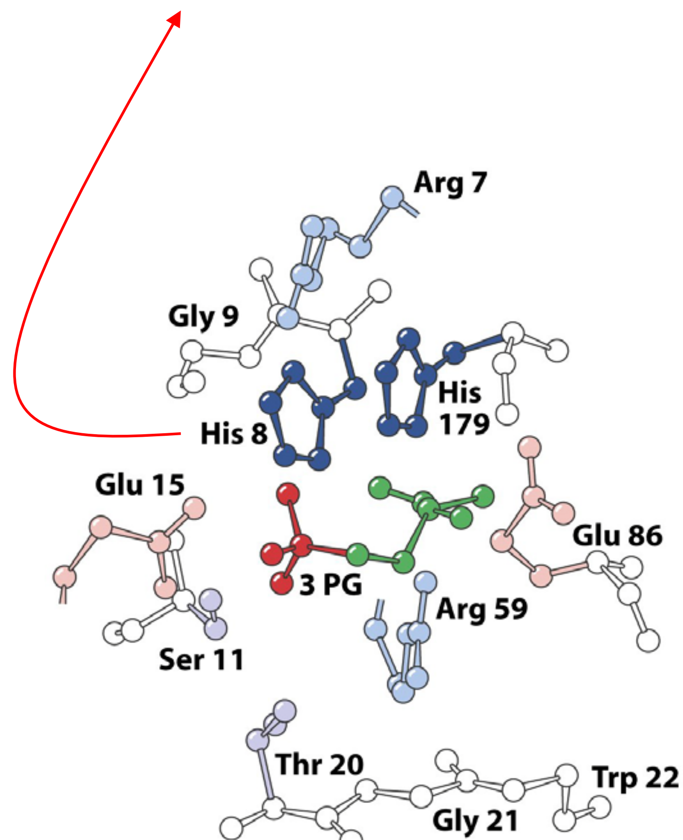
Catalytic amount of 2,3-BPG is required



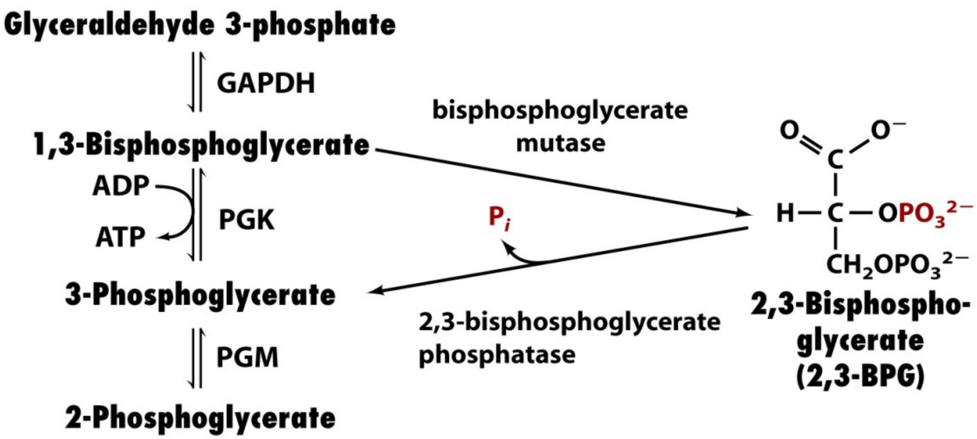
Phospho-His residue



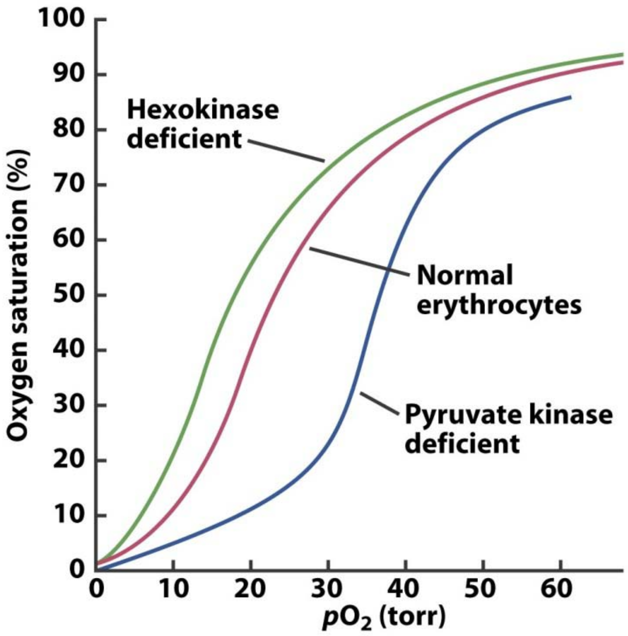
(in erythrocyte)



