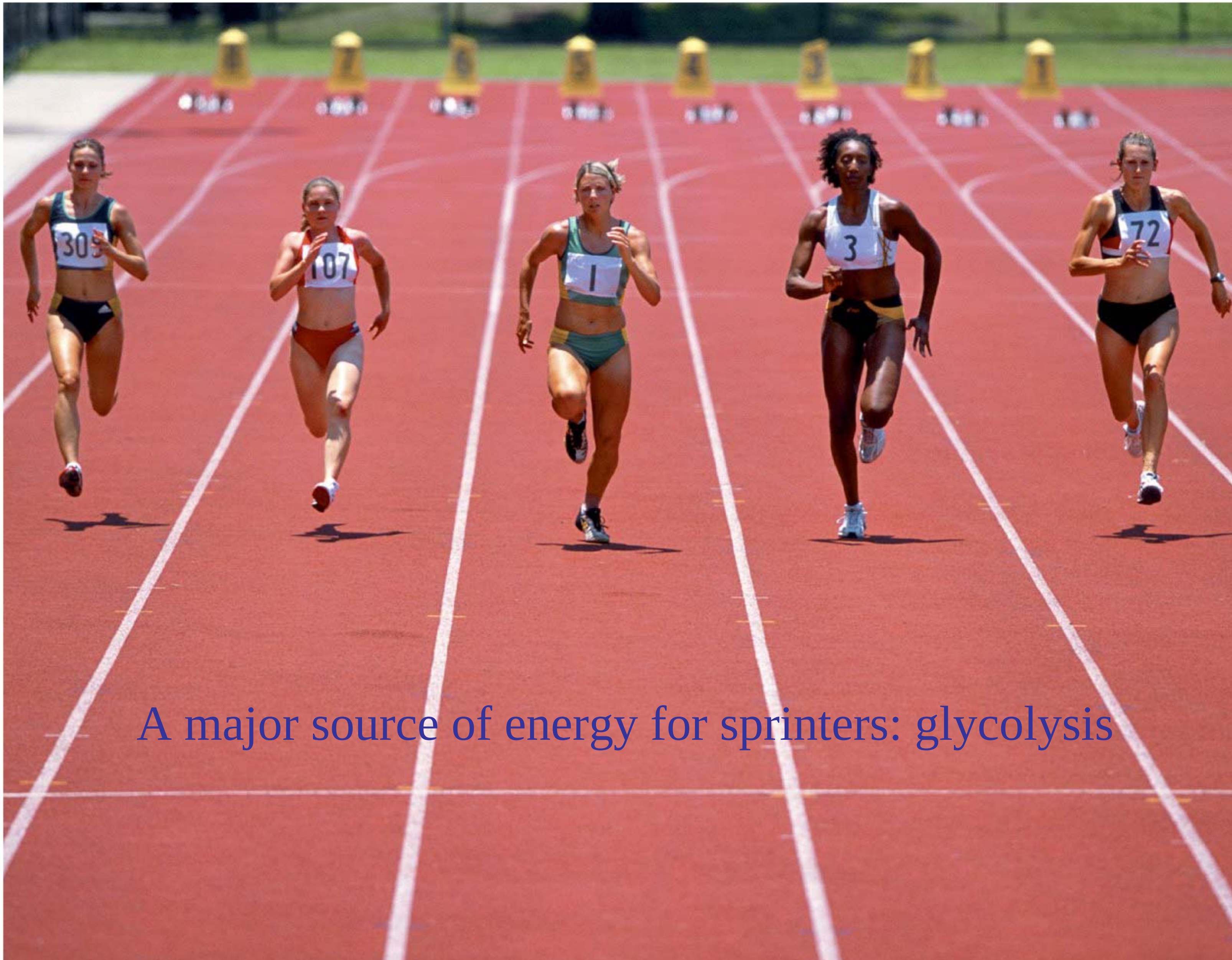
Glucose Catabolism



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

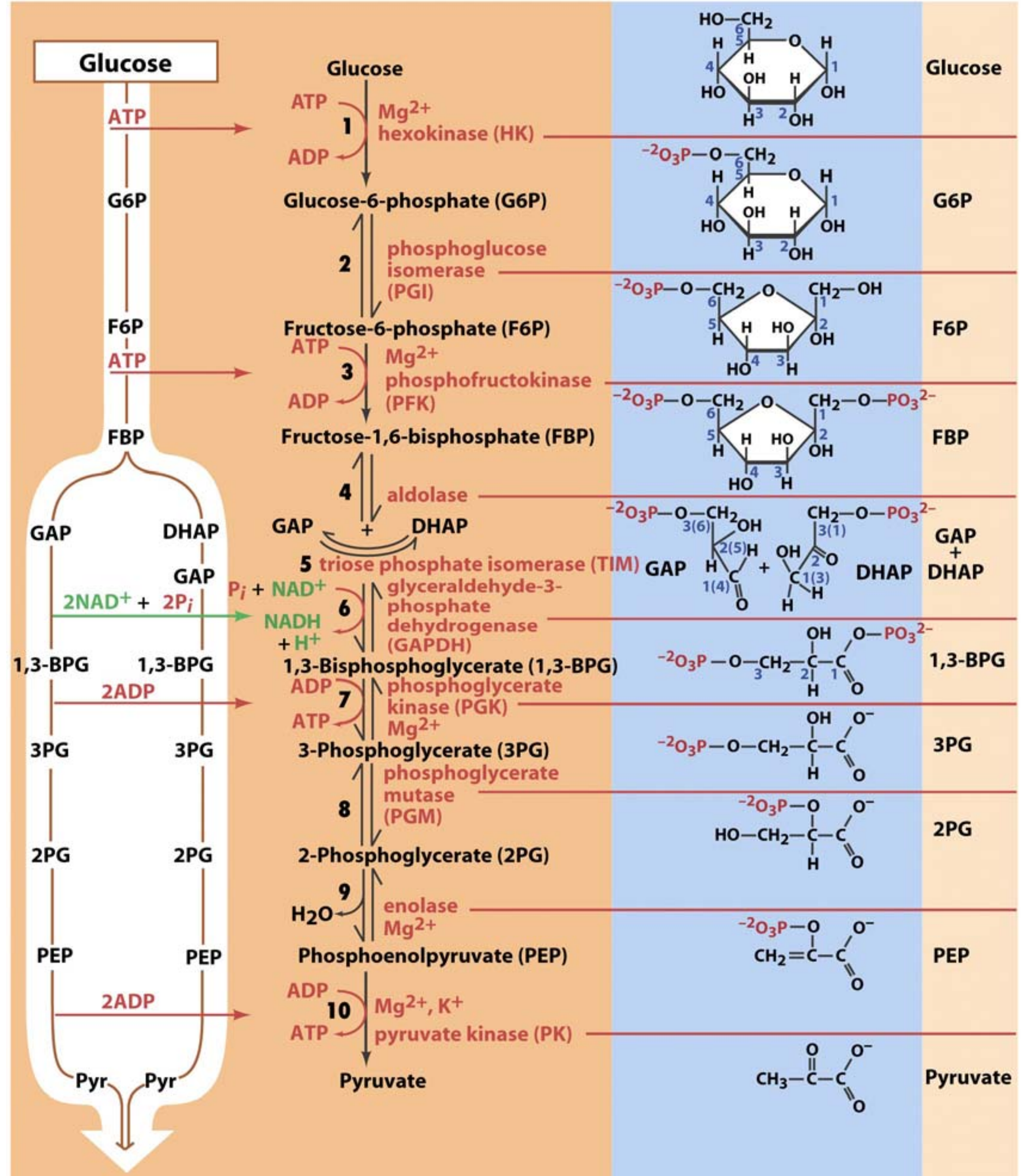


Figure 14-1 Fundamentals of Biochemistry, 2/e

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)

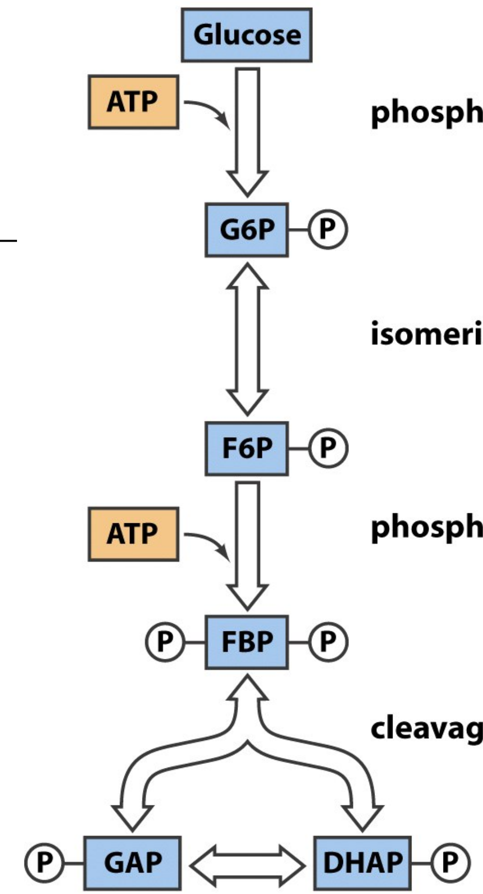
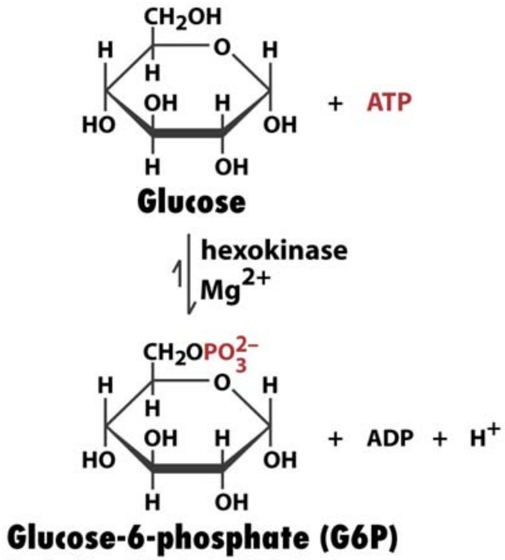


Figure 14-7 Fundamentals of Biochemistry, 2/e

Hexokinase

Nonspecific enzyme
- low Km

Glucokinase
- Liver enzyme
- high Km
- blood glucose control



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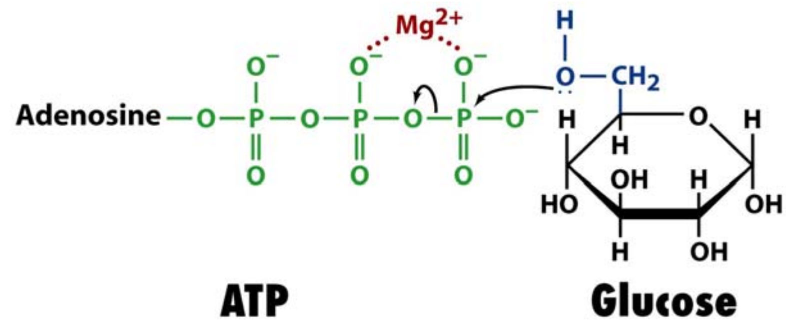

