Metabolism of carbohydrates

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PÉCS

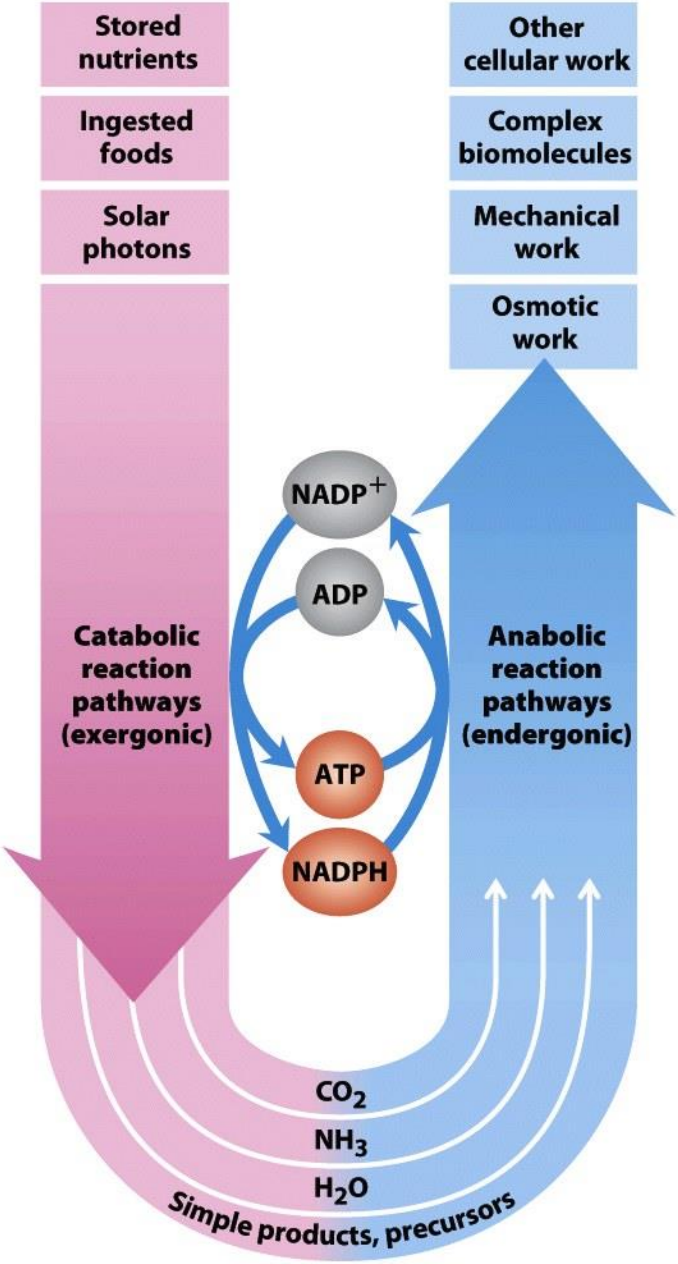


Figure 1-28
Lehninger Principles of Biochemistry, Fifth Edition

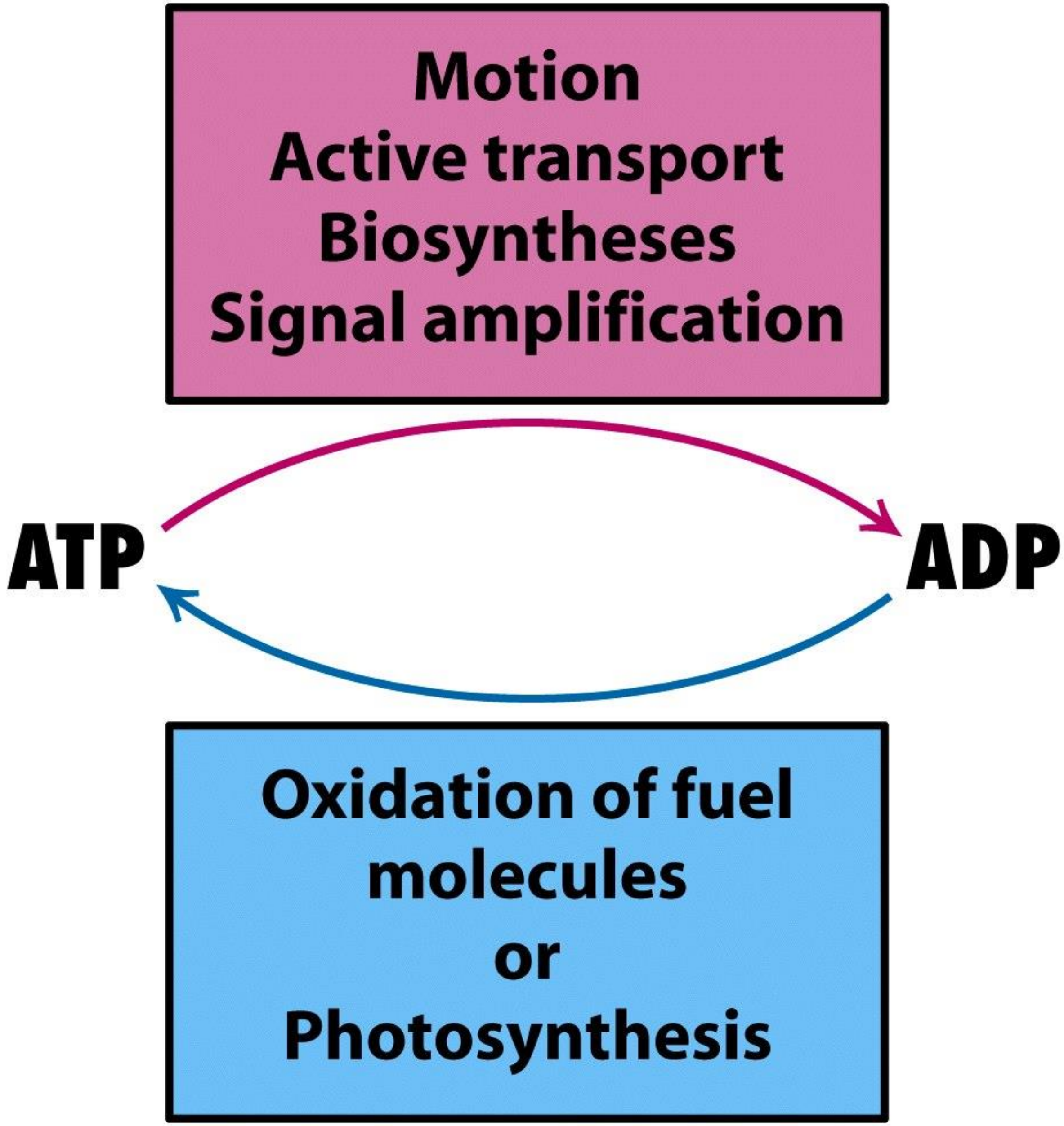
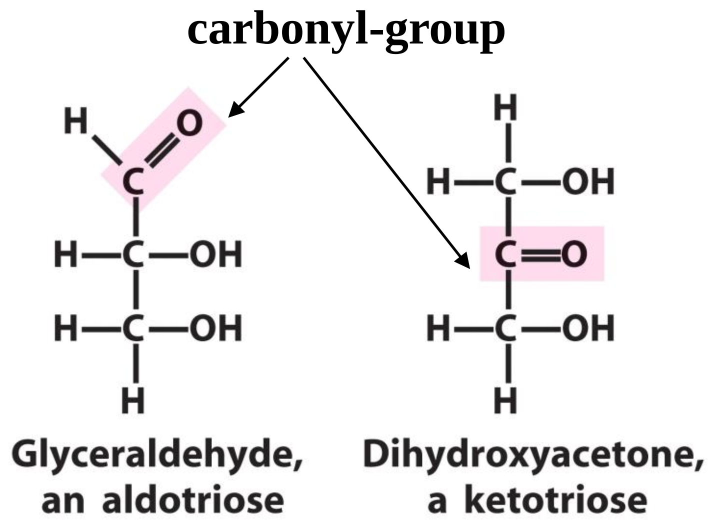
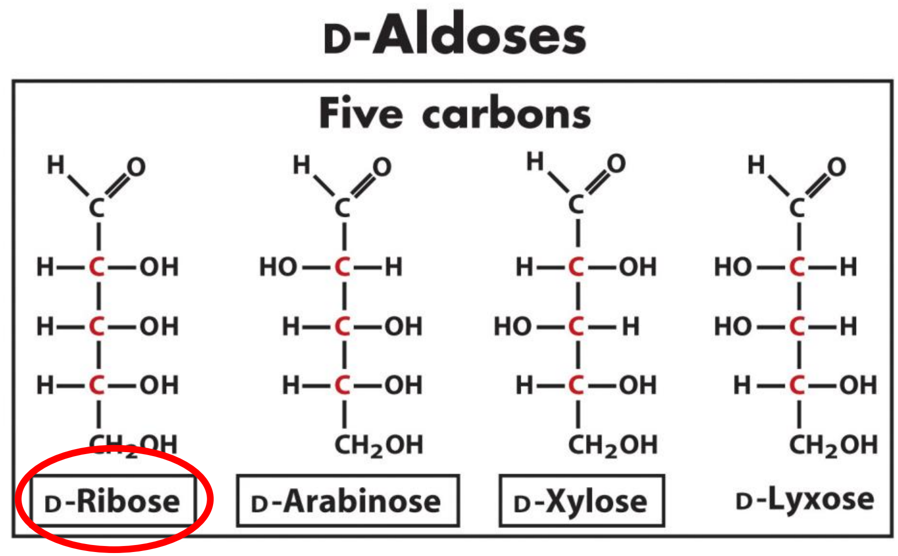


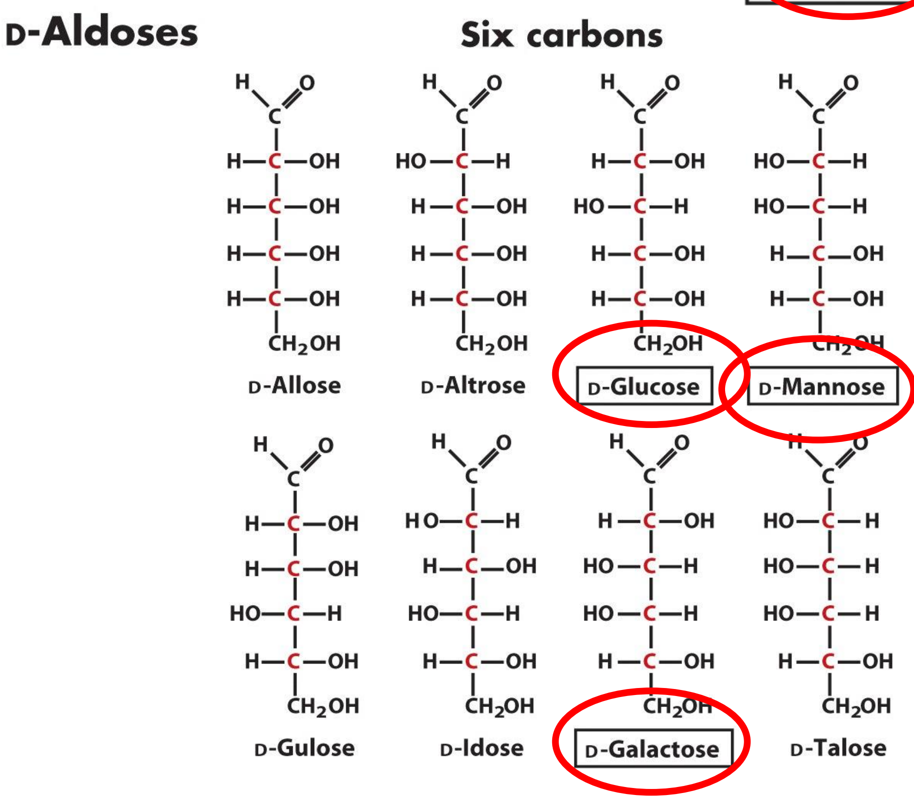
Figure 15-8
Biochemistry, Sixth Edition



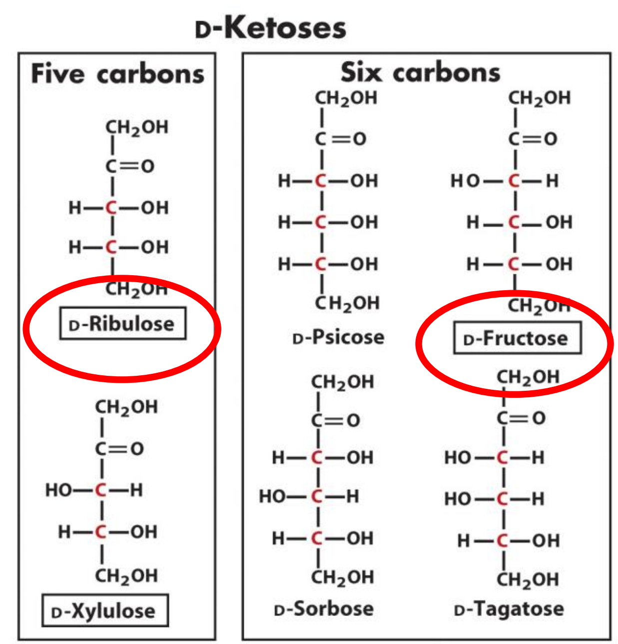
carbonyl-group
Glyceraldehyde, an aldotriose
Dihydroxyacetone, a ketotriose



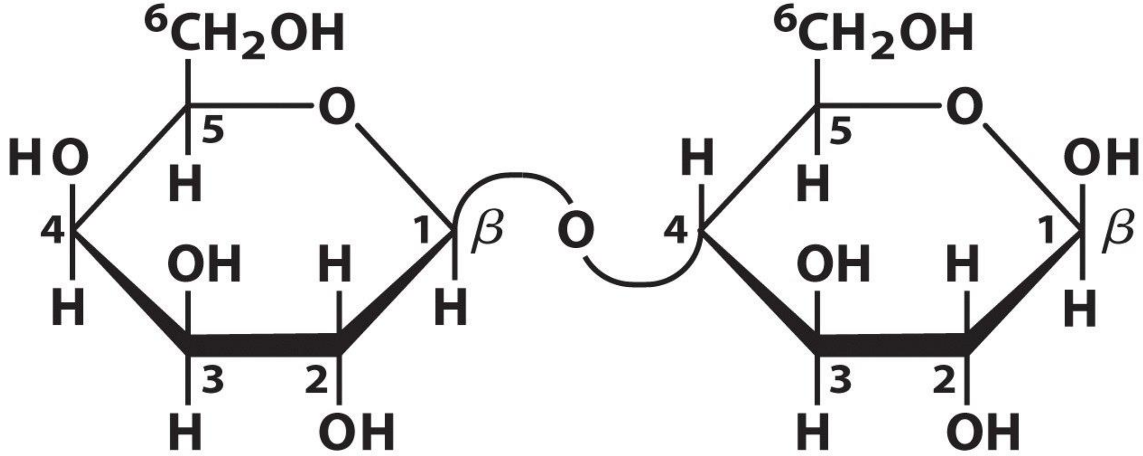
D-Aldoses
Five carbons
D-Ribose
D-Arabinose
D-Xylose
D-Lyxose



D-Aldoses
Six carbons
D-Allose
D-Altrose
D-Glucose
D-Mannose
D-Gulose
D-Idose
D-Galactose
D-Talose



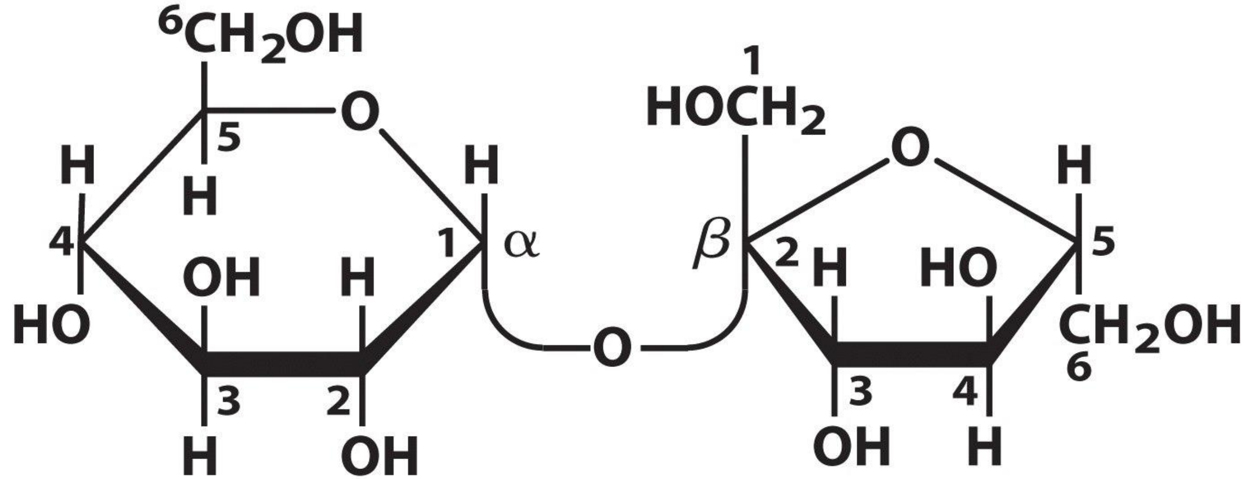
D-Ketoses
Five carbons
D-Ribulose
D-Xylulose
Six carbons
D-Psicose
D-Fructose
D-Sorbose
D-Tagatose



Lactose (*β* form)

β-D-galactopyranosyl-(1→4)-β-D-glucopyranose

Gal(β1→4)Glc



Sucrose

α-D-glucopyranosyl β-D-fructofuranoside

Glc(α1↔2β)Fru

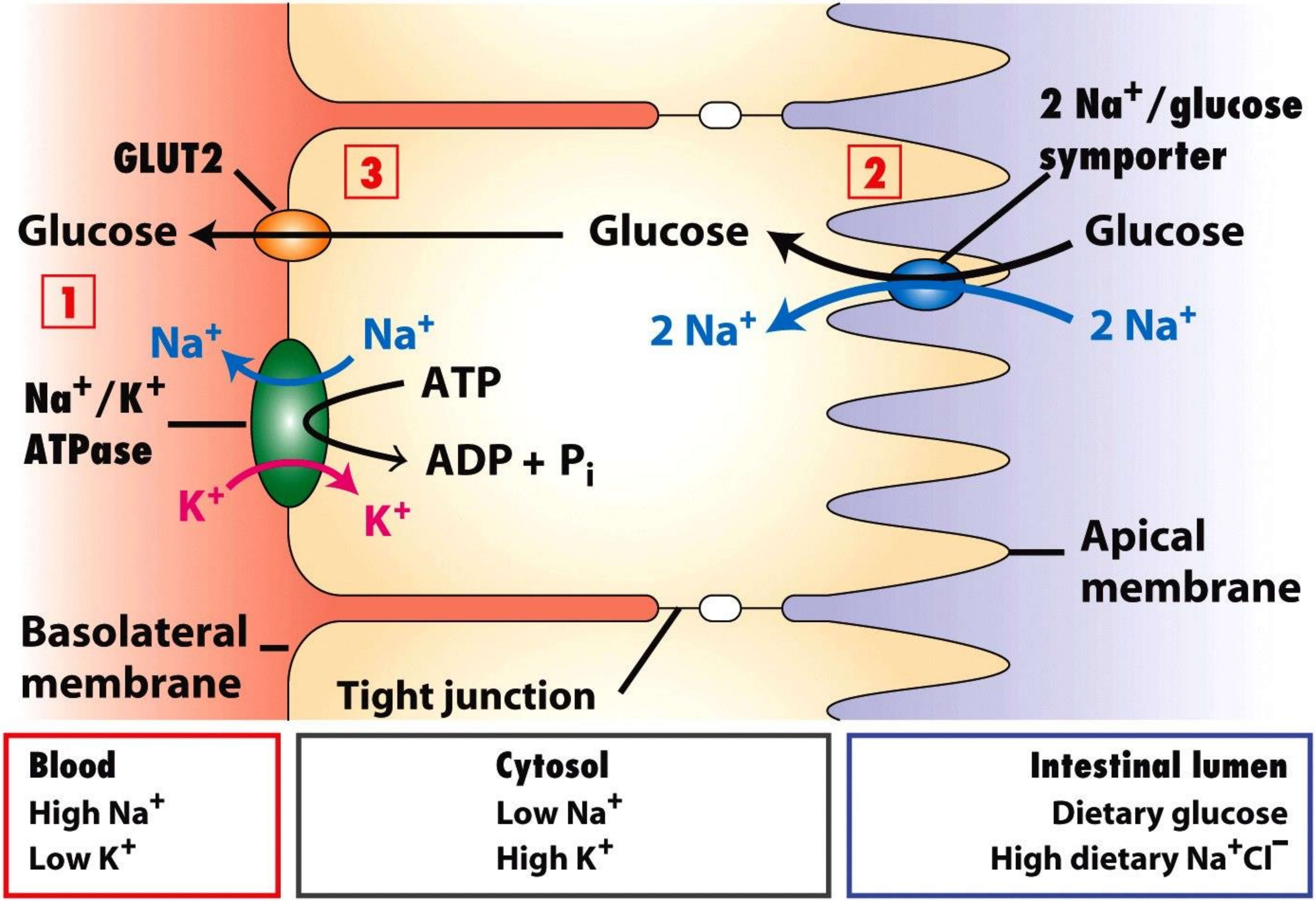


Figure 11-29
Molecular Cell Biology, Sixth Edition

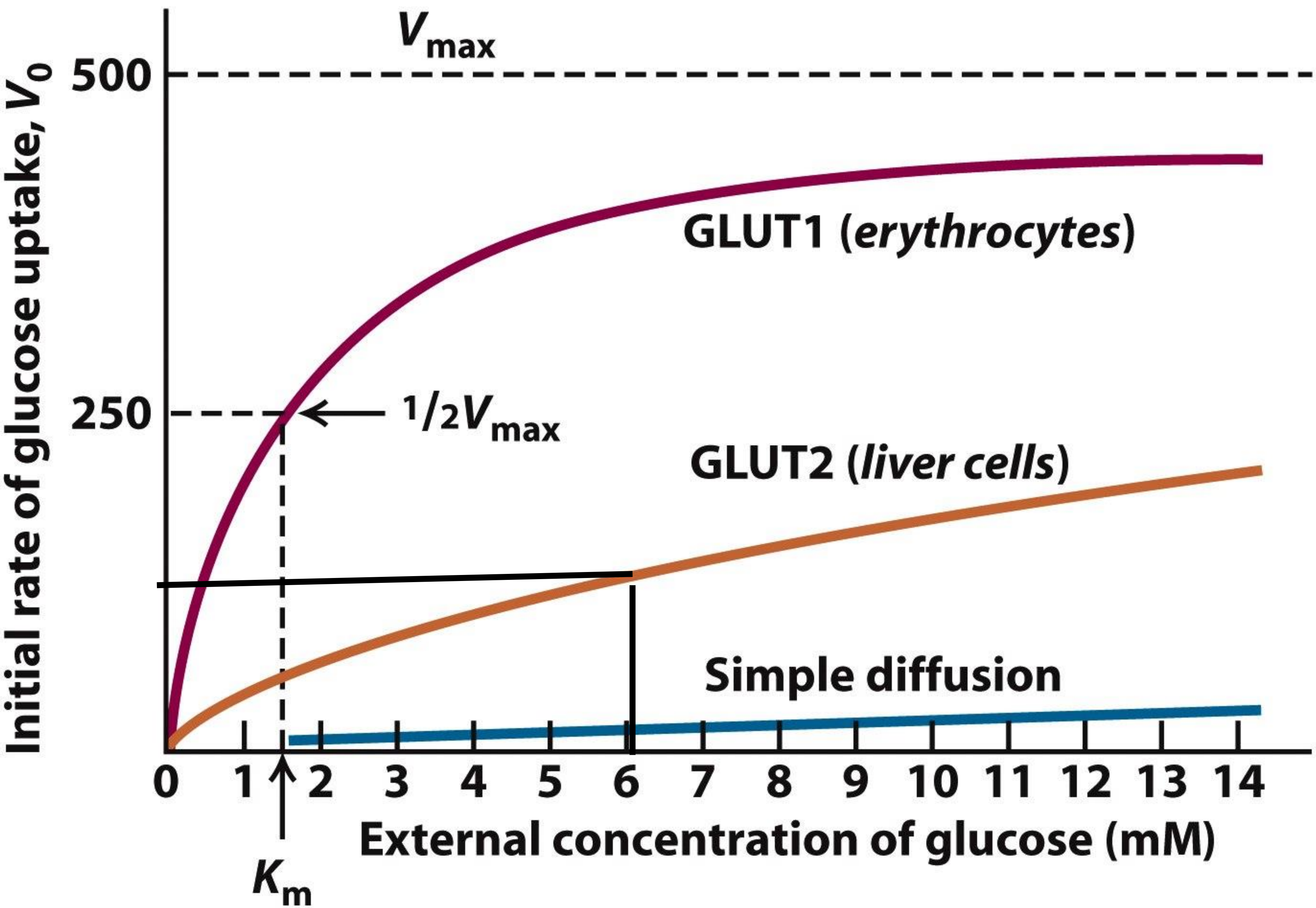


Figure 11-4
Molecular Cell Biology, Sixth Edition

GLUCOSE TRANSPORT

INSULIN INDEPENDENT

GLUT 1

GLUT 2

GLUT 3

TABLE 11–4 Glucose Transporters in the Human Genome

Transporter	*Tissue(s) where expressed*	*Gene*	*Role**
GLUT1	Ubiquitous	*SLC2A1*	Basal glucose uptake
GLUT2	Liver, pancreatic islets, intestine	*SLC2A2*	In liver, removal of excess glucose from blood; in pancreas, regulation of insulin release
GLUT3	Brain (neuronal)	*SLC2A3*	Basal glucose uptake
GLUT4	Muscle, fat, heart	*SLC2A4*	Activity increased by insulin
GLUT5	Intestine, testis, kidney, sperm	*SLC2A5*	Primarily fructose transport
GLUT6	Spleen, leukocytes, brain	*SLC2A6*	Possibly no transporter function
GLUT7	Liver microsomes	*SLC2A7*	—
GLUT8	Testis, blastocyst, brain	*SLC2A8*	—
GLUT9	Liver, kidney	*SLC2A9*	—
GLUT10	Liver, pancreas	*SLC2A10*	—
GLUT11	Heart, skeletal muscle	*SLC2A11*	—
GLUT12	Skeletal muscle, adipose, small intestine	*SLC2A12*	—

*Dash indicates role uncertain.

