Chapter 2-II:

Glucose Catabolism

Control of glycolysis

Different tissues control glycolysis in different ways

3 kinase reactions: large negative free E changes

HK

PFK

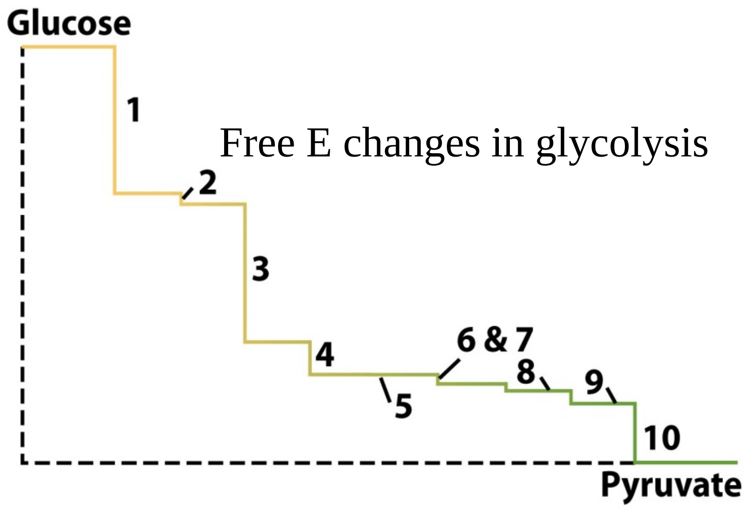
PK

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 regulatory 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]= ~10 & [ATP]/[AMP]= ~50,

meaning greater fluctuation in [ADP] & [AMP]

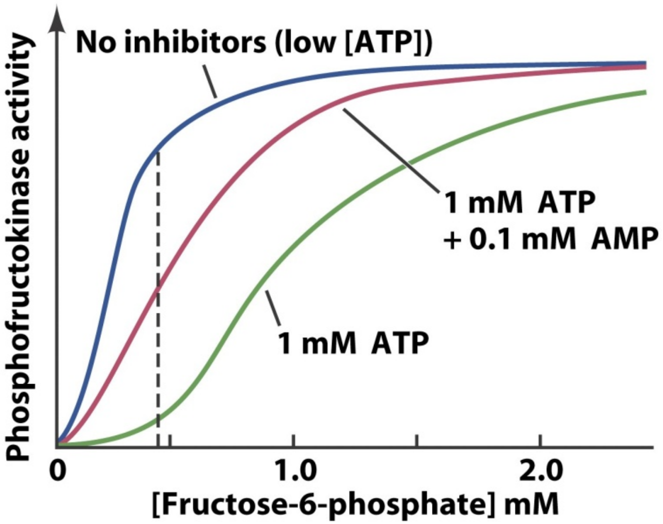


Figure 14-23 Fundamentals of Biochemistry, 2/e

Allosteric changes (T, blue)

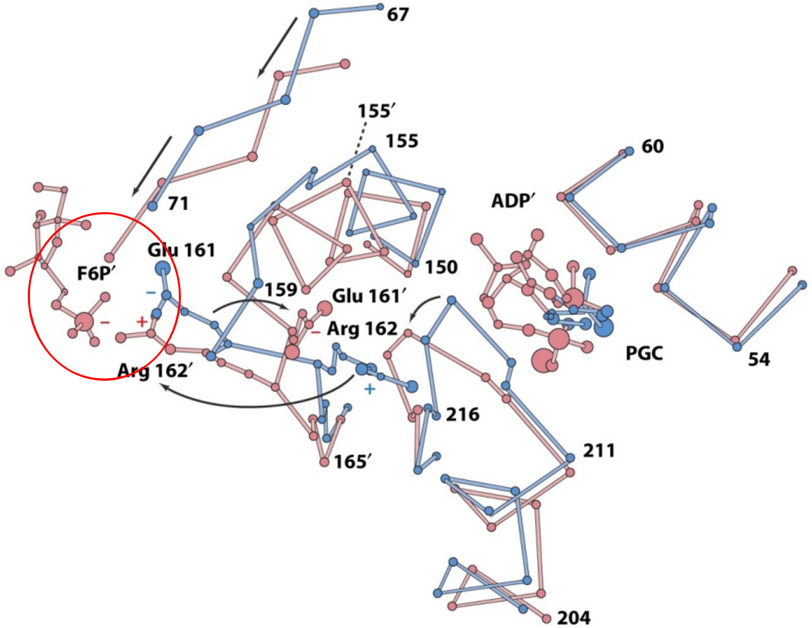


Figure 14-24 Fundamentals of Biochemistry, 2/e

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)