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Substrate induced conformational change
prevent ATP hydrolysis

glucose

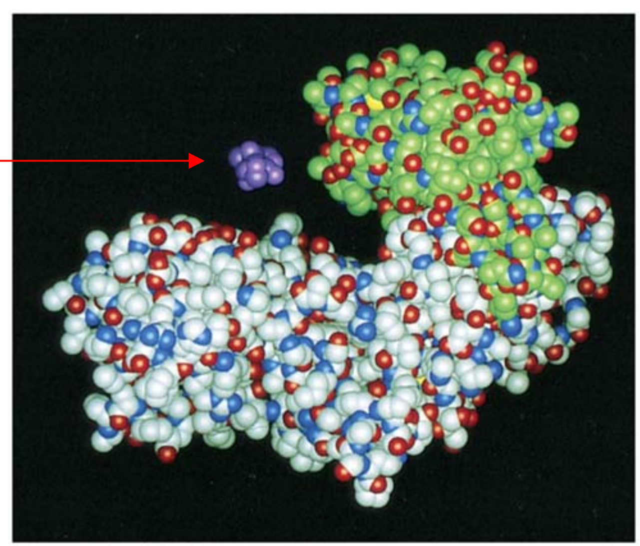


Figure 14-2a Fundamentals of Biochemistry, 2/e

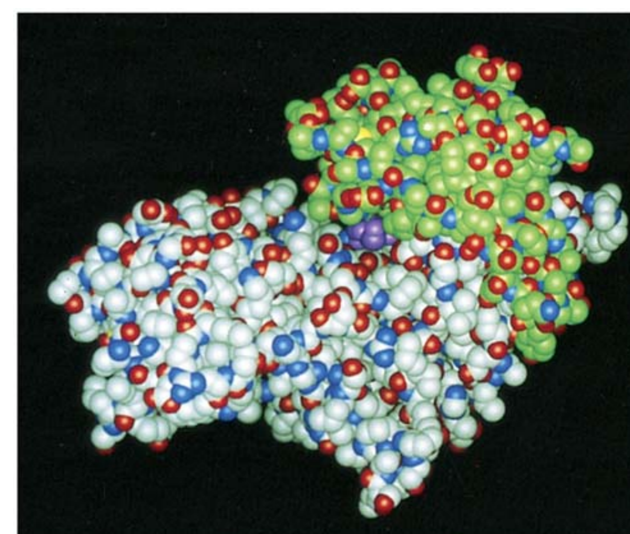
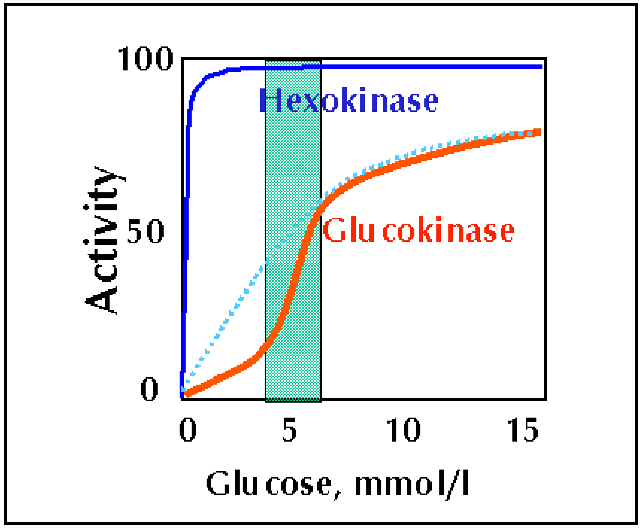
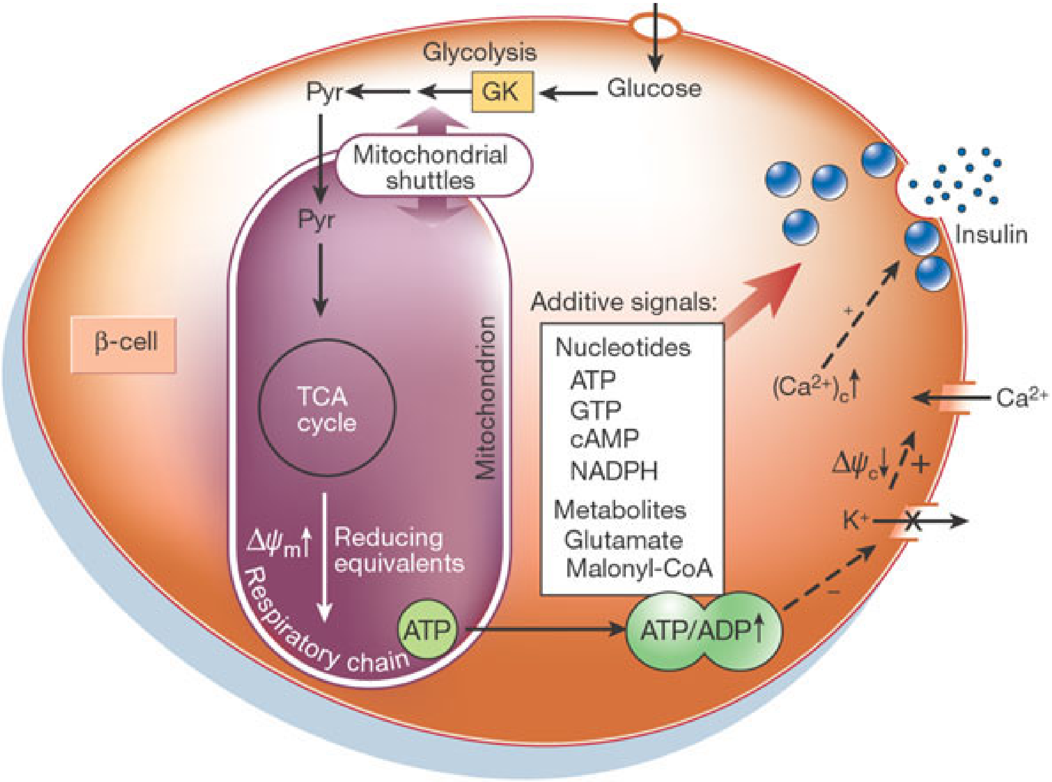


Figure 14-2b Fundamentals of Biochemistry, 2/e

Glucokinase: a glucose sensor

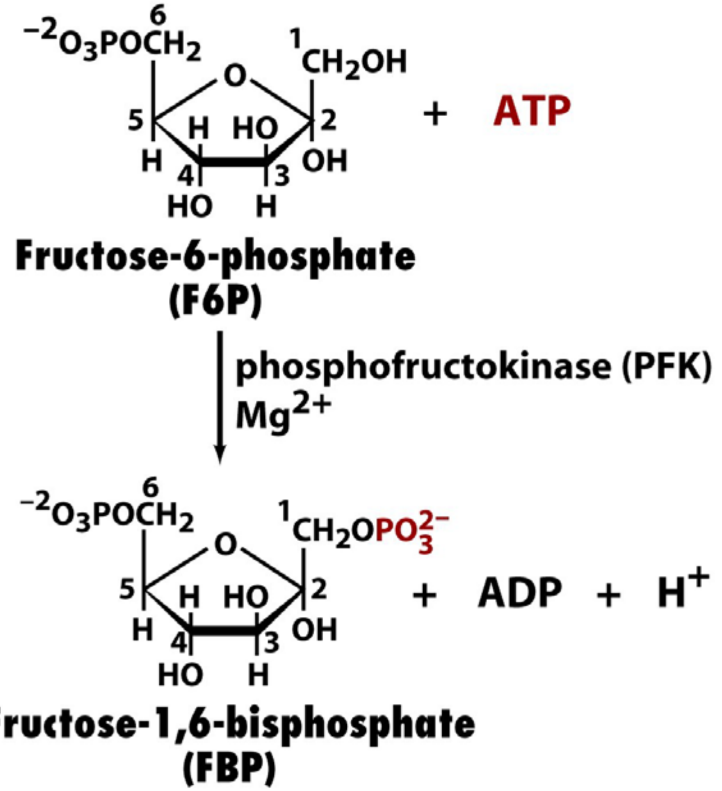




Phosphofructokinase (PFK)

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

Allosteric regulation



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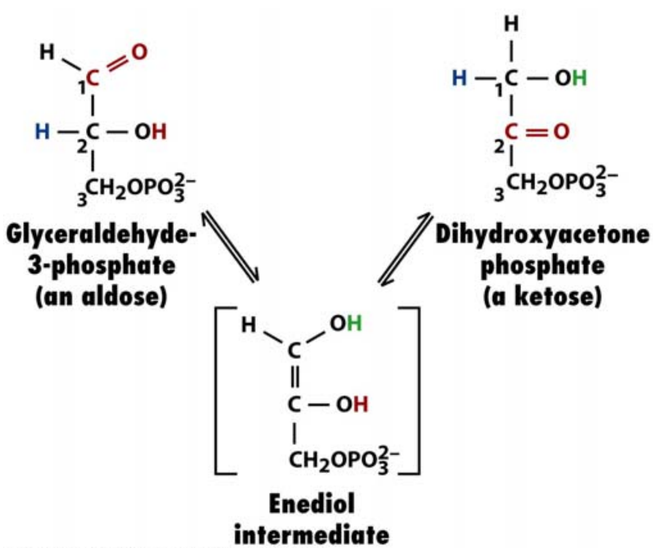
Triose phosphate isomerase (TIM)

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}



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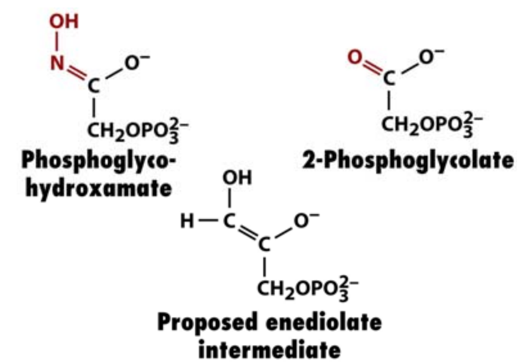

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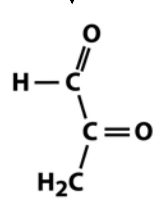
in solution



Methylglyoxal

flexible loop

prevent dephosphorylation

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)

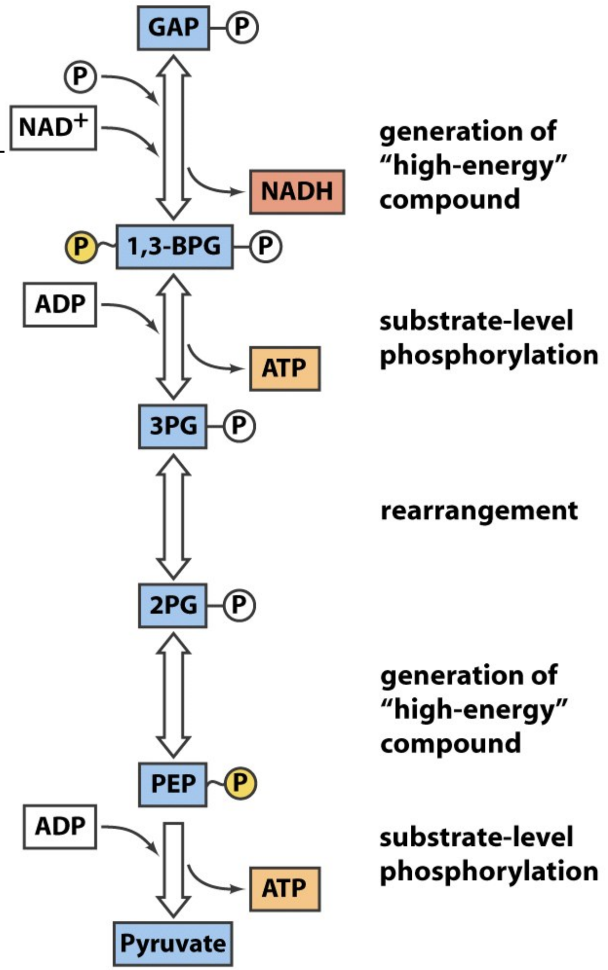
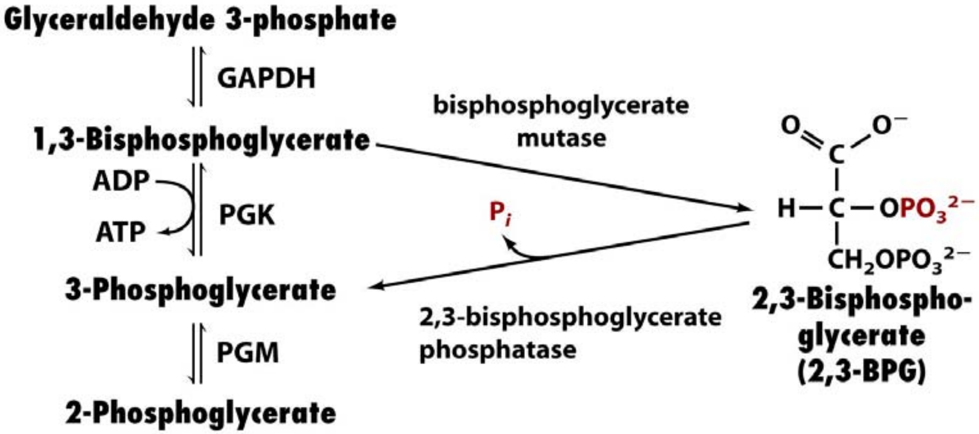
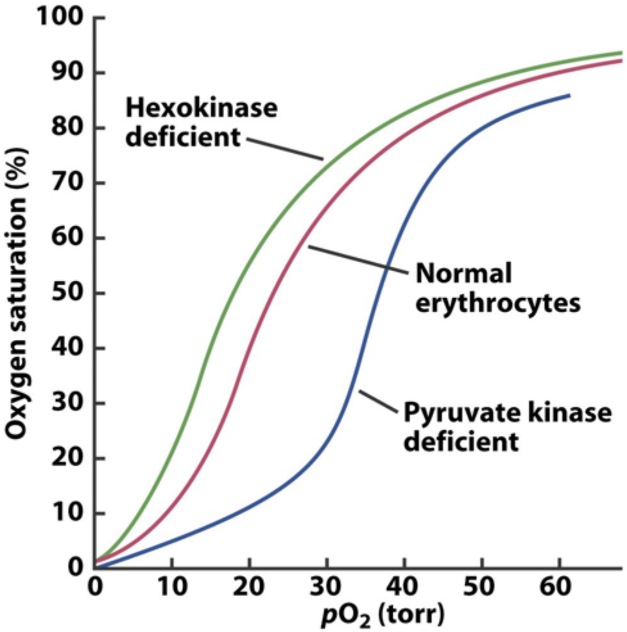