INSULIN DEPENDENT

GLUT 4 (MUSCLE, ADIPOSE)

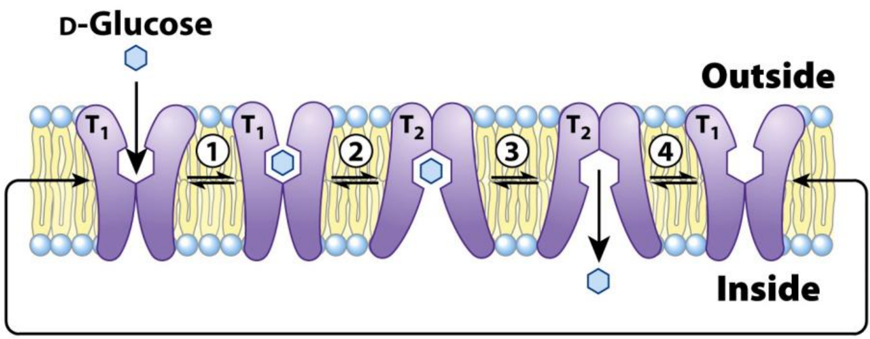


Figure 11-31
Lehninger Principles of Biochemistry, Fifth Edition

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 the 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 mem-
brane			
			increases with endurance training
GLUT5	Small intestine	—	Primarily a fructose transporter

Table 16-4
Biochemistry, Sixth Edition

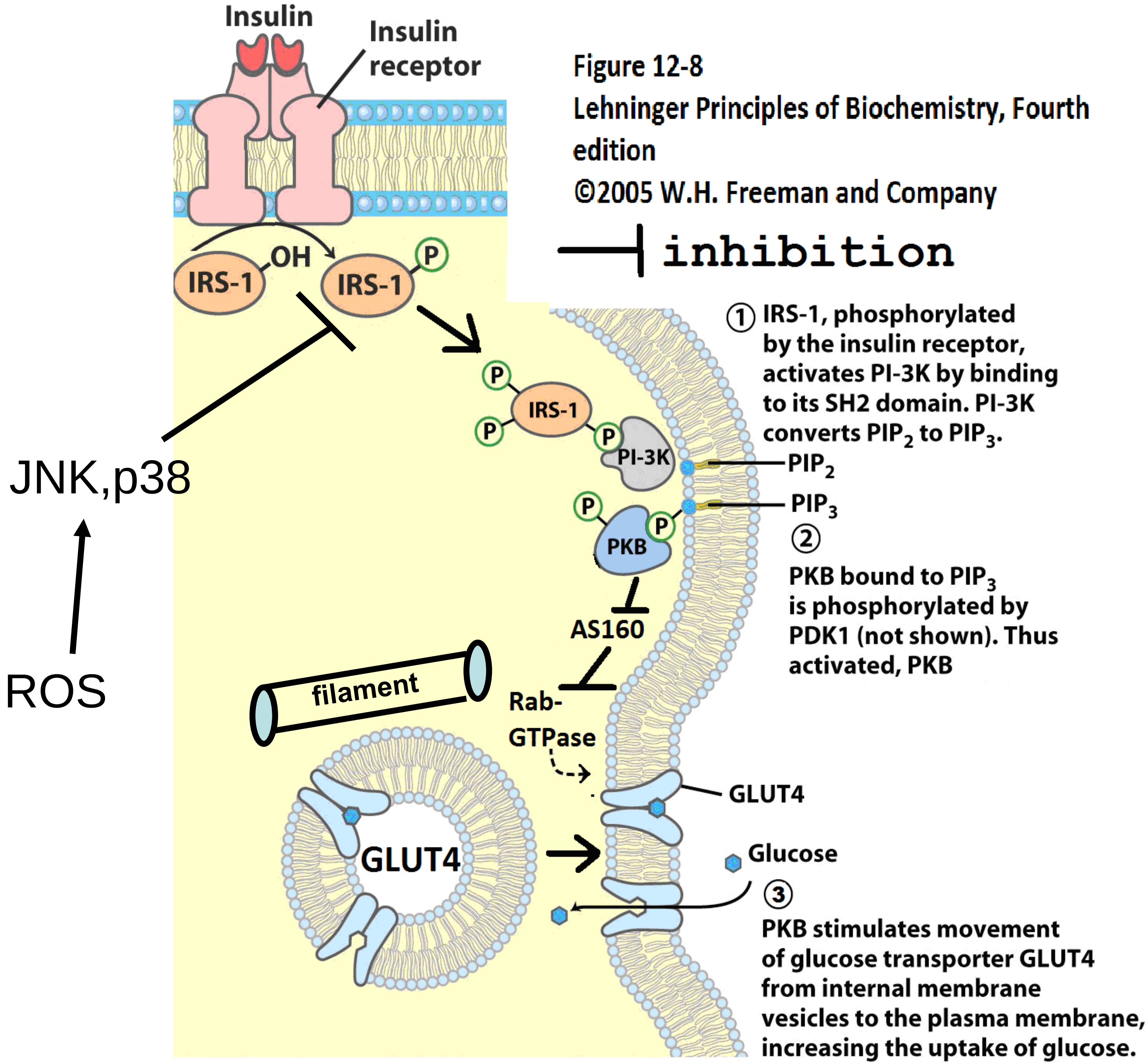
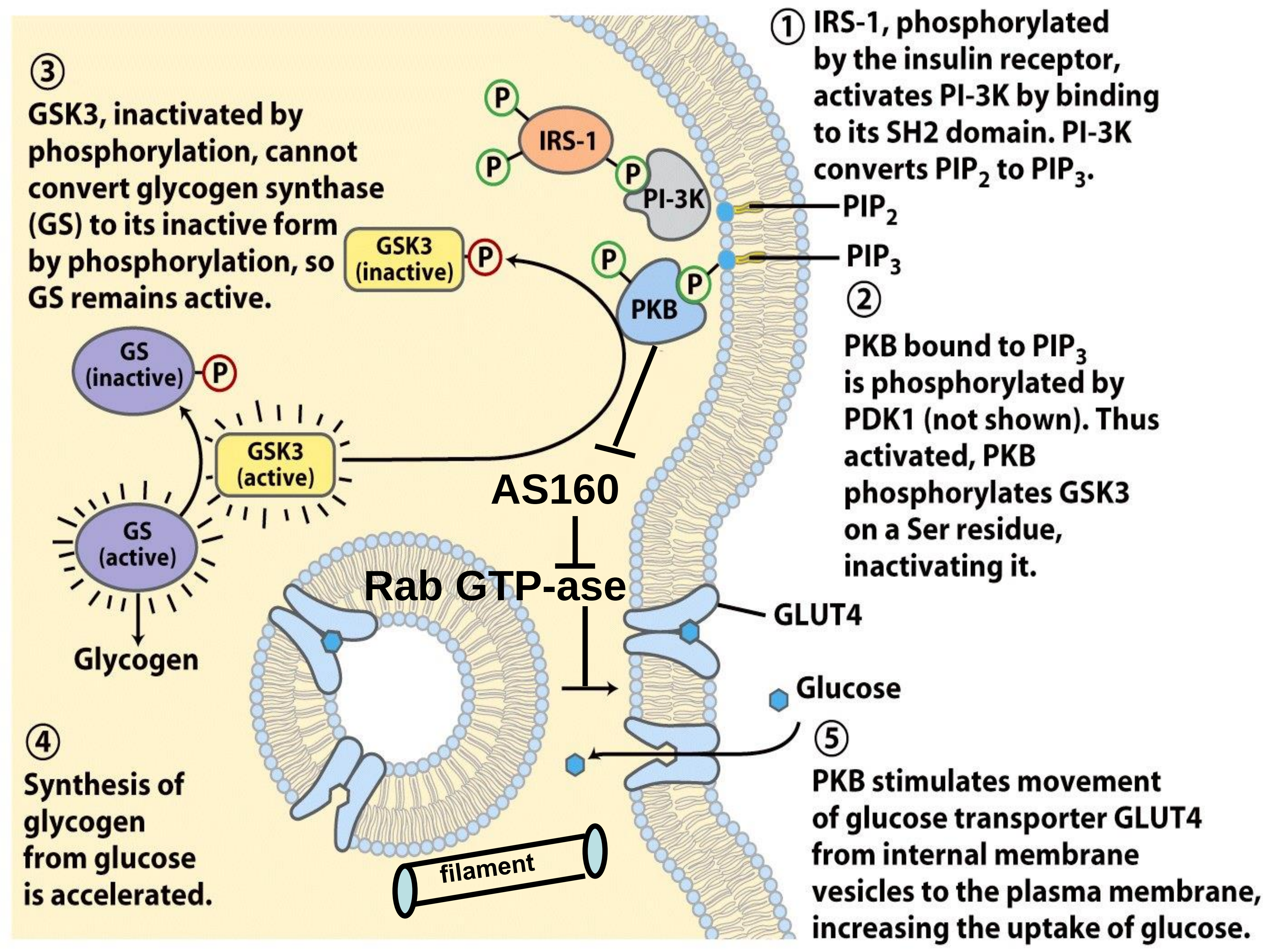


Figure 12-8
Lehninger Principles of Biochemistry, Fourth edition



① IRS-1, phosphorylated by the insulin receptor, activates PI-3K by binding to its SH2 domain. PI-3K converts PIP_2 to PIP_3.
P
IRS-1
P
P
PI-3K
PIP_2
PIP_3
② PKB bound to PIP_3 is phosphorylated by PDK1 (not shown). Thus activated, PKB phosphorylates GSK3 on a Ser residue, inactivating it.
P
PKB
P
③ GSK3, inactivated by phosphorylation, cannot convert glycogen synthase (GS) to its inactive form by phosphorylation, so GS remains active.
GSK3 (inactive)
P
GS (inactive)
P
GSK3 (active)
GS (active)
Glycogen
AS160
Rab GTP-ase
GLUT4
Glucose
④ Synthesis of glycogen from glucose is accelerated.
filament
⑤ PKB stimulates movement of glucose transporter GLUT4 from internal membrane vesicles to the plasma membrane, increasing the uptake of glucose.

Catabolism of proteins, fats, and carbohydrates in the three stages of cellular respiration

Stage 1: oxidation of fatty acids, glucose, and some amino acids yields acetyl-CoA.

Stage 2: oxidation of acetyl groups in the citric acid cycle includes four steps in which electrons are abstracted.

Stage 3: electrons carried by NADH+H^+ and $FADH_2$ are funneled into a chain of mitochondrialelectron carriers
the respiratory chain ultimately reducing O_2 to H_2O.This electron flow drives the production of ATP.

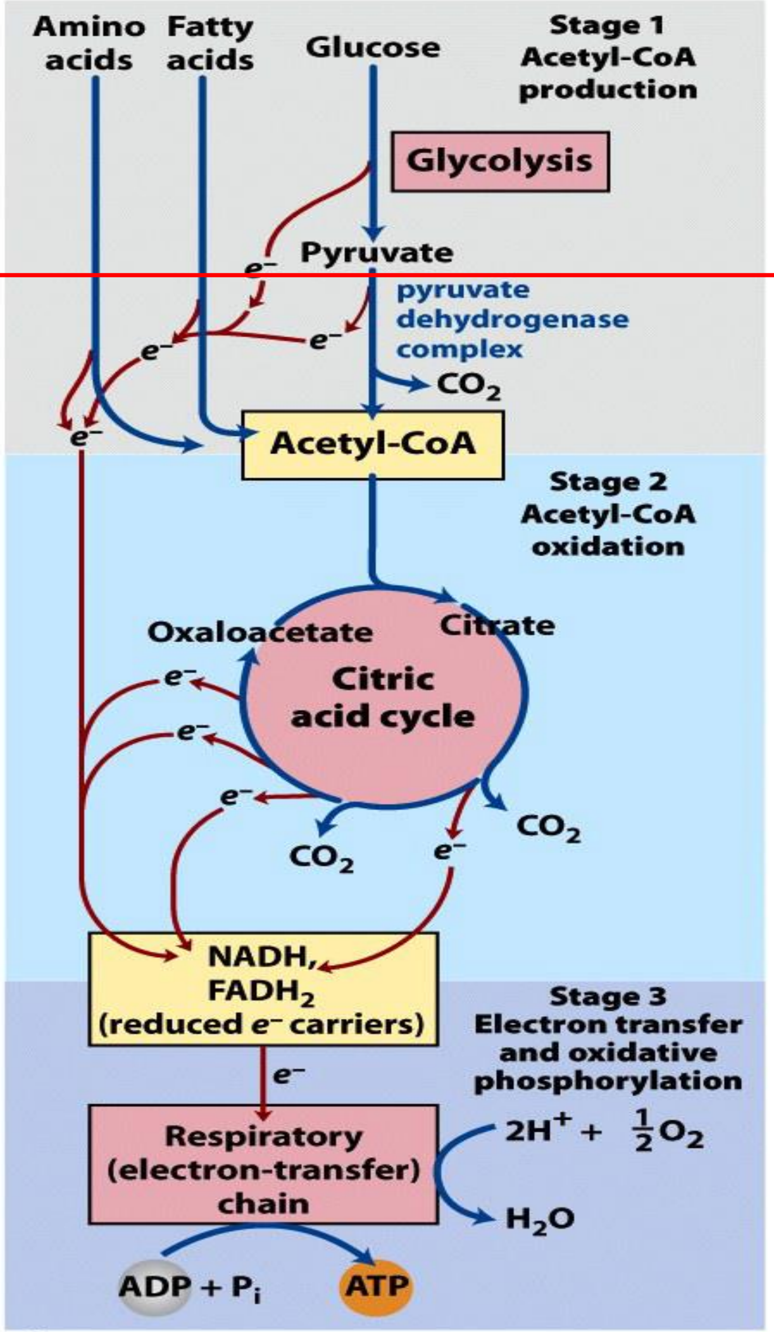


Figure 16-1
Lehninger Principles of Biochemistry, Fifth Edition

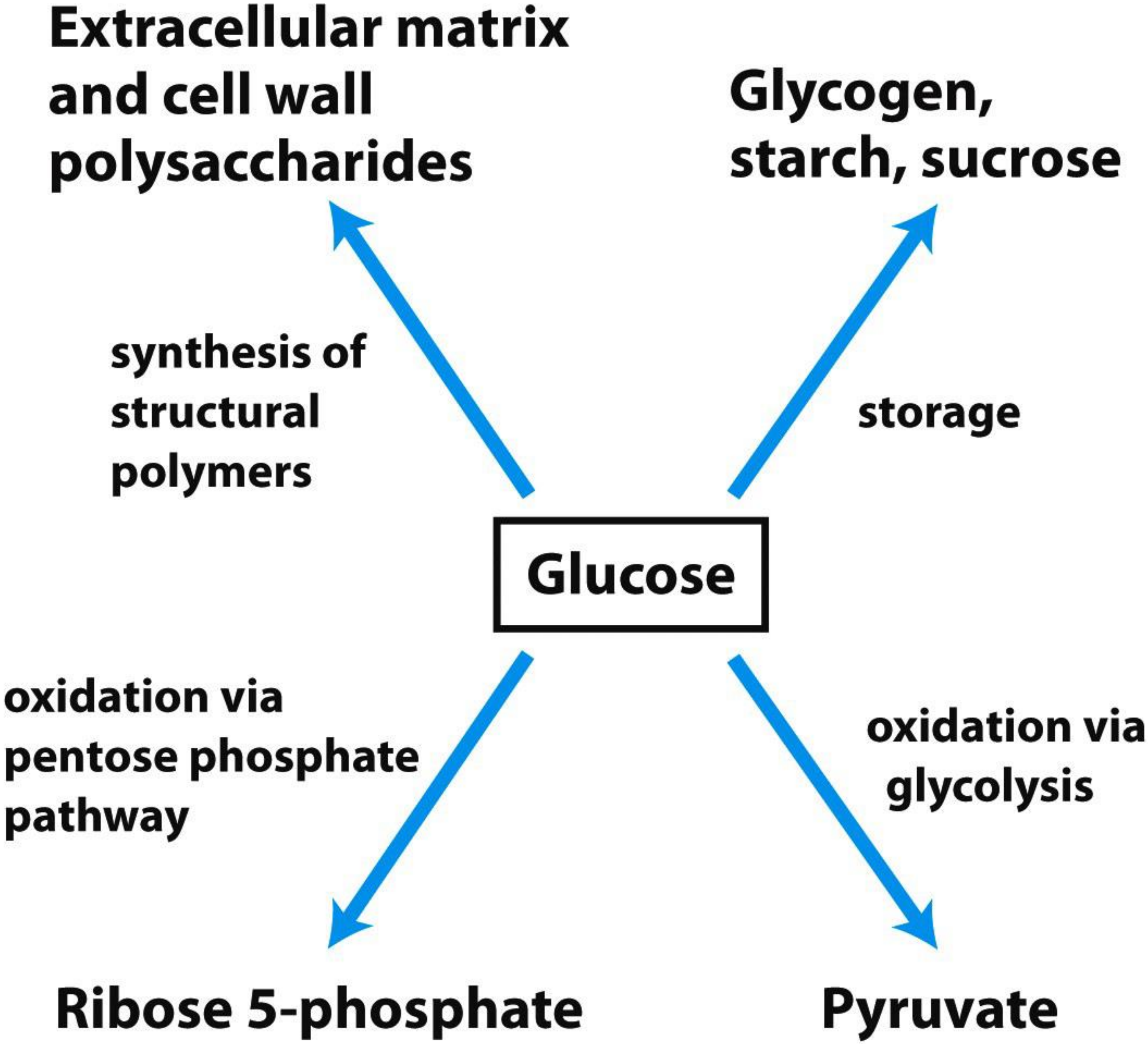


Figure 14-1
Lehninger Principles of Biochemistry, Fifth Edition

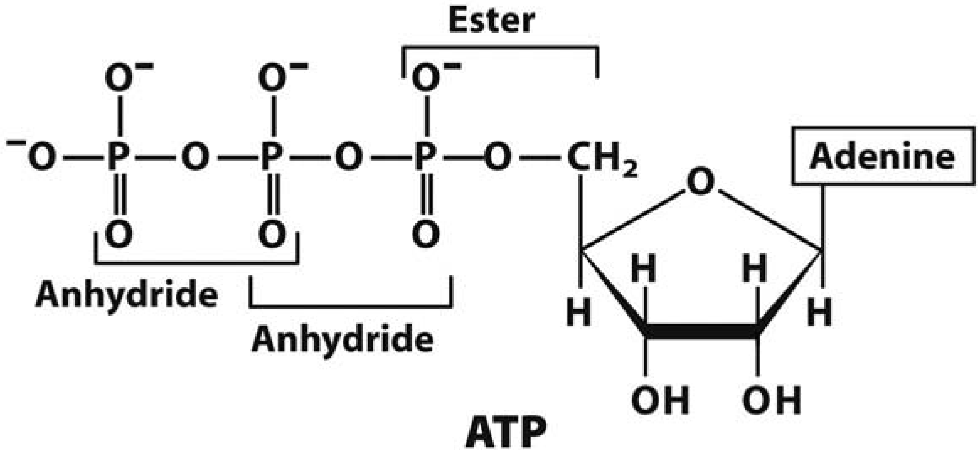
Glycolysis:

-Glycolysis is an almost universal central pathway of glucose catabolism, the pathway with the largest flux of carbon in most cells.

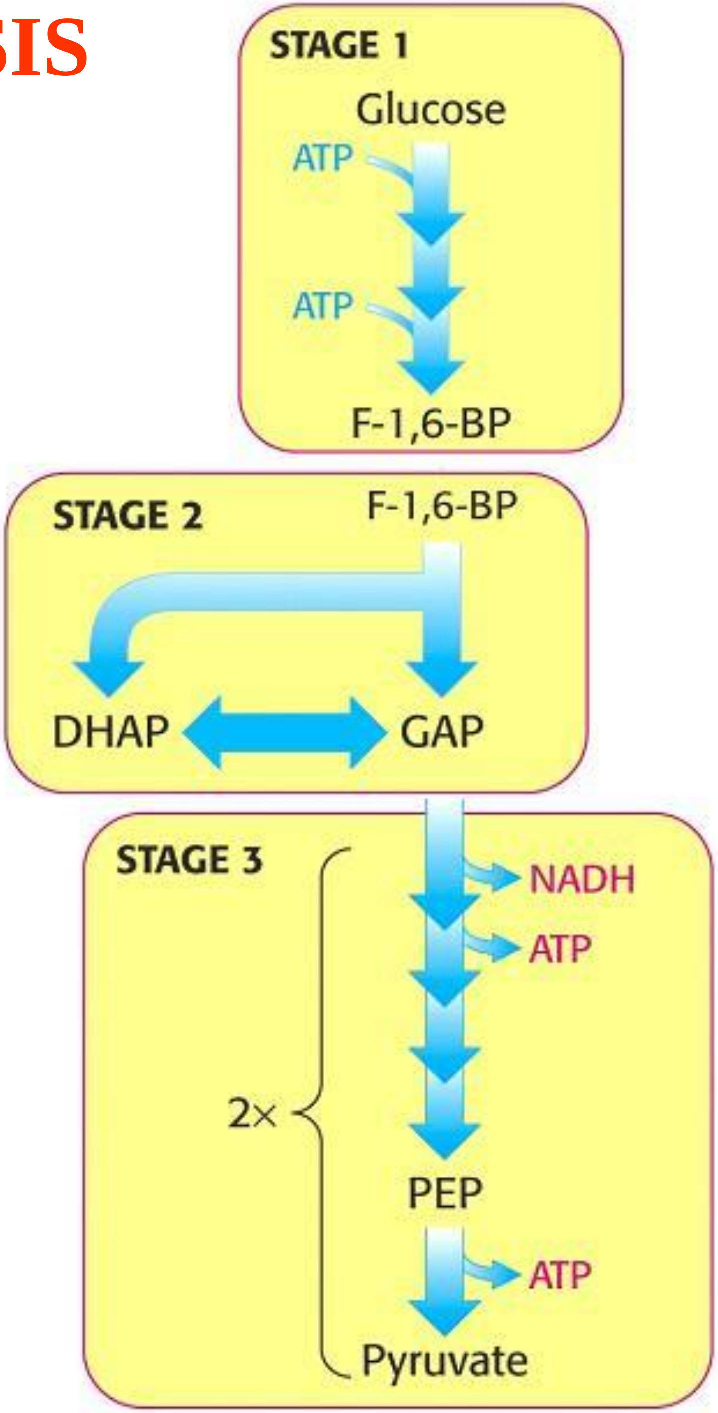
-Glycolysis takes place inside the cytoplasm of the cell

-Glycolytic intermediates are phosphorylated / glycolytic intermediates can't leave the cells.

-Most glycolytic enzymes require Mg^{2+} for activity.



STAGE OF GLYCOLYSIS



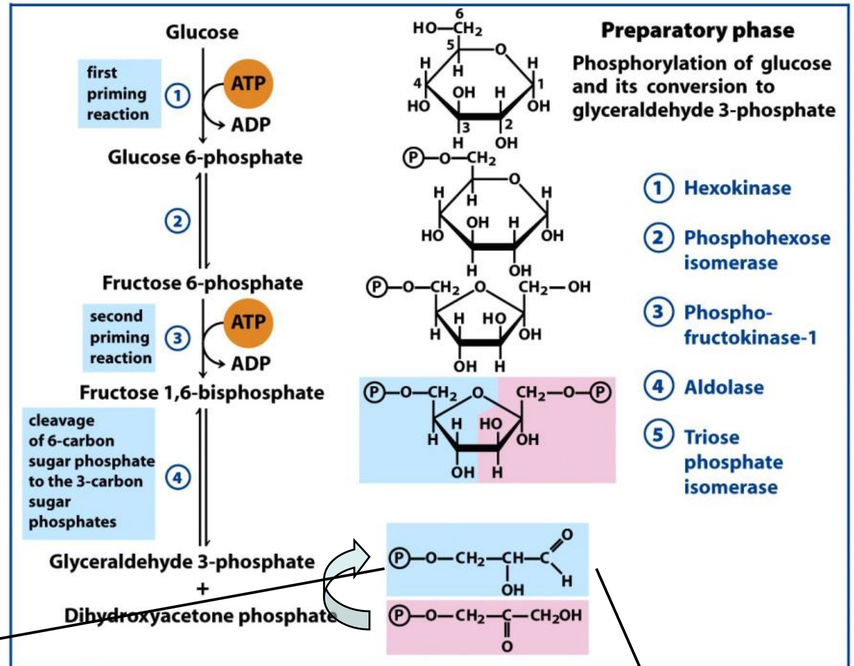


Figure 14-2a
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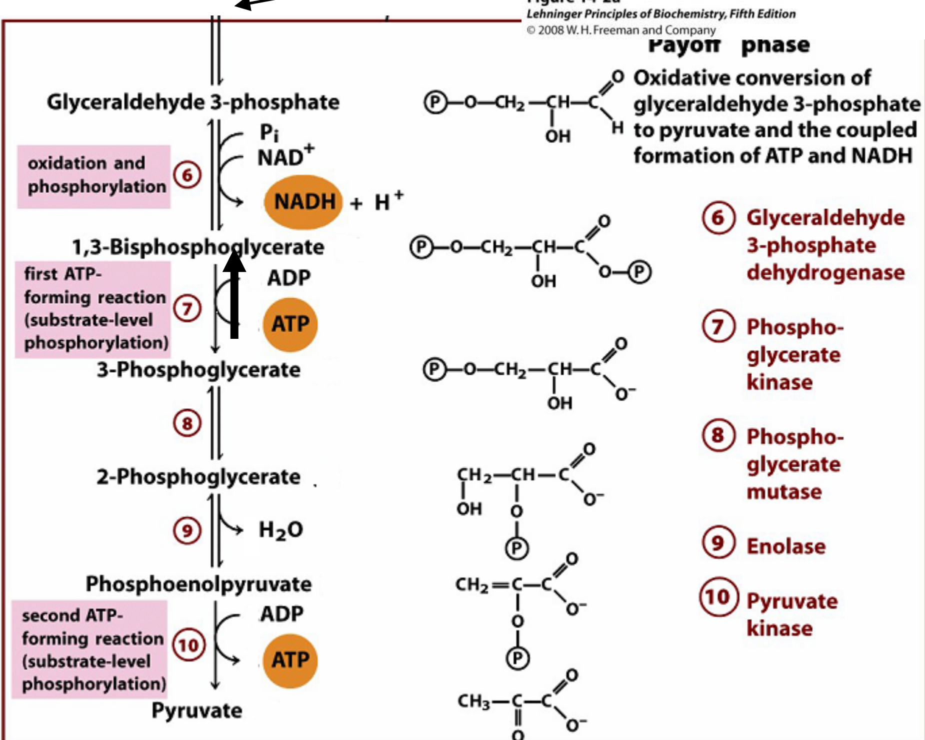

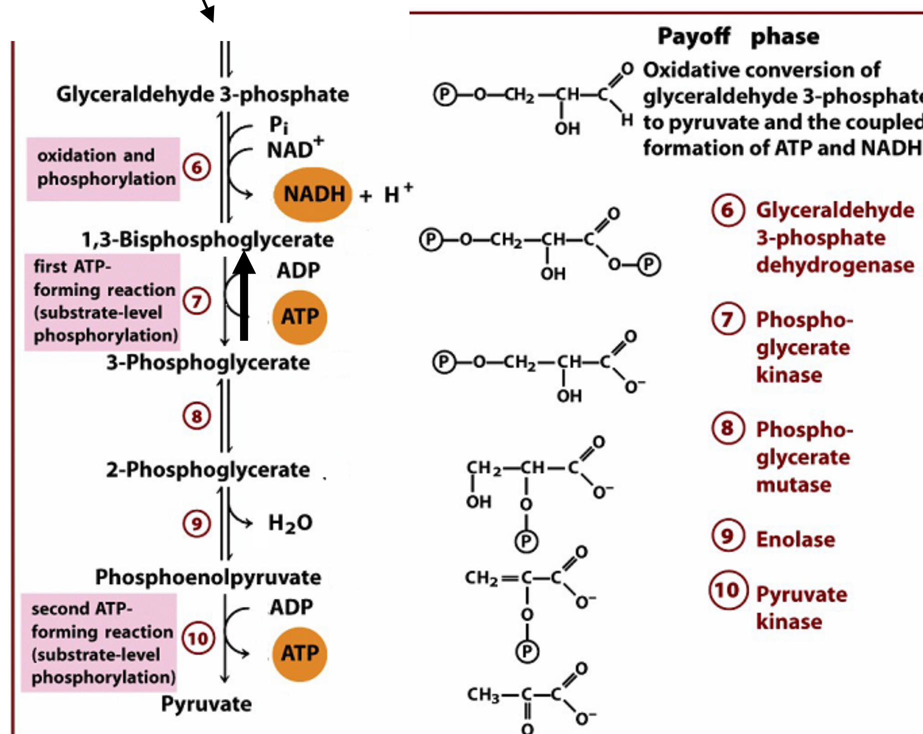

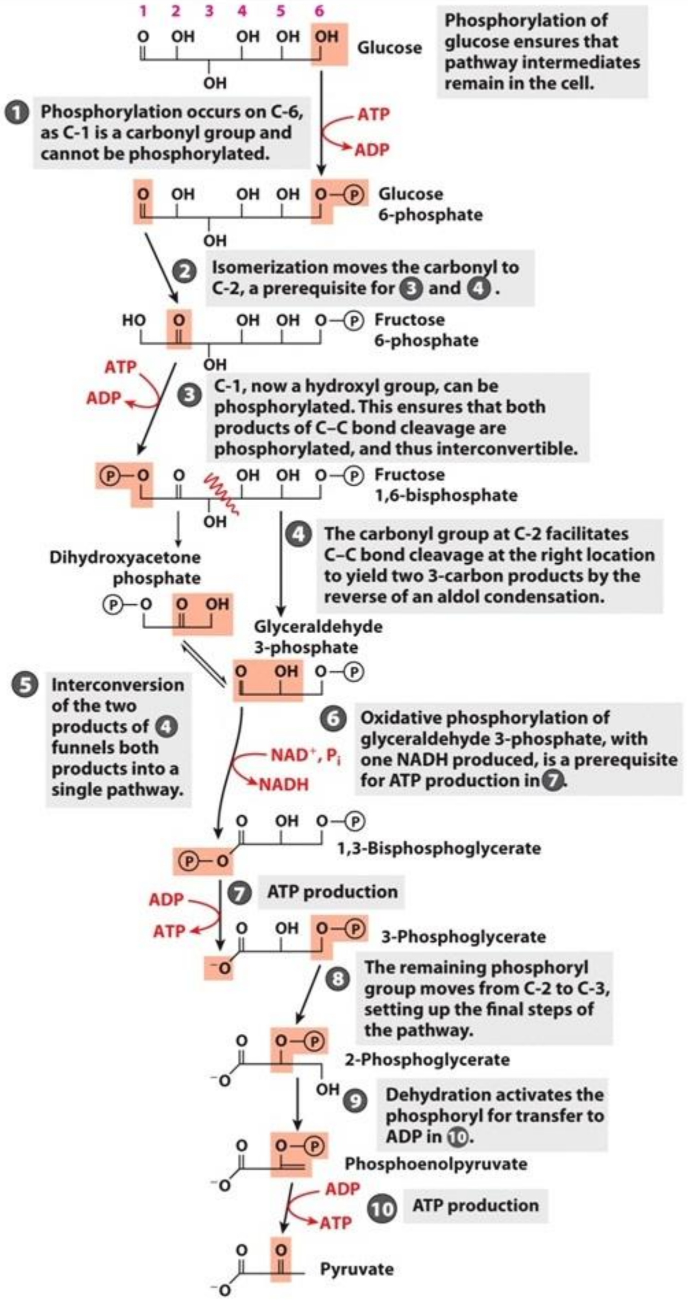

Figure 14-3

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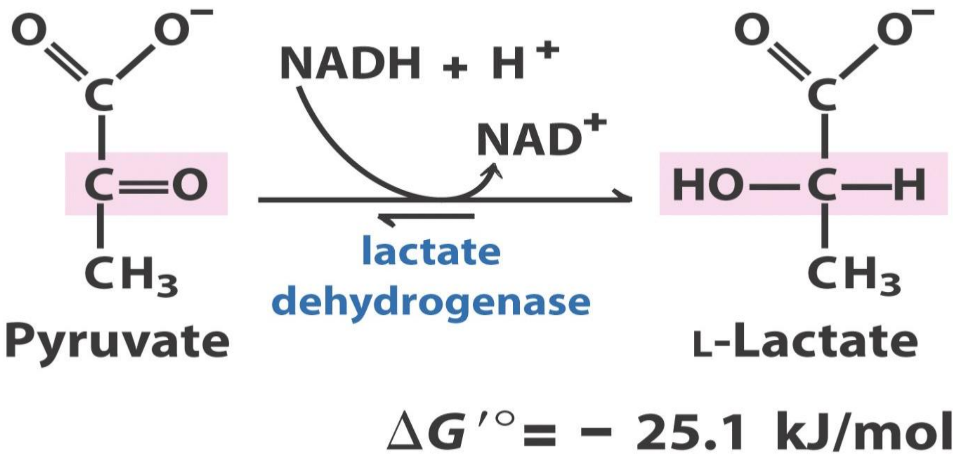
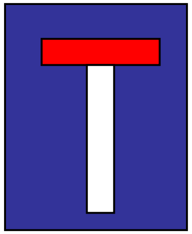
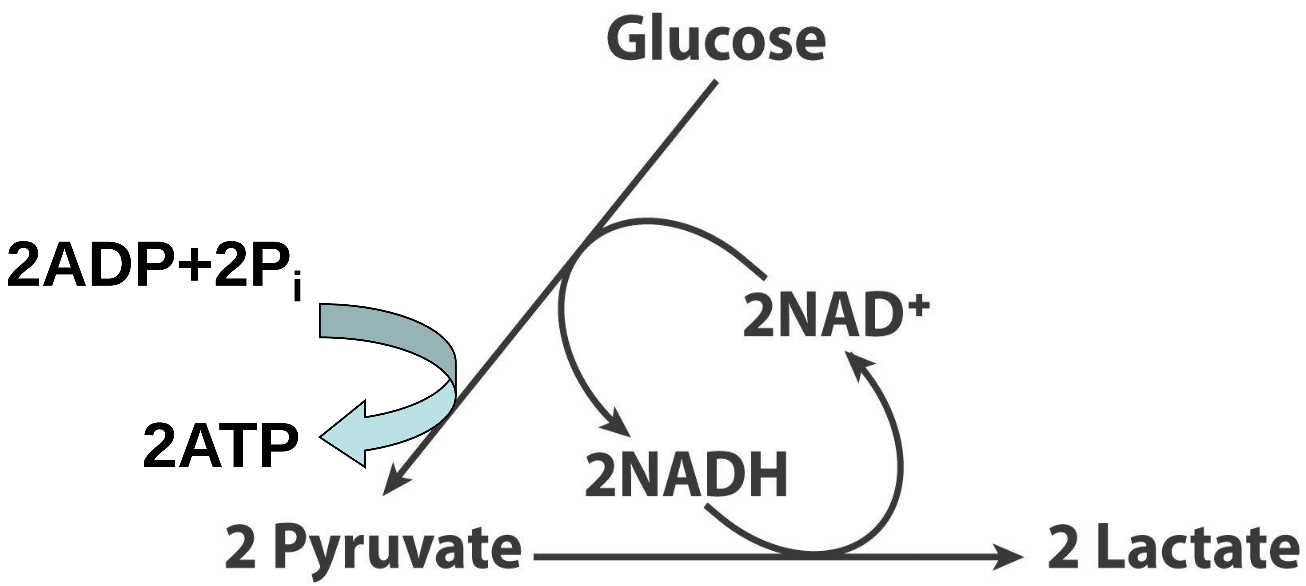
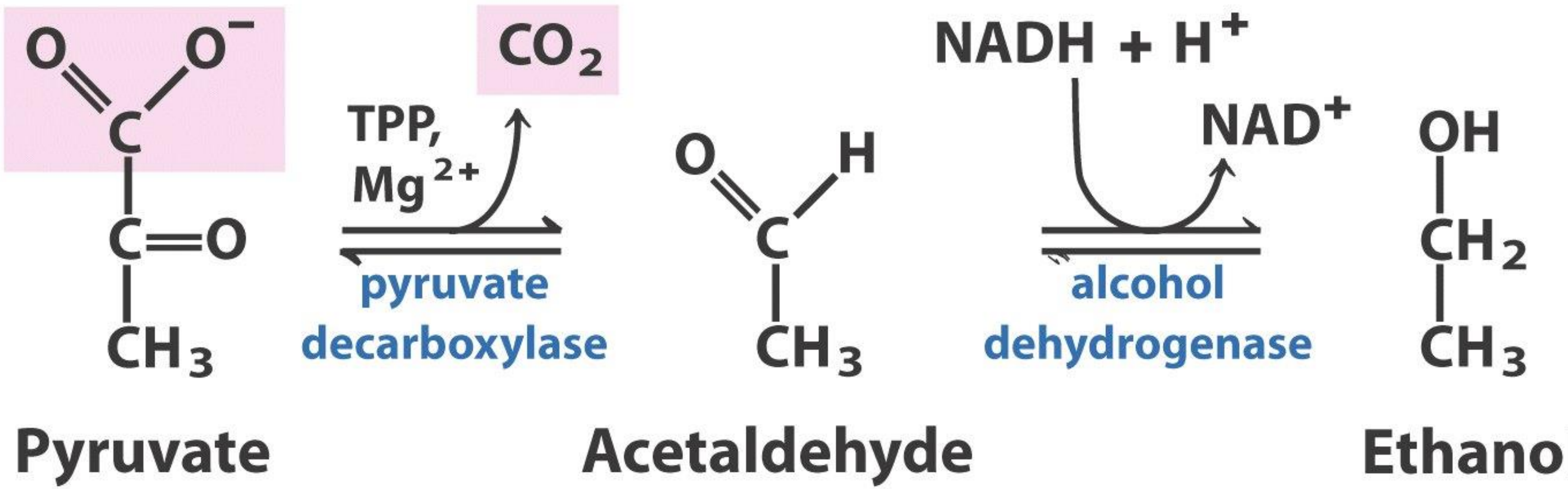
ANAEROB CONDITION