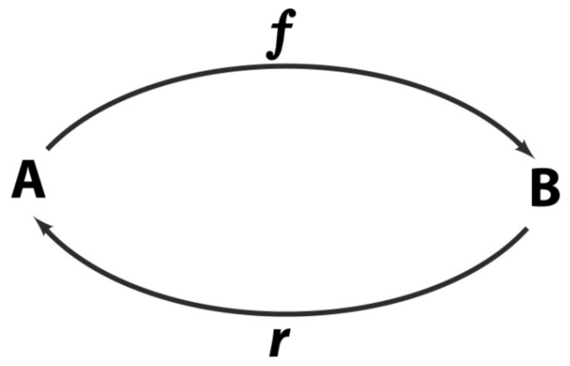
dose not increase the maximum flux, but decrease the minimum flux

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

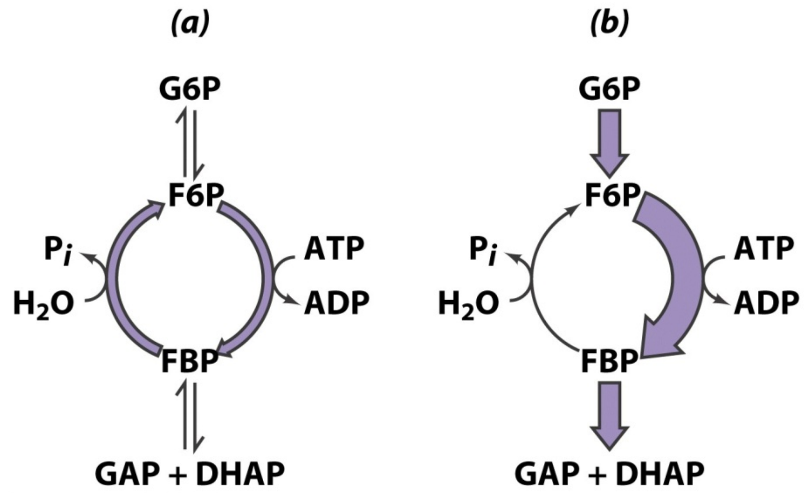
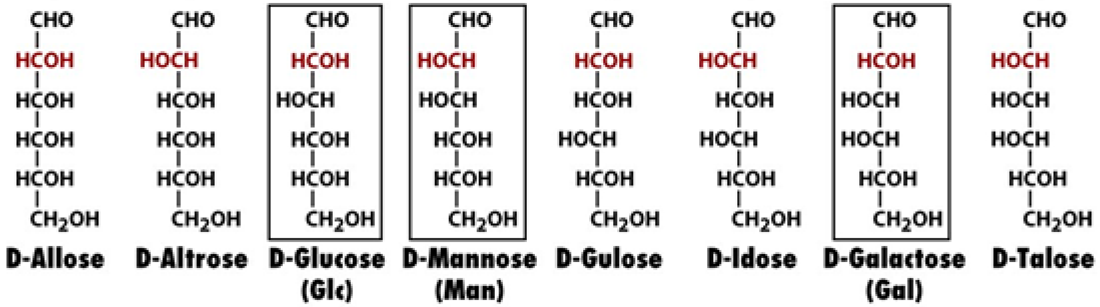