Figure 14-15 Fundamentals of Biochemistry, 2/e

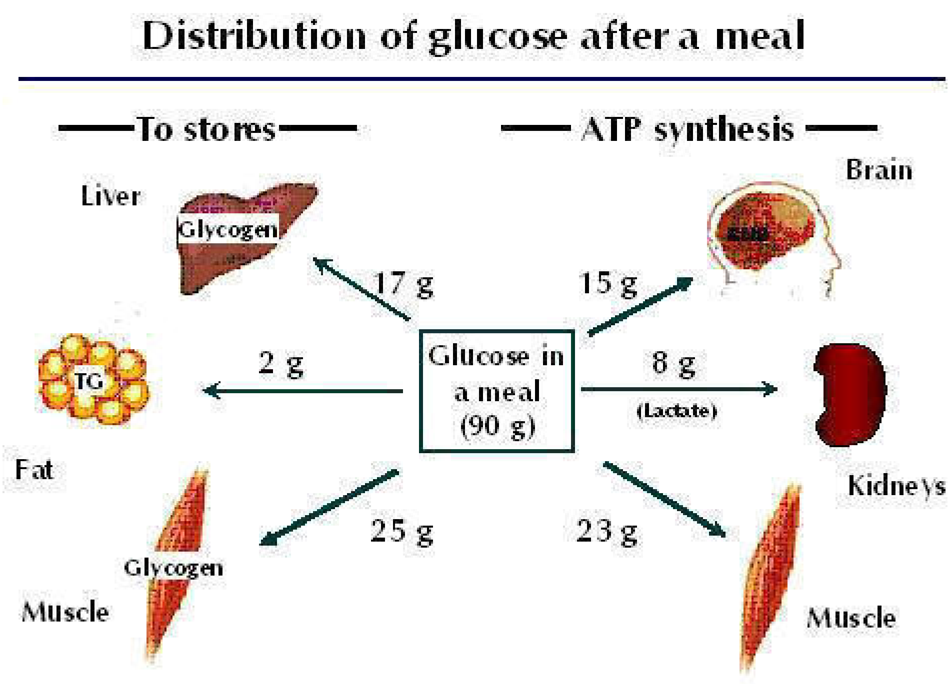
2,3-BGP in erythrocyte





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+

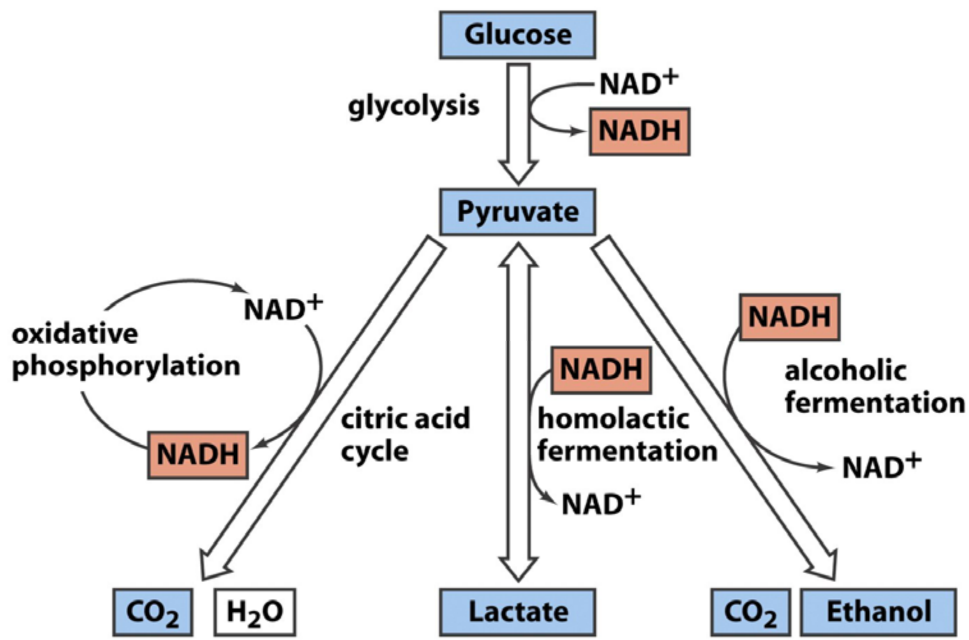
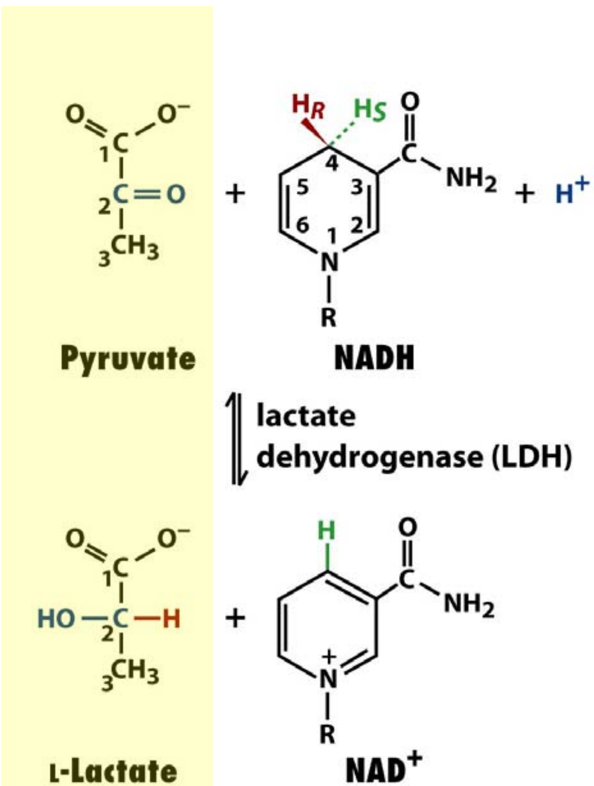


Figure 14-16 Fundamentals of Biochemistry, 2/e

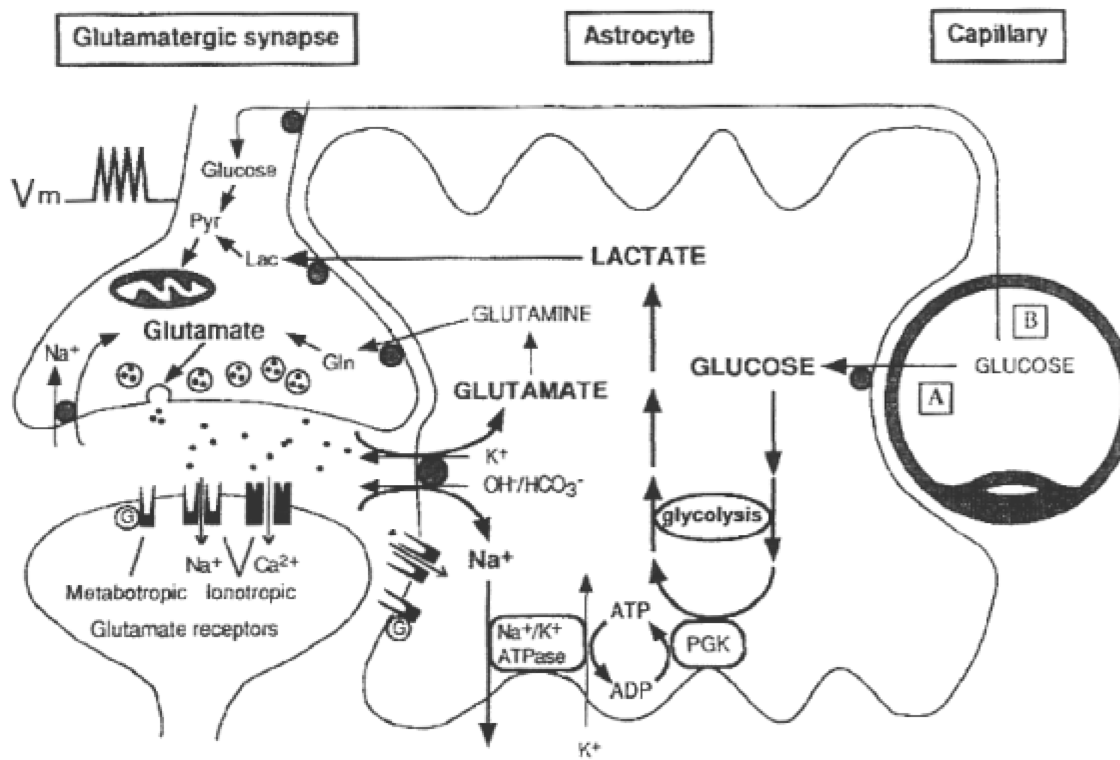
muscle
erythrocyte

Lactate fermentation

Lactate dehydrogenase (LDH)
Freely reversible
Transport of lactate from muscle to liver

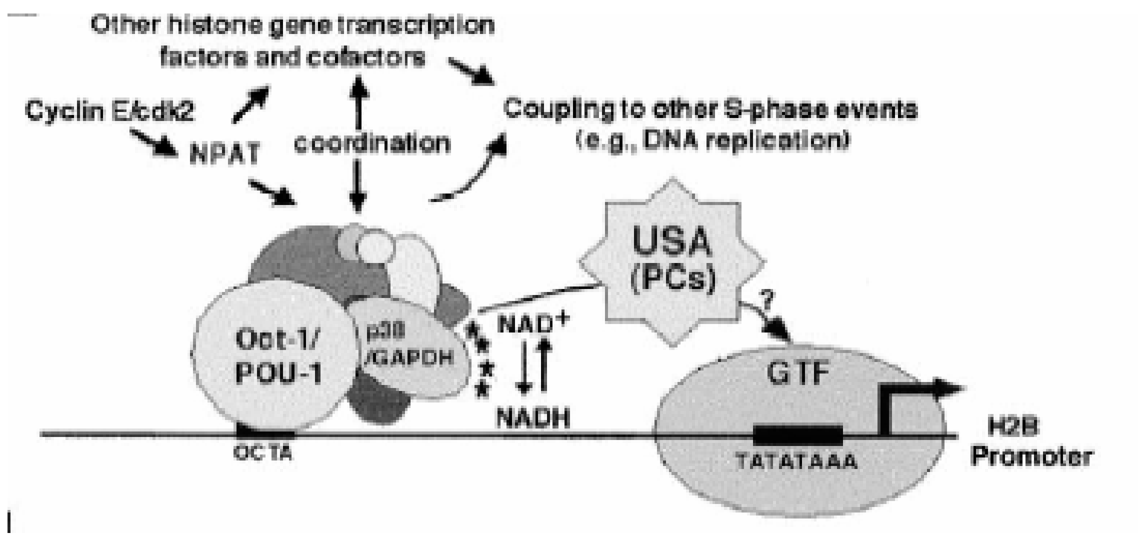


Lactate dependent cells
Lactate metabolism in brain



Cell, Vol. 114, 255–266, July 25, 2003, Copyright ©2003 by Cell Press

S Phase Activation of the Histone H2B Promoter by OCA-S, a Coactivator Complex that Contains GAPDH as a Key Component