2,3-BPG in erythrocyte



Box 14-2 figure 1 Fundamentals of Biochemistry, 2/e

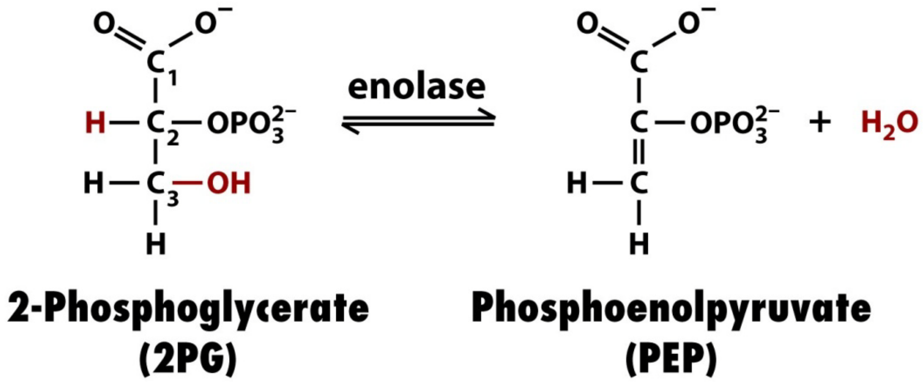


Box 14-2 figure 2 Fundamentals of Biochemistry, 2/e

Explain the figure

Enolase

Generation of 2nd high-E intermediate
Dehydration rxn to produce unstable enol form
2PG hydrolysis release insufficient free E

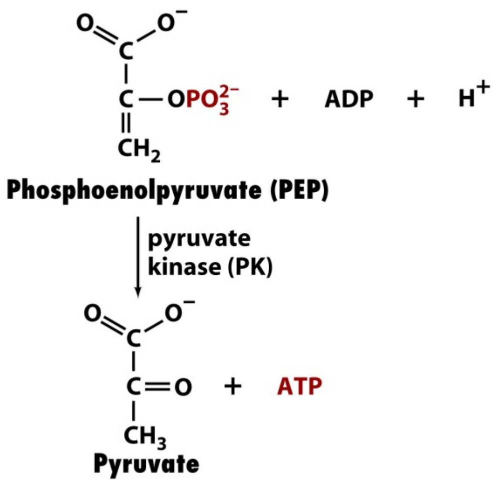


Unnumbered figure pg 442b Fundamentals of Biochemistry, 2/e

Pyruvate kinase (PK)