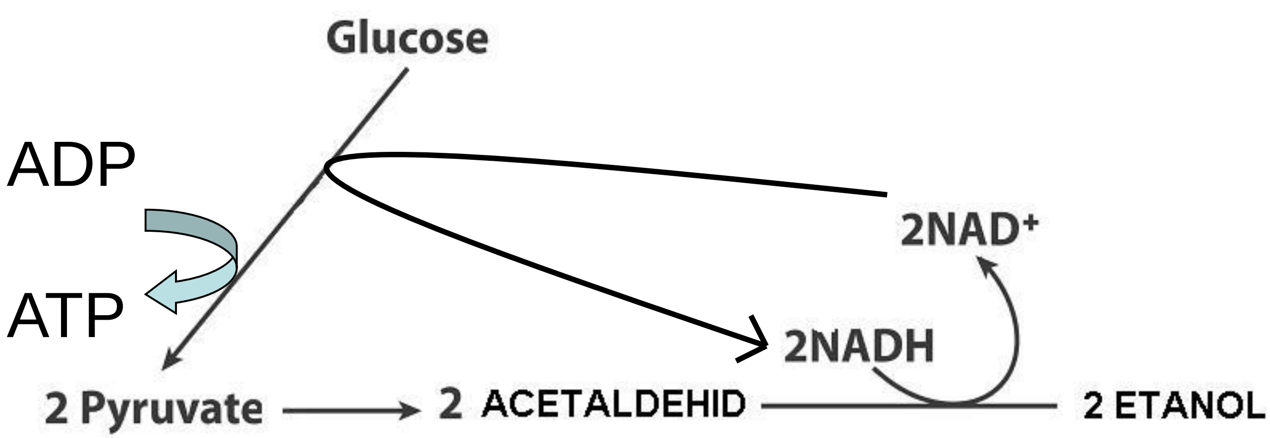






ANAEROB CONDITION





Glycolysis

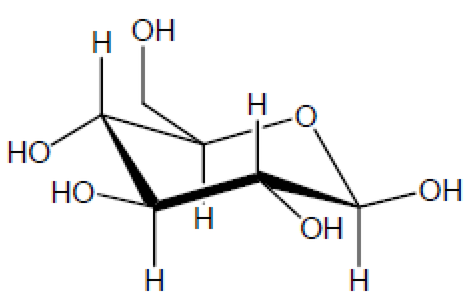
$$\text{glucose} + 2\ \text{NAD}^+ + 2\ \text{ADP} + 2\ \text{P}_i \rightarrow 2\ \text{pyruvate} + 2\ \text{NADH} + 2\ \text{H}^+ + 2\ \text{ATP} + 2\ \text{H}_2\text{O}$$

A redox reaction:

$$\text{glucose} + 2\ \text{NAD}^+ \rightarrow 2\ \text{pyruvate} + 2\ \text{NADH} + 2\ \text{H}^+$$

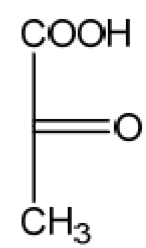
glucose is oxidized:

$\Delta G°' = -146$ kJ/mol



0 +1 -2

$C_6H_{12}O_6$ $\longrightarrow$

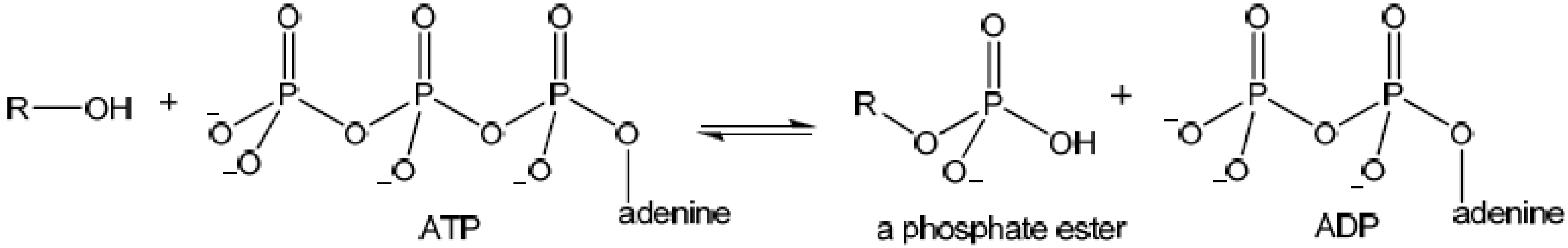


+2/3 +1 -2

$C_3H_4O_3$

The enzymes of glycolysis, and the reactions they catalyse

kinase: phosphorylation by using an ATP



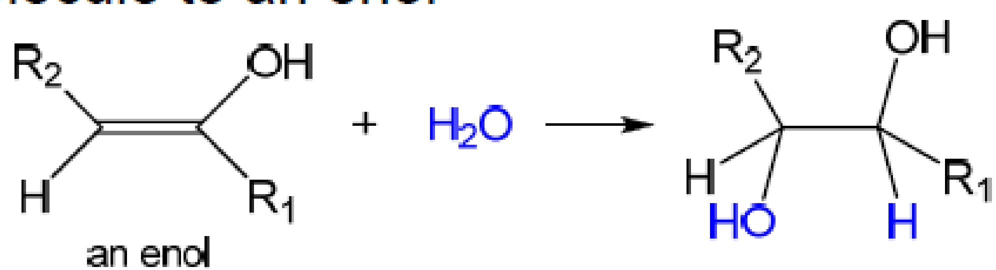
isomerase: isomerisation of the substrate

aldolase: aldol dimerisation

dehydrogenase: oxidation by removing 2 H atoms

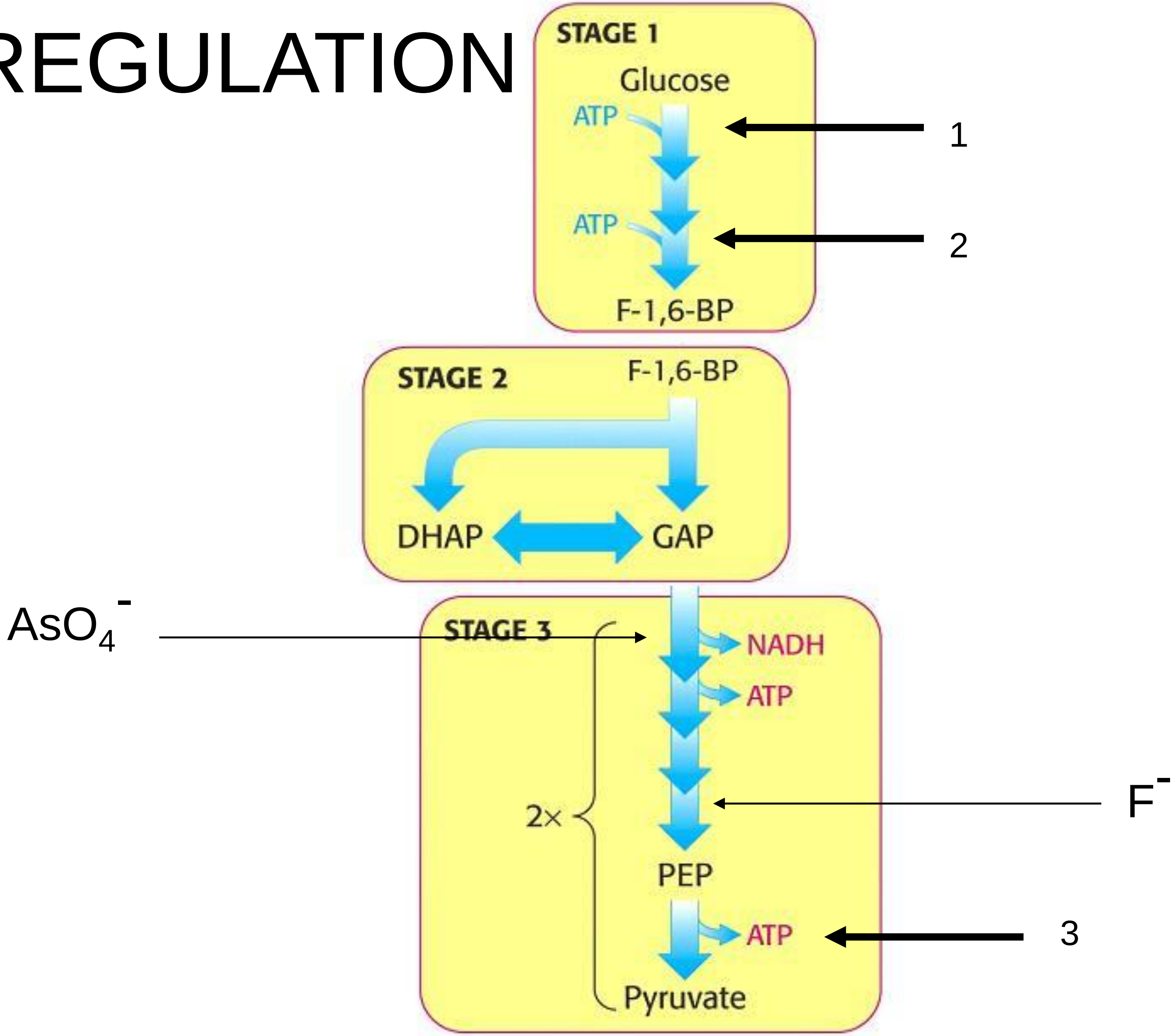
mutase: isomerisation of the substrate by shifting a particular group in a molecule from a position to another one

enolase: addition of a water molecule to an enol



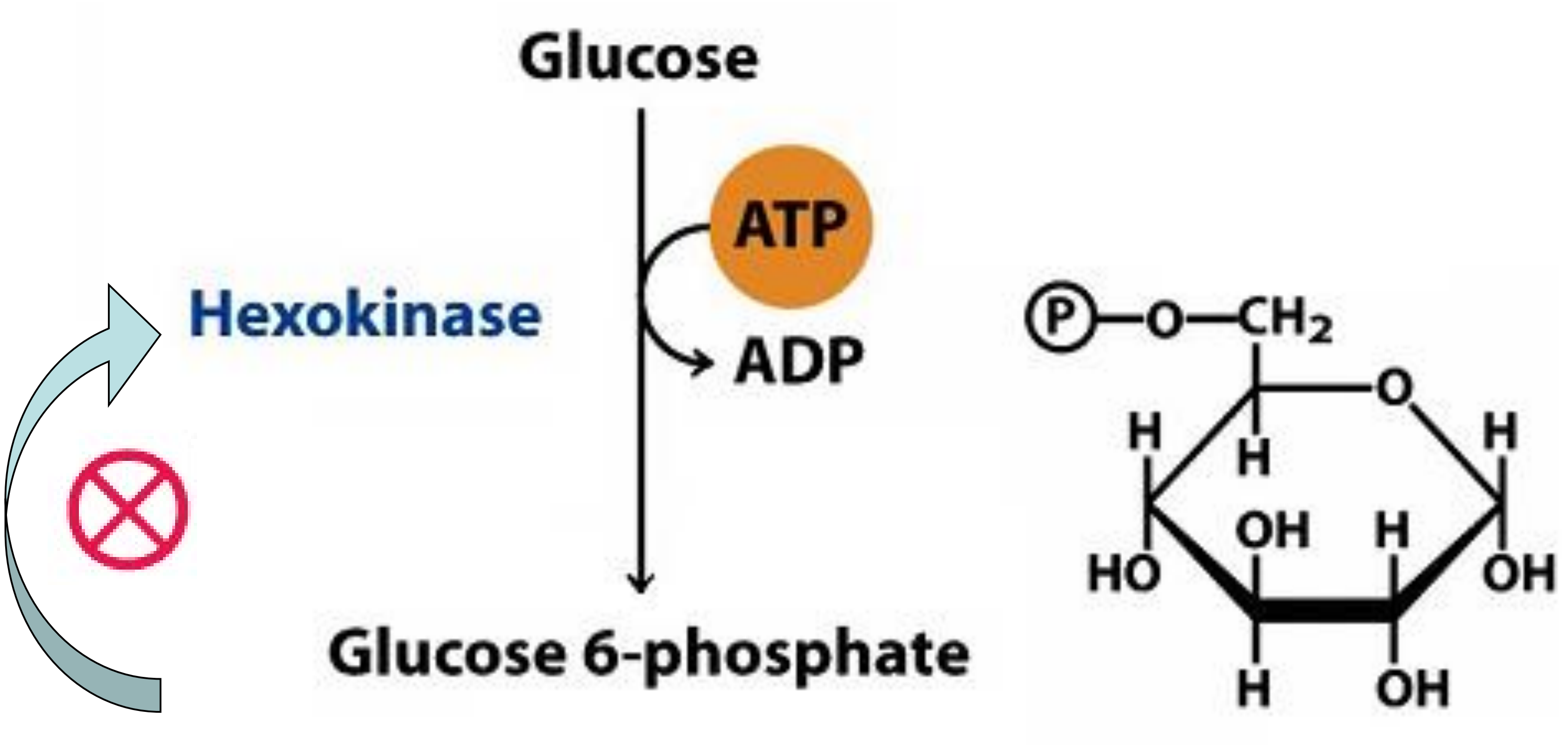
The enzymes catalyse the reactions and their reverse, too!

REGULATION



STAGE 1
Glucose
ATP
ATP
F-1,6-BP
1
2
STAGE 2
F-1,6-BP
DHAP
GAP
AsO_4^-
STAGE 3
NADH
ATP
2×
F^-
PEP
ATP
3
Pyruvate

1. HEXOKINASE OR GLUCOKINASE ?



1. Regulation of HEXOKINASE IV (GLUCOKINASE) by sequestration in the LIVER nucleus

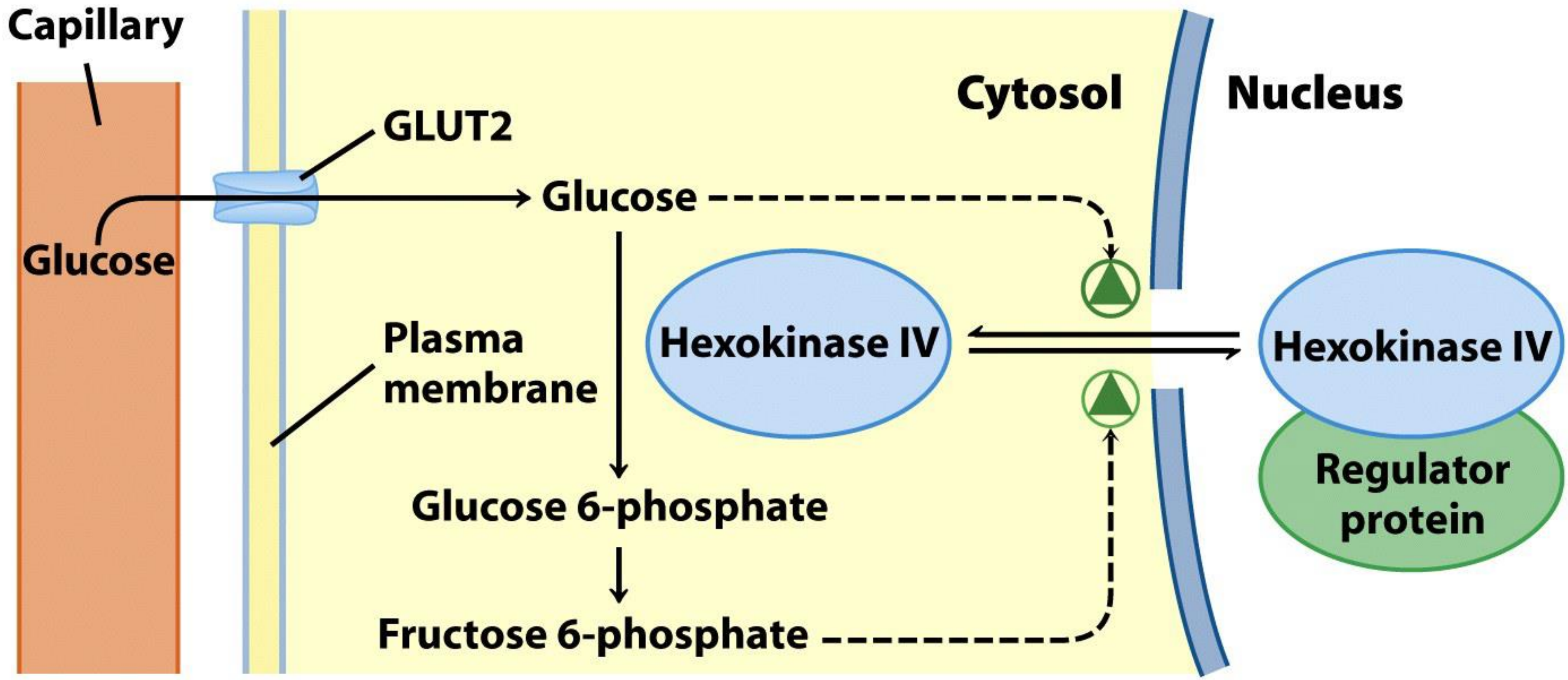


Figure 15-13
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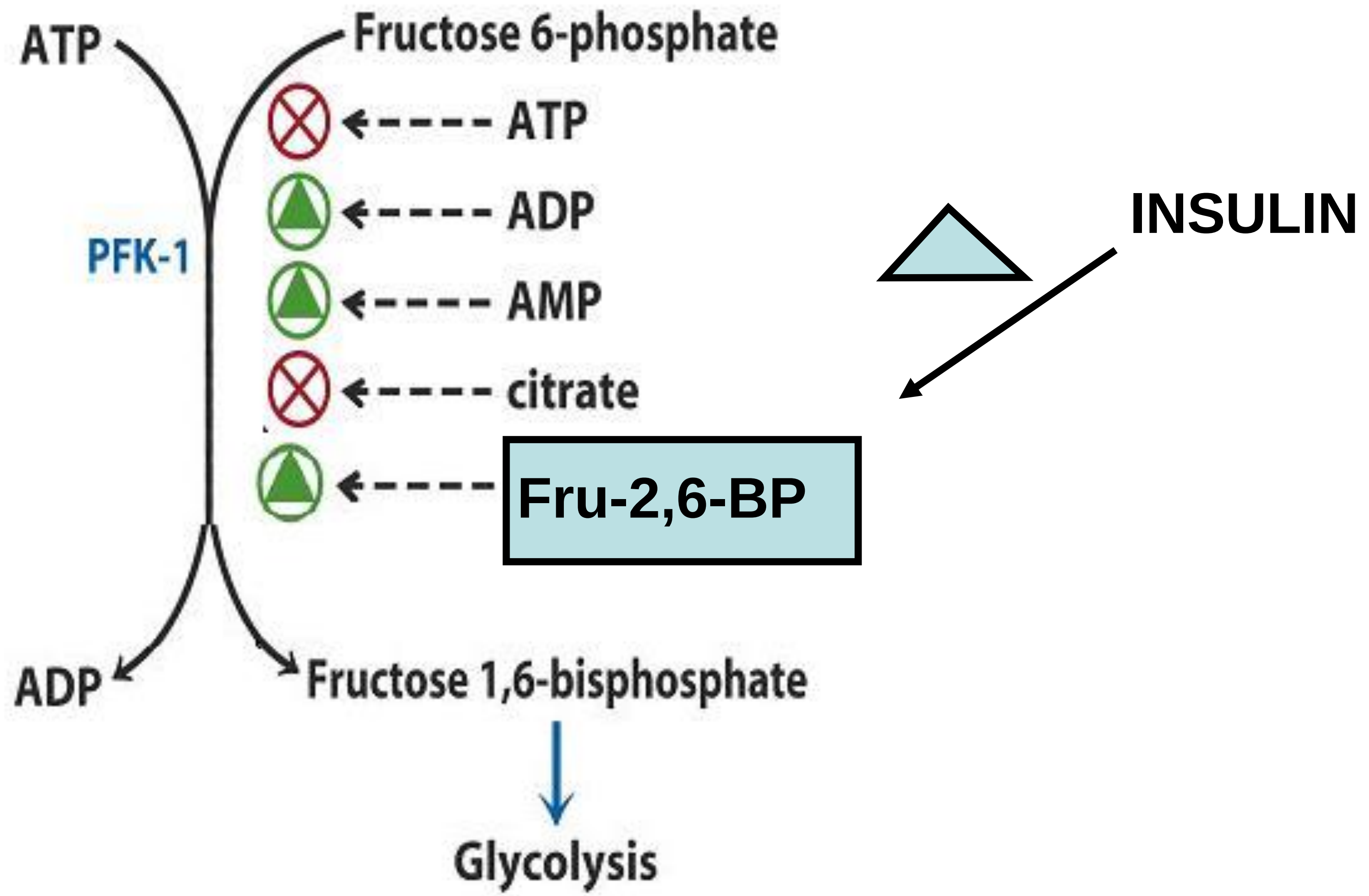
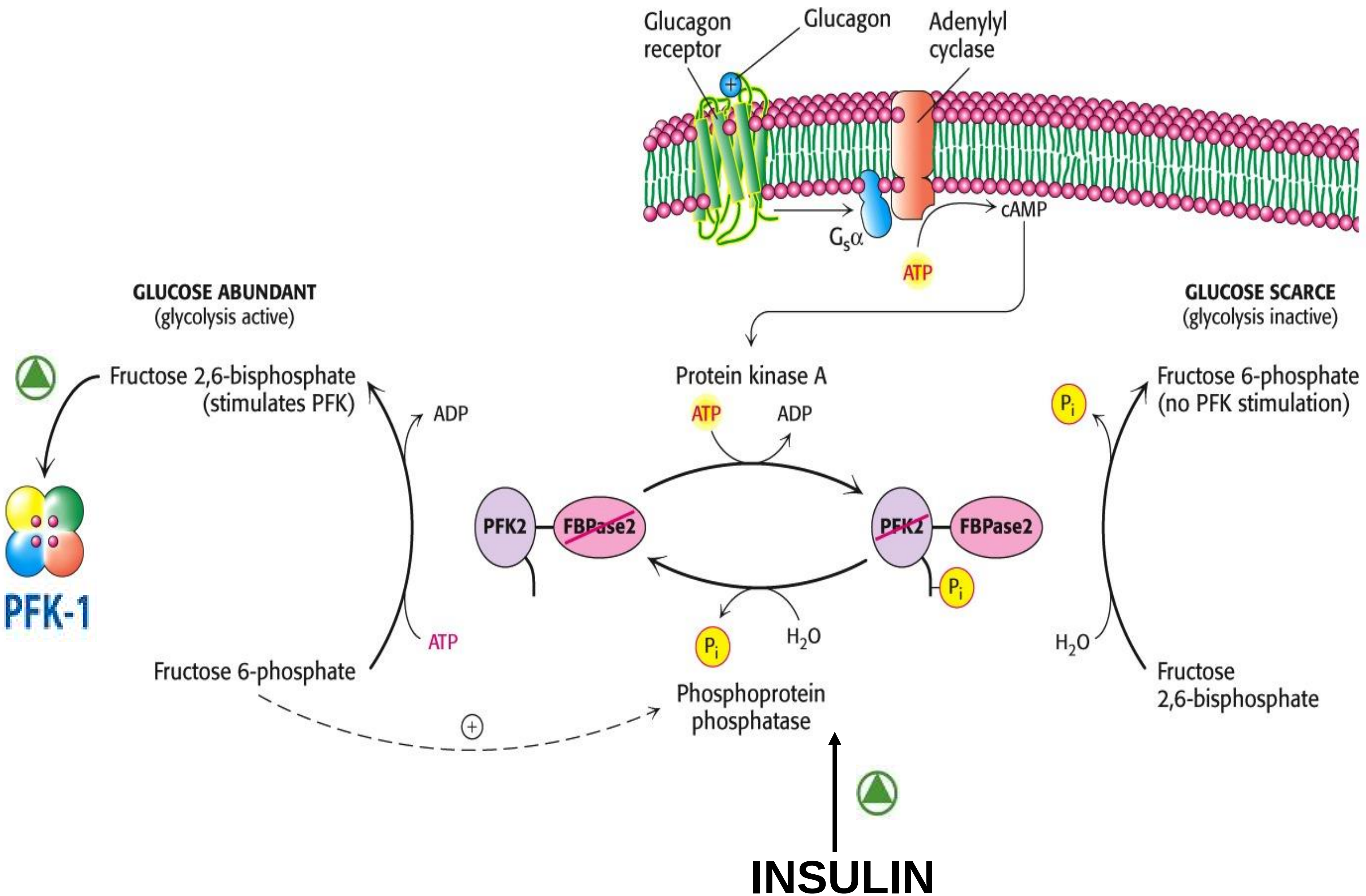
2. ALLOSTERIC REGULATION OF PFK-1