Journal of Cellular Biochemistry 95:45–52 (2005)

New Nuclear Functions of the Glycolytic Protein, Glyceraldehyde-3-Phosphate Dehydrogenase, in Mammalian Cells

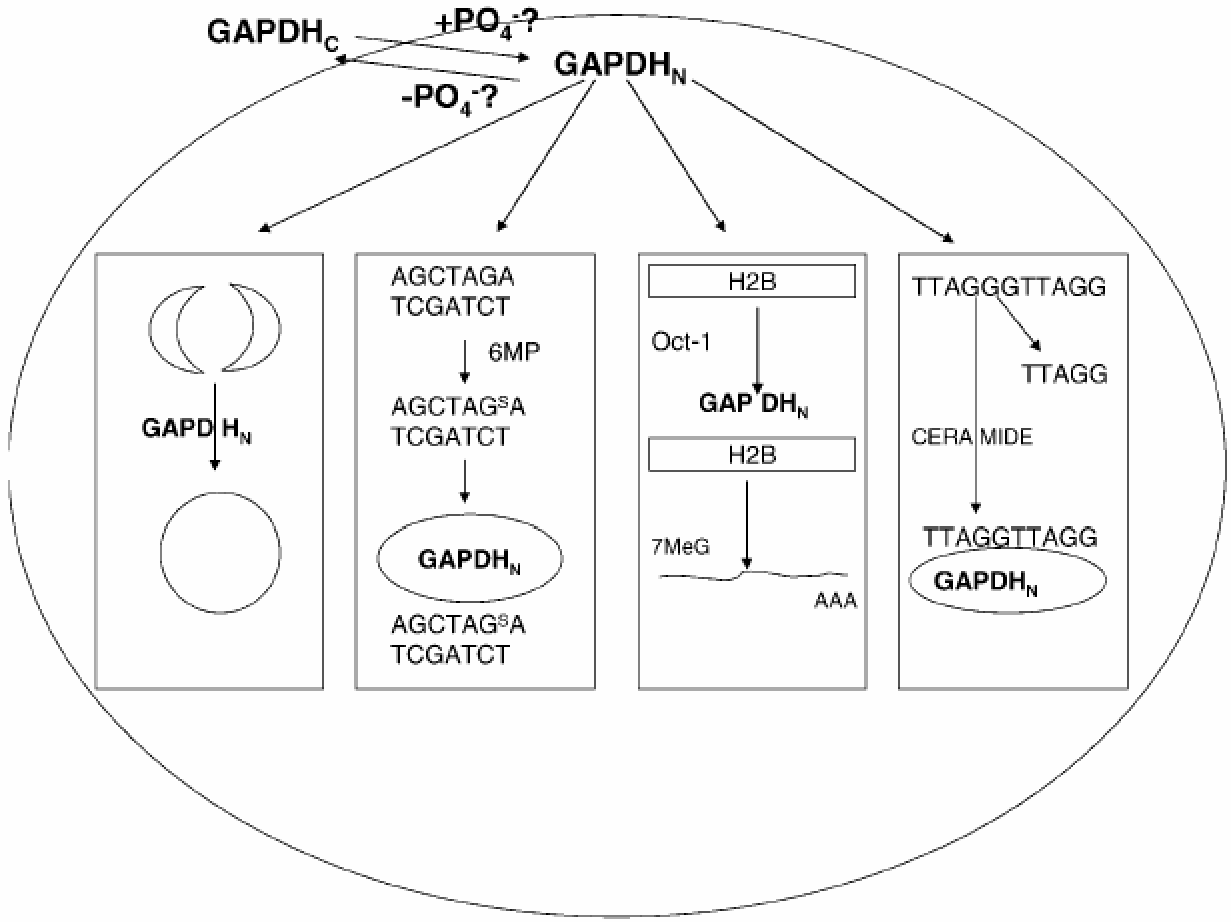
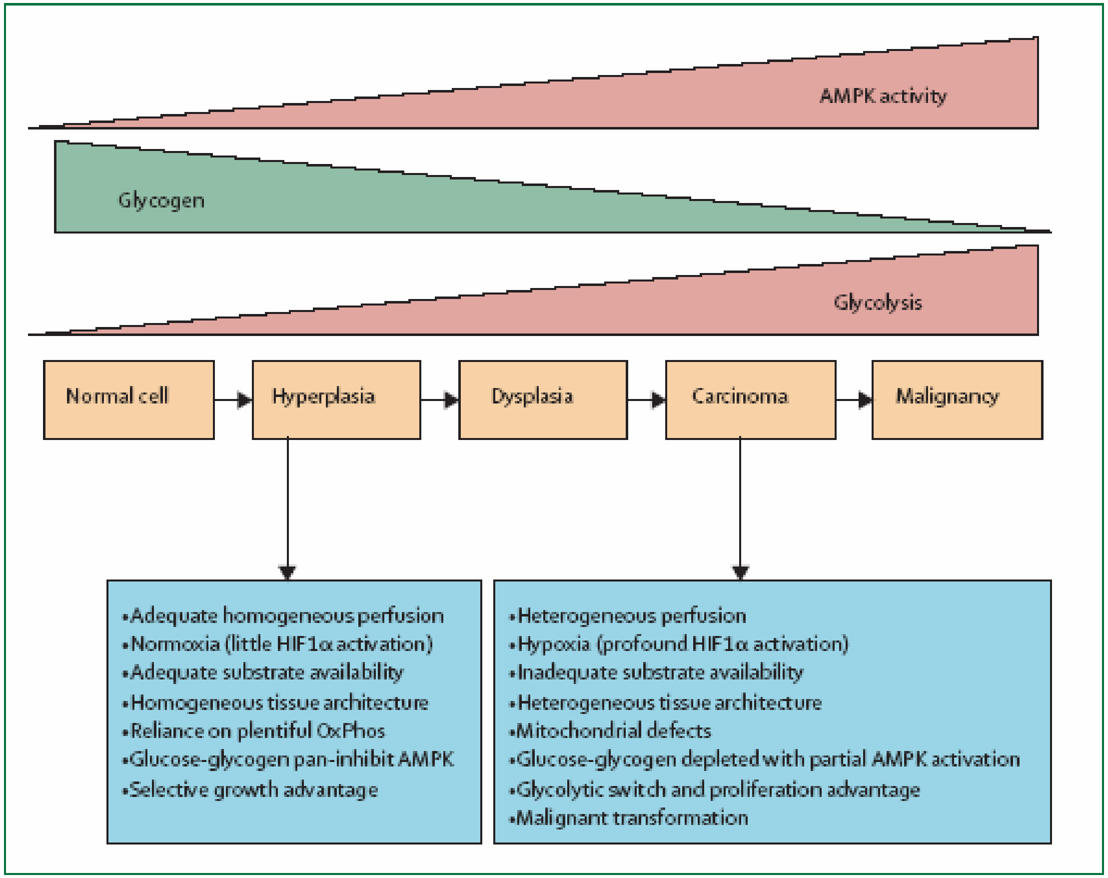


Fig. 1. Post-translational modification of GAPDH. Nuclear translocation of GAPDH$_C$ and its conversion to GAPDH$_N$ is indicated as is the new functions of GAPDH$_N$ (Left to right: Membranefusion, binding to fraudulent DNA, regulation of histone 2B gene expression, maintenance oftelomere structure). Previously reported functions of GAPDH$_N$ are not illustrated [rev. in Sirover, 1999].

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):

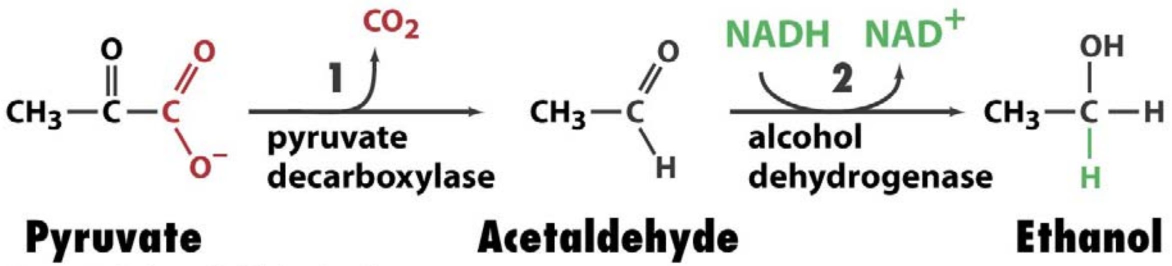


Figure 14-18 Fundamentals of Biochemistry, 2/e

Control of glycolysis

Different tissues control glycolysis in different ways

3 kinase reactions: large negative free E changes

HK

PFK

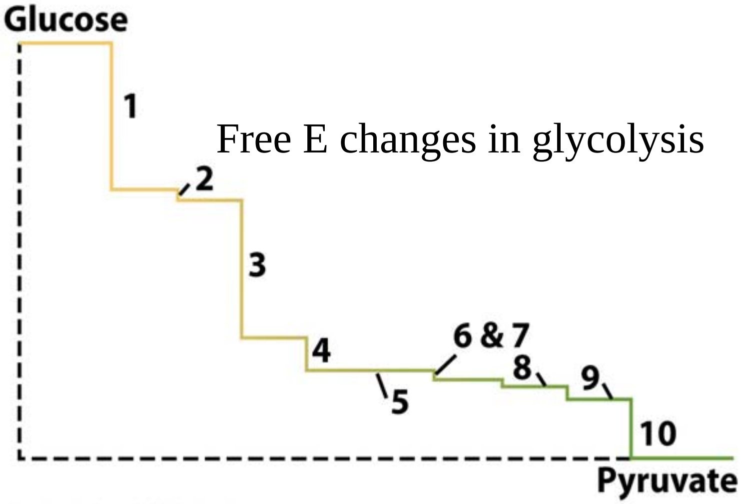
PK

Table 14-1 $\Delta G^{\circ\prime}$ 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).

Table 14-1 Fundamentals of Biochemistry, 2/e



Free E changes in glycolysis

Figure 14-21 Fundamentals of Biochemistry, 2/e

PFK: the major flux controlling enzyme in muscle

HK is not required when glycogen is a source for glucose

Tetrameric enzyme in R & T conformations
Allosteric inhibitors: ATP (at regulatroy site)
Allosteric activators: F26BP, ADP, AMP

Figure 14-22 Fundamentals of Biochemistry, 2/e

AMP and ADP overcome the ATP inhibition

Low metabolic demand: high ATP & PFK inhibition
High metabolic demand: low ATP & PFK activation
Metabolic demand variation: 100-fold level but [ATP] variation is <10%
In muscle [ATP]/[ADP]= ~50 & [ATP]/[AMP]= ~10,
meaning greater fluctuation in [ADP] & [AMP]

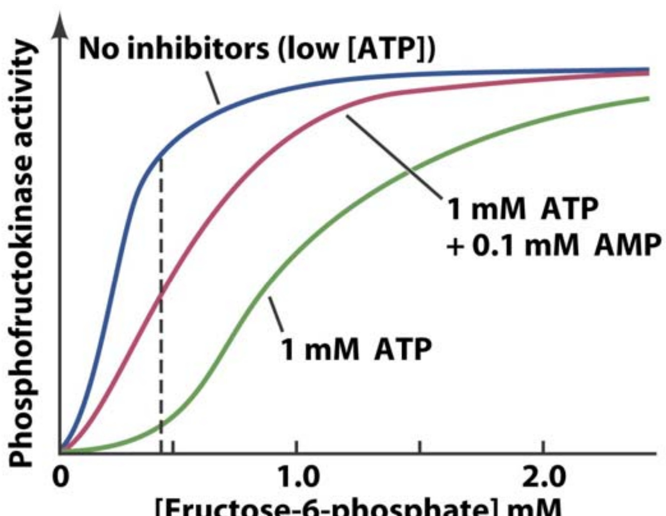


Figure 14-23 Fundamentals of Biochemistry, 2/e

Allosteric changes (T, blue)