Figure 14-25 Fundamentals of Biochemistry, 2/e

Metabolism of hexoses other than glucose
Fructose, galactose, mannose



Entry into glycolysis

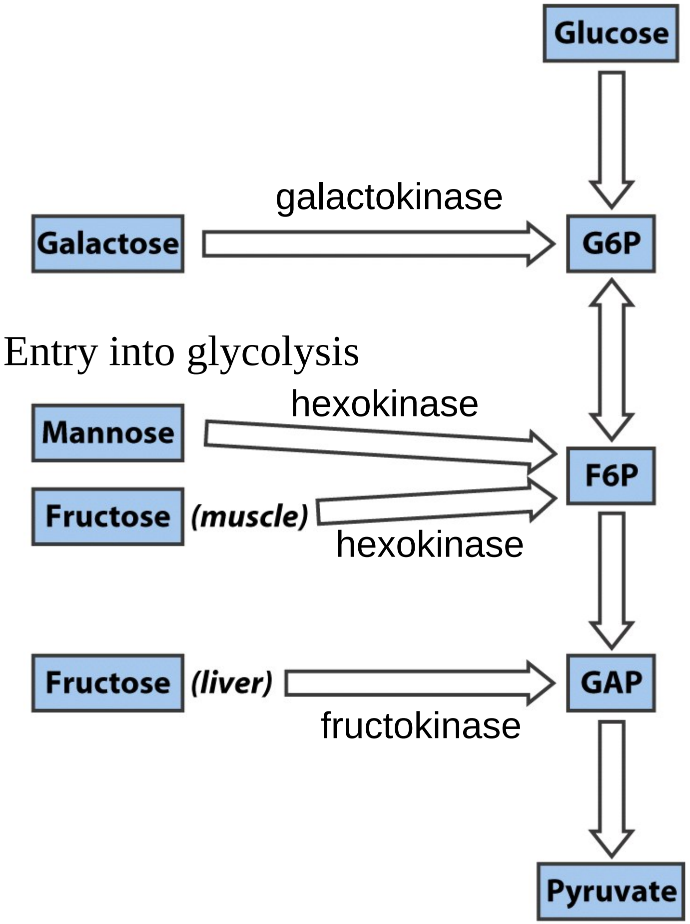


Figure 14-26 Fundamentals of Biochemistry, 2/e

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

Aldolase A: muscle
Aldolase B: liver
Aldolase C: brain
A&C prefer FBP, while B both

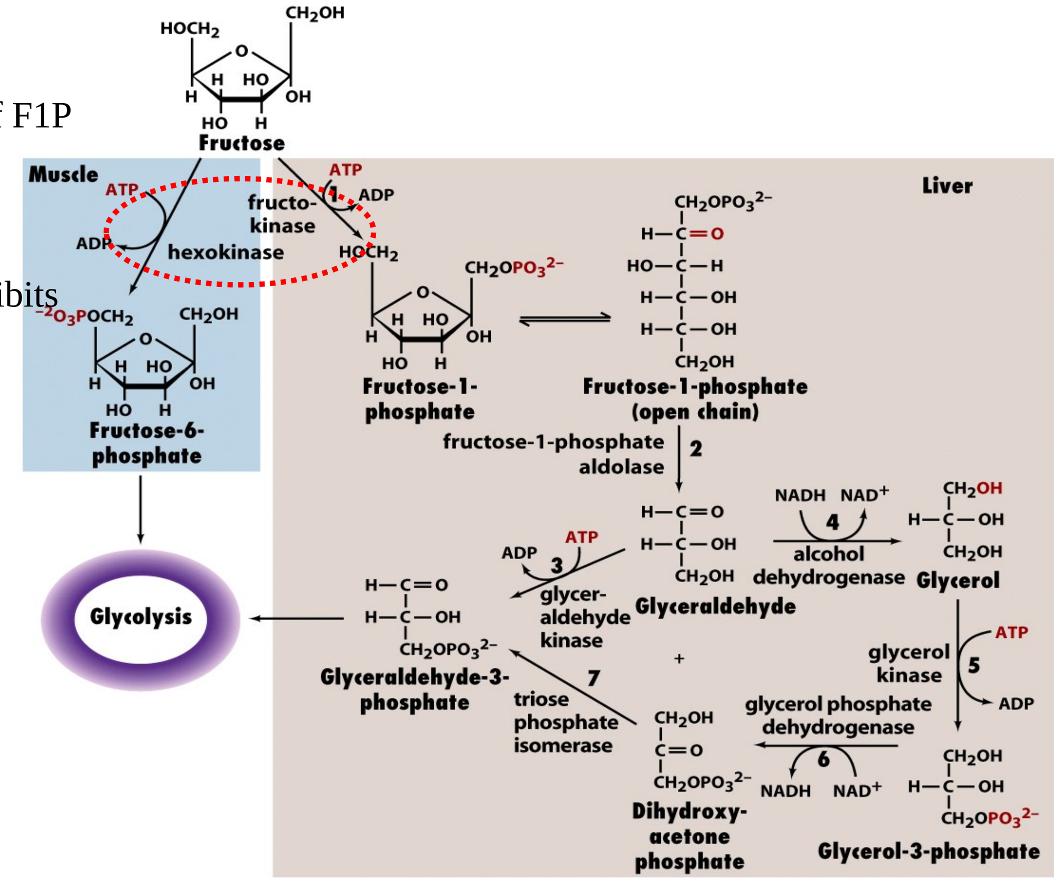
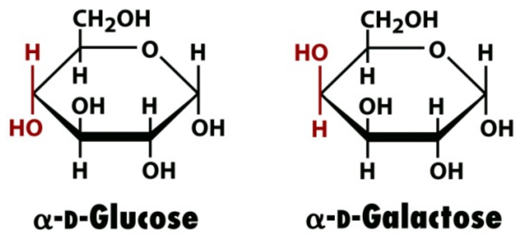