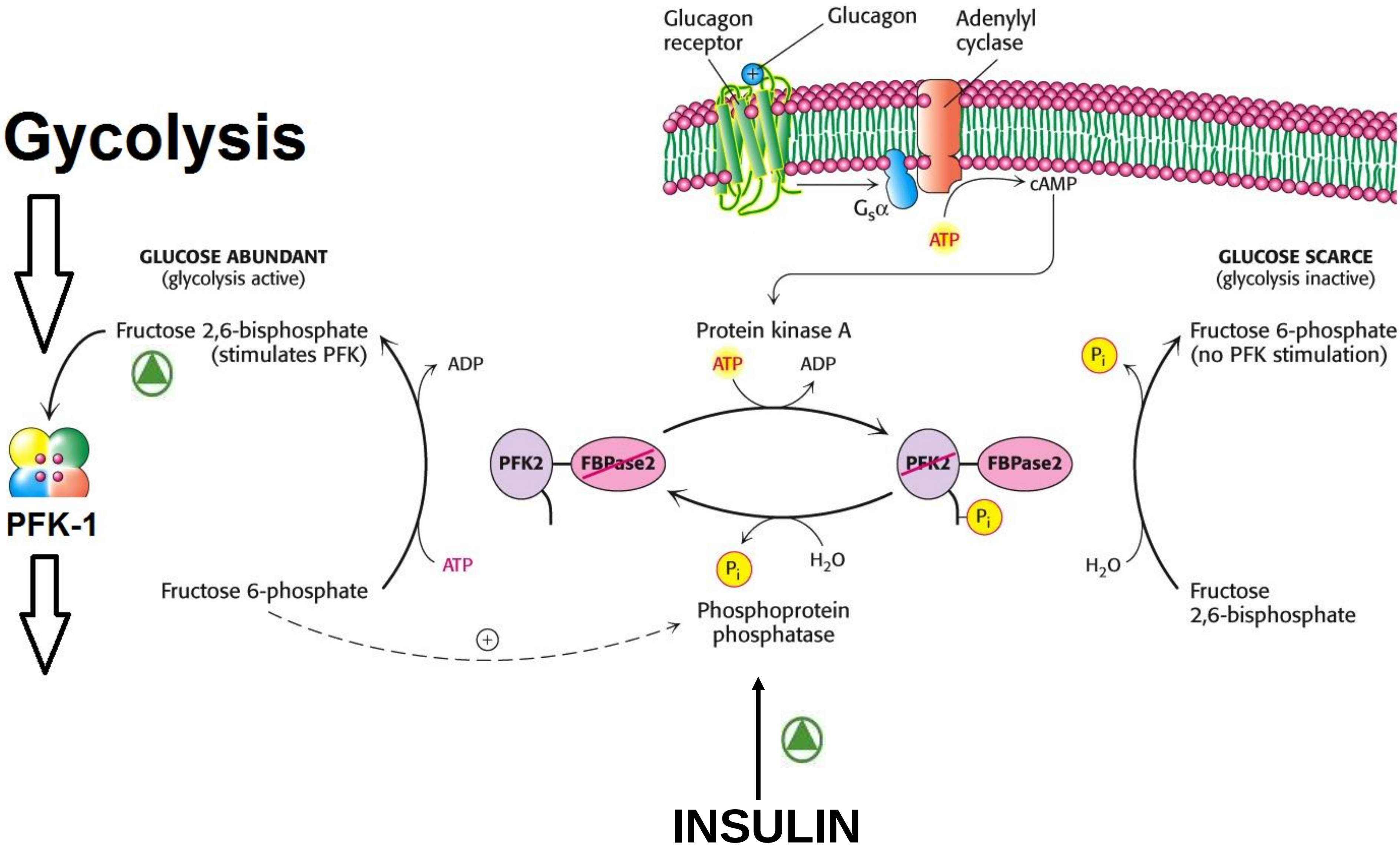


F-15-15 5th

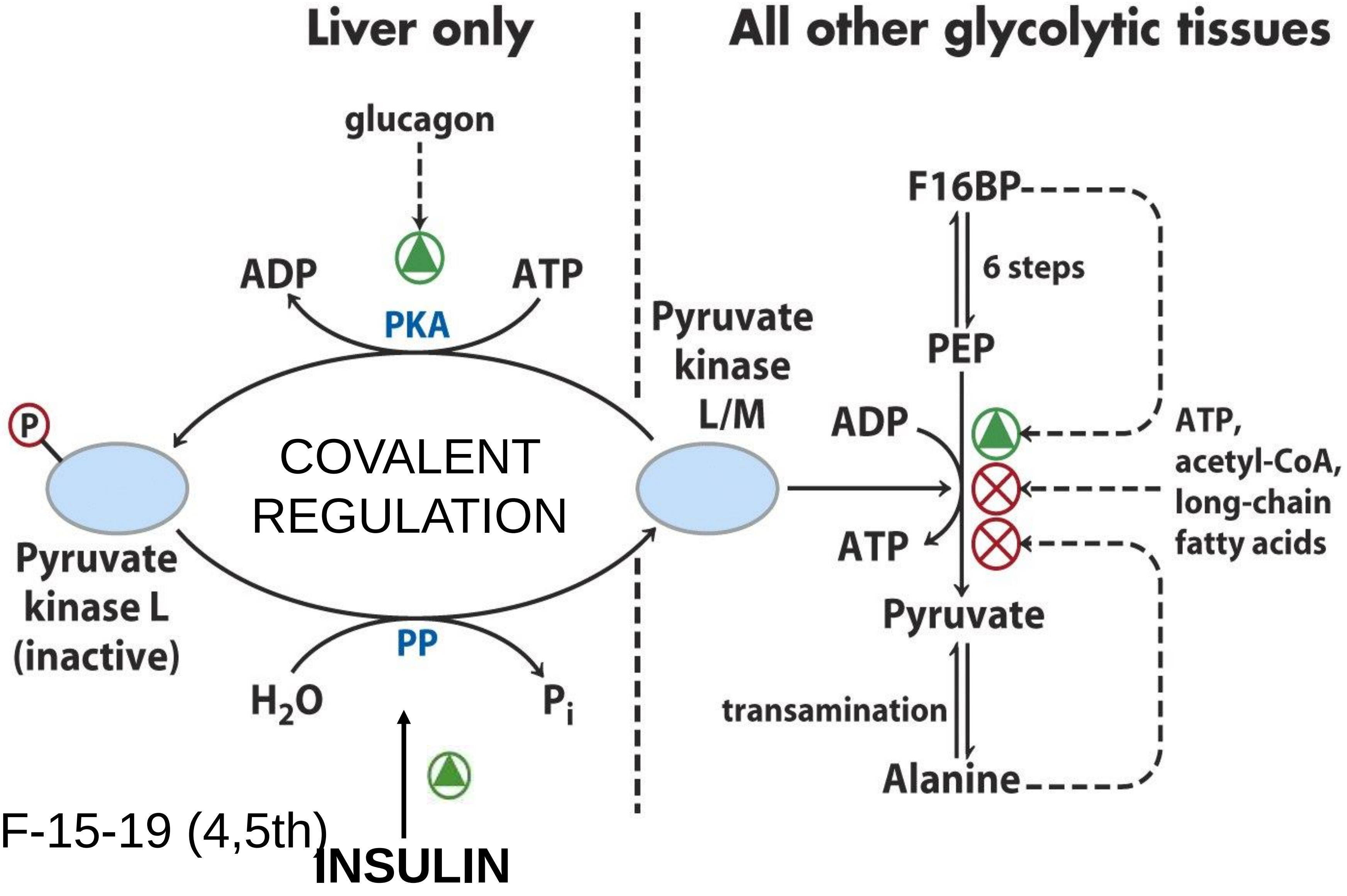
2. HORMONAL REGULATION OF PFK-2



2. HORMONAL REGULATION OF PFK-2 LIVER



3. REGULATION OF PYRUVATE KINASE



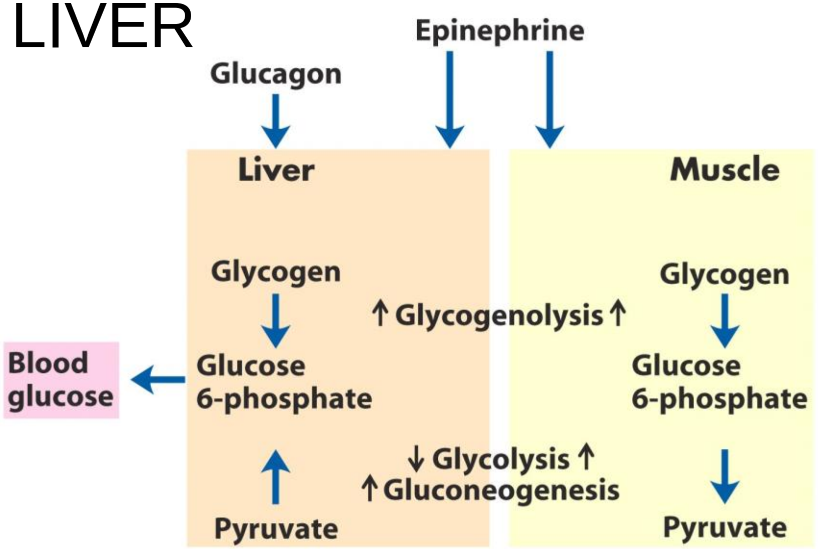
F-15-19 (4,5th)

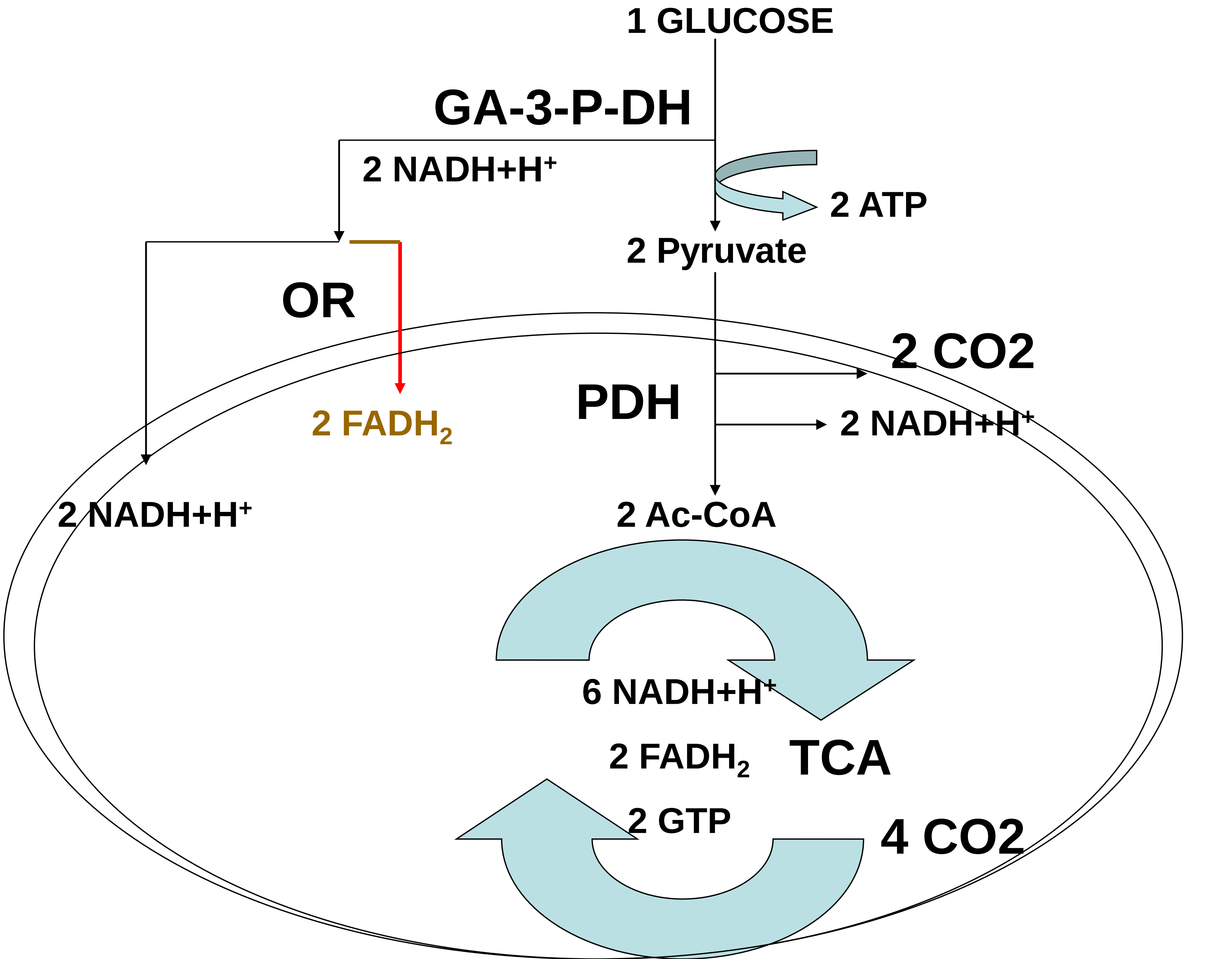
HORMONAL REGULATION OF GLYCOLYSIS

Glucagon, ephinephrin :
GLYCOLYSIS (LIVER) ↓

ephinephrin
GLYCOLYSIS (MUSCLE) ↑ ↓ LIVER

insulin
GLYCOLYSIS ↑
(MUSCLE, ADIPOSE, LIVER)




1 GLUCOSE
GA-3-P-DH
2 NADH+H+
2 ATP
2 Pyruvate
OR
2 FADH2
2 CO2
PDH
2 NADH+H+
2 NADH+H+
2 Ac-CoA
6 NADH+H+
2 FADH2
TCA
2 GTP
4 CO2

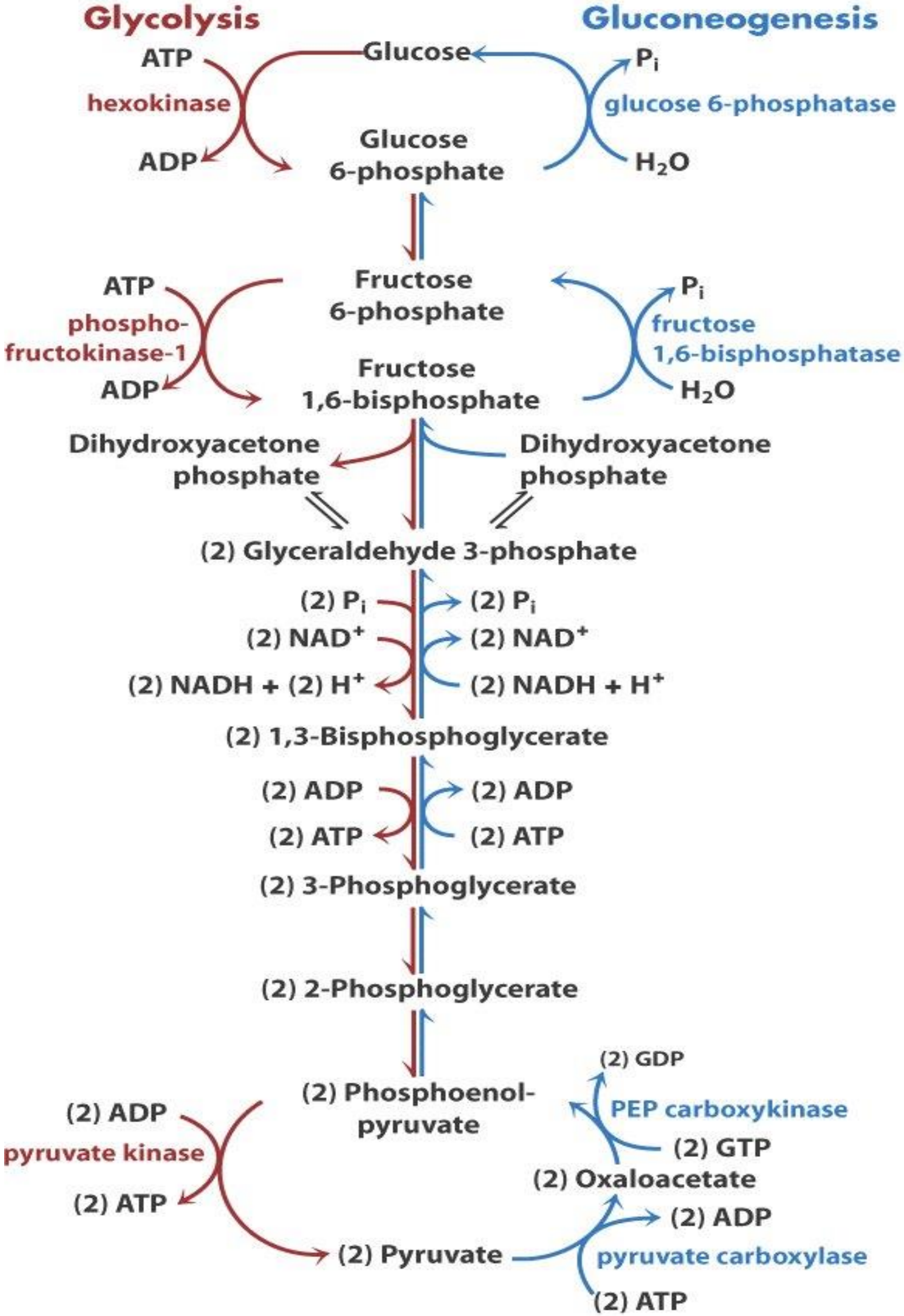
GLUCONEOGENESIS

LIVER

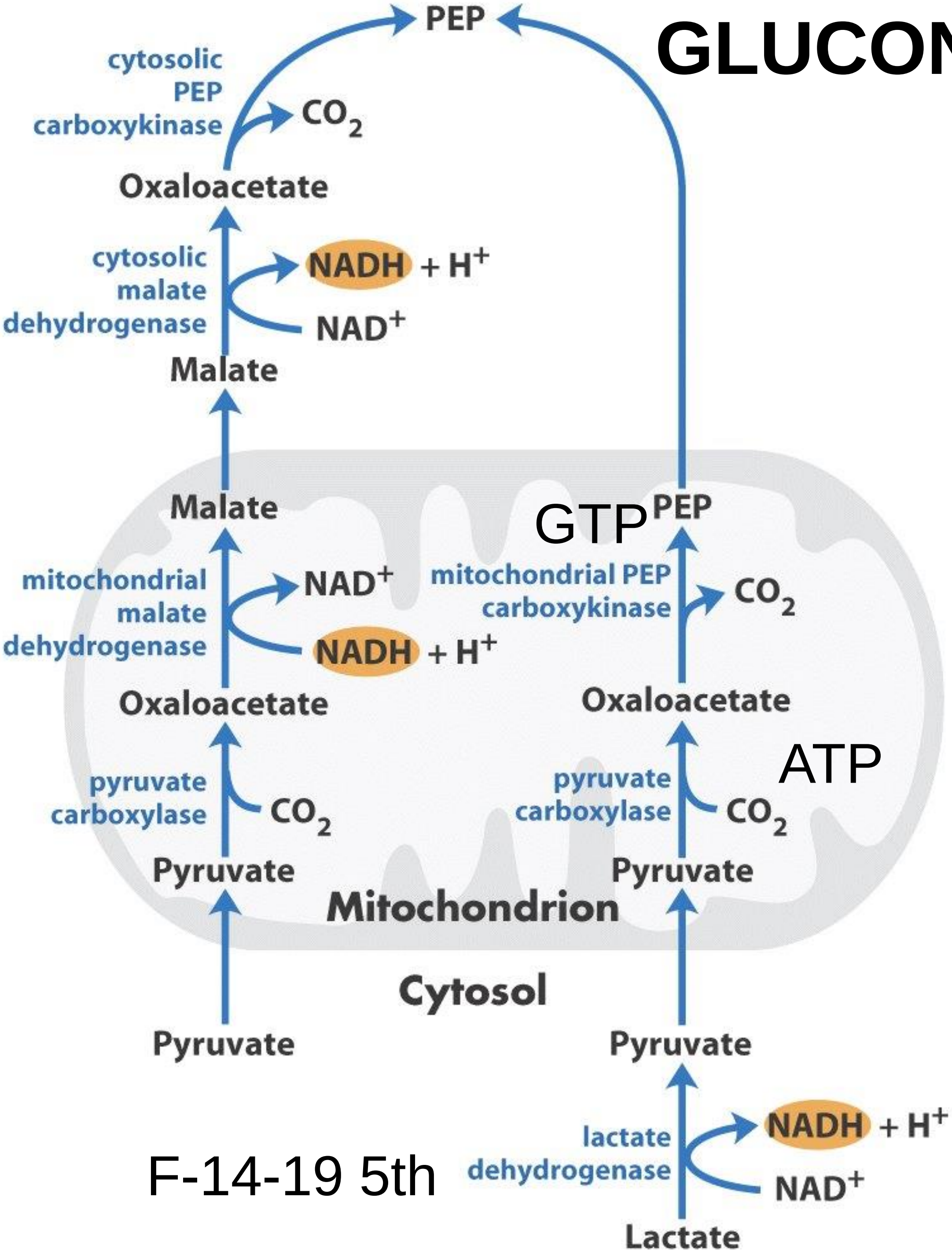
GLUCONEOGENESIS

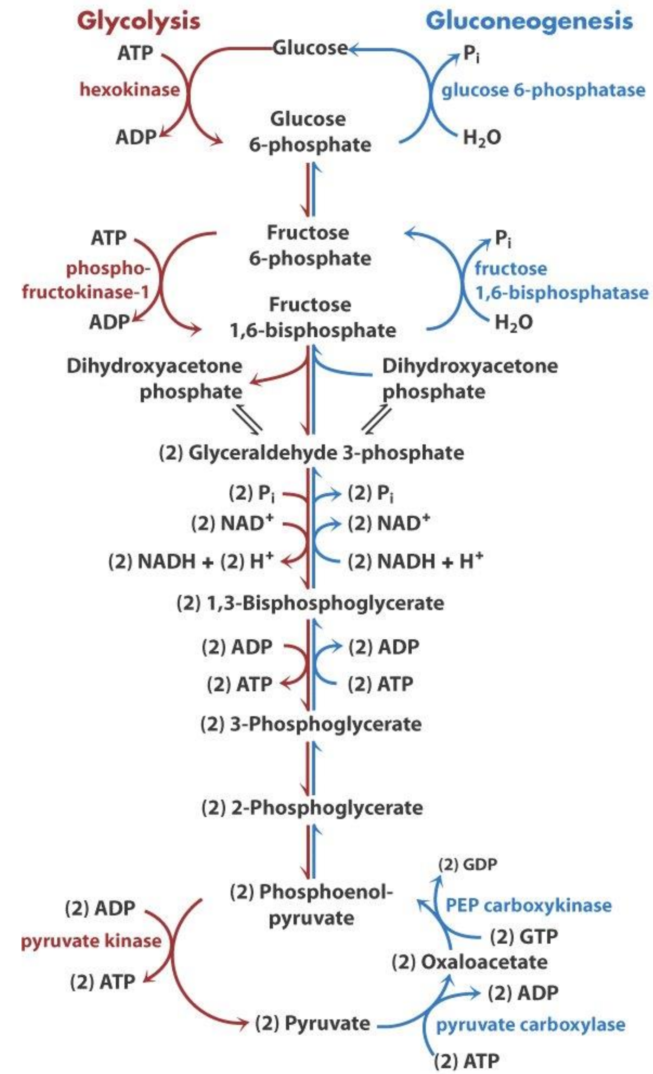
LIVER

F-15-11



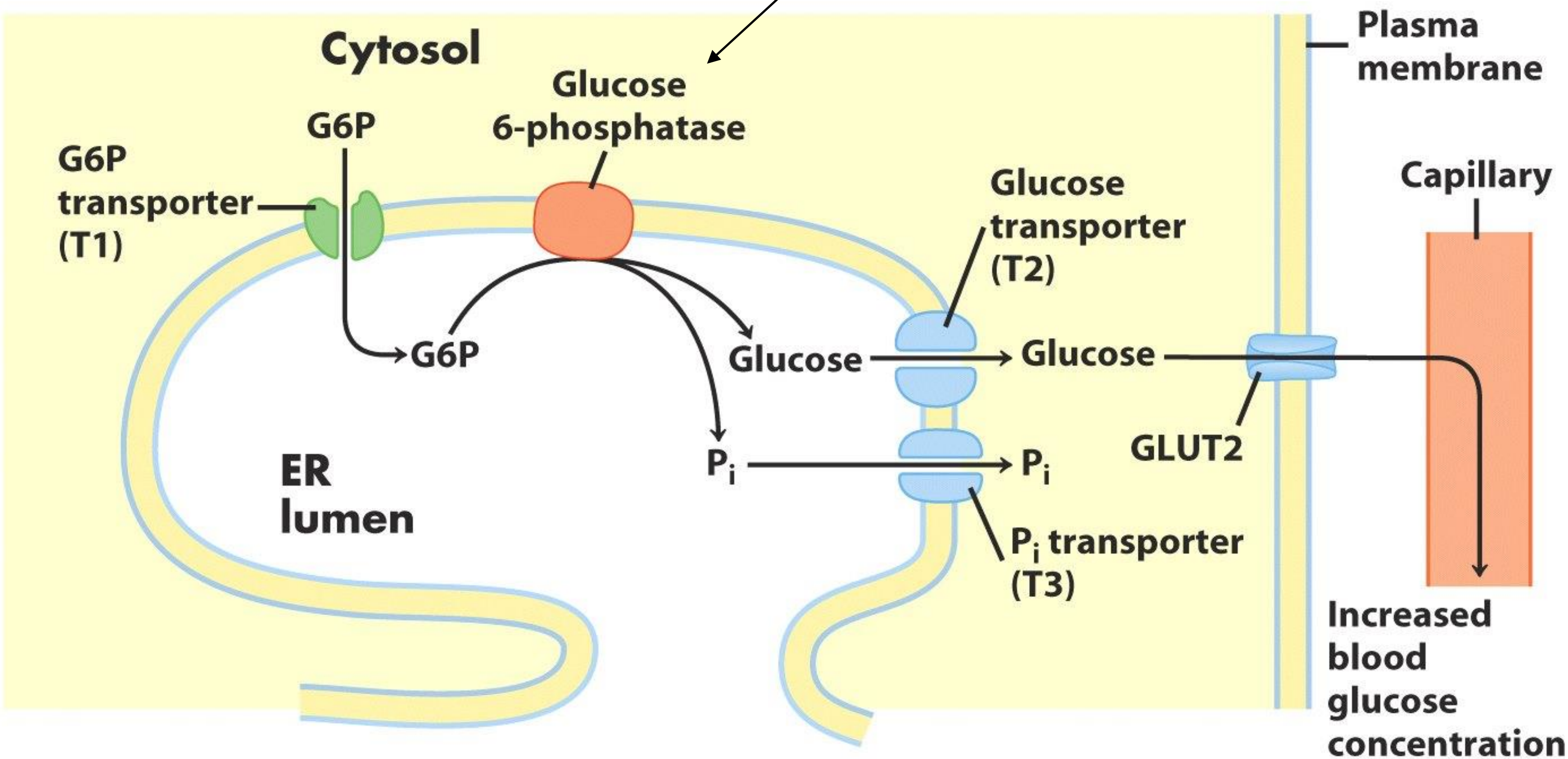
GLUCONEOGENESIS





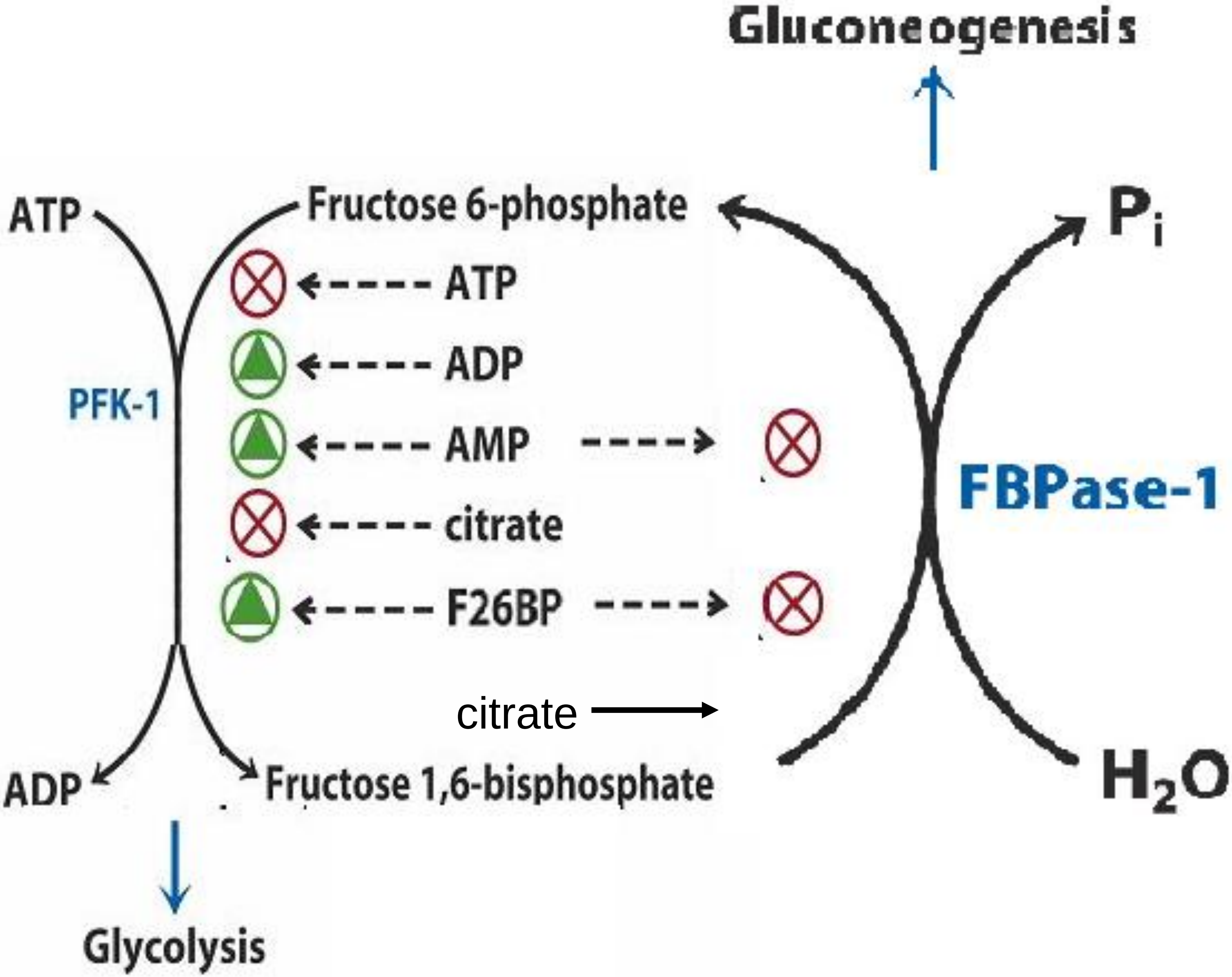
GLUCONEOGENESIS

LIVER



F-15-28 5th

F-15-6 4th



Gluconeogenesis
ATP
Fructose 6-phosphate
ATP
ADP
PFK-1
AMP
citrate
F26BP
FBPase-1
Pi
citrate
ADP
Fructose 1,6-bisphosphate
H2O
Glycolysis