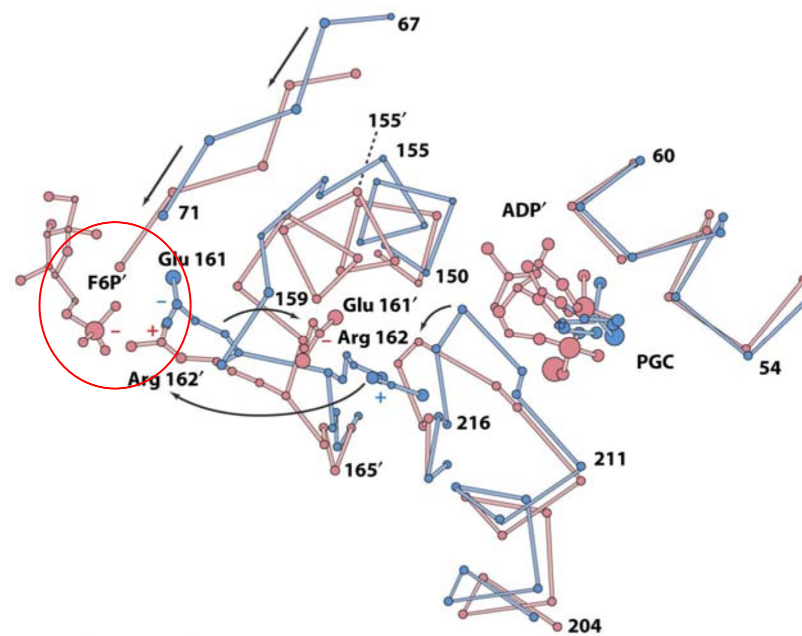


Figure 14-24 Fundamentals of Biochemistry, 2/e

Substrate cycling

Futile cycle? (net reaction: ATP hydrolysis by the combined actions of PFK & FBPase)

<u>Additional control of PFK</u>

greater fractional effect on pathway flux (vf-vr)

than allosteric control on a single enzyme (ex. F26P activates PFK but inhibits FBPase)

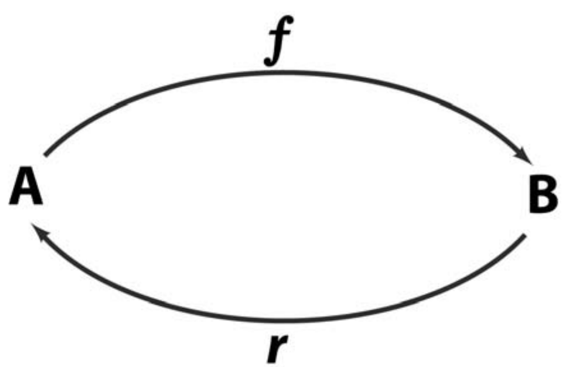
dose not increase the maximum flux, but decrease the minimum flux

holding pattern (energetic price for rapid change from a resting to active state)

<u>Generation of body heat</u> (nonshivering thermogenesis)

substrate cycling is controlled by thyroid hormones, which stimulate metabolism)

cold sensitive and obesity



Unnumbered figure pg 456 Fundamentals of Biochemistry, 2/e

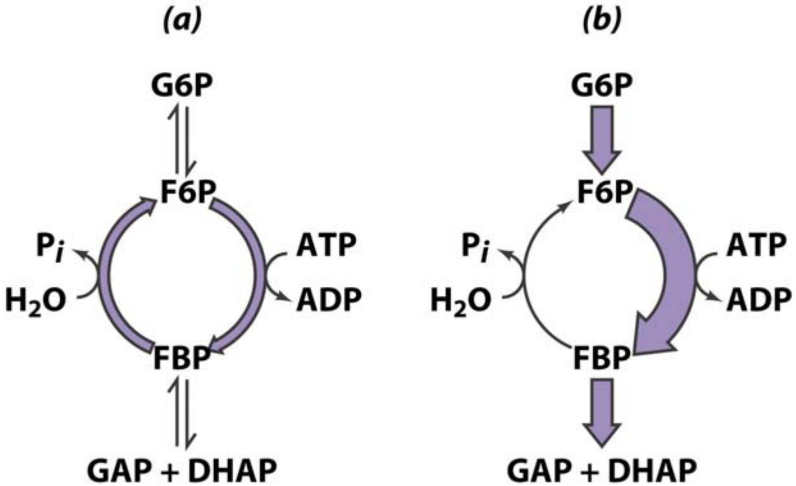


Figure 14-25 Fundamentals of Biochemistry, 2/e

Metabolism of hexoses other than glucose

Fructose, galactose, mannose

Entry into glycolysis

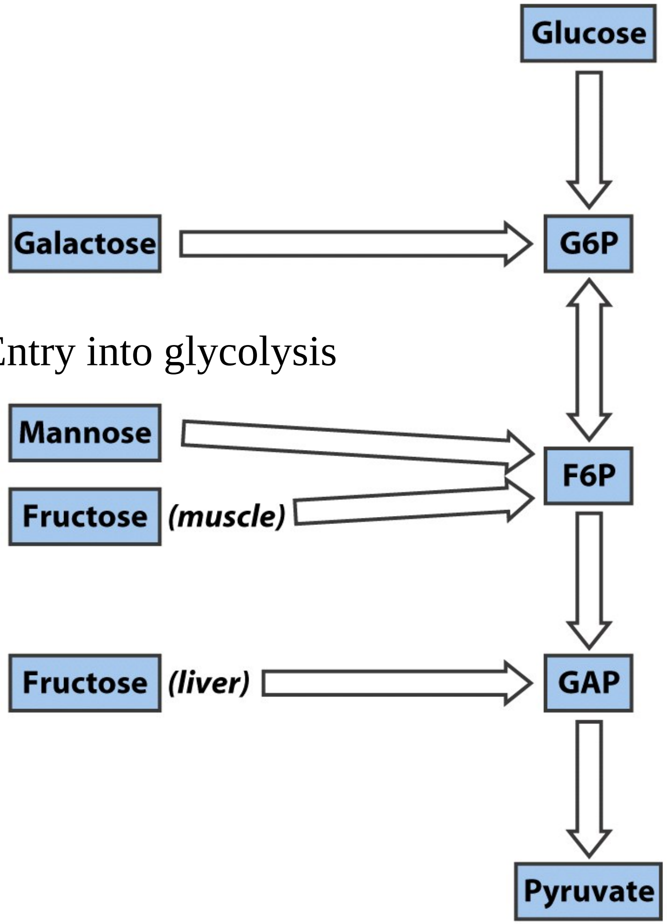


Figure 14-26 Fundamentals of Biochemistry, 2/e

Fructose

A major fuel in diets
Different metabolism in muscle and liver
Increasing fructose consumption
    High fructose as a sweetner
    Harmful? Bypass of PFK control
    may be directed to lipid synthesis
  in low ATP demand

Fructose intolerance
  deficiency of type B aldolase: accumulation of F1P
    depletion of liver Pi
    [ATP] drop
    liver damage
    causing hypoglycemia, because [F1P] inhibits
    glycogen phosphorylase & FBPase
  However the deficiency develops distaste
    for sweet

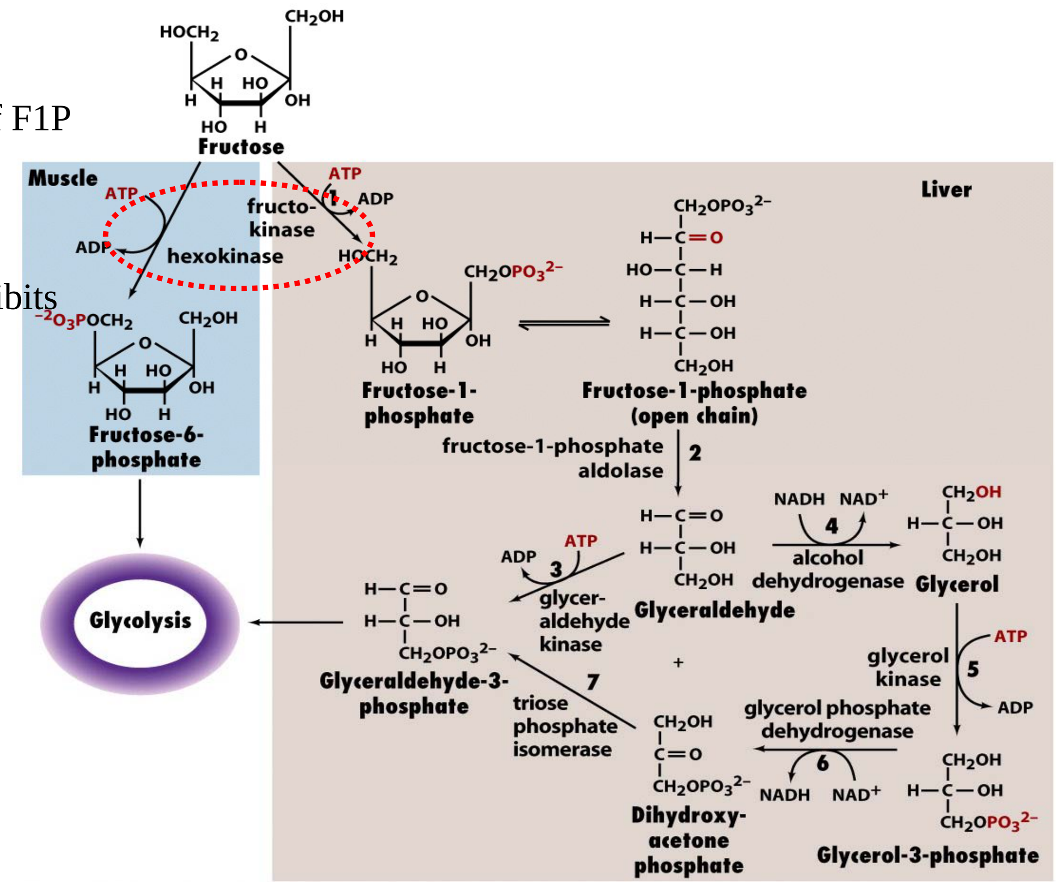
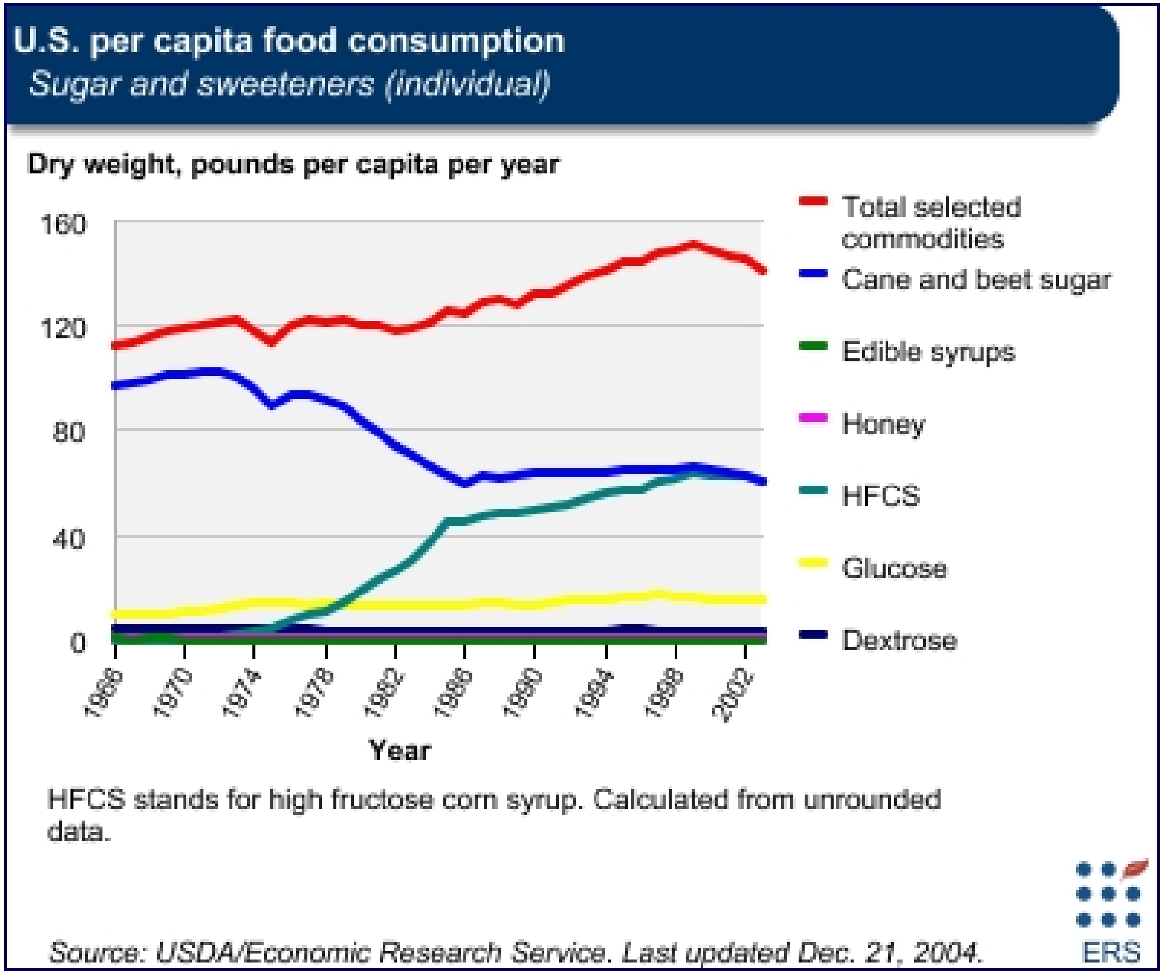
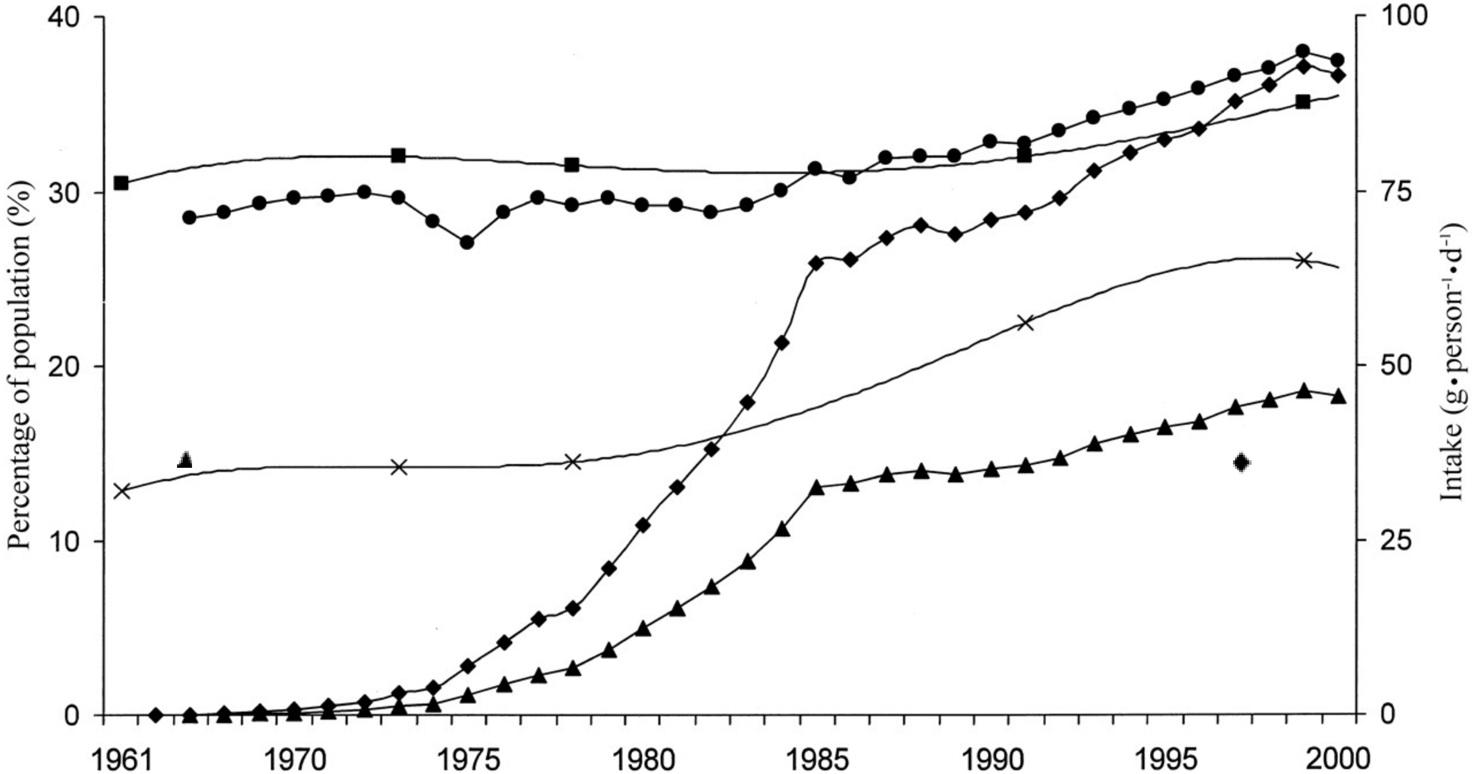