Conversion of unstable enol to keto form

Generation of ATP



Unnumbered figure pg 443 Fundamentals of Biochemistry, 2/e

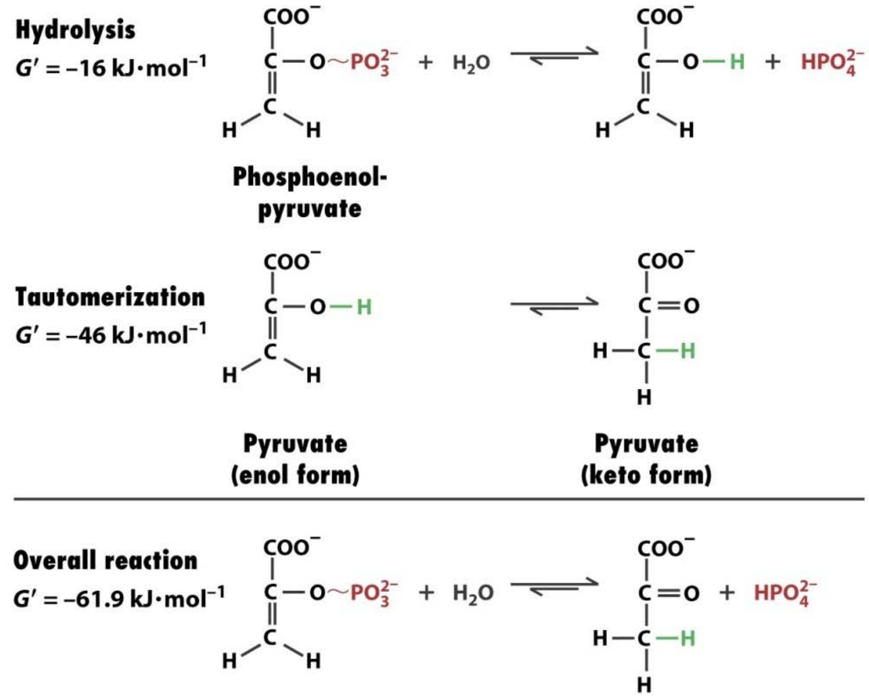


Figure 14-14 Fundamentals of Biochemistry, 2/e

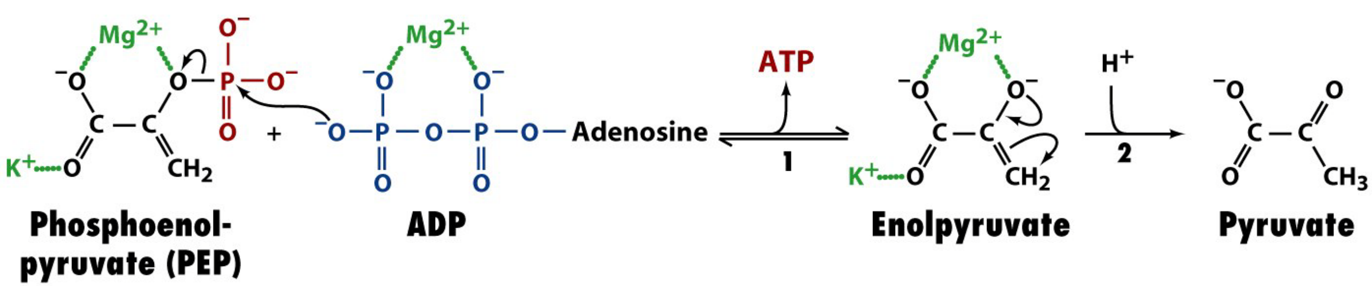
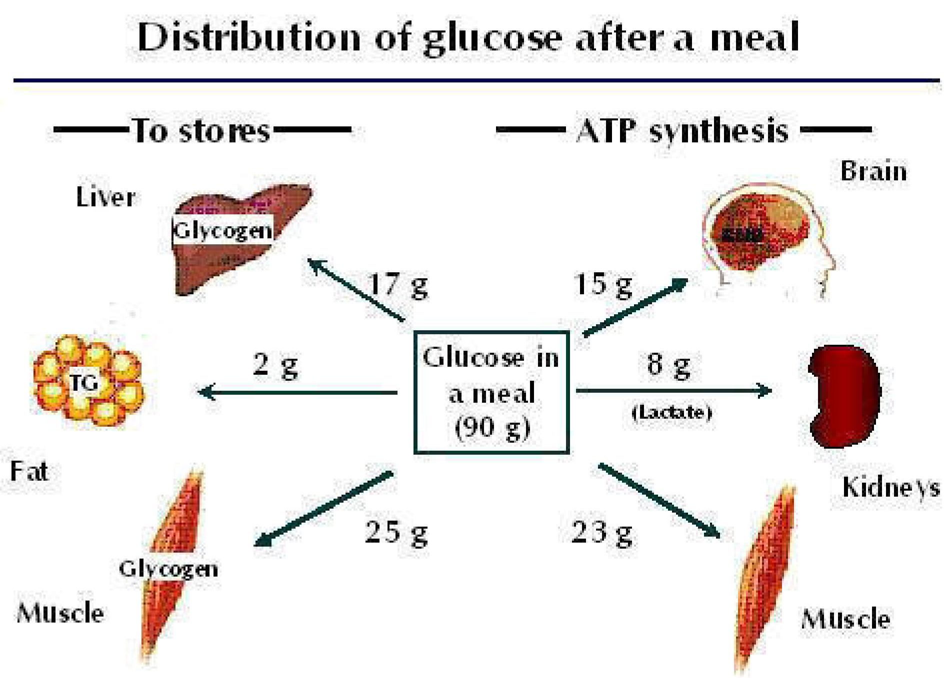