Figure 14-27 Fundamentals of Biochemistry, 2/e

Galactose

Lactose hydrolysis
Epimerization to glucose
Galactosemia: mostly deficiency in G1PUT
High galctose in blood: reduction to galactitol
- cataract
- mental retardation
- liver damage



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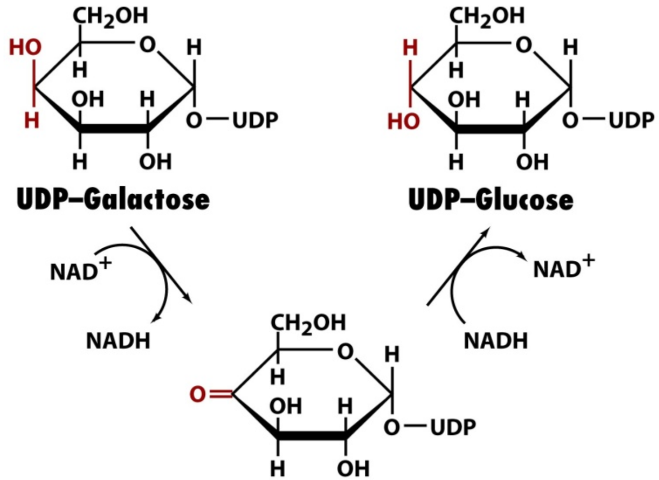

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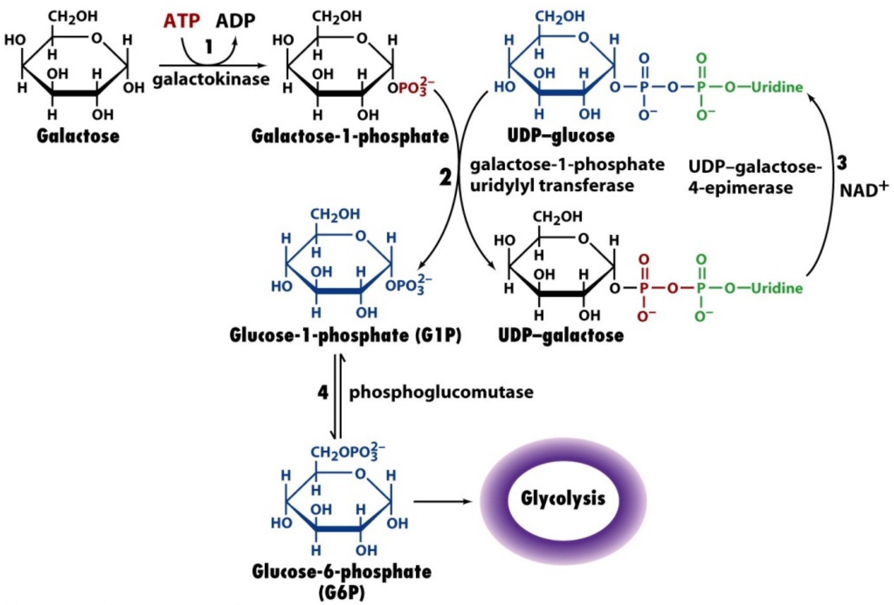
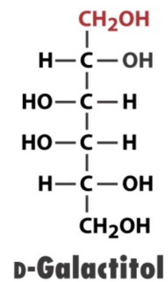


Figure 14-28 Fundamentals of Biochemistry, 2/e



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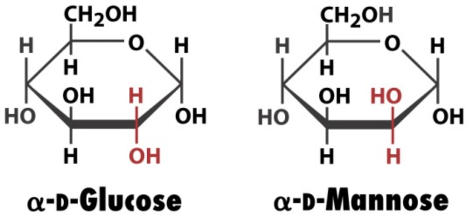
Mannose