Figure 14-27 Fundamentals of Biochemistry, 2/e



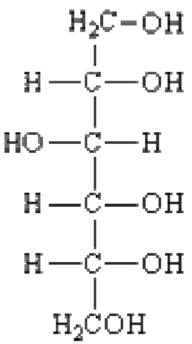
http://en.wikipedia.org/wiki/High_fructose_corn_syrup



Estimated intakes of total fructose (●), free fructose (▲), and high-fructose corn syrup (HFCS, ◆) in relation to trends in the prevalence of overweight (■) and obesity (x) in the United States. American Journal of Clinical Nutrition, Vol. 79, No. 4, 537-543, April 2004

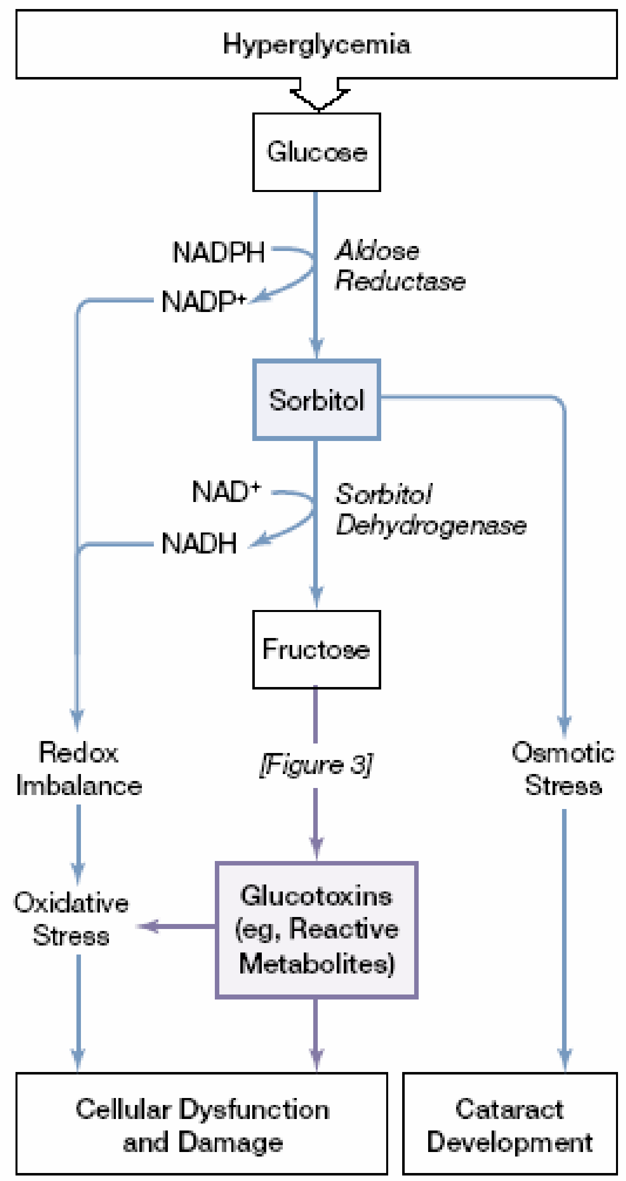
Glucose in diabetes

Aldose reductase



Sorbitol

Figure 2. Aldose Reductase Pathway Theory



Pentose phosphate pathway

30% of glucose oxidation

Principal products

- Reducing power: NADPH
- Not interchangeable with NADH

- Ribose-5-phosphate

<u>3 stages</u>

Oxidative reactions

Isomerization and epimerization

C-C cleavage and formation

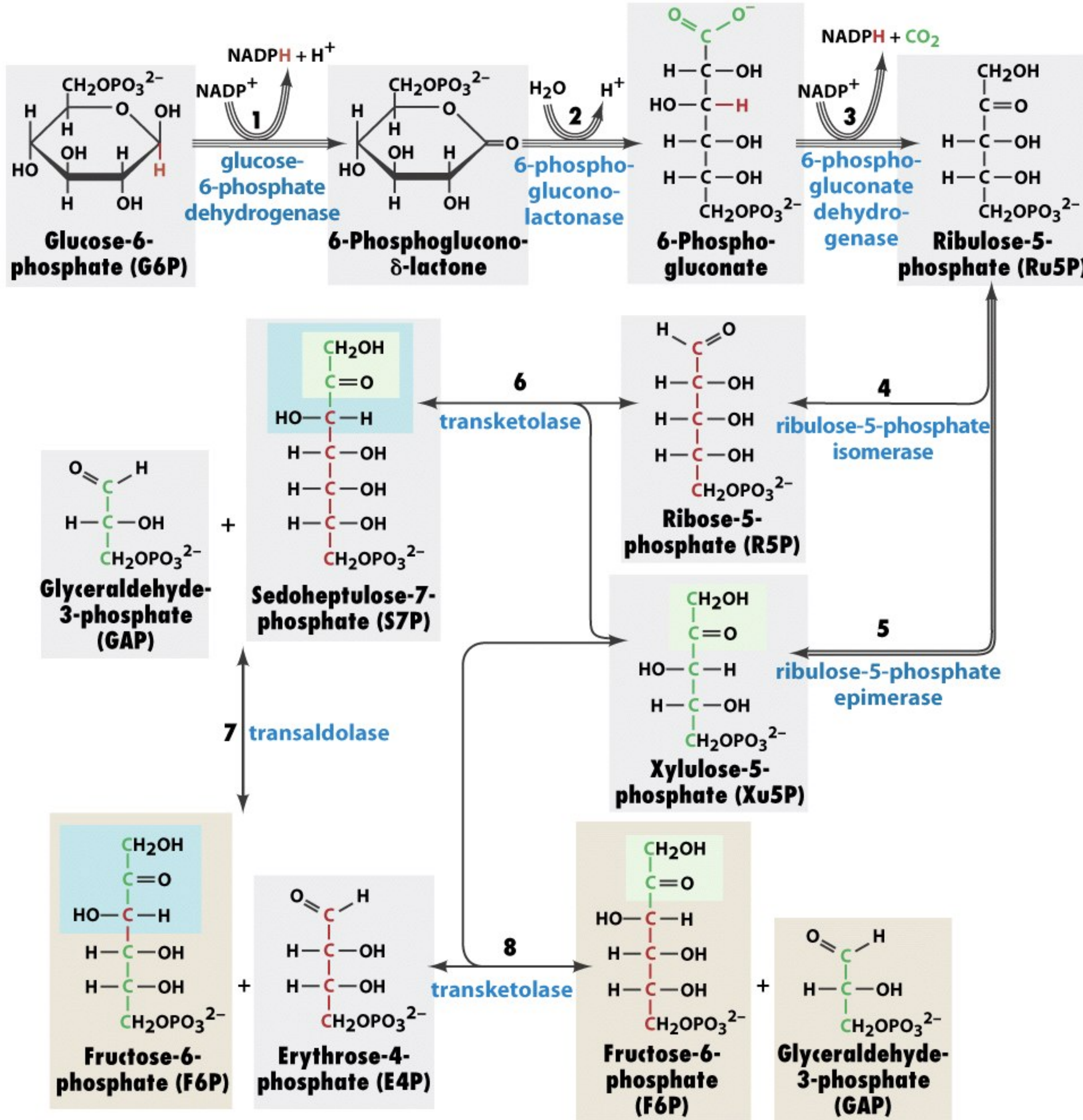


Figure 14-30 Fundamentals of Biochemistry, 2/e

Control of pentose phosphate pathway

Depends on the requirements of ATP, NADPH, R5P

G6P dehydrogenase: the first committed step
- regulation by [NADP+]
- enzyme synthesis control by hormone
- enzyme deficiency