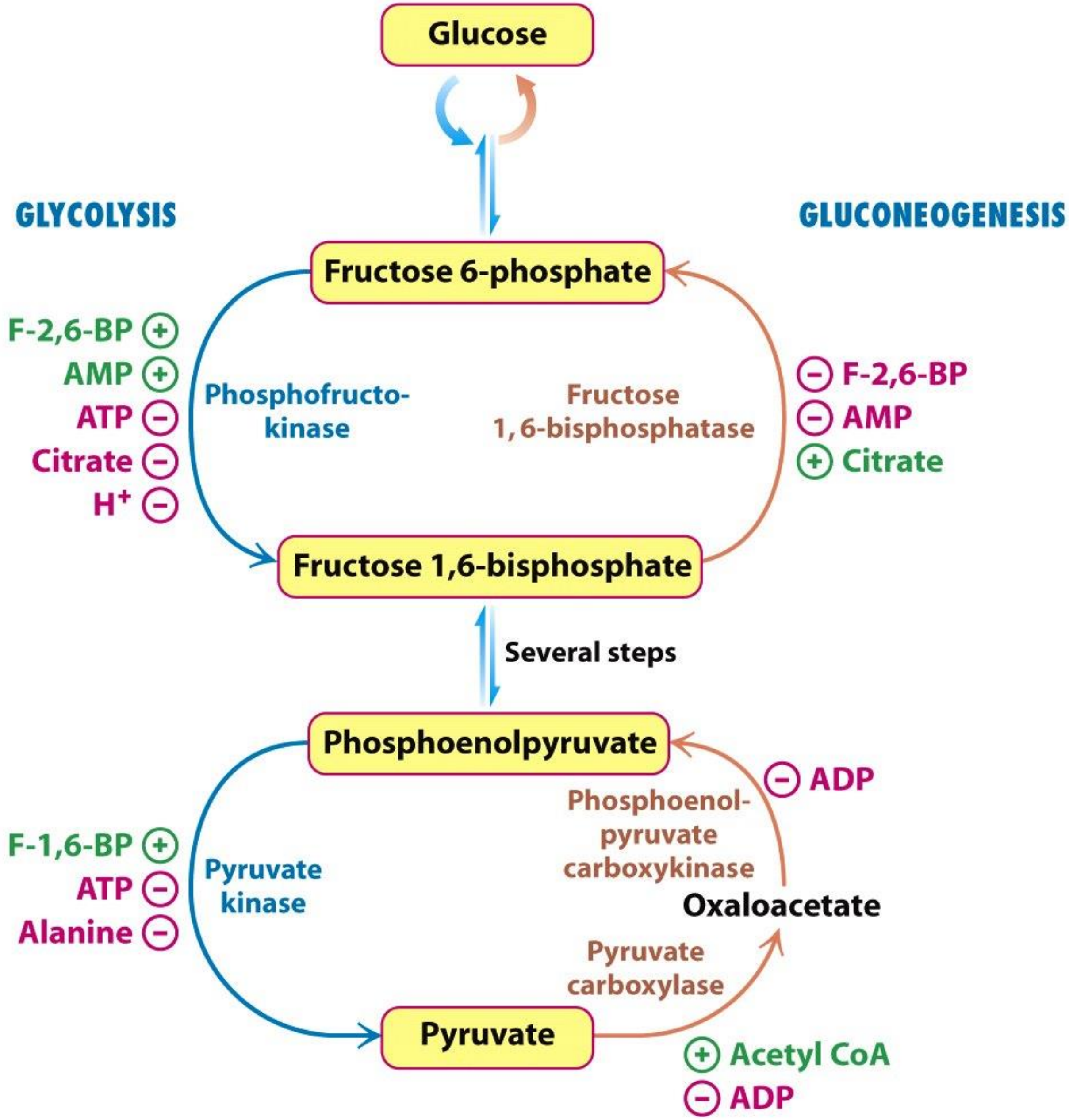
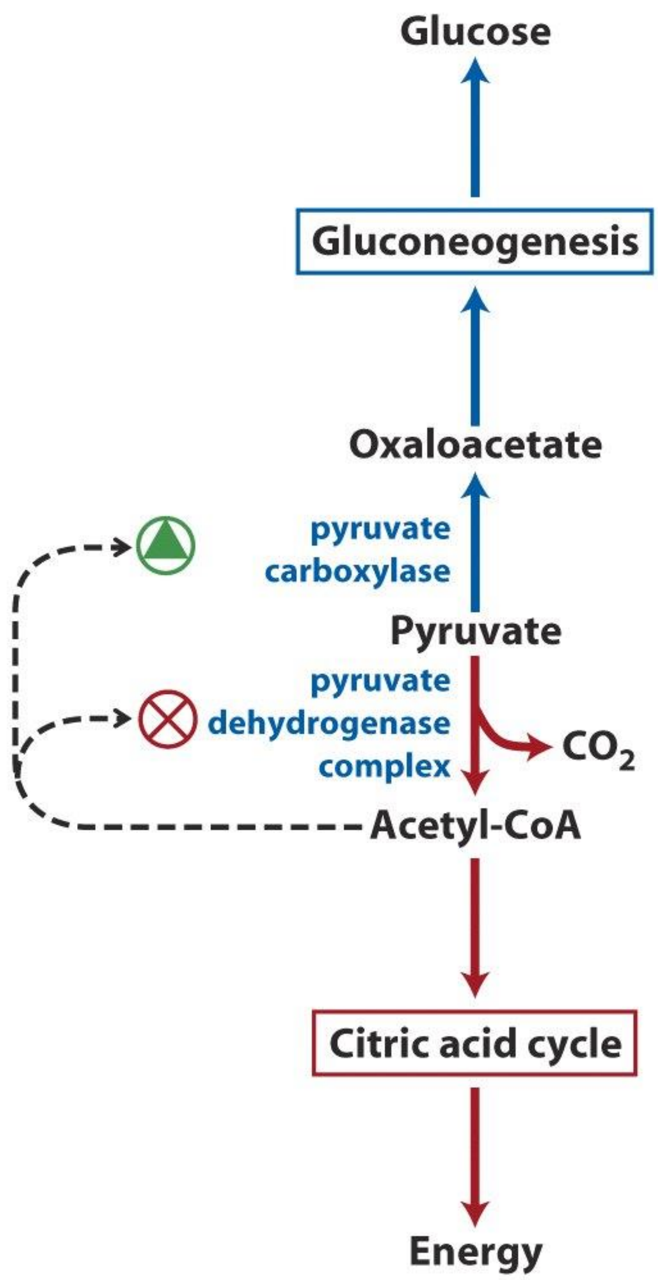
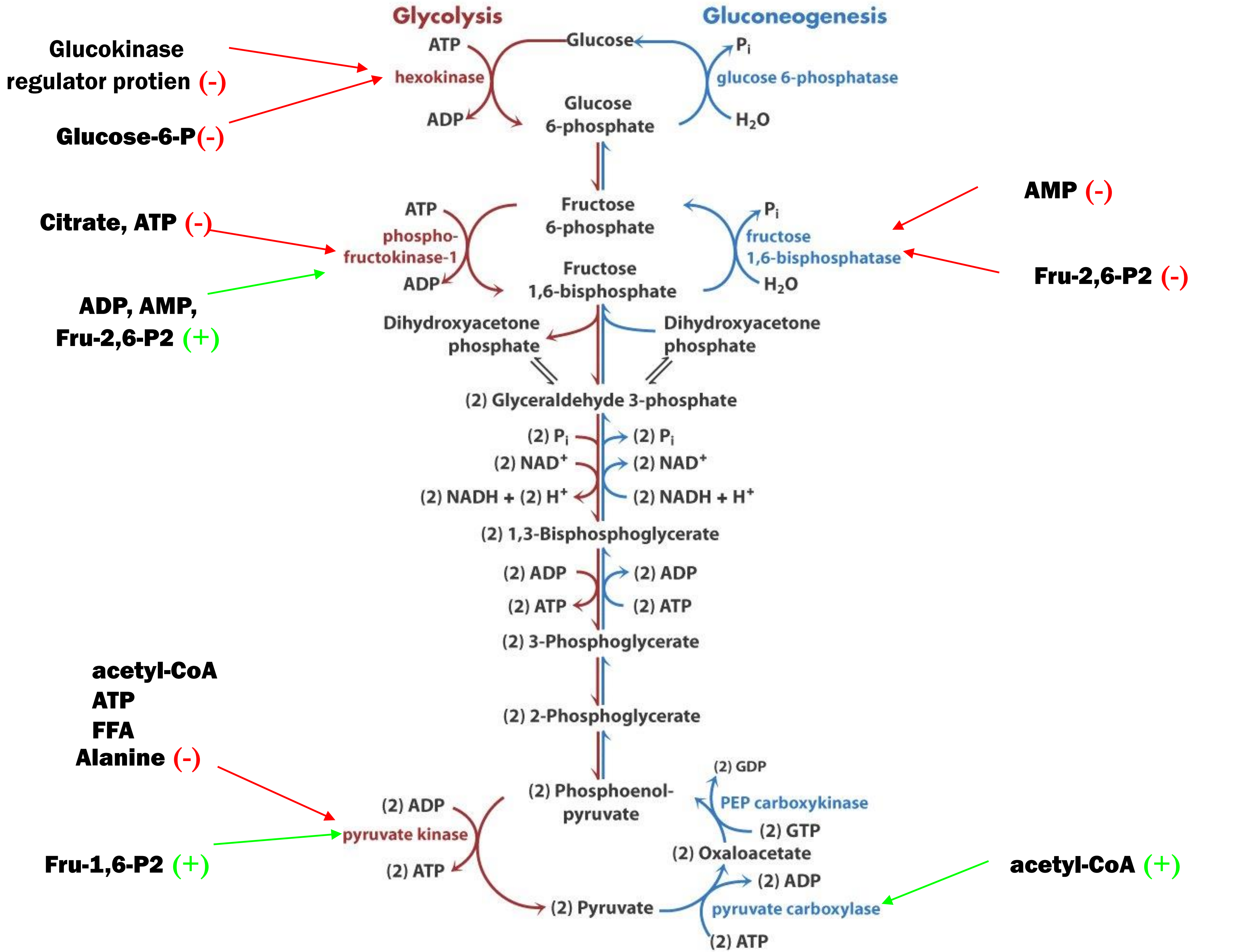


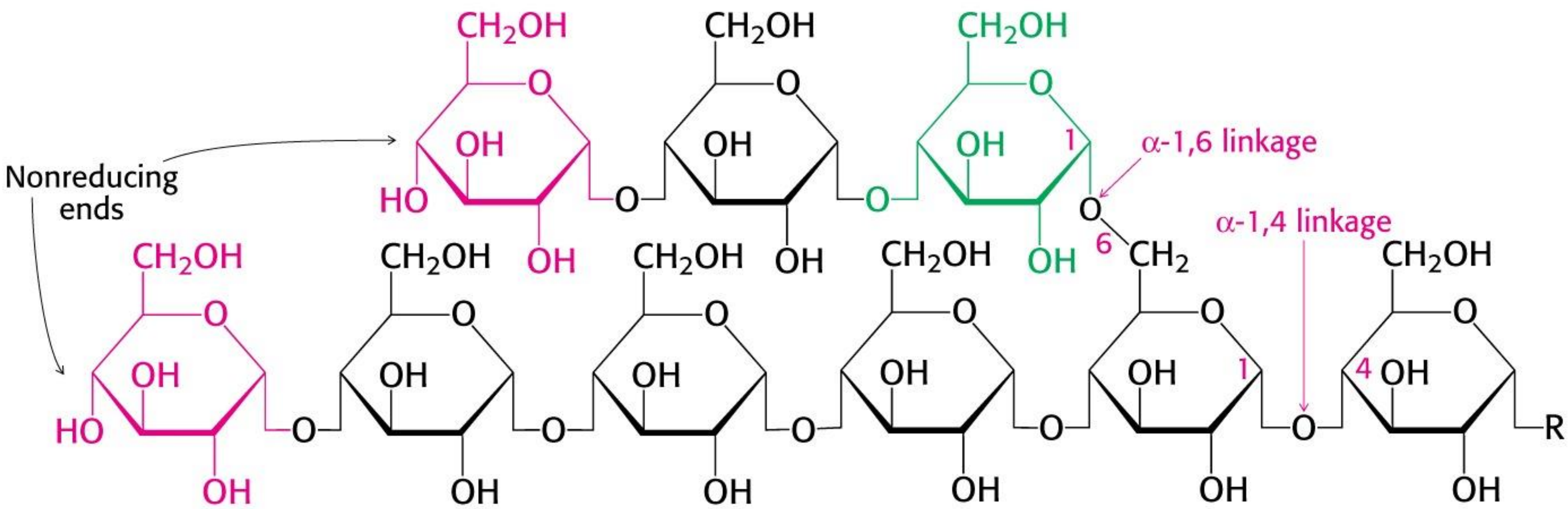
Figure 16-28
Biochemistry, Sixth Edition

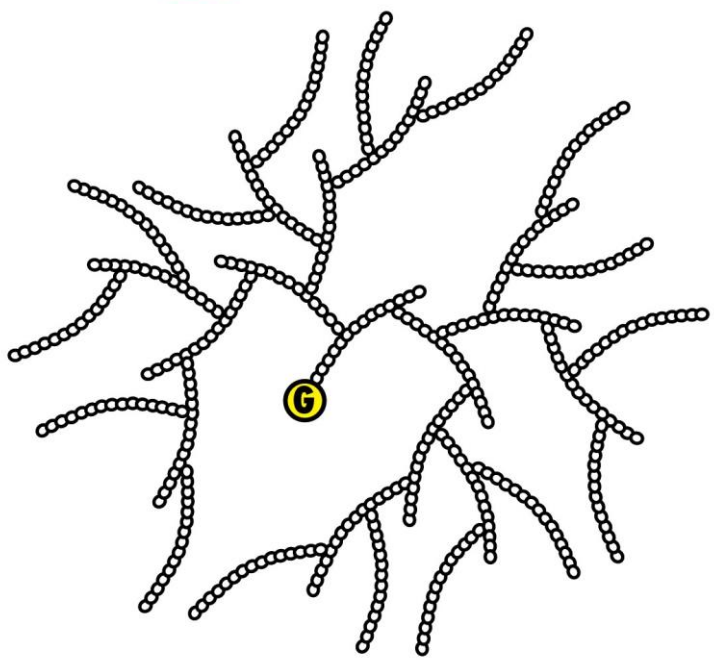

Glucose
Gluconeogenesis
Oxaloacetate
pyruvate
carboxylase
Pyruvate
pyruvate
dehydrogenase
complex
CO_2
Acetyl-CoA
Citric acid cycle
Energy


Glycolysis
Gluconeogenesis
Glucokinase regulator protien (-)
Glucose-6-P(-)
ATP
hexokinase
ADP
Glucose
Glucose 6-phosphate
P_i
glucose 6-phosphatase
H_2O
Citrate, ATP (-)
ADP, AMP, Fru-2,6-P2 (+)
ATP
phospho-fructokinase-1
ADP
Fructose 6-phosphate
Fructose 1,6-bisphosphate
P_i
fructose 1,6-bisphosphatase
H_2O
AMP (-)
Fru-2,6-P2 (-)
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) NAD^+
(2) NADH + (2) H^+
(2) P_i
(2) NAD^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
acetyl-CoA
ATP
FFA
Alanine (-)
Fru-1,6-P2 (+)
(2) ADP
pyruvate kinase
(2) ATP
(2) Phosphoenol-pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) Oxaloacetate
(2) ADP
(2) Pyruvate
pyruvate carboxylase
(2) ATP
acetyl-CoA (+)

GLYCOGEN SYNTHESIS AND DEGRADATION

Structure of glycogen





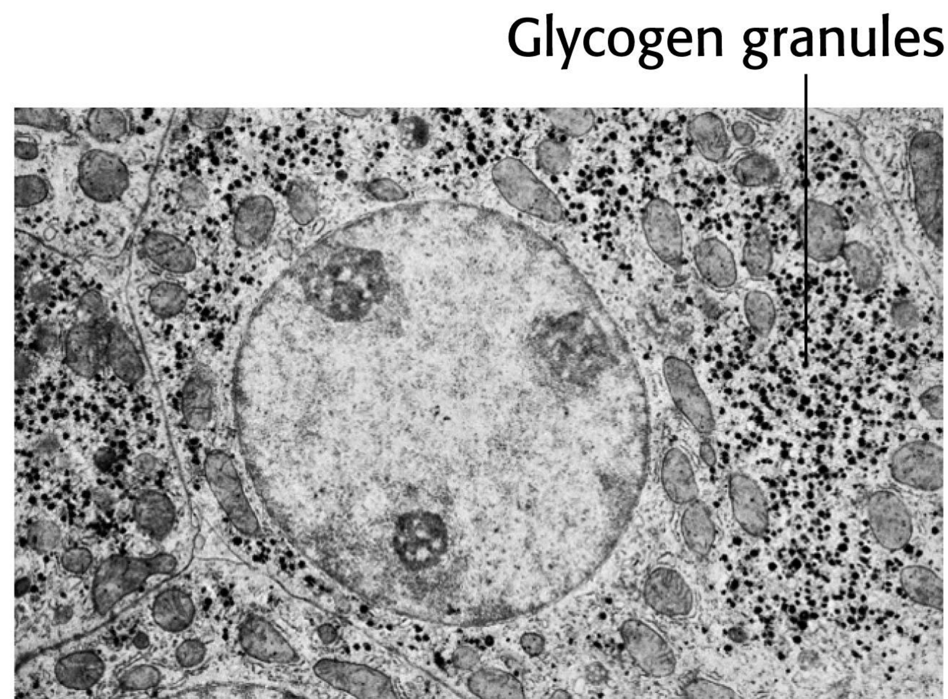


Figure 21-16
Biochemistry, Sixth Edition

Synthesis of glycogen **Muscle, liver:**

(hexokinase, glucokinase)

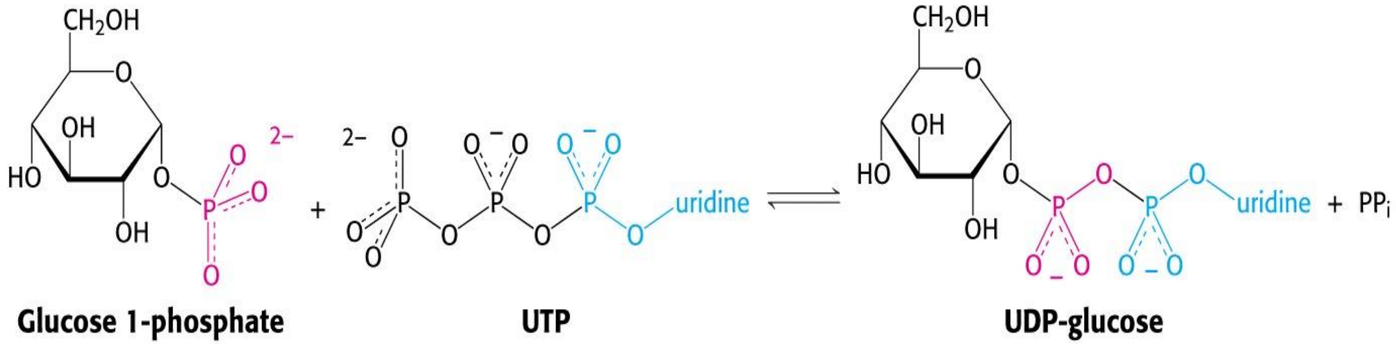
D-glucose + ATP → D-glucose-6-phosphate + ADP

(phosphoglucomutase)

glucose-6-phosphate ↔ glucose-1-phosphate

(UDP-glucose pyrophosphorylase)

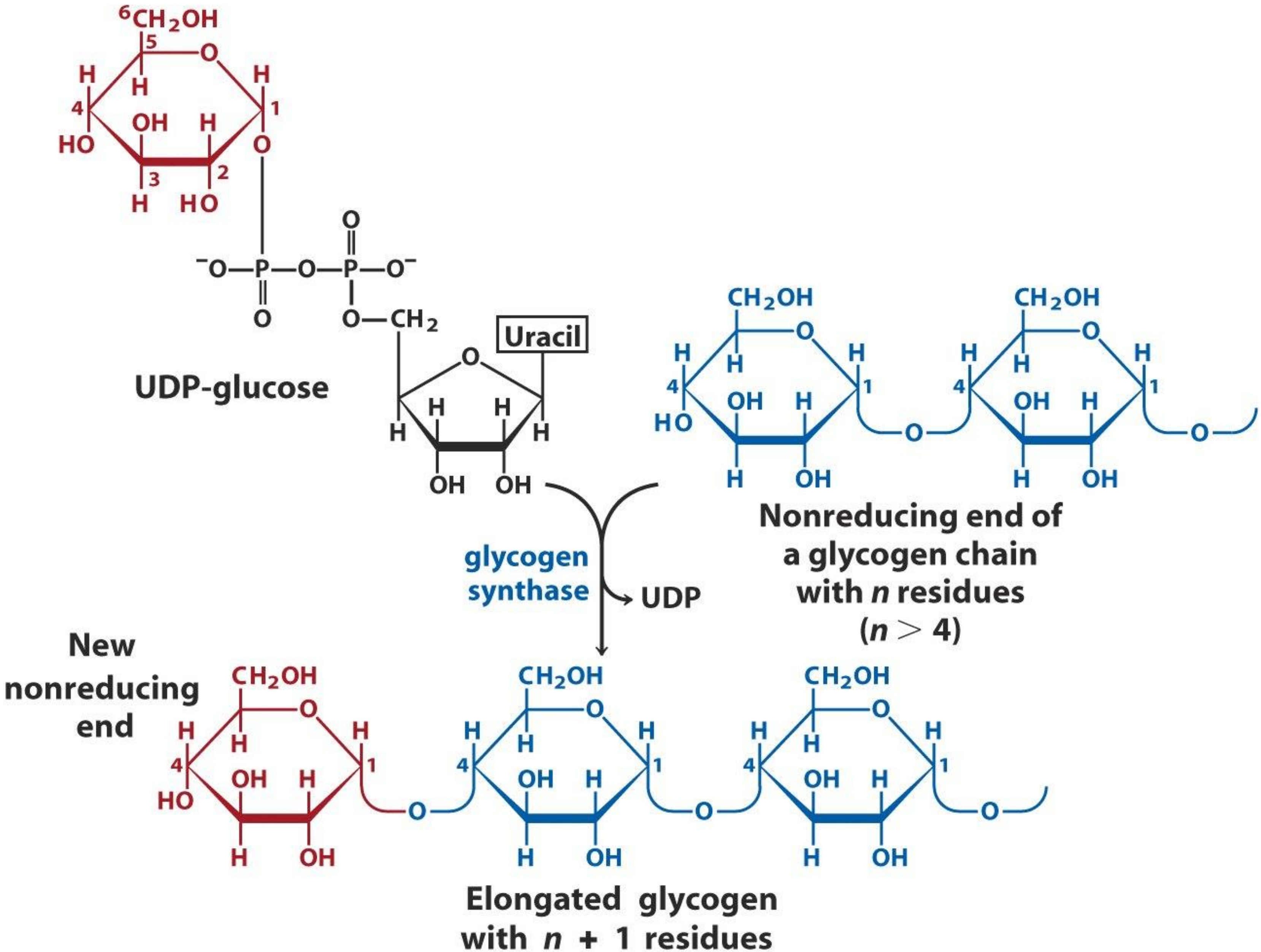
glucose-1-phosphate + UTP → UDP-glucose + PP_i

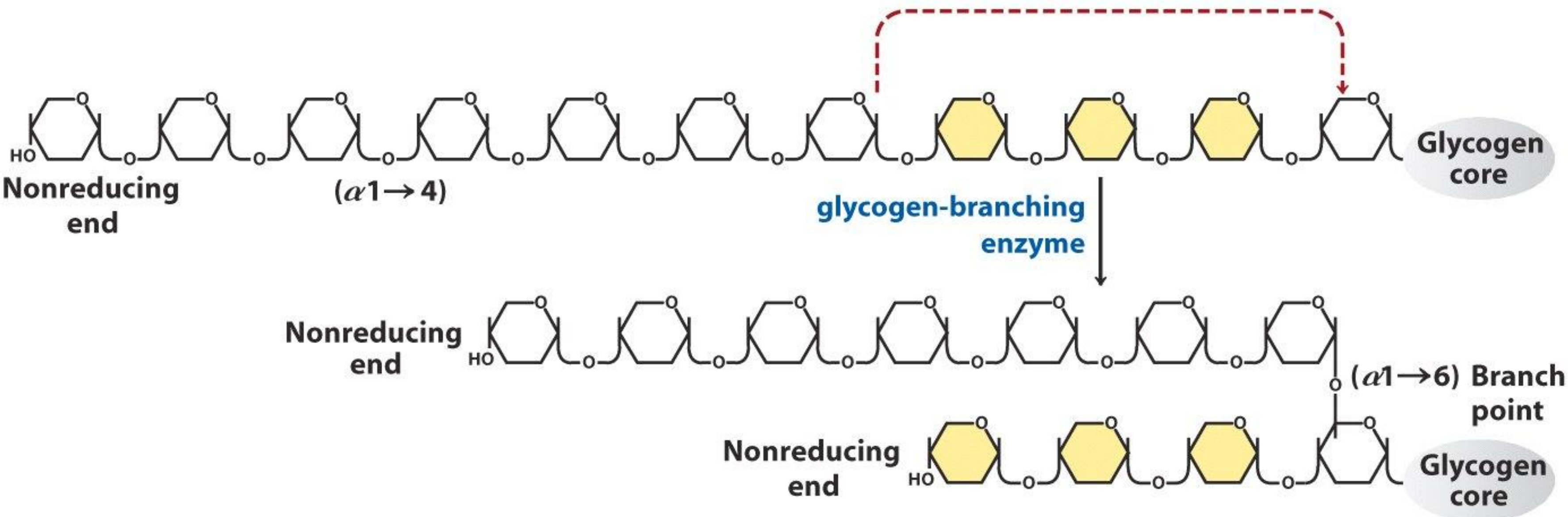


(Glycogen synthase)

(Gycogenin)

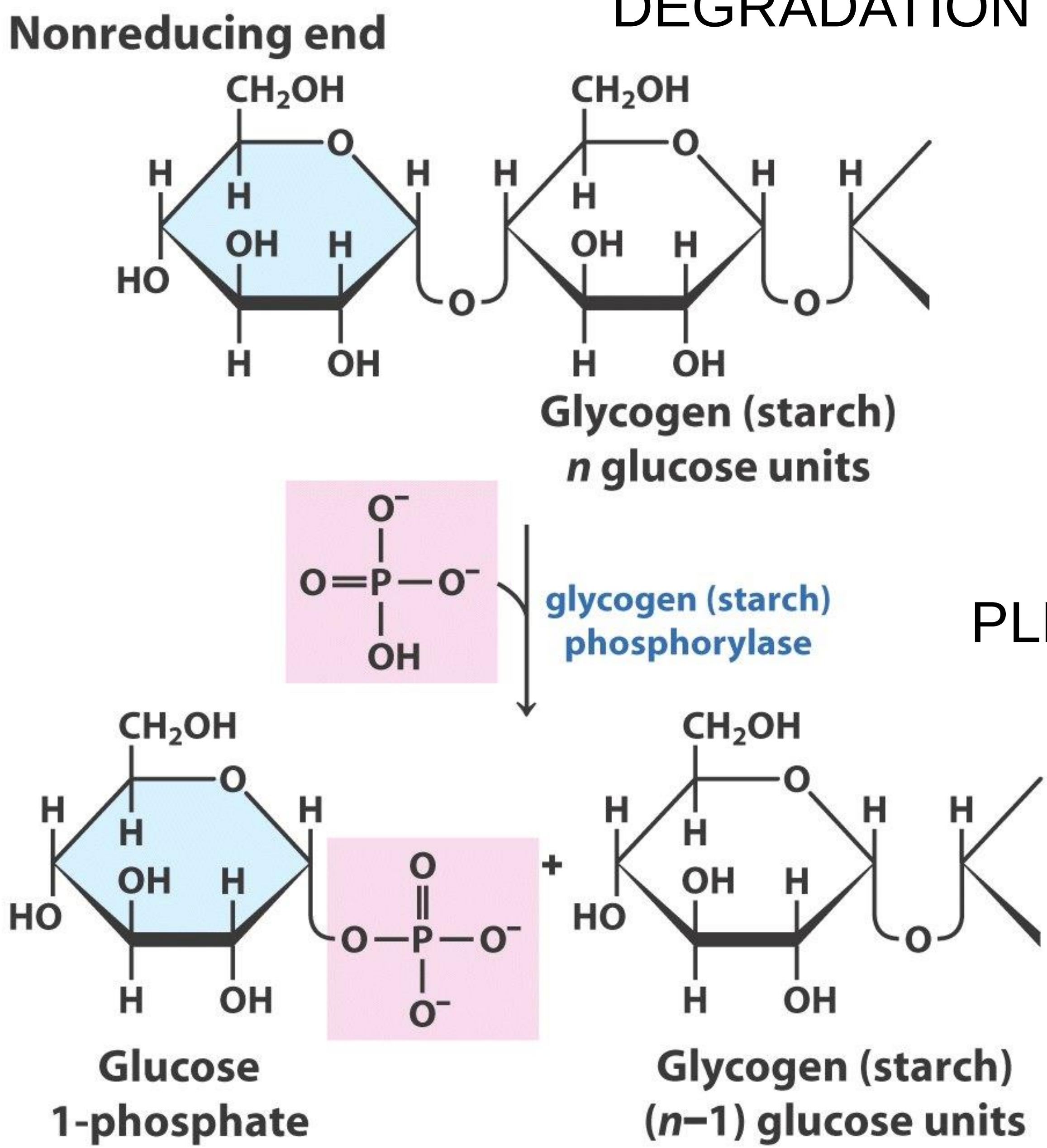
(Branchig enzyme)


UDP-glucose
Uracil
glycogen synthase
UDP
Nonreducing end of a glycogen chain with n residues (n > 4)
New nonreducing end
Elongated glycogen with n + 1 residues



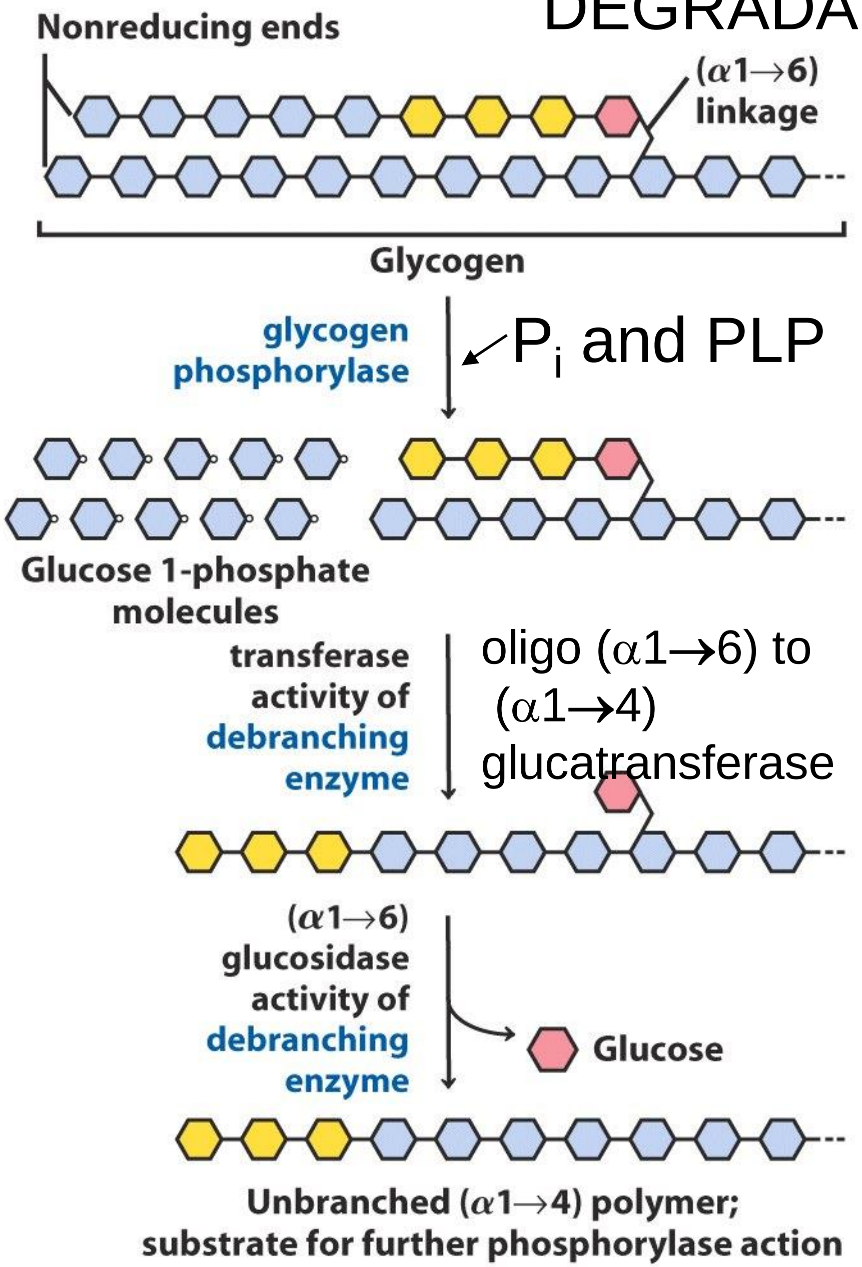
HO
Nonreducing end
(α1→4)
Glycogen core
glycogen-branching enzyme
Nonreducing end
HO
(α1→6) Branch point
Nonreducing end
HO
Glycogen core