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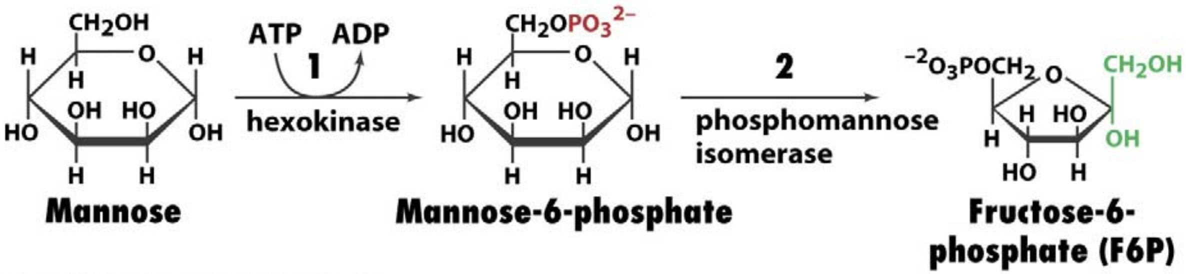
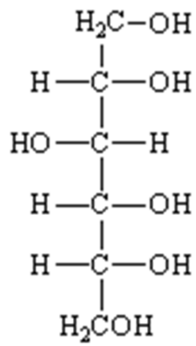