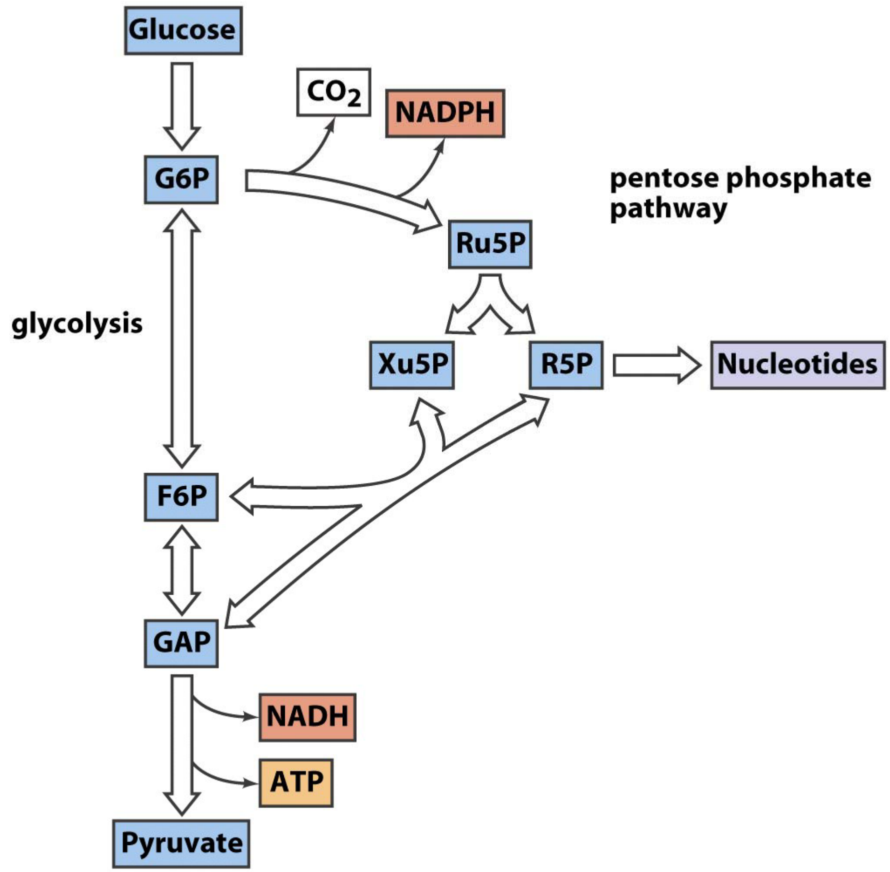


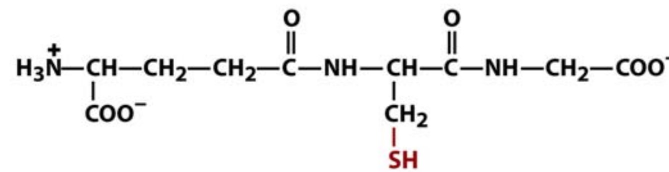
Figure 14-35 Fundamentals of Biochemistry, 2/e

G6PD deficiency

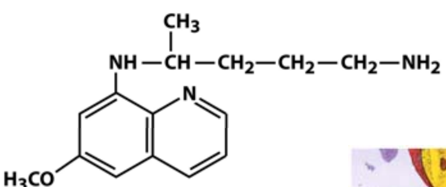
Common in African, Asian, Mediterranean
Deficiency of NADPH (for biosynthesis & ROS elimination)
In erythrocytes
- glutathione (GSH) regeneration

Hemolytic anemia when ingest drugs (such as antimalarial drug primaquine) or eat fava beans
- increase peroxide formation
- accelerated breakdown of mutant enzymes
- membrane damage

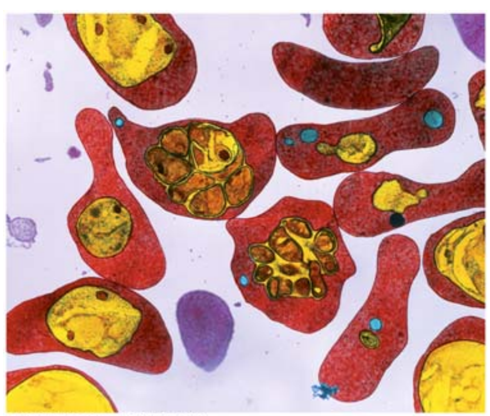
High prevalence
~400 G6PD variants
Selective advantage to malaria

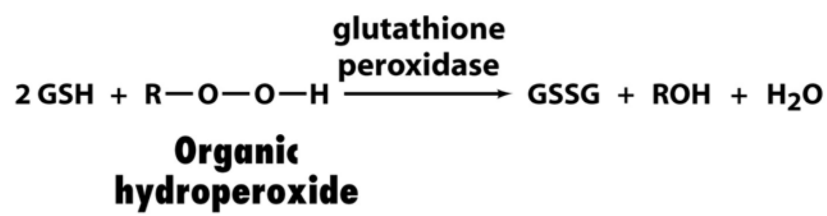


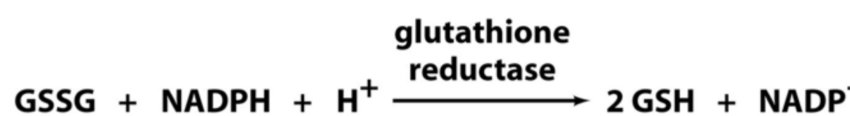
Glutathione (GSH)
(γ-L-glutamyl-L-cysteinylglycine)



Primaquine







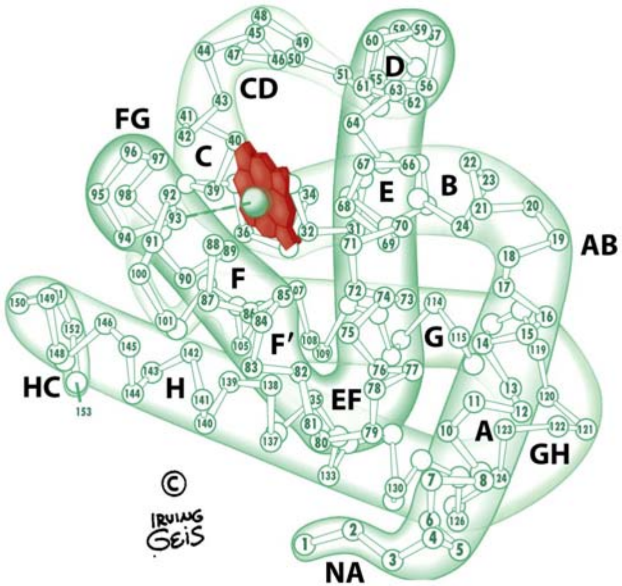


Figure 7-1 Fundamentals of Biochemistry, 2/e

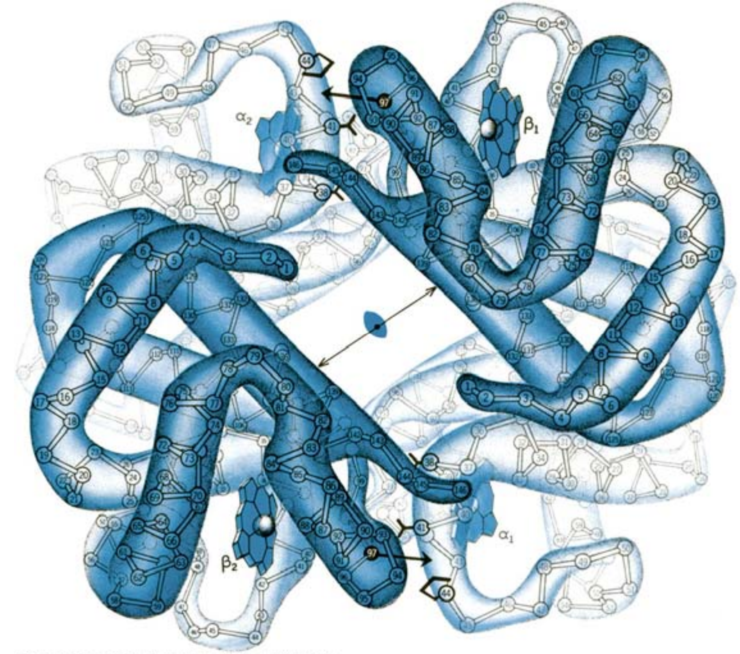


Figure 7-5 part 1 Fundamentals of Biochemistry, 2/e

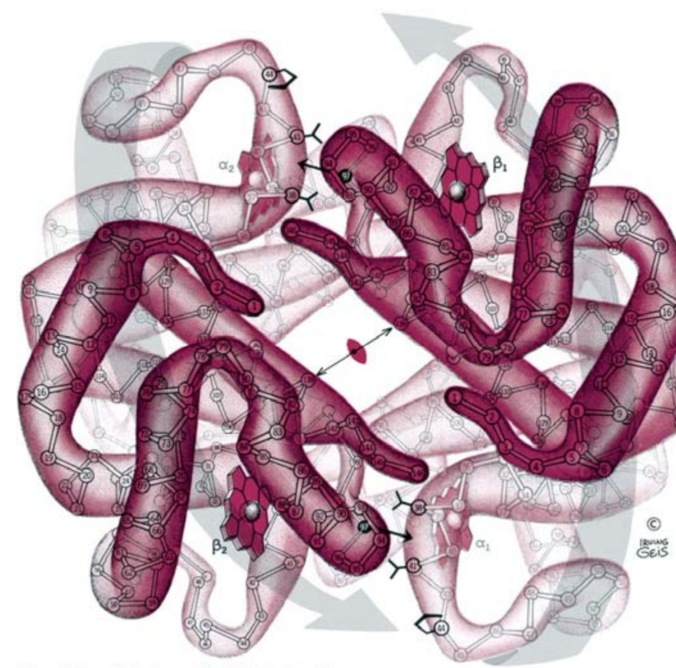
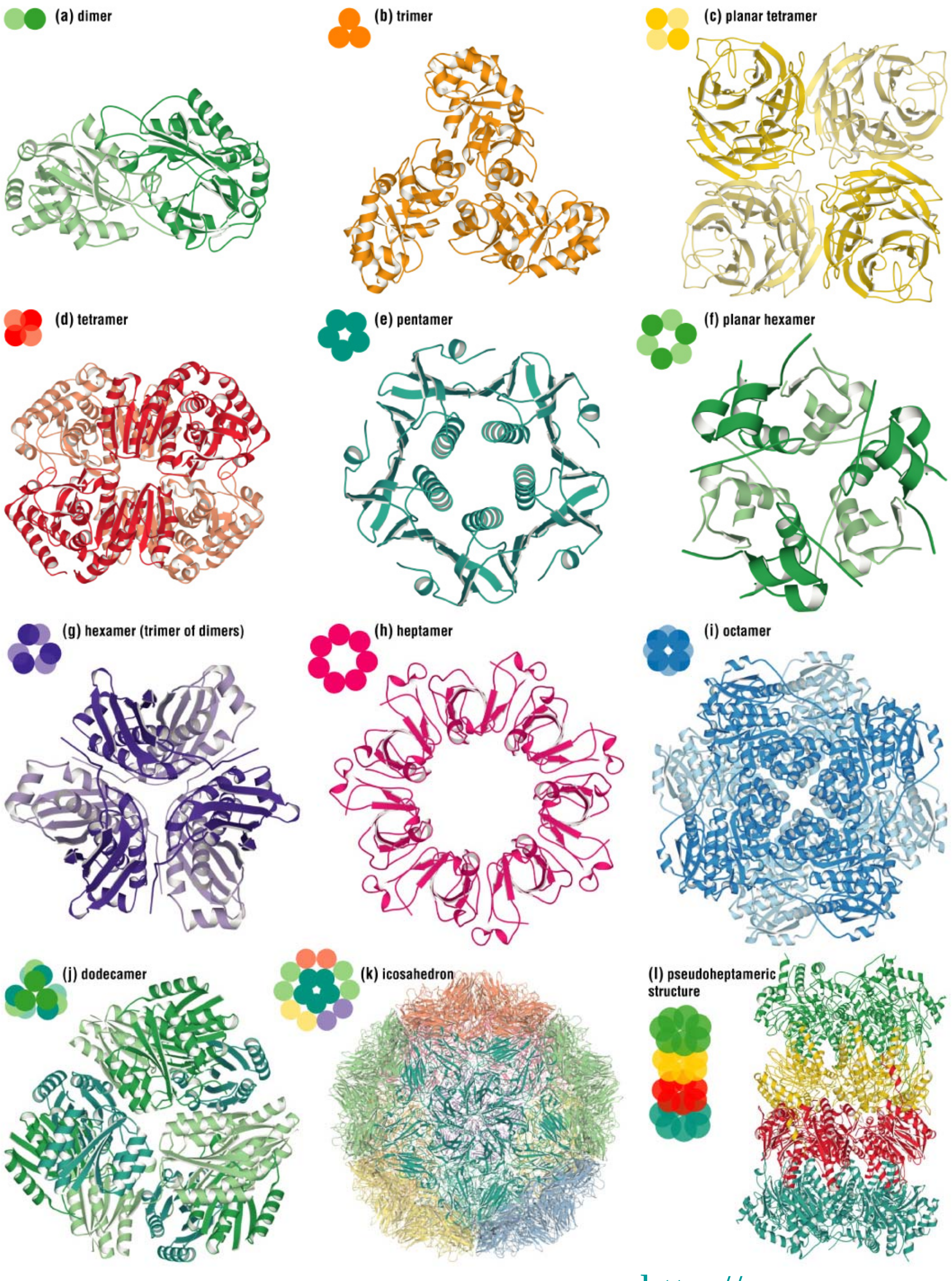