Figure 14-13 Fundamentals of Biochemistry, 2/e

3 glycolytic products

ATP
NADH: electron transport
Pyruvate: fermentation



Fermentation: the anaerobic fate of pyruvate

- Aerobic condition: pyruvate to citric acid cycle
- Anaerobic condition: lactate or alcohol fermentation
  - reduction of pyruvate
  - regeneration of NAD+

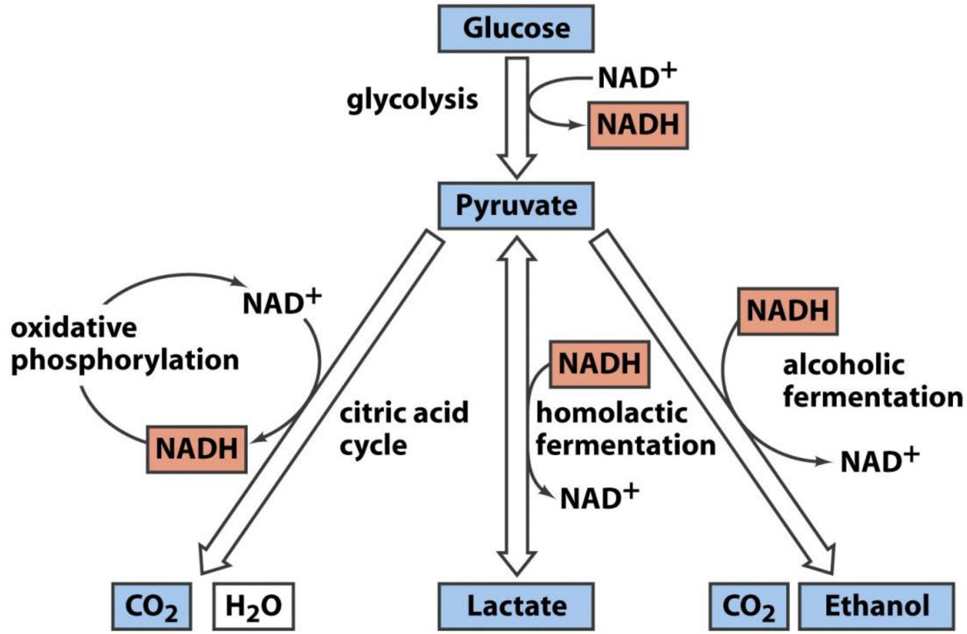
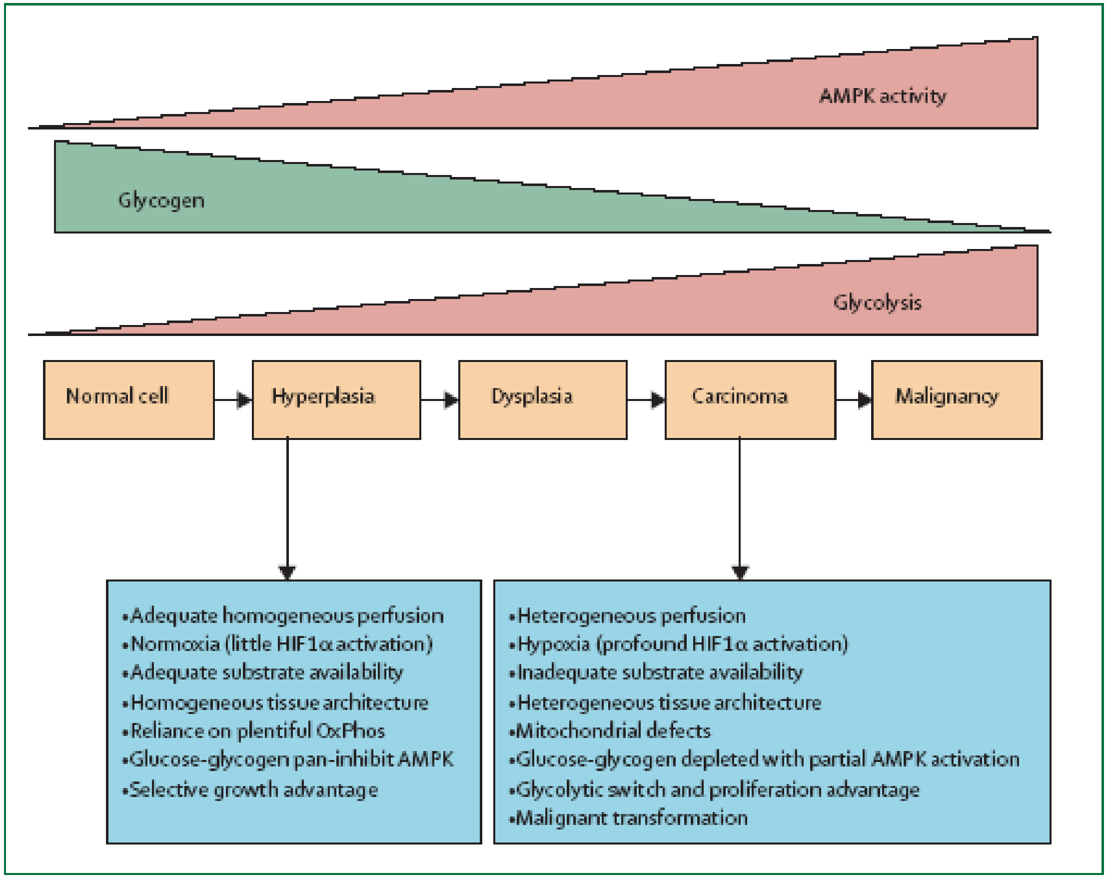