Figure 14-29 Fundamentals of Biochemistry, 2/e

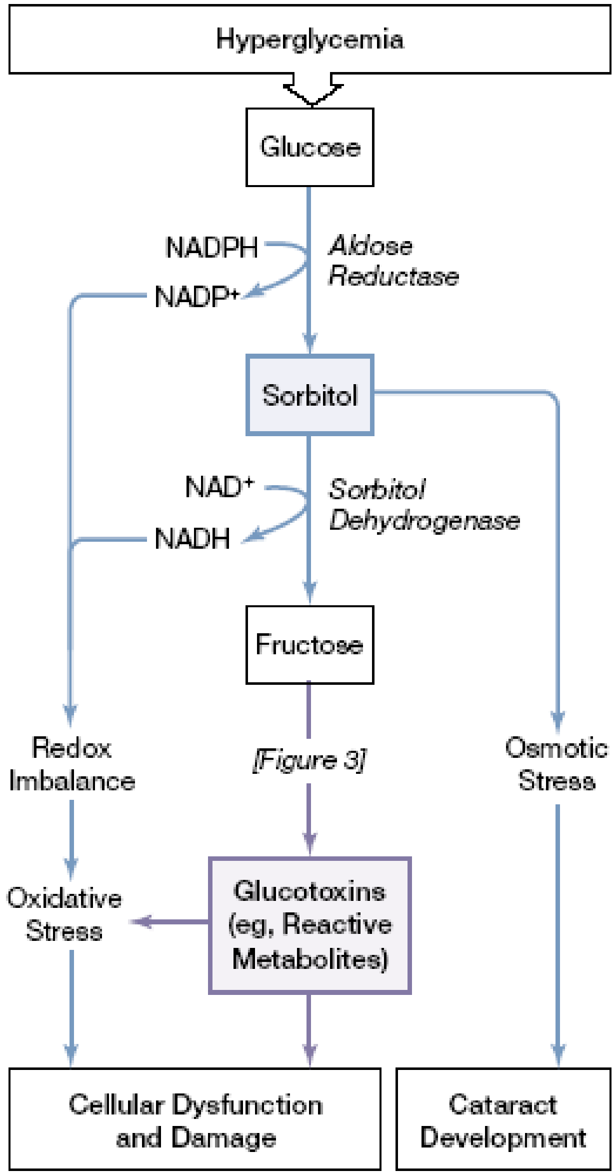
Glucose in diabetes

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

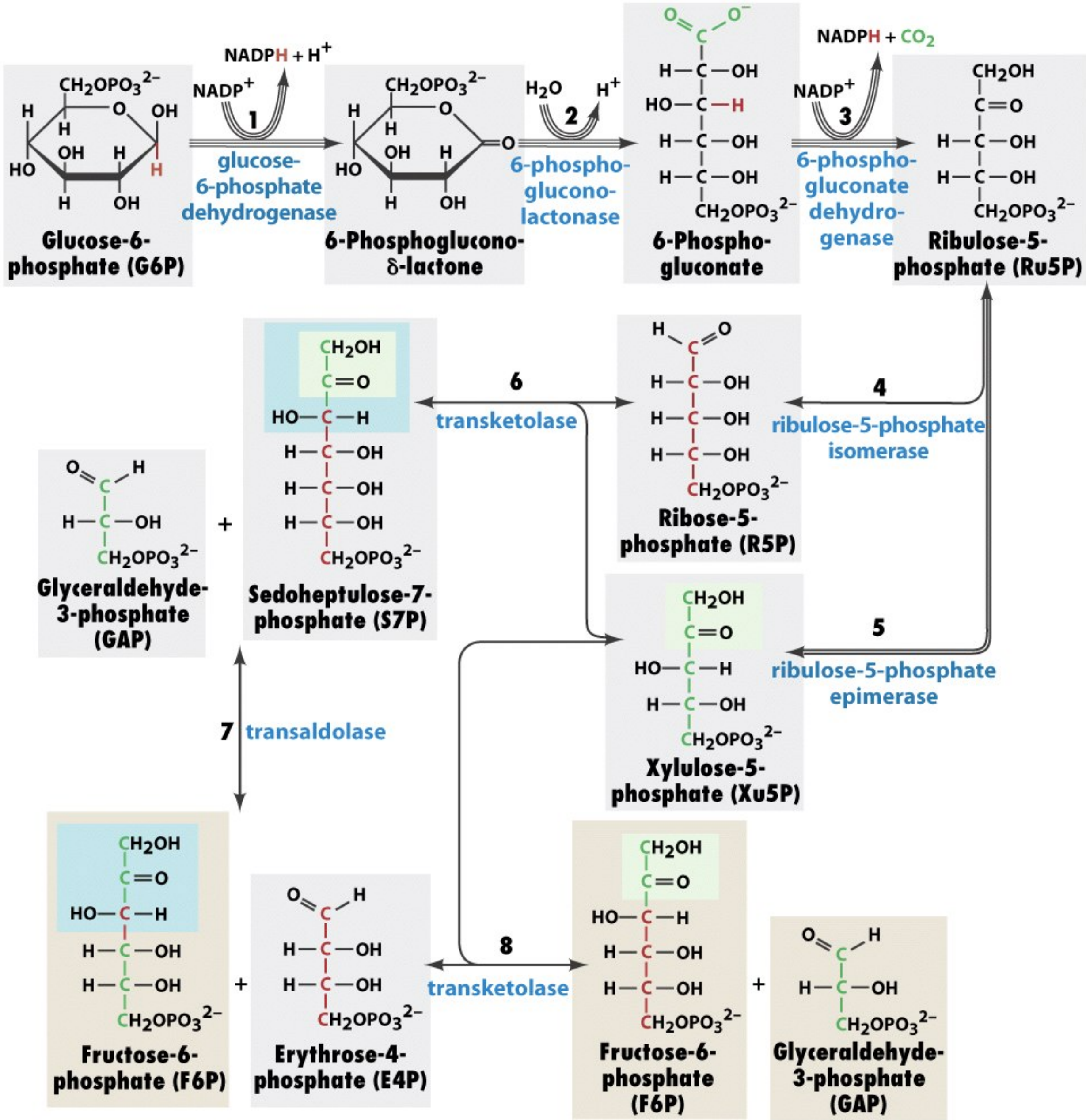
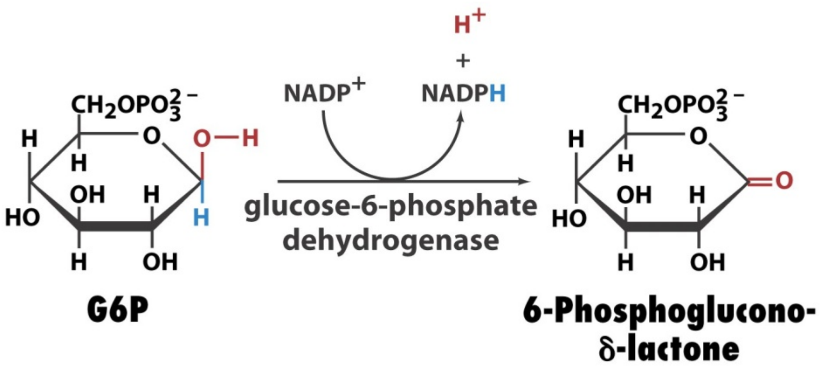