Figure 7-5 part 2 Fundamentals of Biochemistry, 2/e

From **Protein Structure and Function** by Gregory A Petsko and Dagmar Ringe



http://www.new-science-press.com/browse/protein/illustrations/1/

Oxygen-binding curve of hemoglobin

Sigmoidal

YO2 = 0.95 at 100 torr
YO2 = 0.55 at 30 torr

Cooperativity

cooperative interaction
between binding sites

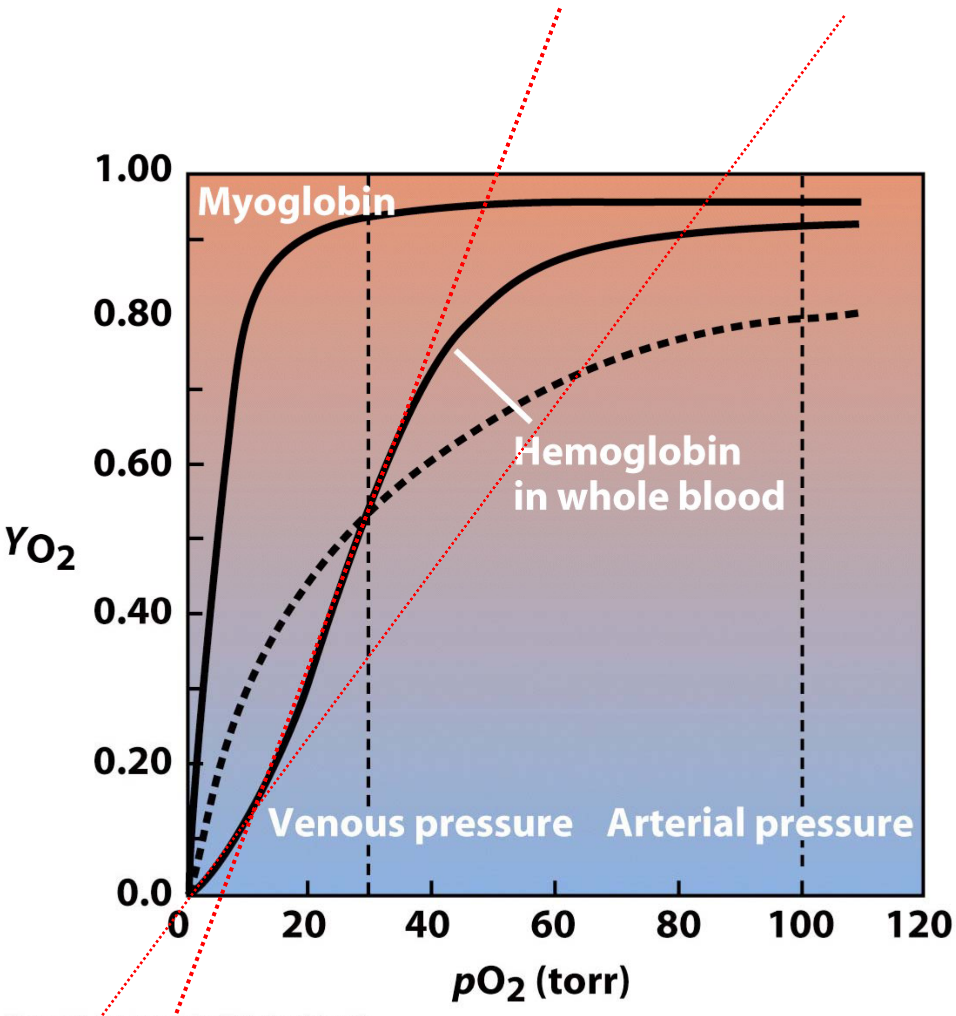


Figure 7-7 Fundamentals of Biochemistry, 2/e

The Bohr effect

The O_2 affinity of Hb increases with increasing pH
In T state oxygen binding decrease the pK's of several groups
  + charged groups in T state participate in ion pairs
    α subunits N-terminal amino groups
    β subunits C-terminal His
Under physiological condition, Hb releases ~0.6 protons for each O_2 binding

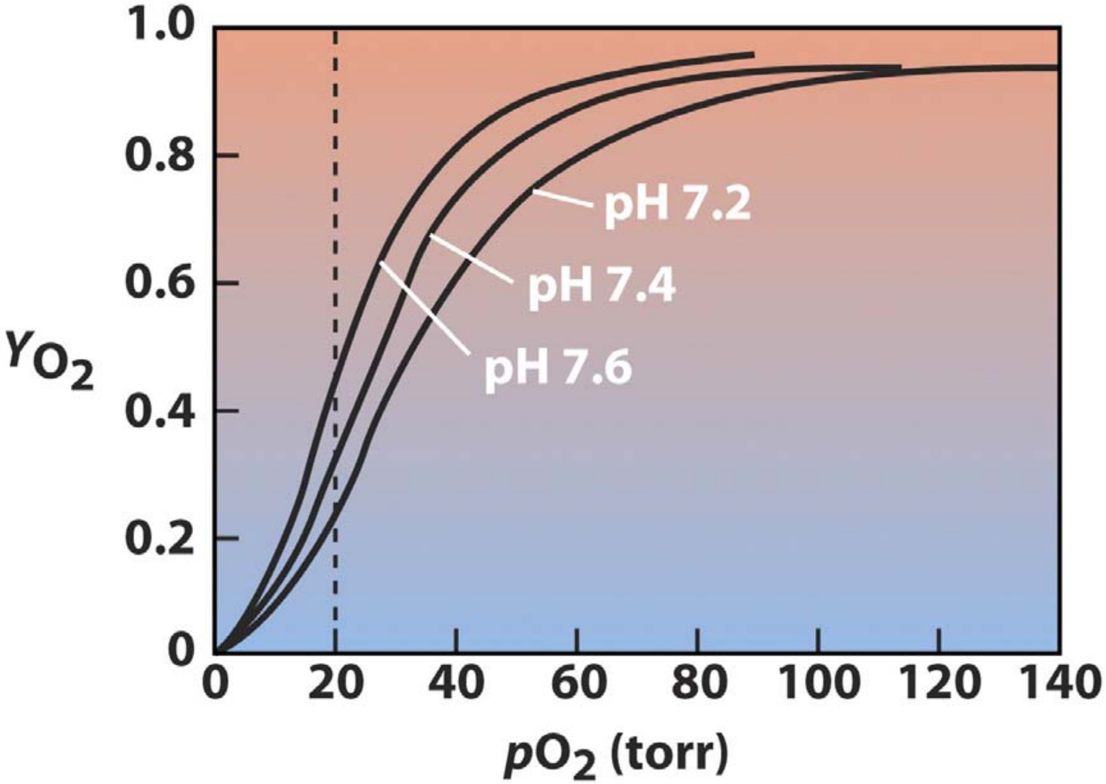


Figure 7-12 Fundamentals of Biochemistry, 2/e

The roles of hemoglobin and myoglobin in transporting O2 from the lungs to respiring tissues and CO2 (as HCO_3^-) from the tissues to the lungs

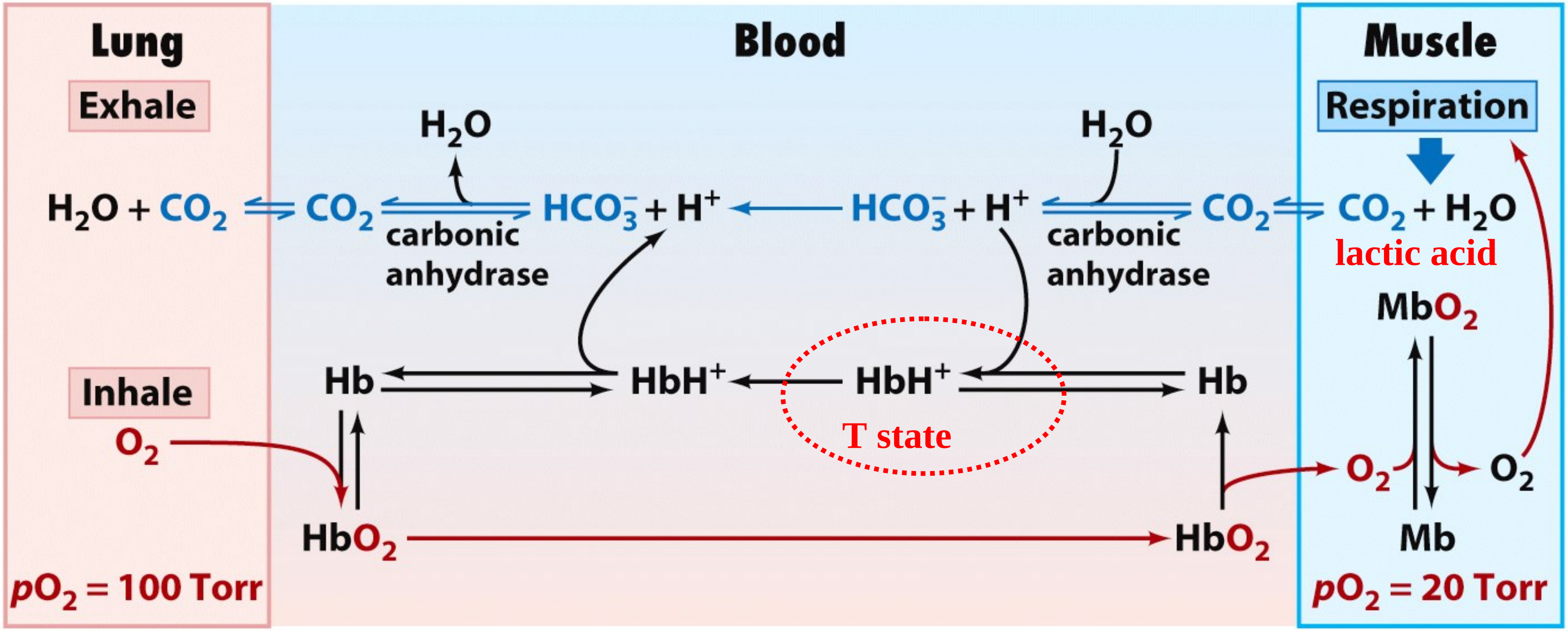


Figure 7-13 Fundamentals of Biochemistry, 2/e