Figure 14-16 Fundamentals of Biochemistry, 2/e

muscle
erythrocyte

Otto Warburg (1931)

Cancer cells have increased glycolysis and impaired OXPHOS
Tumor cell glycolysis >>> normal cells (~80% of glucose)
AMPK (AMP-activated protein kinase) senses AMP/ATP ratio drives glycolysis via HK, GLUT1 induction



Lancet 2006; 367: 618–21

Alcoholic fermentation

Pryuvate to ethanol and CO_2
Two consecutive reactions via acetaldehyde
Pyruvate decarboxylase: TPP (thiamine pyrophosphate) as a coenzyme
Alcohol dehydrogenase (ADH):

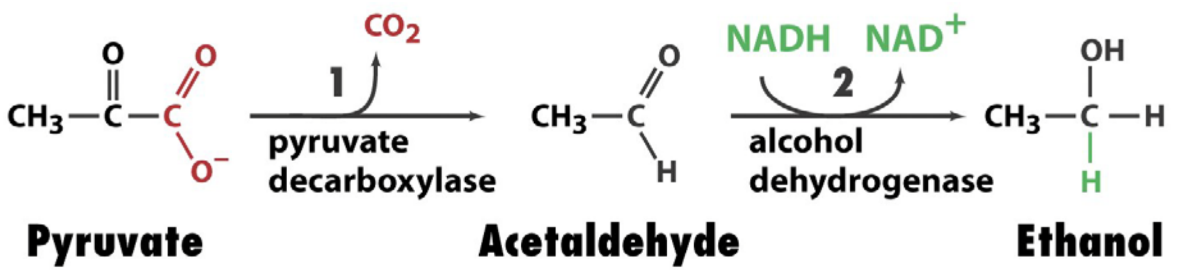
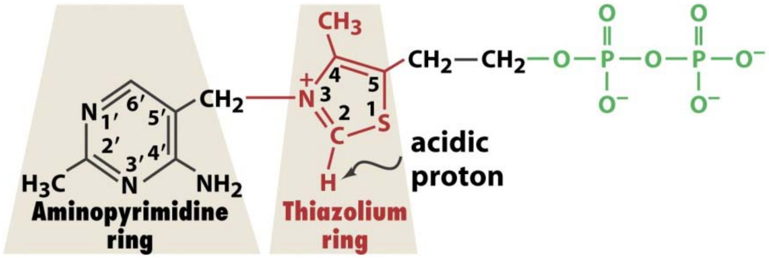
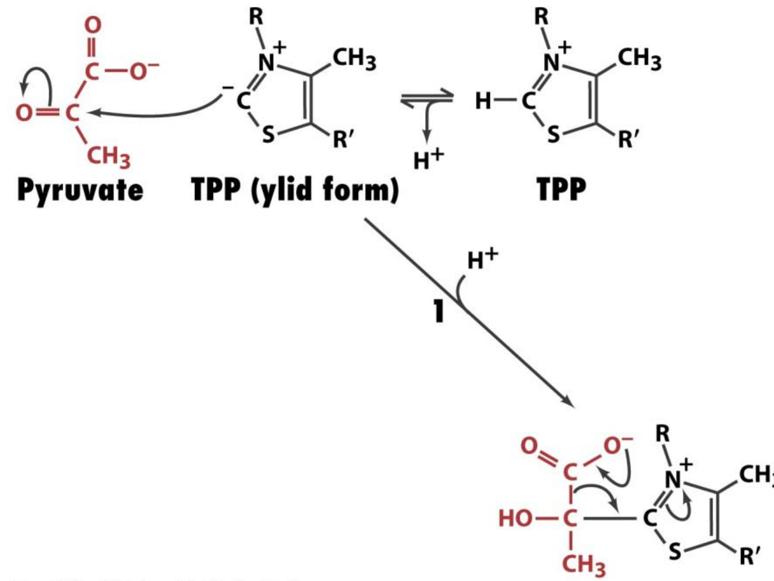


Figure 14-18 Fundamentals of Biochemistry, 2/e



Thiamine pyrophosphate (TPP)

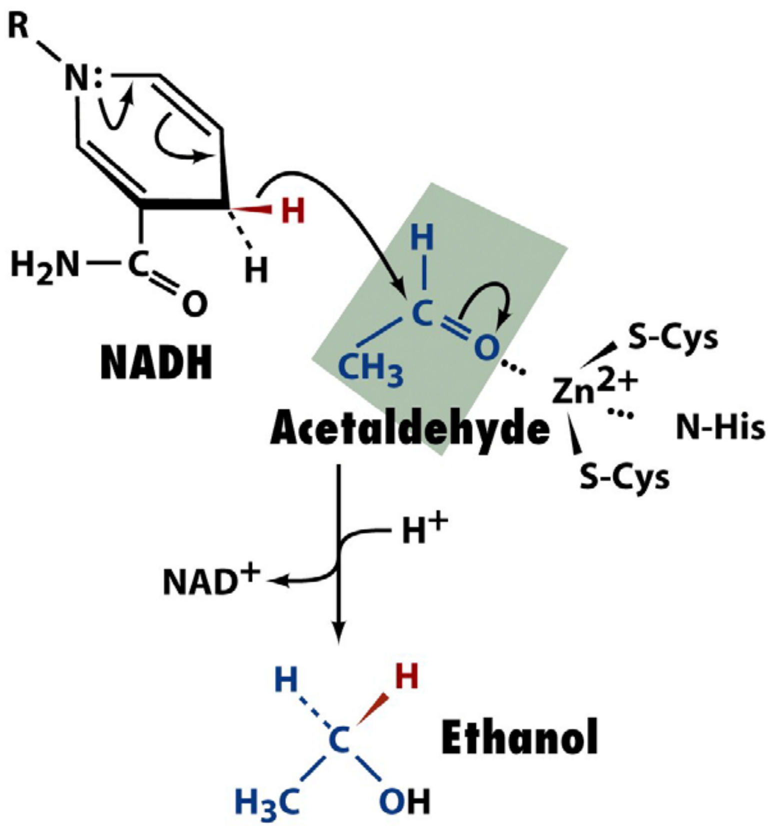
Thiamine (vitamine B1) deficiency



Electron sink

ADH

Zn enzyme
Stabilize the developing negative charge in the transition state
Acetaldehyde to ethanol and the reverse