DEGRADATION



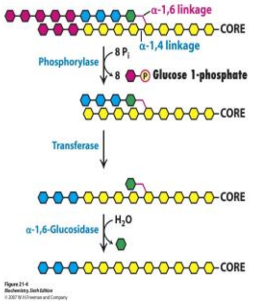
PLP

DEGRADATION



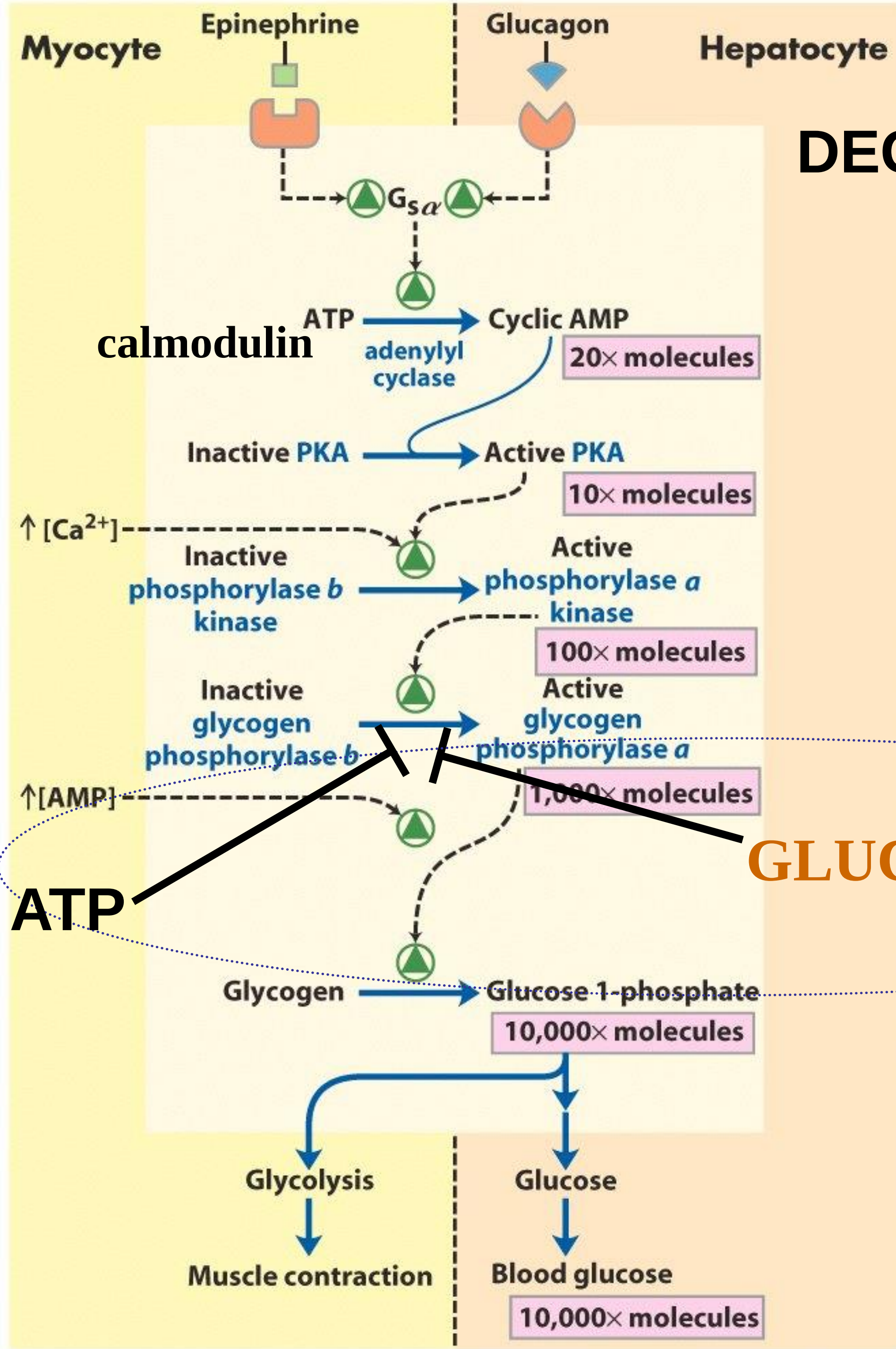
P_i and PLP

oligo (α1→6) to
(α1→4)
glucatransferase



F-15-26 5th

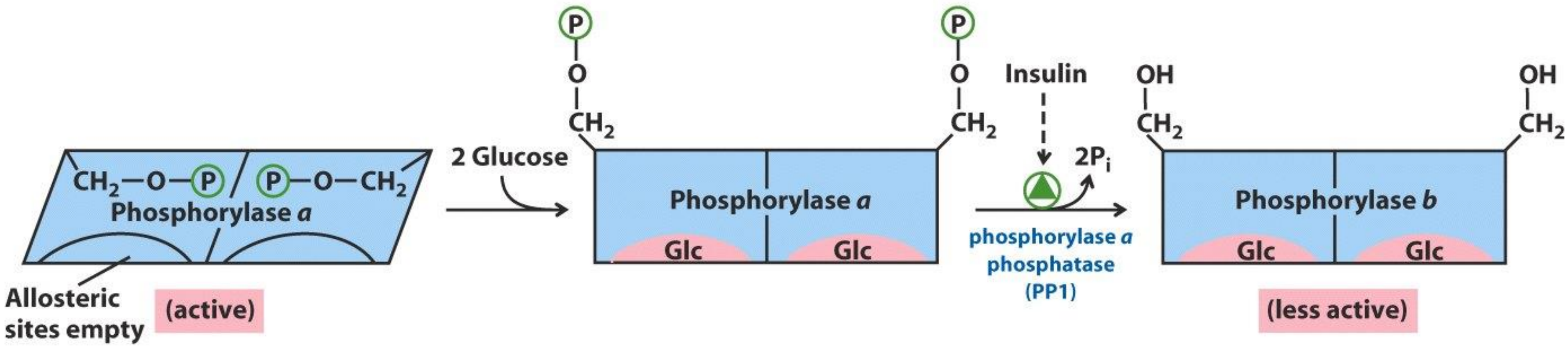
DEGRADATION



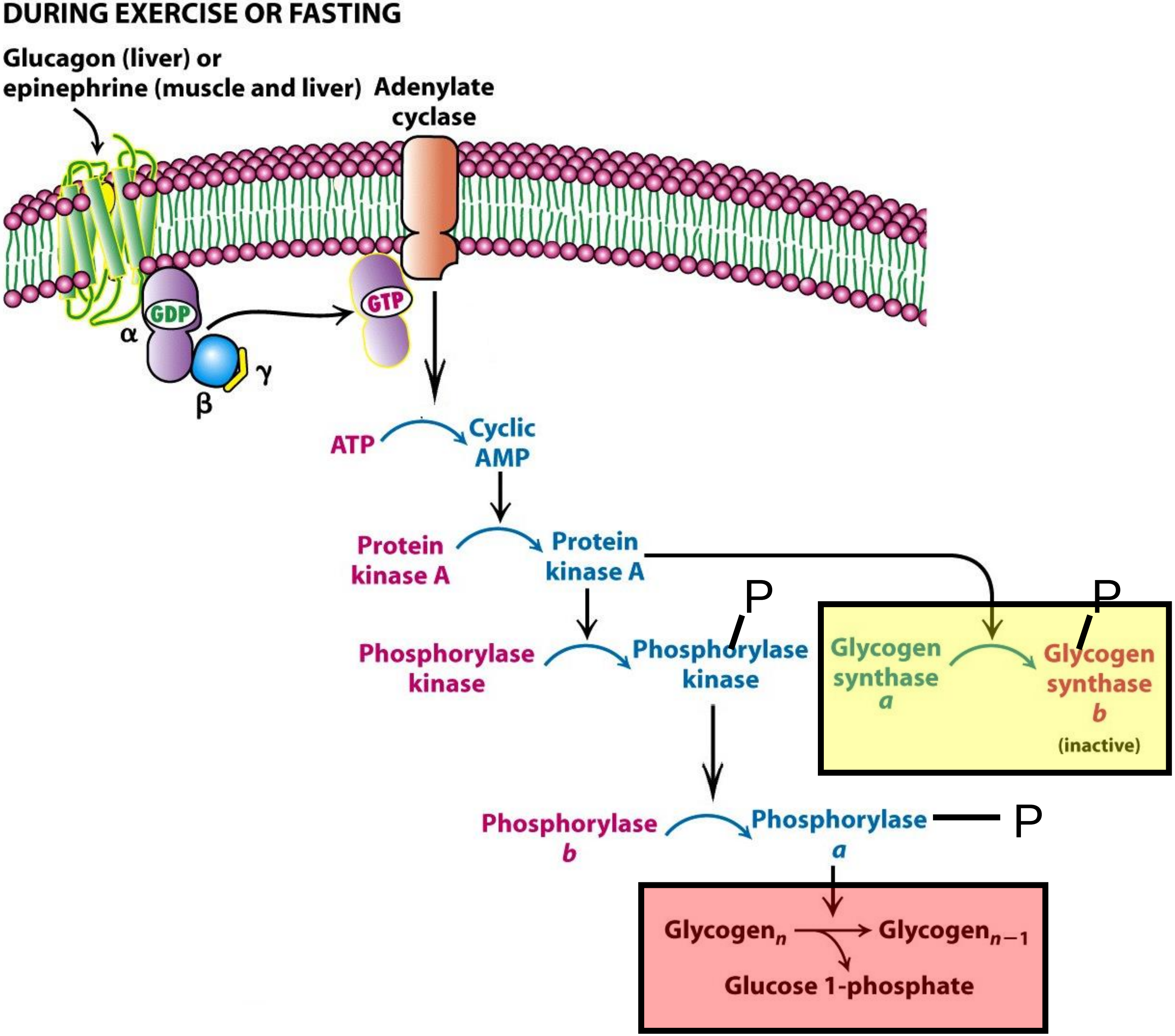
F-15-35 5th

Glycogen phosphorylase of liver as a glucose sensor

DEGRADATION



F-15-36 5th



DURING EXERCISE OR FASTING
Glucagon (liver) or
epinephrine (muscle and liver)
Adenylate
cyclase
GDP
α
β
γ
GTP
ATP
Cyclic
AMP
Protein
kinase A
Protein
kinase A
Phosphorylase
kinase
P
Phosphorylase
kinase
Glycogen
synthase
a
P
Glycogen
synthase
b
(inactive)
Phosphorylase
b
Phosphorylase
a
P
Glycogen$_n$
Glycogen$_{n-1}$
Glucose 1-phosphate

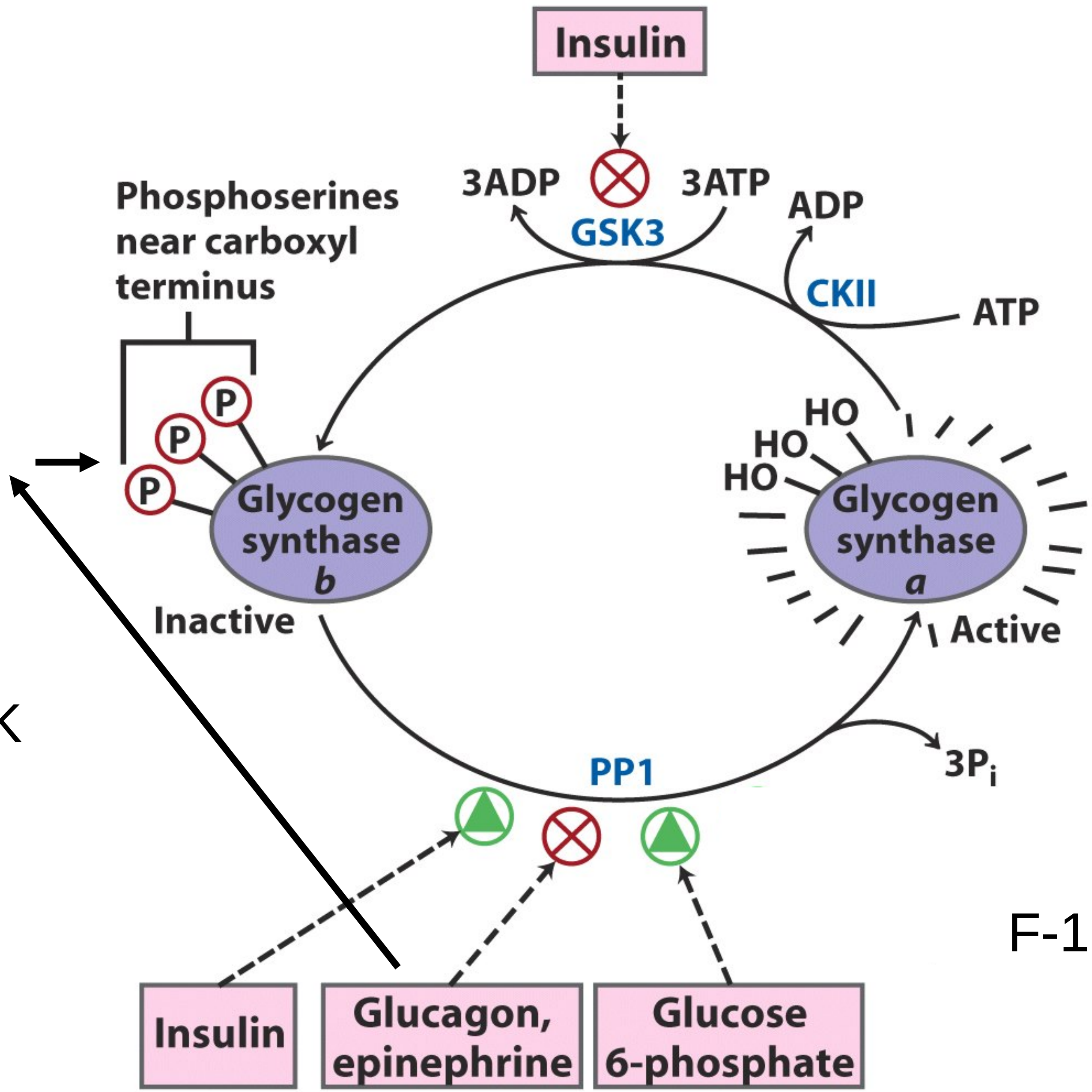
Effect of GSK3 on glycogen synthase activity

PKA

PKC

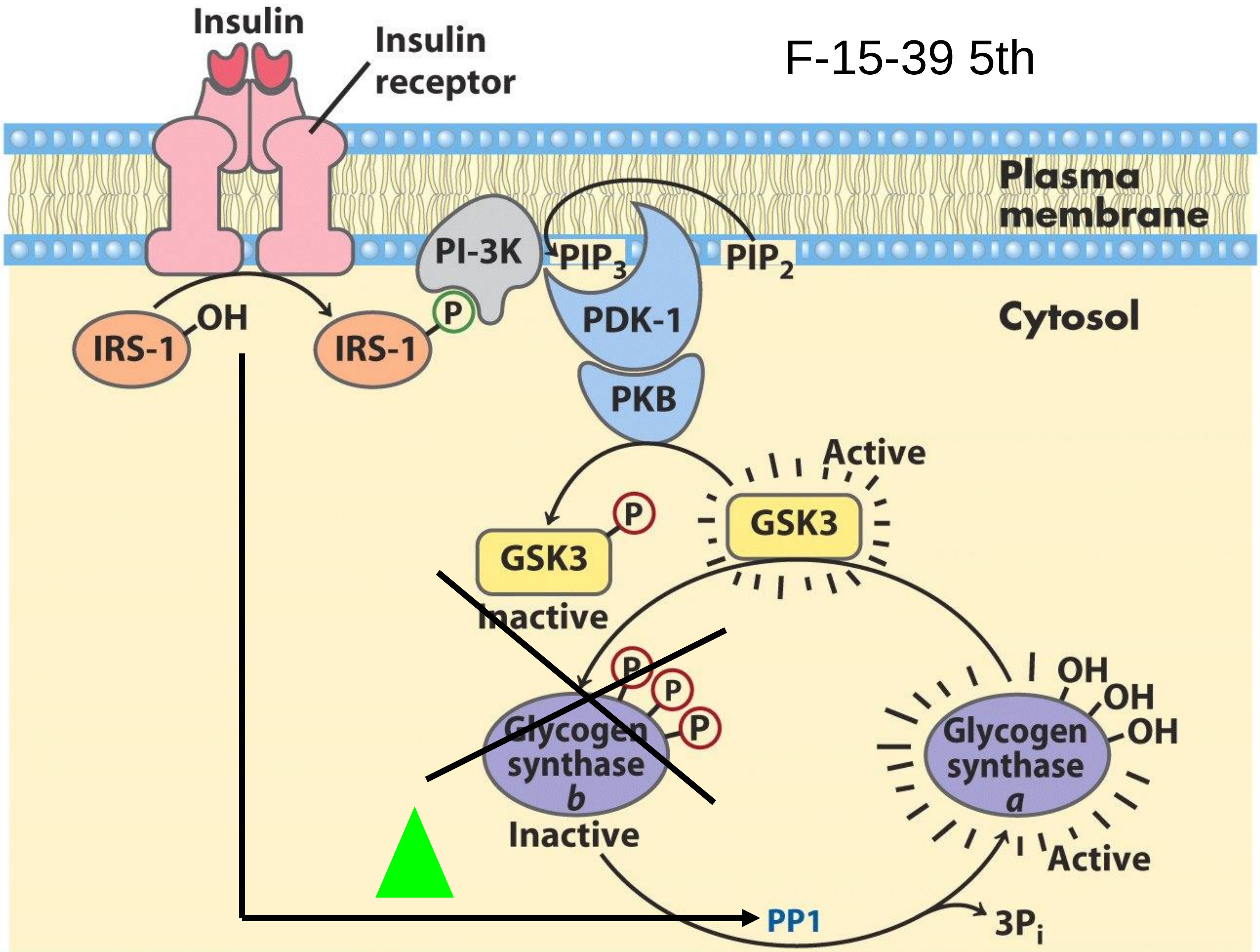
PKG

AMPK



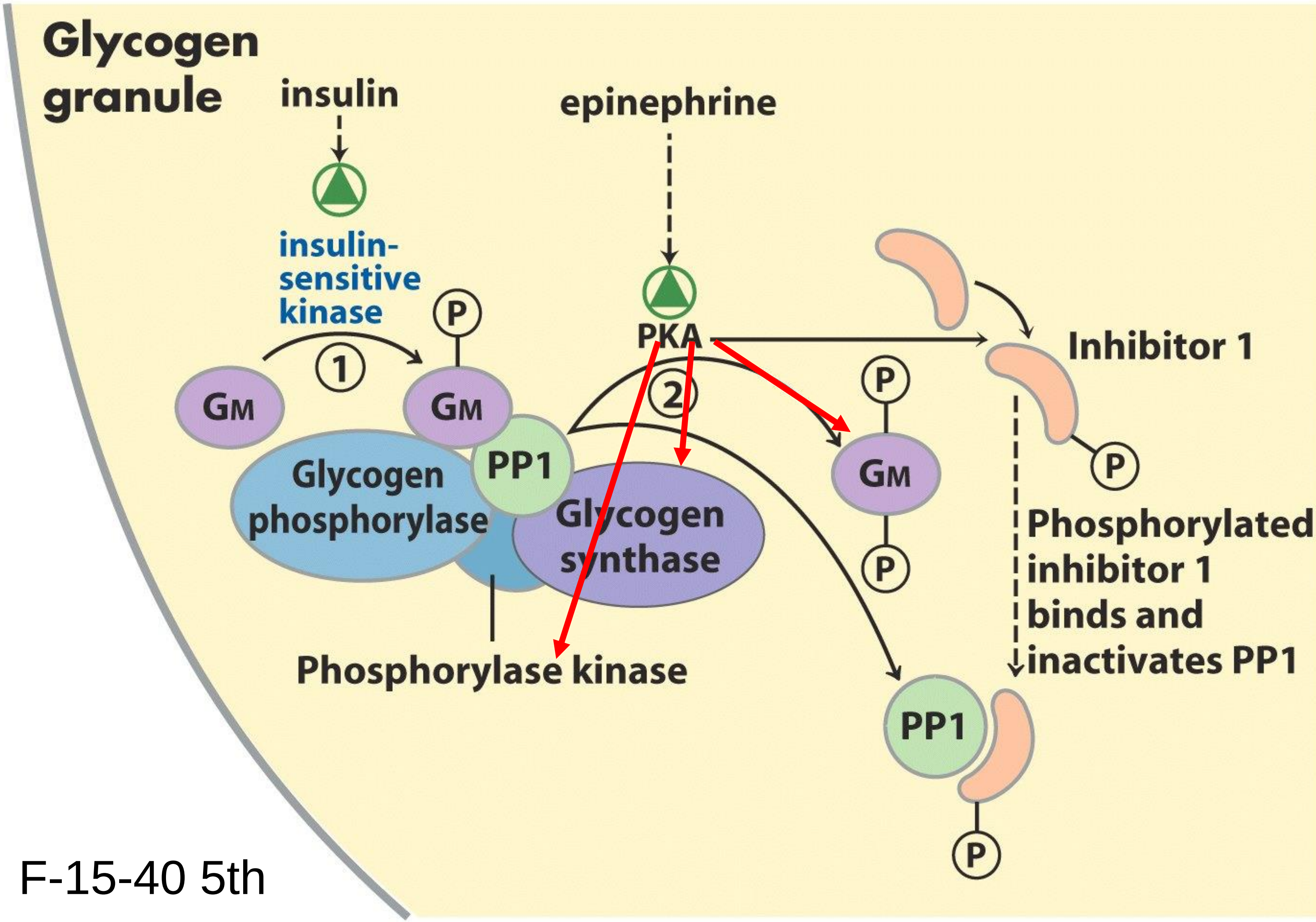
F-15-37 5th

F-15-39 5th



Insulin
Insulin receptor
Plasma membrane
Cytosol
PI-3K
PIP3
PIP2
PDK-1
PKB
IRS-1
OH
IRS-1
P
Active
GSK3
GSK3
P
Inactive
P
P
P
Glycogen synthase b
Inactive
OH
OH
OH
Glycogen synthase a
Active
PP1
3Pi

Glycogen-targeting protein G_M



F-15-40 5th

DURING EXERCISE OR FASTING

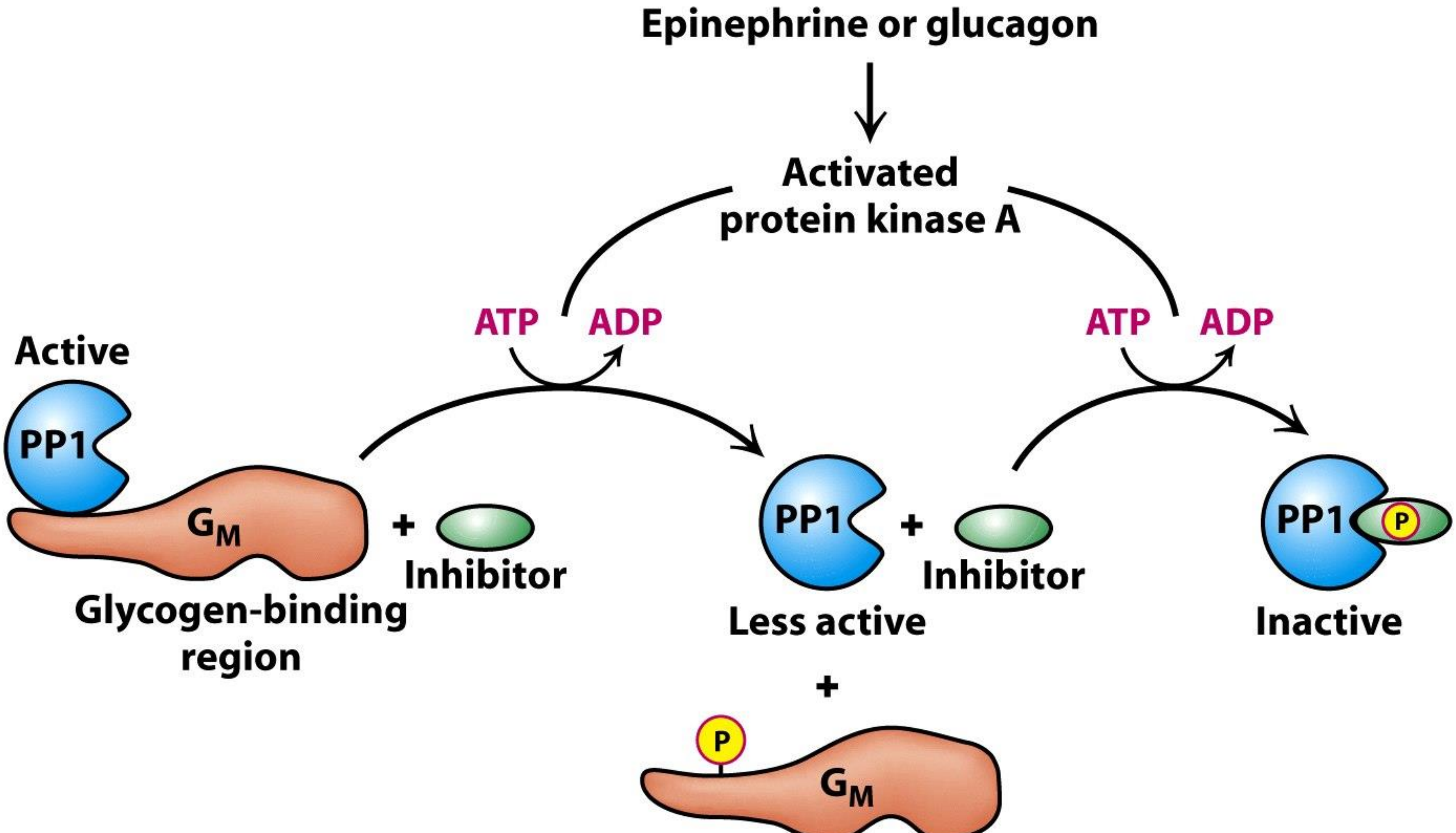
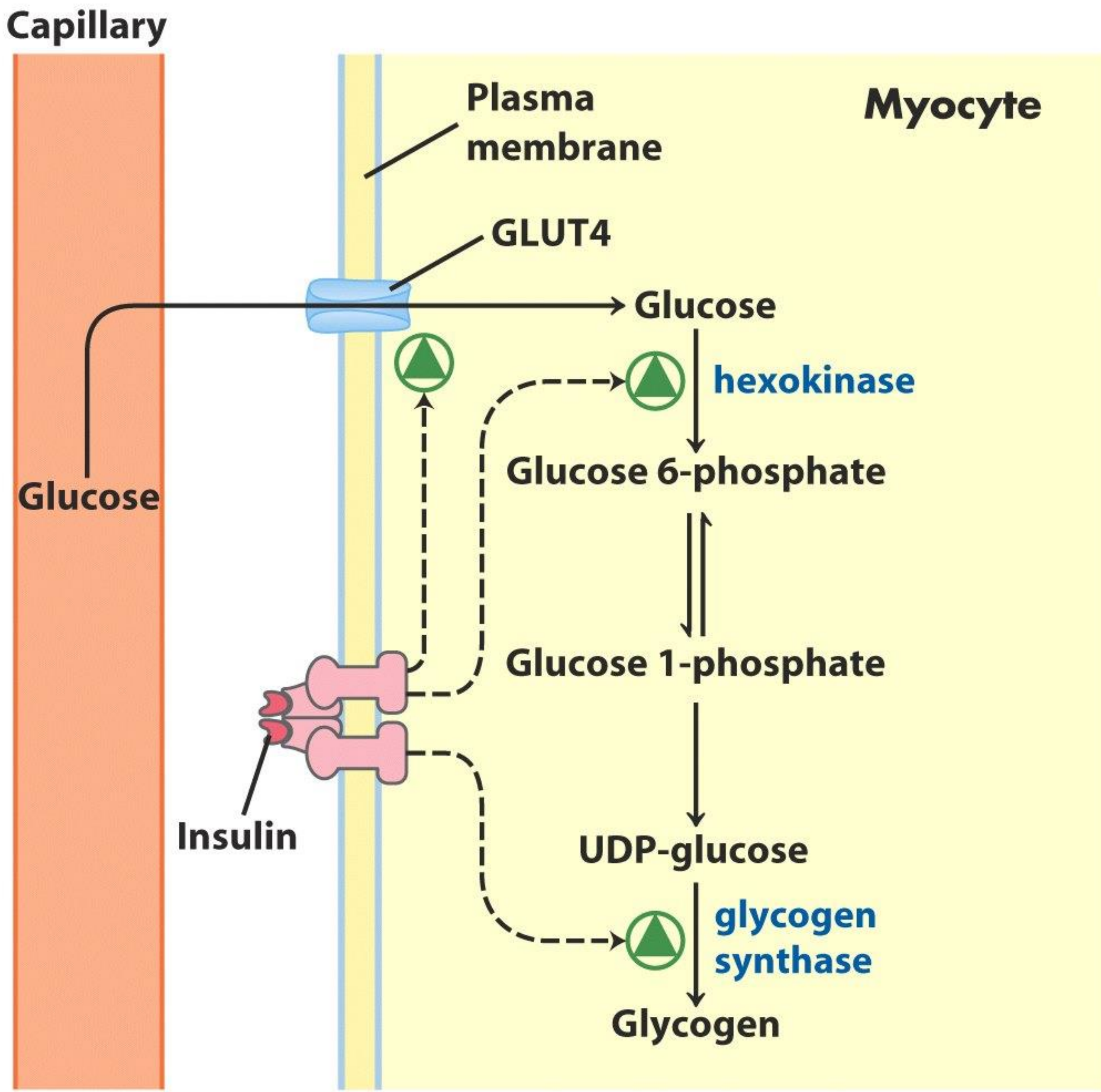
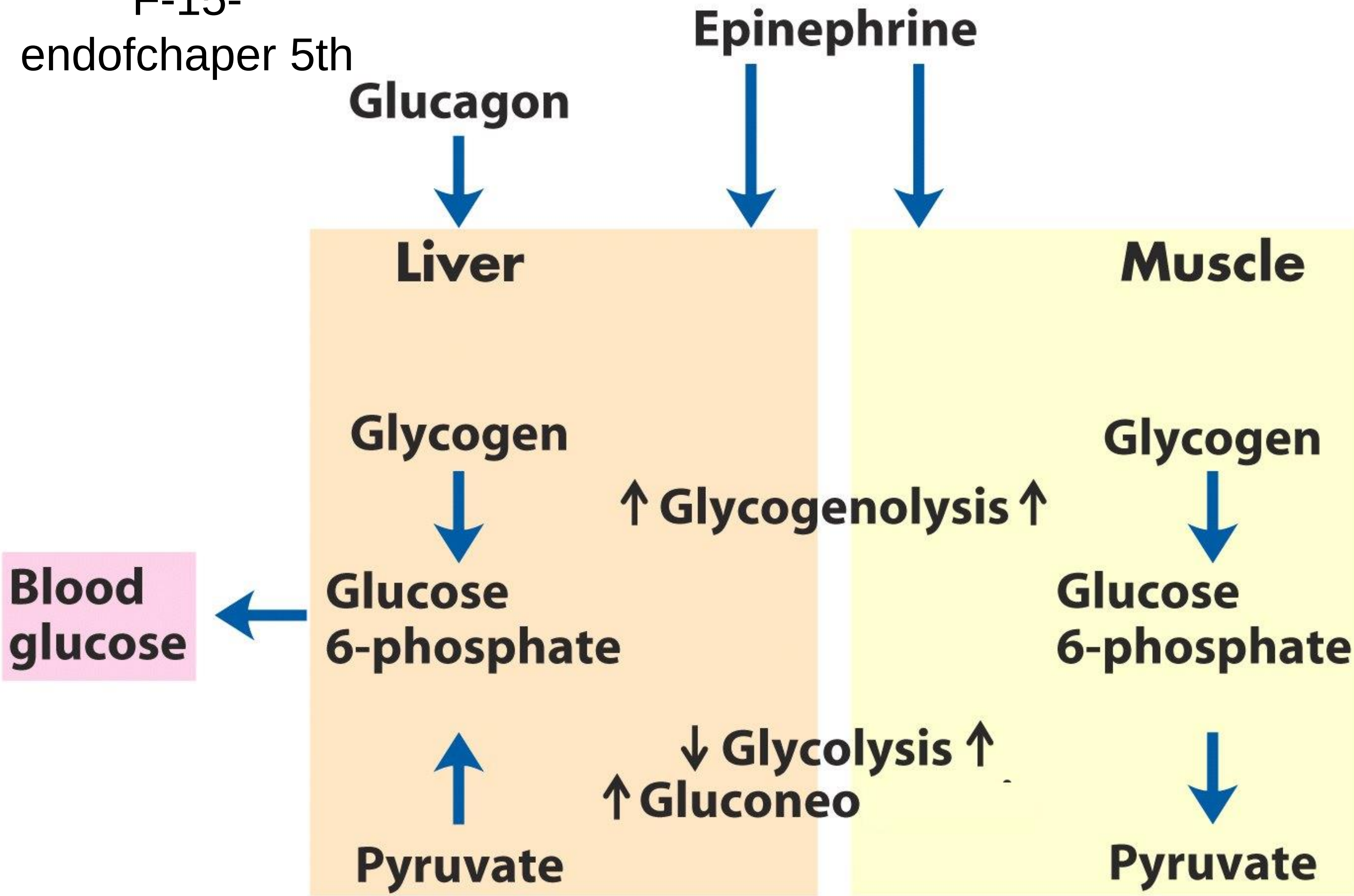