Figure 14-30 Fundamentals of Biochemistry, 2/e



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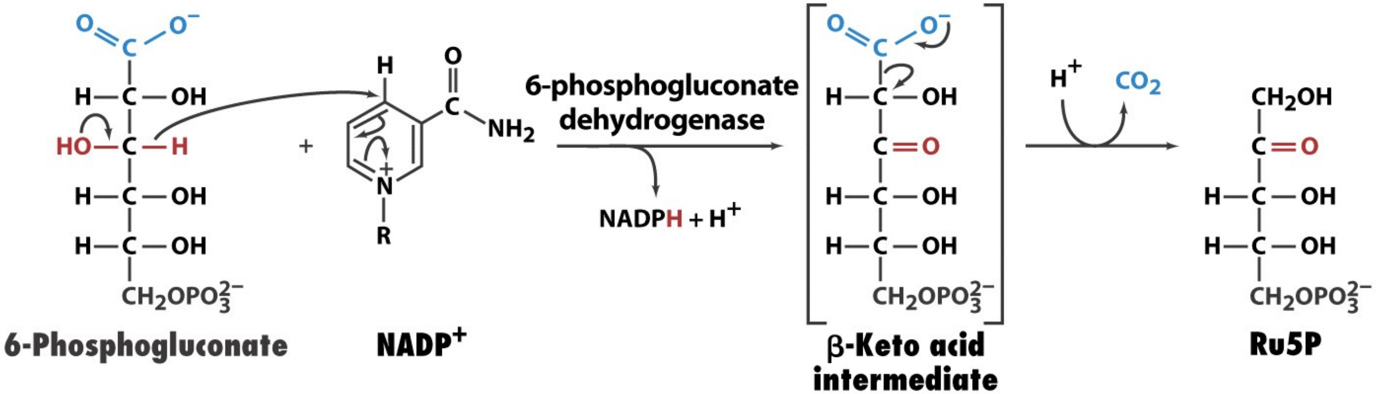