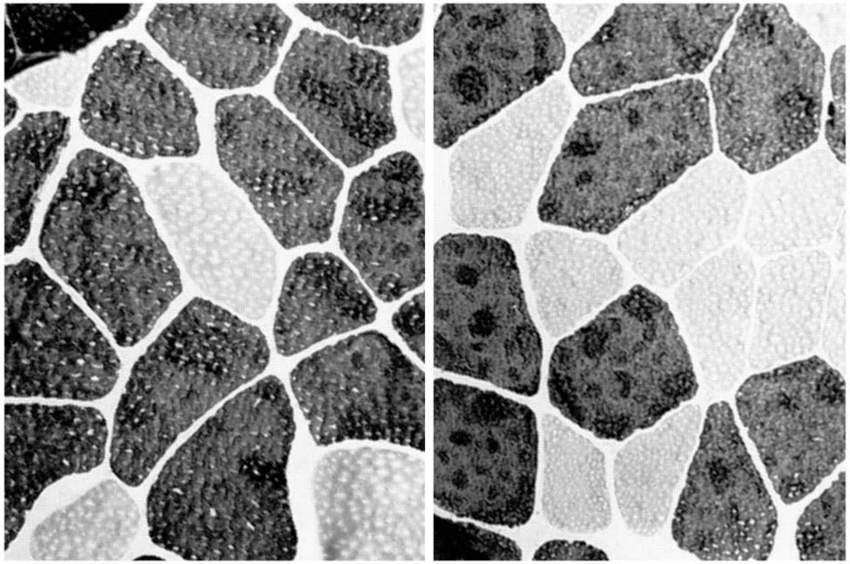
Unnumbered figure pg 451 Fundamentals of Biochemistry, 2/e

Glycolysis in skeletal muscles

Slow-twitching (type I)
rich in mitochondria (red fiber: heme-containing cytochrome)

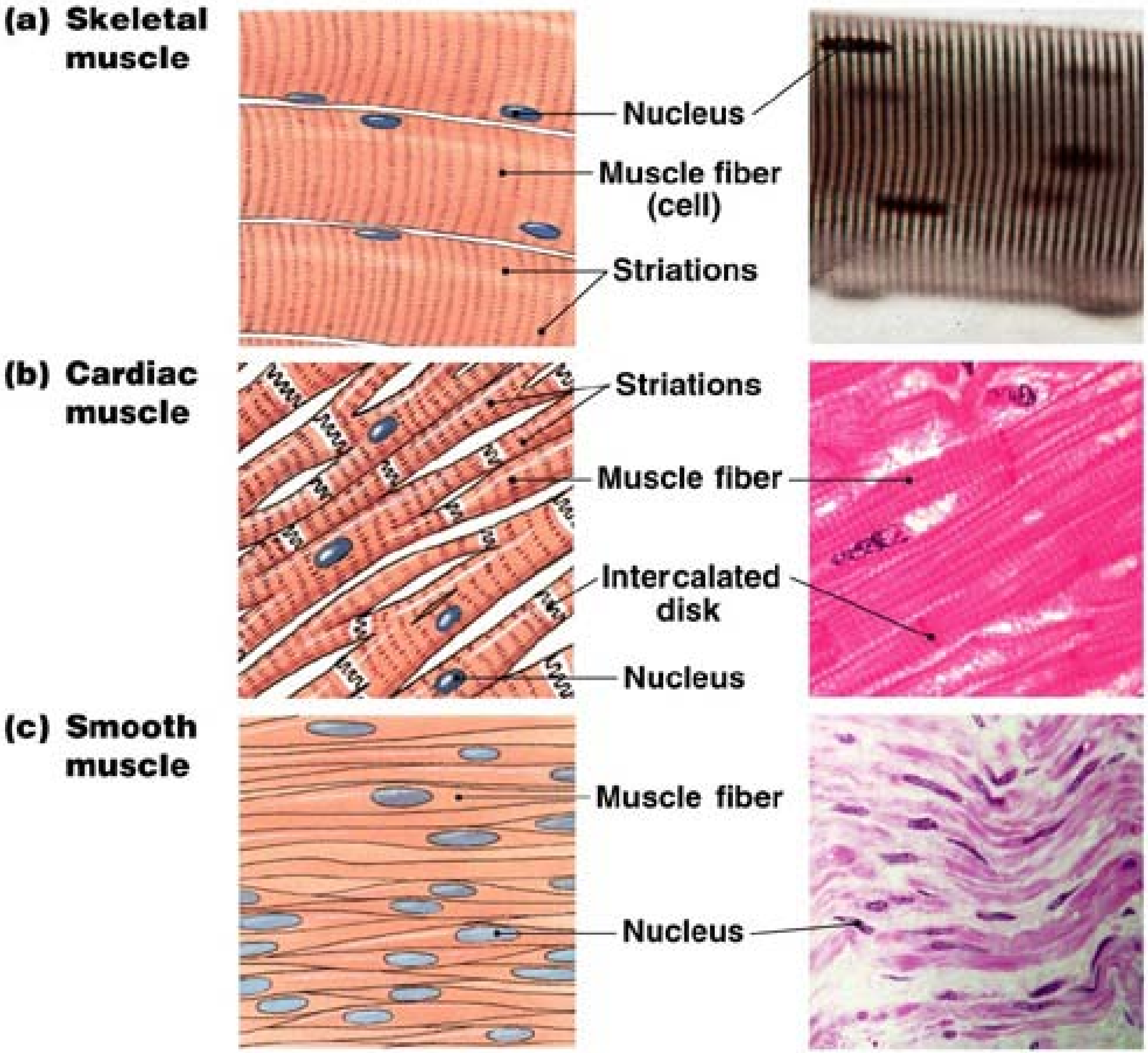
Fast-twitching (type II)
devoid of mitochondria (white fiber)