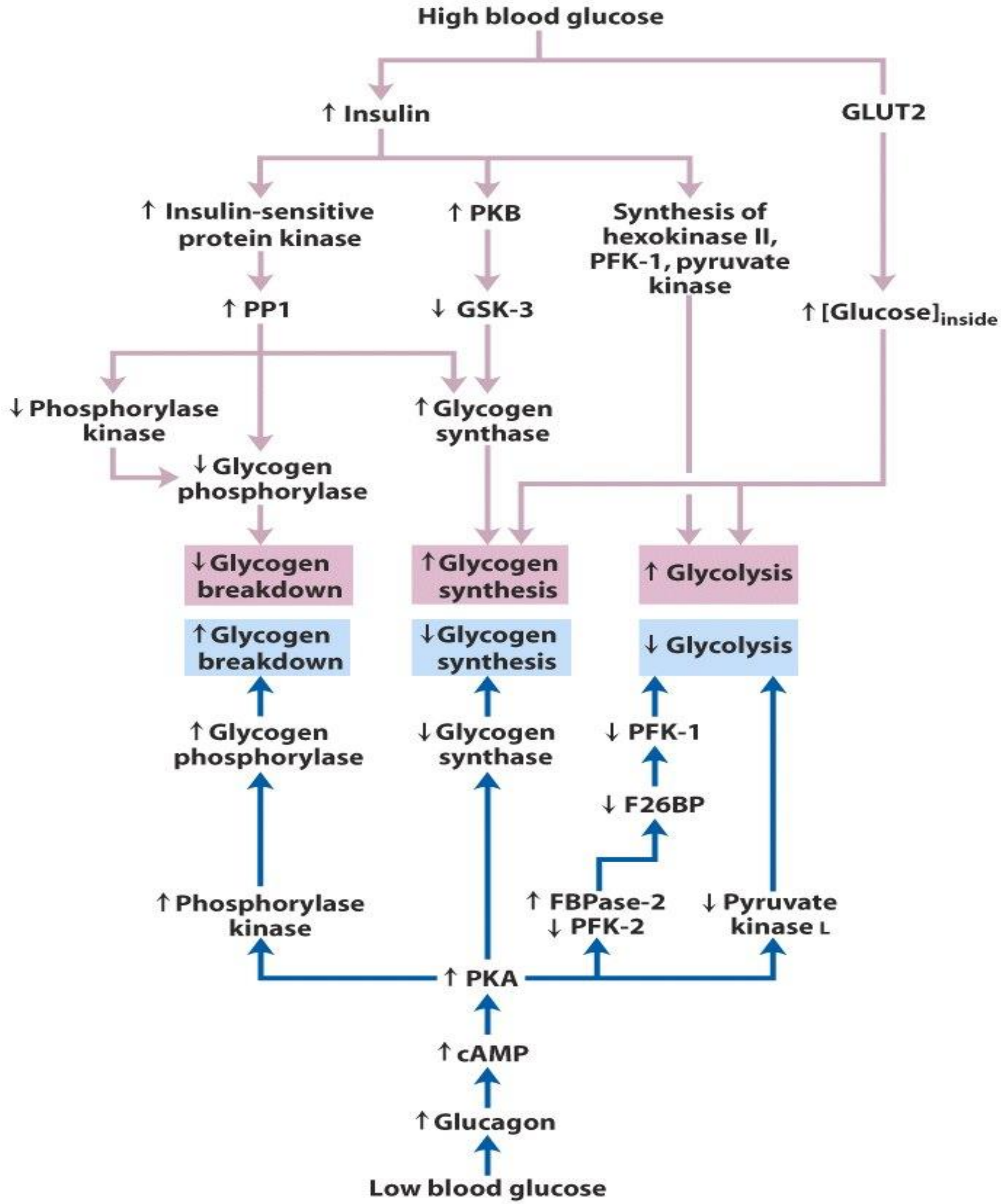
Figure 21-19
Biochemistry, Sixth Edition


Capillary
Plasma
membrane
Myocyte
GLUT4
Glucose
hexokinase
Glucose 6-phosphate
Glucose
Glucose 1-phosphate
UDP-glucose
Insulin
glycogen
synthase
Glycogen

F-15-
endofchaper 5th



Regulation of carbohydrate metabolism in the hepatocyte



F-15-41 5th

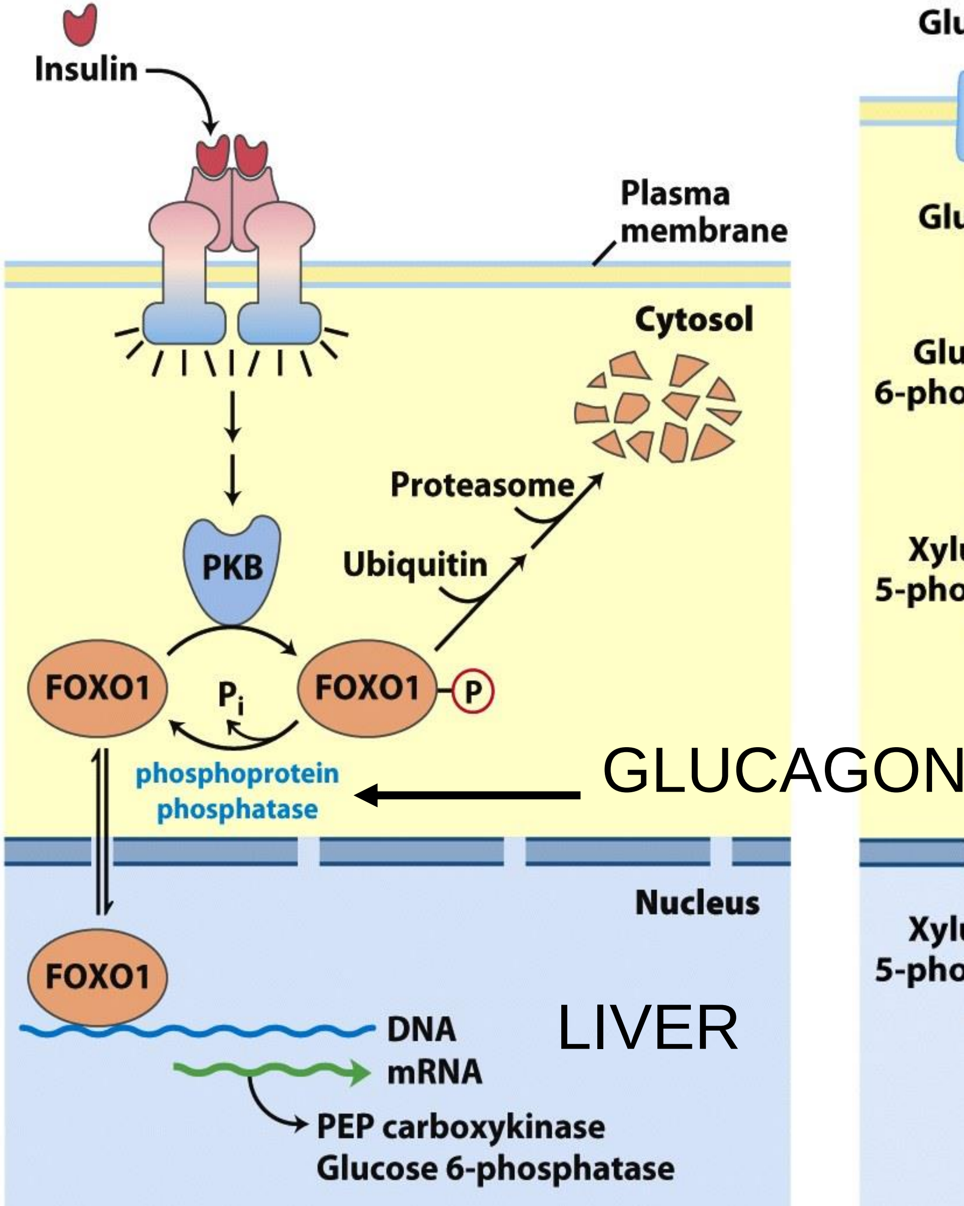


Figure 15-22
Lehninger Principles of Biochemistry, Fifth Edition

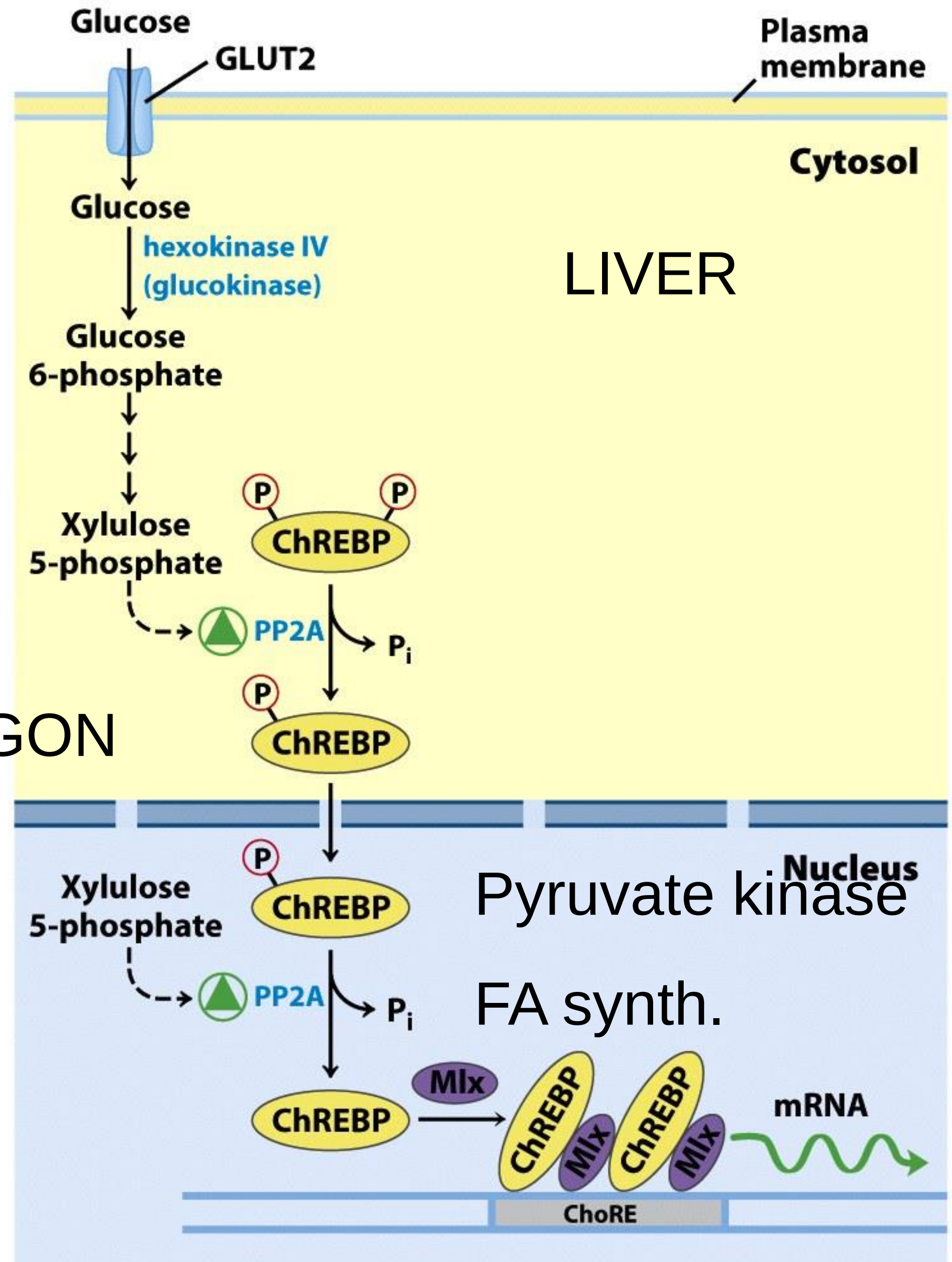


Figure 15-21
Lehninger Principles of Biochemistry, Fifth Edition

Although insulin and glucagon play important roles in regulating the response of cells to nutrients, cells also respond to carbohydrates through transcriptional regulation by the glucose responsive transcription factor ChREBP. ChREBP, carbohydrate responsive element binding protein, is a transcription factor that is activated by high levels of carbohydrates and repressed by cAMP. The activation of ChREBP by elevated carbohydrate levels increases the activity of genes involved in glucose metabolism such as pyruvate kinase, a rate-limiting enzyme in glycolysis, increasing the overall rate of utilization of carbohydrates. Excess carbohydrates also increase the transcription of genes that convert carbohydrates to triglycerides in the liver for storage in adipose tissue. cAMP regulates ChREBP activity by activating PKA, which phosphorylates ChREBP. Phosphorylation of ChREBP at ser(196) inactivates nuclear import and phosphorylation at Thr(666) prevents DNA binding by ChREBP. A metabolite of glucose activates protein phosphatase PP2A that then dephosphorylates both sites on ChREBP in response to increased glucose levels and increases ChREBP activity. Other pathways also regulate ChREBP activity and response to nutrients. High fat diets repress ChREBP activation by increasing AMP in liver cells, activating the AMP kinase. Phosphorylation of ChREBP by AMP kinase inactivates ChREBP and blocks glucose induction of ChREBP, linking dietary fatty acids to the regulation of carbohydrate metabolism.

Glycogen storage disorders (Glycogenosis)

- 12 different disorders
- defects in the enzymes or regulation of glycogen synthesis or breakdown
- Pathological glycogen accumulation in the liver, heart and skeletal muscle, kidney
- Hypoglycemia is the leading symptom in each type
- Definitive diagnosis: tissue biopsy

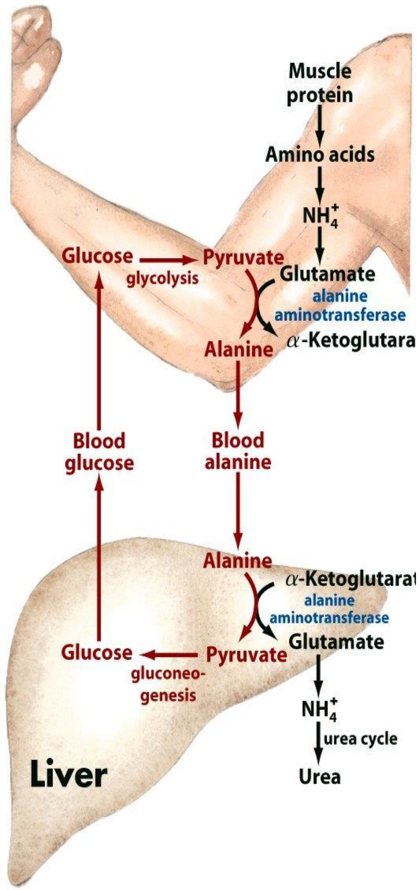
Glycogen storage disorders (Glycogenosis)

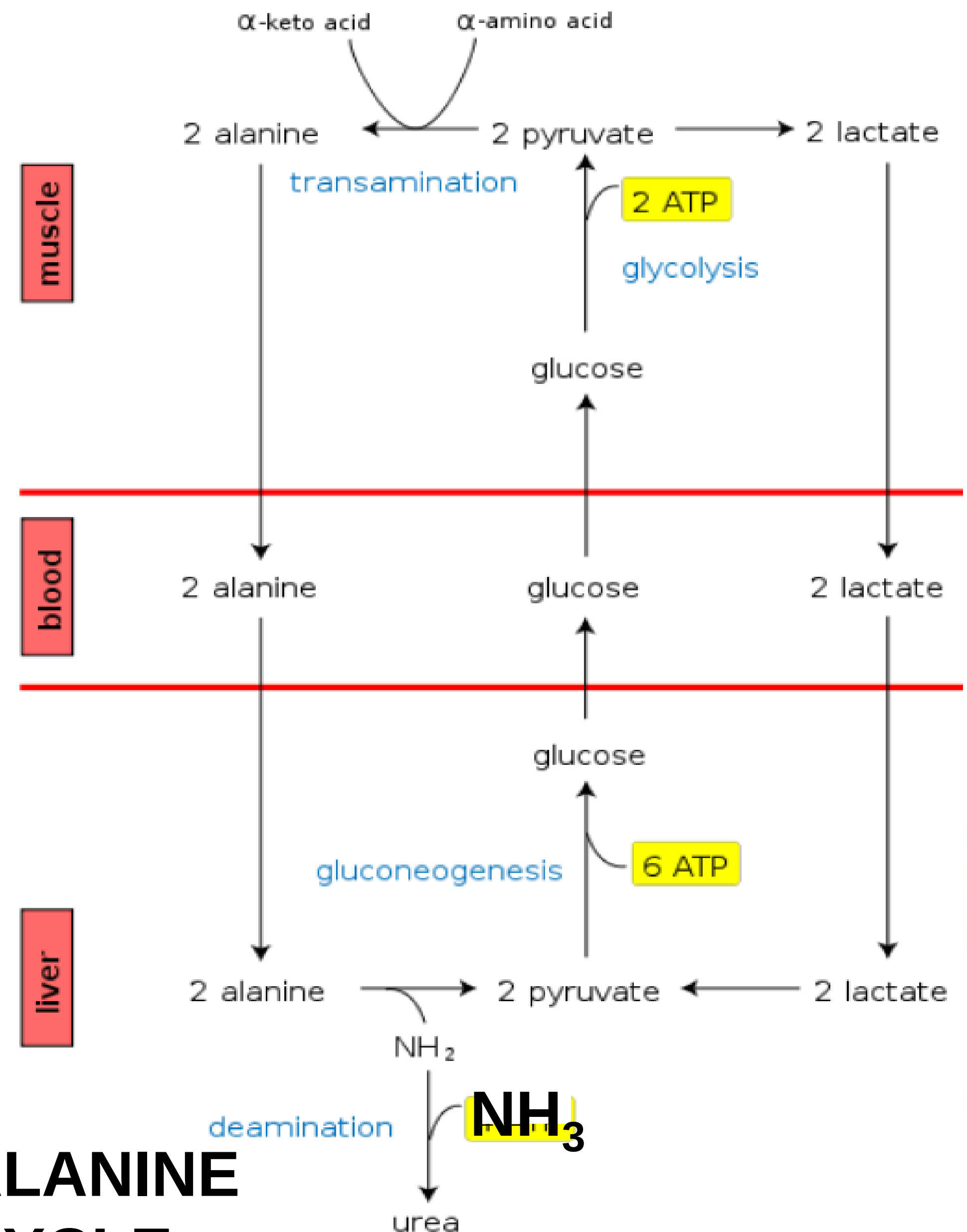
TABLE 1 Glycogen Storage Diseases of Humans

T 15-1

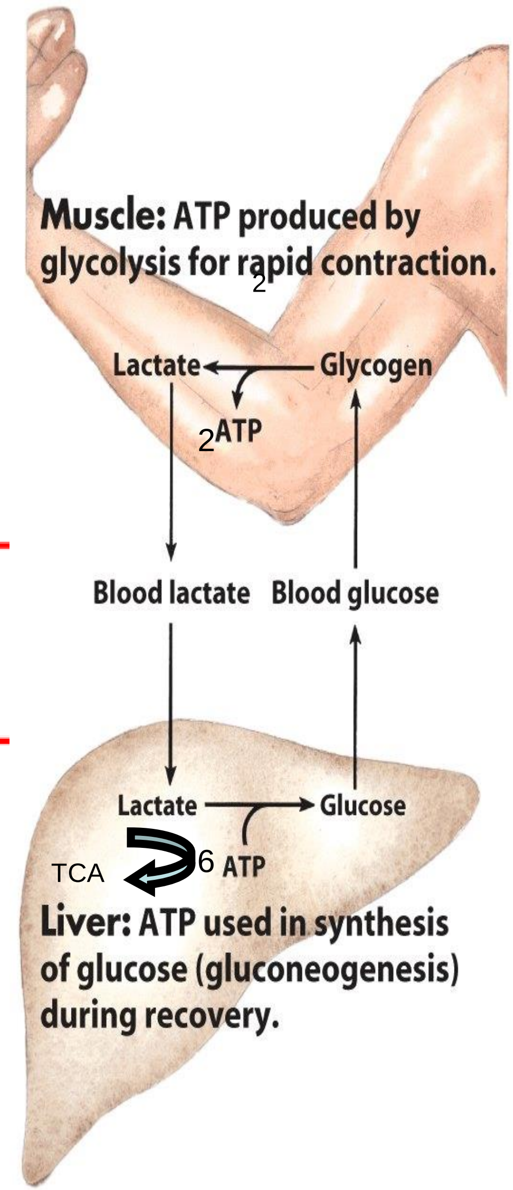
Type (name)	*Enzyme affected*	*Primary organ affected*	*Symptoms*
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone bodies, early death
Type Ia (von Gierke's)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P_i transporter	Liver	As in Ia
Type II (Pompe's)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori's or Forbes's)	Debranching enzyme	Liver, skeletal and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen's)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle's)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers's)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui's)	Muscle PFK-1	Muscle, erythrocytes	As in V; also hemolytic anemia
Type VIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction

CORI and ALANIN CYCLE



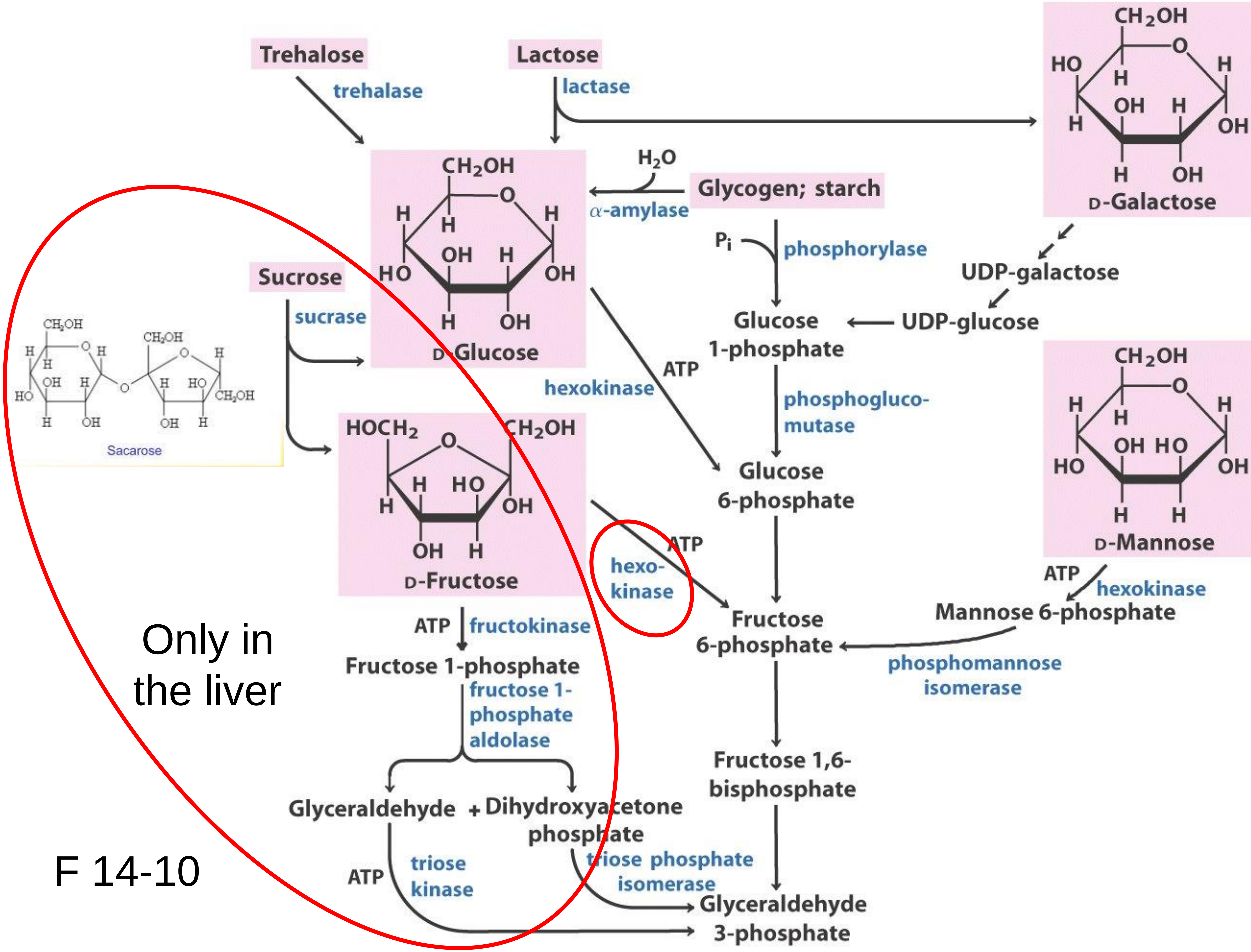


ALANINE CYCLE



CORI CYCLE

Fructose metabolism


Trehalose
trehalase
Lactose
lactase
D-Galactose
Glycogen; starch
H_2O
α-amylase
P_i
phosphorylase
UDP-galactose
UDP-glucose
Glucose 1-phosphate
phosphogluco-mutase
D-Glucose
Sucrose
sucrase
Sacarose
ATP
hexokinase
Glucose 6-phosphate
D-Fructose
ATP
hexo-kinase
Fructose 6-phosphate
D-Mannose
ATP
hexokinase
Mannose 6-phosphate
phosphomannose isomerase
ATP
fructokinase
Fructose 1-phosphate
fructose 1-phosphate aldolase
Fructose 1,6-bisphosphate
Glyceraldehyde + Dihydroxyacetone phosphate
ATP
triose kinase
triose phosphate isomerase
Glyceraldehyde 3-phosphate
Only in the liver

F 14-10

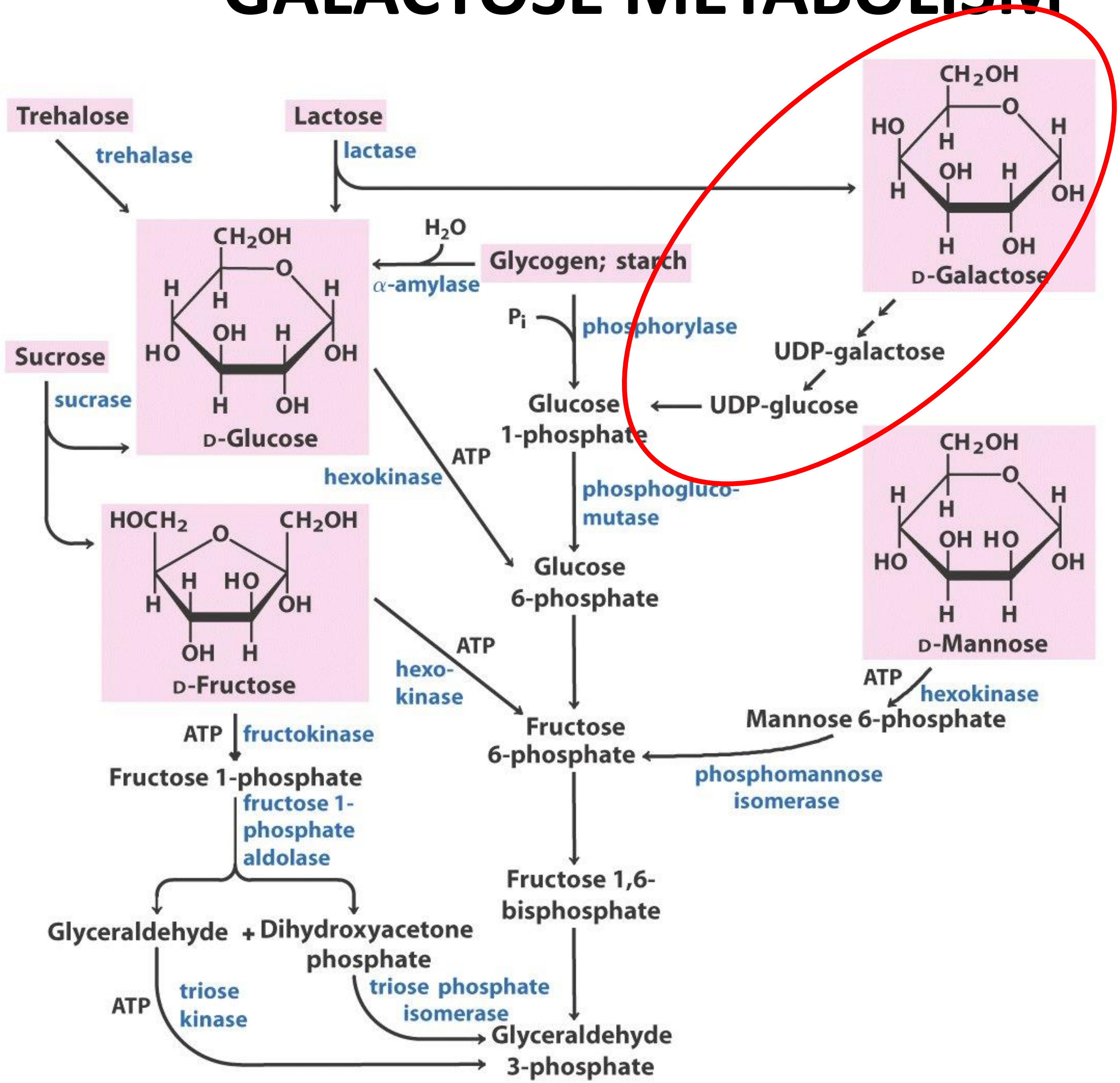
Fructosuria

- essentially benign condition, follows autosomal recessive inheritance
- deficiency of **hepatic fructokinase** enzyme
- as fructose can not be broken down it is excreted in the urine