Figure 14-31 Fundamentals of Biochemistry, 2/e

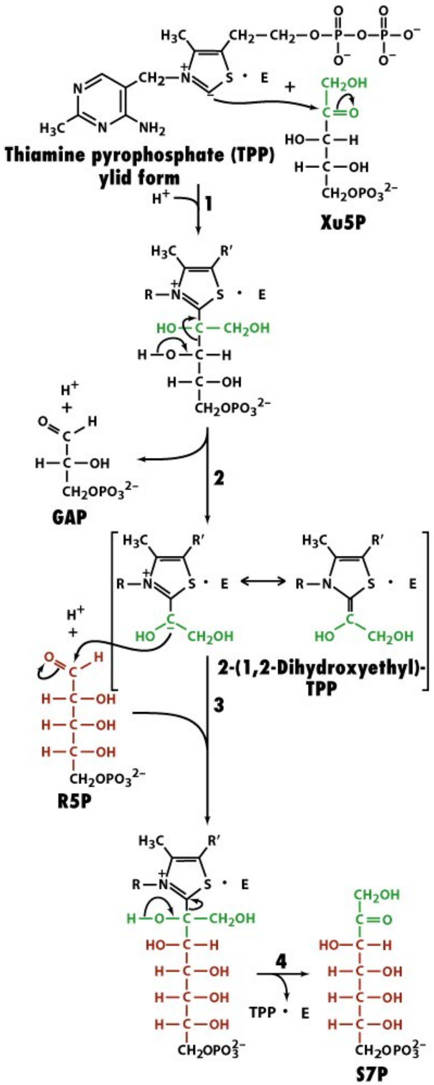


Figure 14-32 Fundamentals of Biochemistry, 2/e

Transketolase: transfer of C2 units

Transaldolase: transfer of C3 units

$$(6)\quad C_5 + C_5 \rightleftharpoons C_7 + C_3$$

$$(7)\quad C_7 + C_3 \rightleftharpoons C_6 + C_4$$

$$(8)\quad C_5 + C_4 \rightleftharpoons C_6 + C_3$$

$$(\text{Sum})\quad 3\,C_5 \rightleftharpoons 2\,C_6 + C_3$$

Figure 14-34 Fundamentals of Biochemistry, 2/e

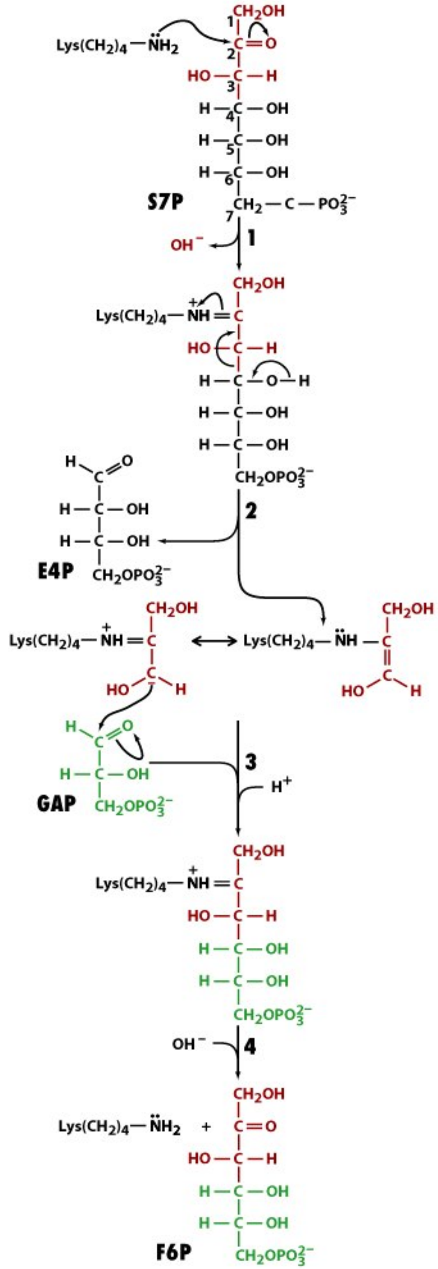


Figure 14-33 Fundamentals of Bioch

Control of pentose phosphate pathway

Depends on the requirements of ATP, NADPH, R5P

G6P dehydrogenase: the first committed step
regulation by [NADP+]: [NADPH]/[NADP]=100:1
enzyme synthesis control by hormone
enzyme deficiency

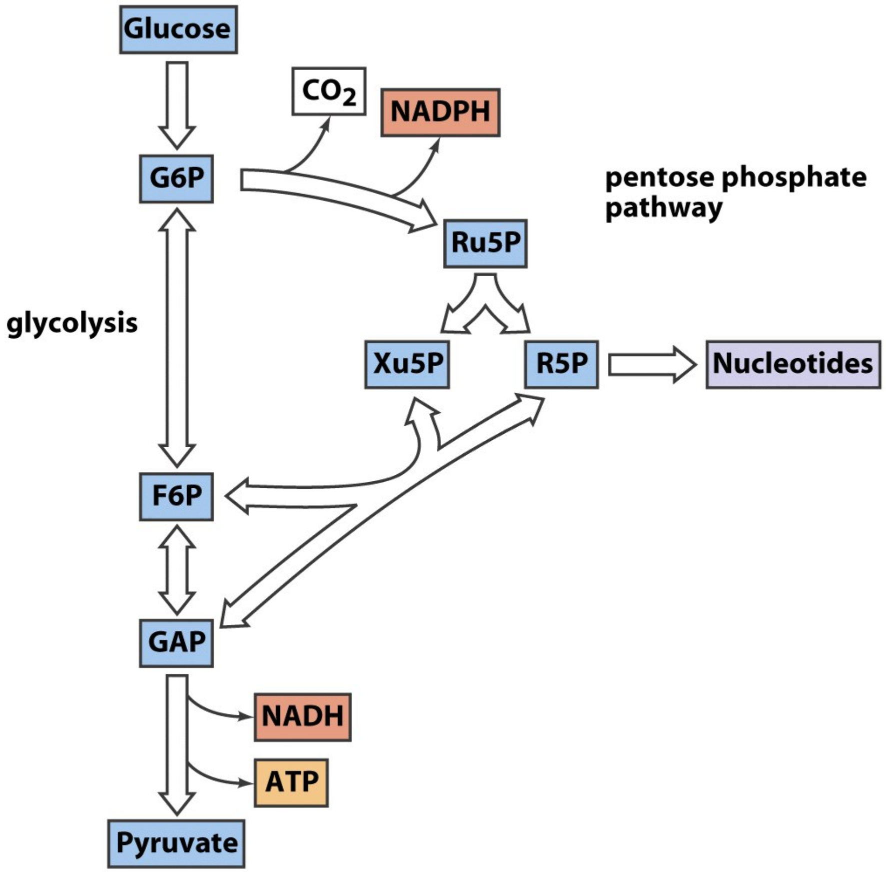


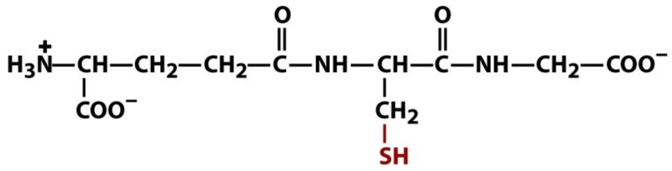
Figure 14-35 Fundamentals of Biochemistry, 2/e

G6PD deficiency

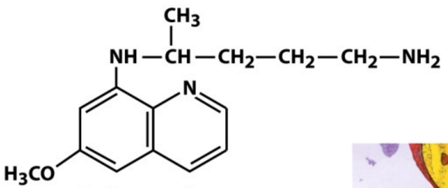
Common in African, Asian, Mediterranean
Deficiency of NADPH (for biosynthesis & ROS elimination)
In erythrocytes
    glutathione (GSH) regeneration

Hemolytic anemia when ingest drugs (such as antimalarial drug primaquine) or eat fava beans
    increased 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