How about birds?
How about sprinters and distance runners?



Slow-twitch muscle fiber   Fast-twitch muscle fiber

Box 14-3 Fundamentals of Biochemistry, 2/e



(a) Skeletal muscle
Nucleus
Muscle fiber (cell)
Striations
(b) Cardiac muscle
Striations
Muscle fiber
Intercalated disk
Nucleus
(c) Smooth muscle
Muscle fiber
Nucleus

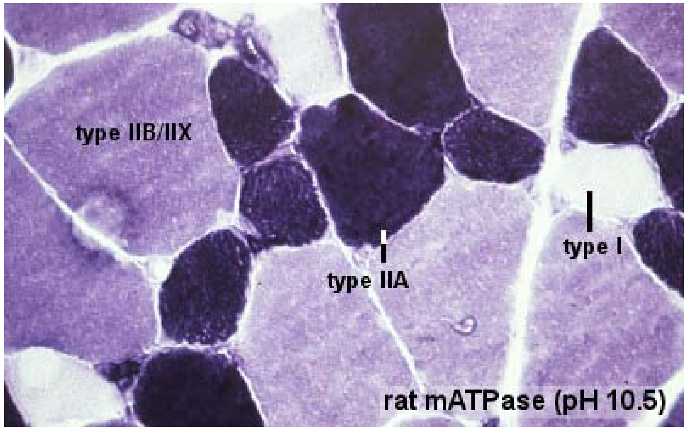
Fig. 12-1

Comparison of Slow and Fast Twitch Fibers

	Type I (slow-oxidative)	Type IIa (fast-oxidative)	Type IIb (fast-glycolytic)
Use (examples)	Posture	Walking	Sprinting
Motor unit size	100+ fibers	2-6 fibers	2-6 fibers
ATPase activity*	Low	High	High
Contraction speed	Slow	Fast	Fast
Fatigue resistance	High	Intermediate	Low
Myoglobin content	High	High	Low
Capillary density	High	Intermediate	Low
Fiber color	Red (dark)	Red	White
Glycolytic enzymes	Low	Intermediate	High
Mitochondrial content	Packed	Intermediate	Sparse

*Rapid breakdown of ATP

See also Table 12-2 in Silverthorn



	Type IIa Oxidative	Type IIb Glycolytic
Marathoners	82%	18%
Distance swimmers	74	26
Couch potatoes	45	55
Sprinters	37	63