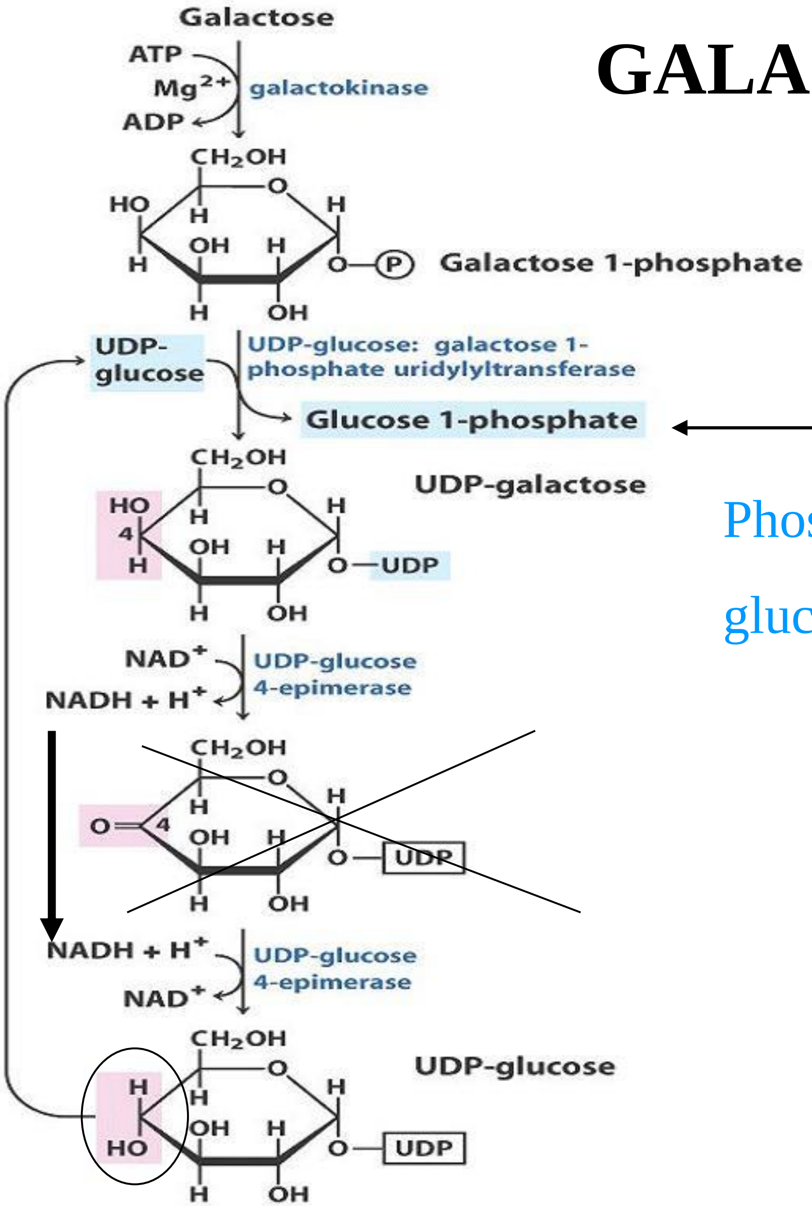
Fructose intolerance(Fructosaemia)

- Deficiency of **Fructose-1-P aldolase** enzyme (Aldolase B) (incidence: 1:20000)
- Fr-1-P accumulation in the liver
- decreased P_i and ATP levels
- Inhibition of glycolysis, glycogenolysis and gluconeogenesis
- Lactic acidosis+ hypoglycemia
- Vomiting, liver malfunction, in severe cases liver and kidney failure
- Treatment: dietary fructose (and cane-sugar) restriction

GALACTOSE METABOLISM



GALACTOSE METABOLISM

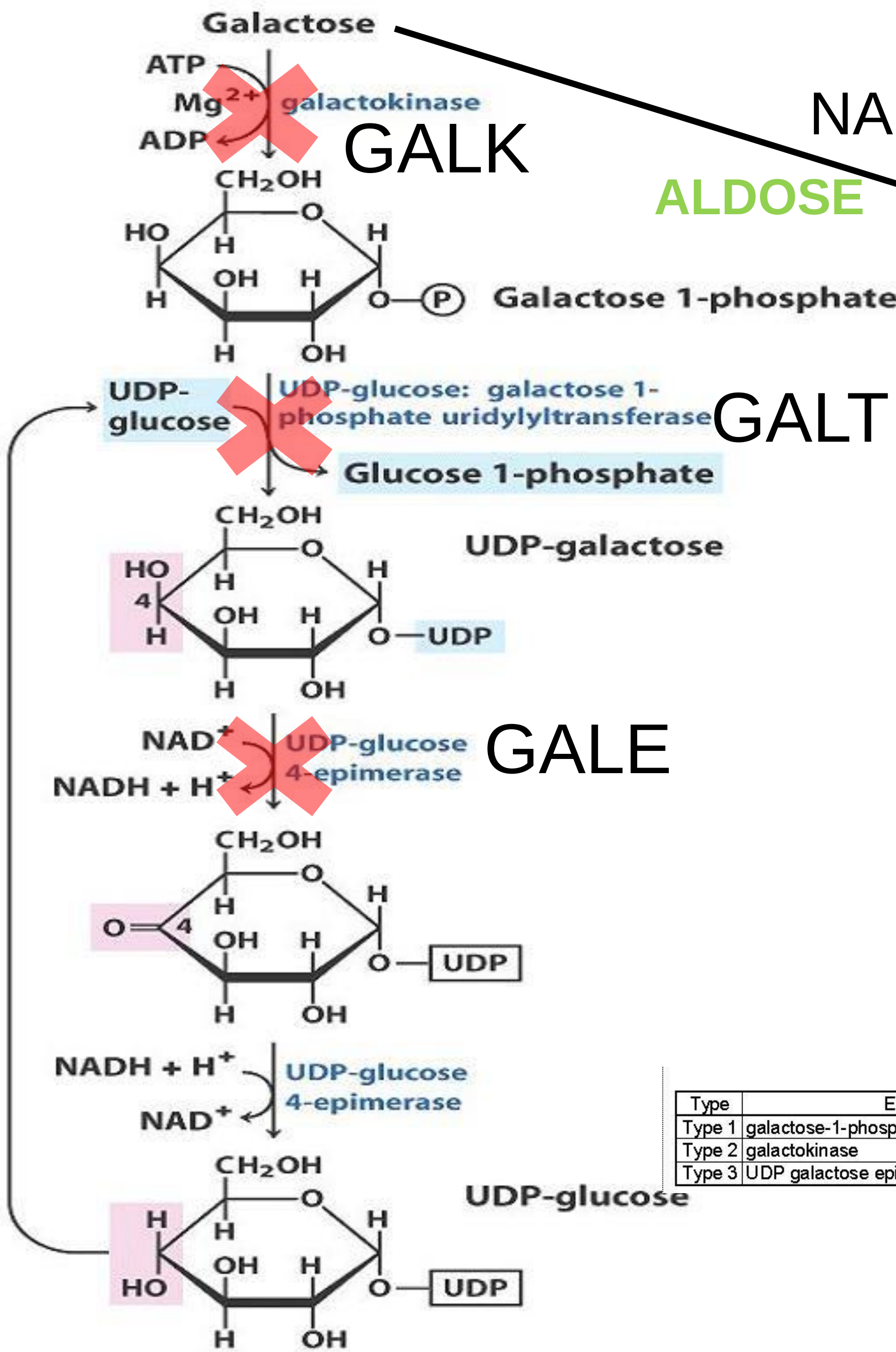


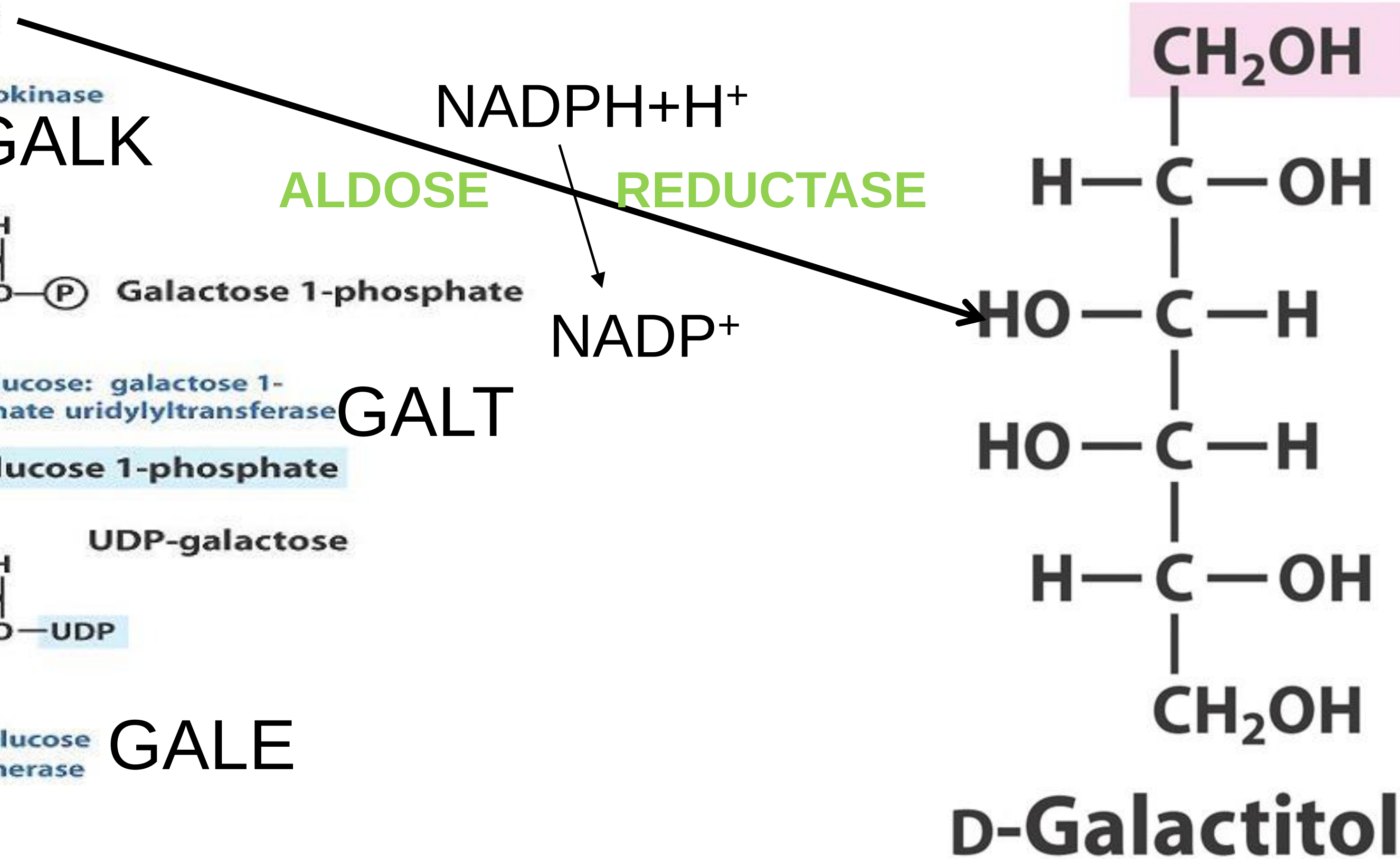
Glu-6-P → **GLYCOLYSIS**

Phospho – glucomutase

F 14-12

GALACTOSEMIAS:





GALACTOSEMIAS:

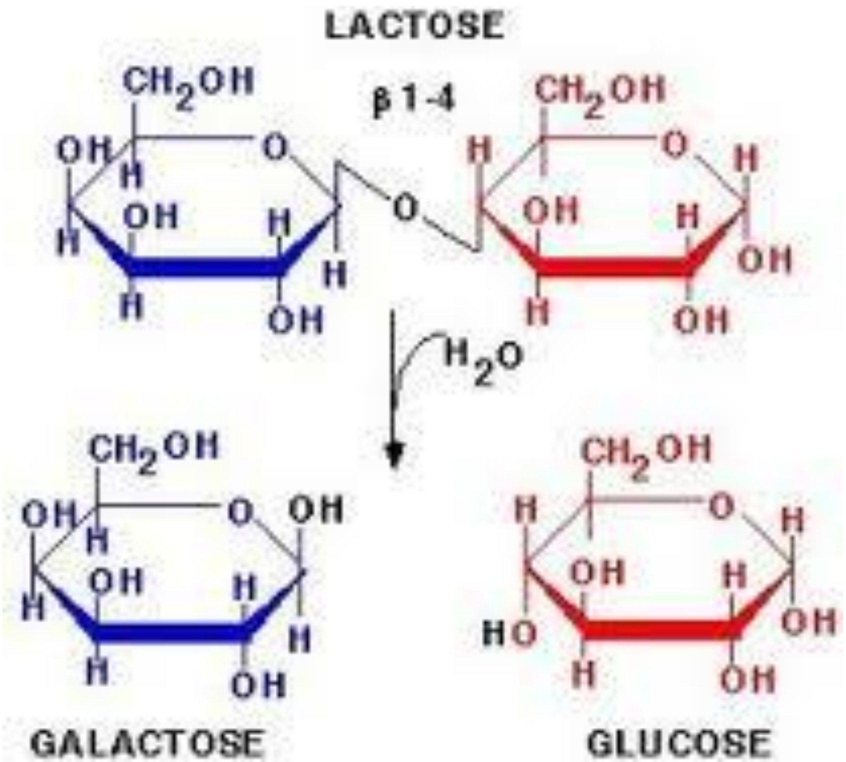
Type	Enzyme	Name
Type 1	galactose-1-phosphate uridyl transferase	classic galactosemia
Type 2	galactokinase	galactokinase deficiency
Type 3	UDP galactose epimerase	galactose epimerase deficiency, UDP-Galactose-4-epimerase deficiency


Normal
cristalin clar
Cataracta
cristalin opac

Lactose intolerance

(Milk sugar intolerance)

Symptoms:
- Osmotic diarrhea
- Abdominal discomfort, bloating, flatulence

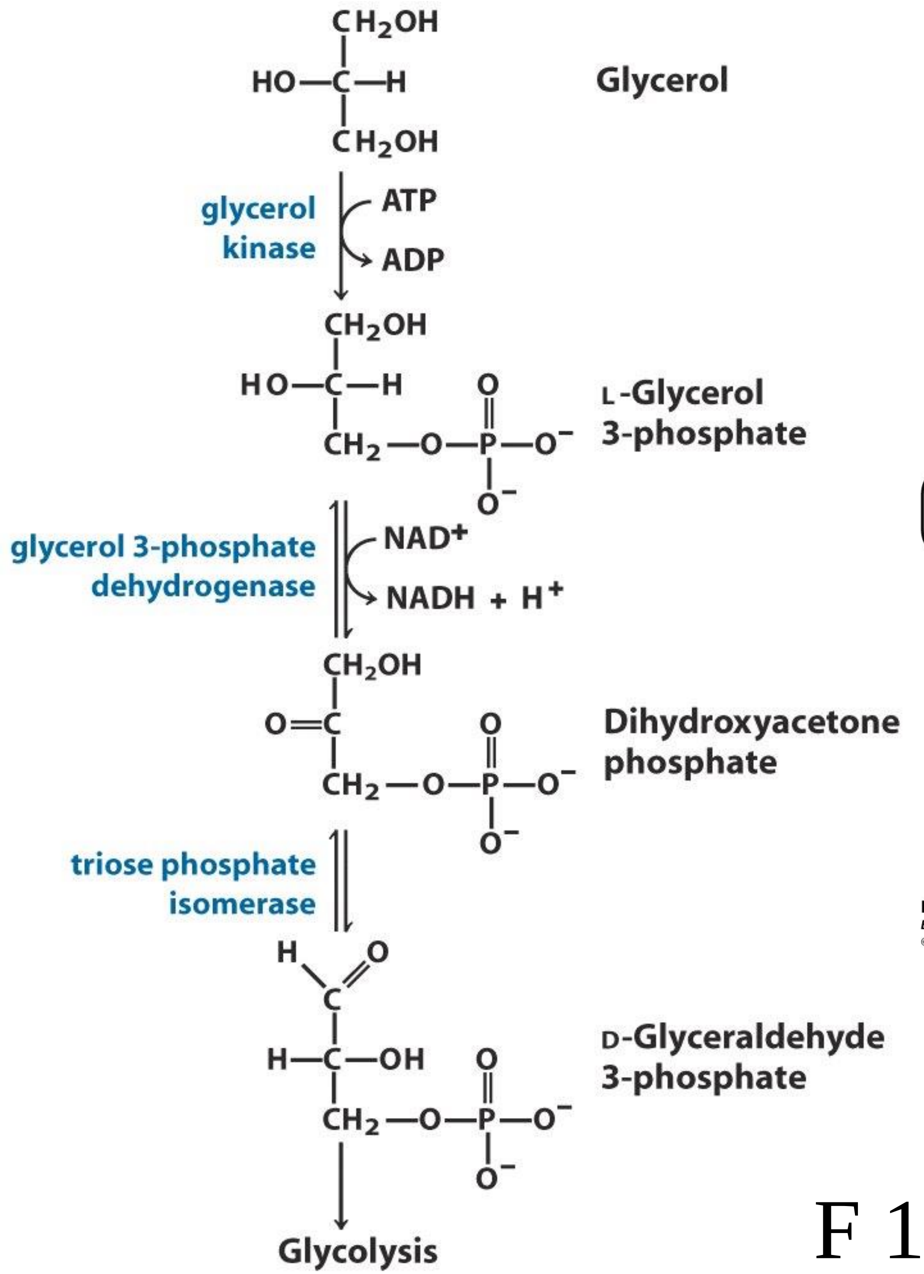


It is NOT milk protein allergy!
(Adverse immune reaction to one or more of the milk proteins)

Required enzyme:
ß-galactosidase = lactase

Treatment:
-Lactose reduced diet
-enzymatic lactase supplementation as intestine soluble capsules (pure enzyme or bacteria)
-Adaptation

Fate of glycerol in liver



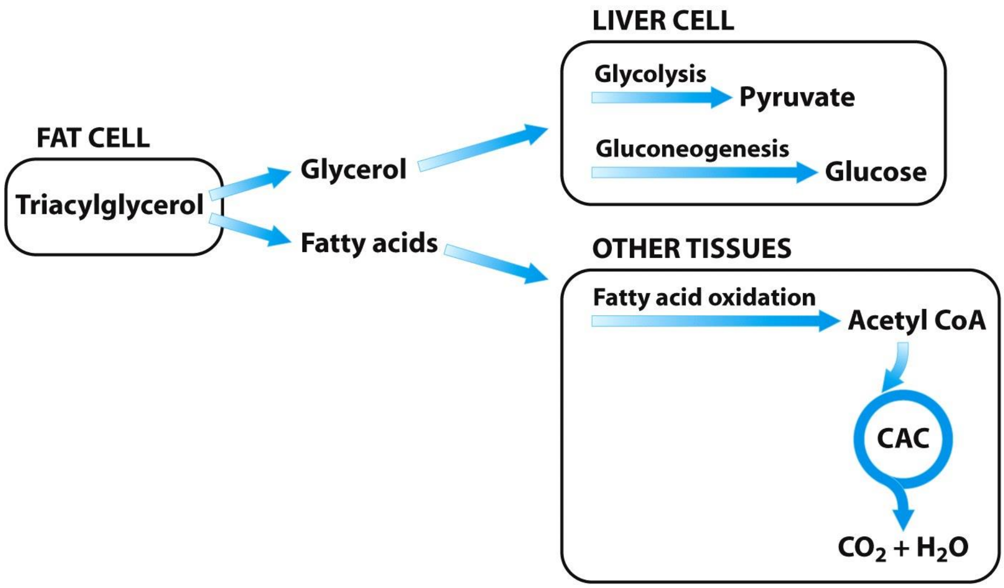


Figure 22.7
Biochemistry, Seventh Edition

F 17-4

Pentose Phosphate Pathway

Pentose Phosphate Pathway

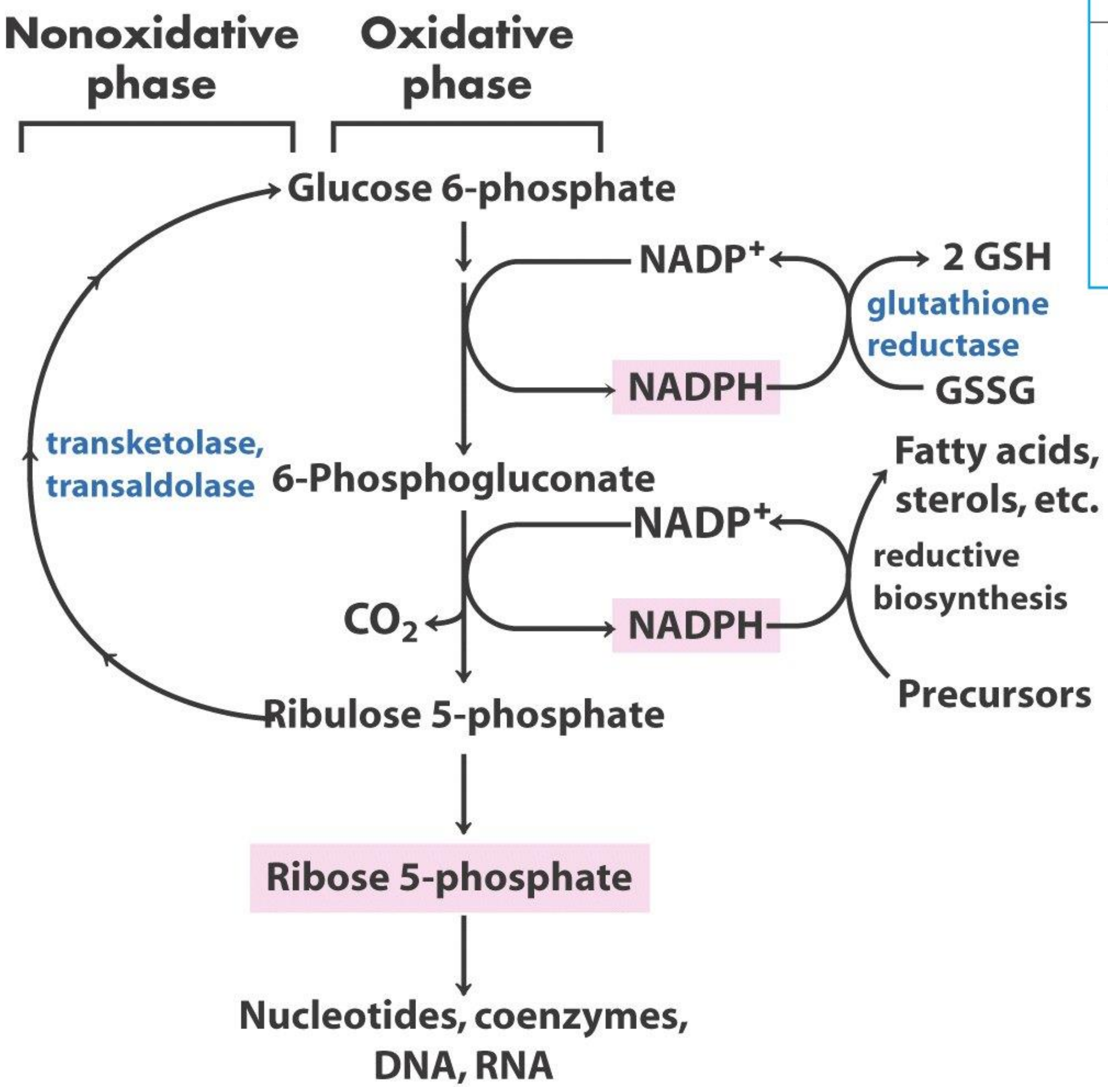


TABLE 20.4 Tissues with active pentose phosphate pathways

Tissue	Function
Adrenal gland	Steroid synthesis
Liver	Fatty acid and cholesterol synthesis
Testes	Steroid synthesis
Adipose tissue	Fatty acid synthesis
Ovary	Steroid synthesis
Mammary gland	Fatty acid synthesis
Red blood cells	Maintenance of reduced glutathione

lens, cornea

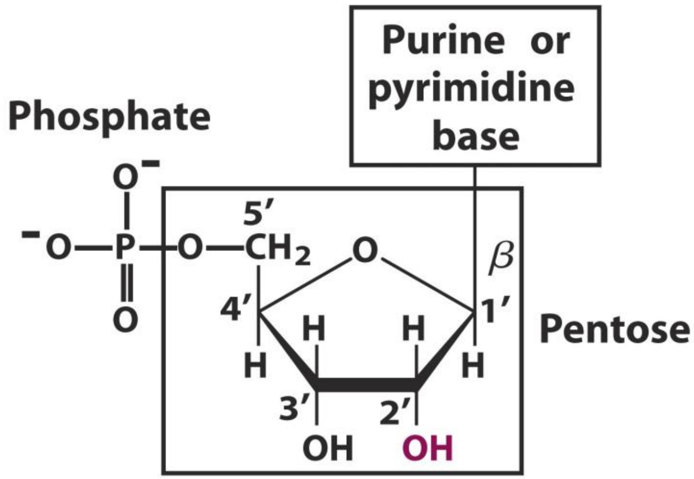
TABLE 20.2 **Pathways requiring NADPH**

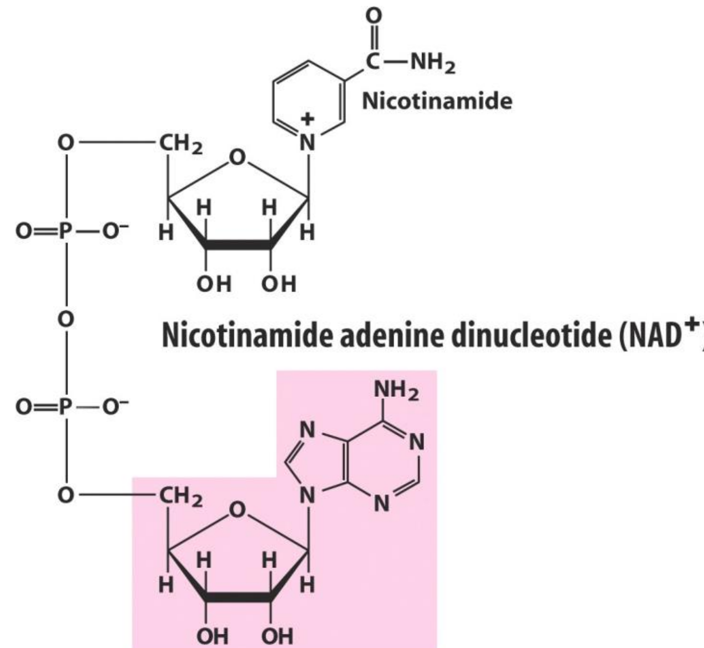
Synthesis
Fatty acid biosynthesis
Cholesterol biosynthesis
Neurotransmitter biosynthesis
Nucleotide biosynthesis
Detoxification
Reduction of oxidized glutathione
Cytochrome P450 monooxygenases

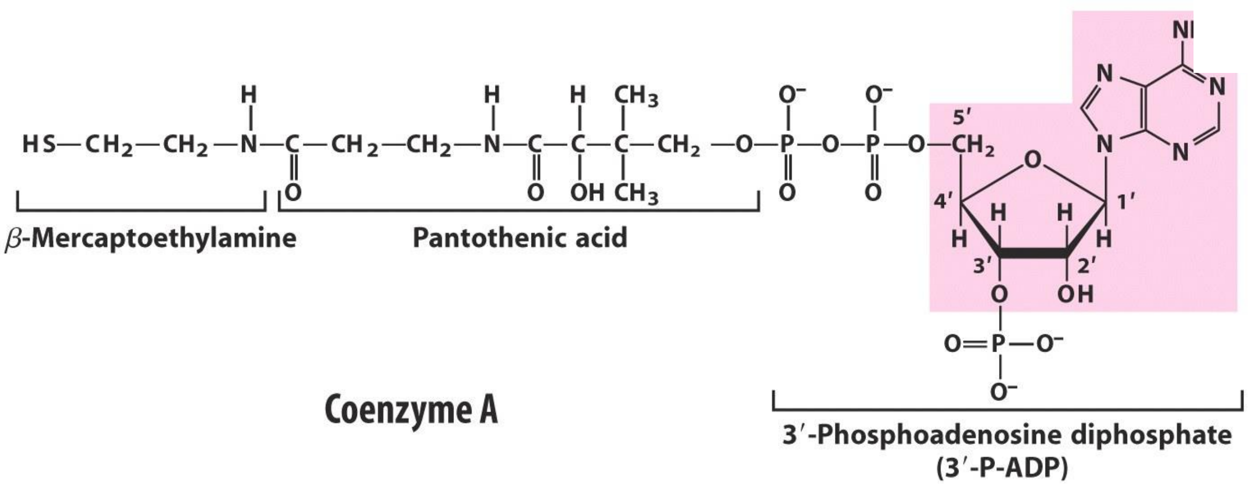
Fates of pentoses

(bone marrow, skin, intestinal mucosa)

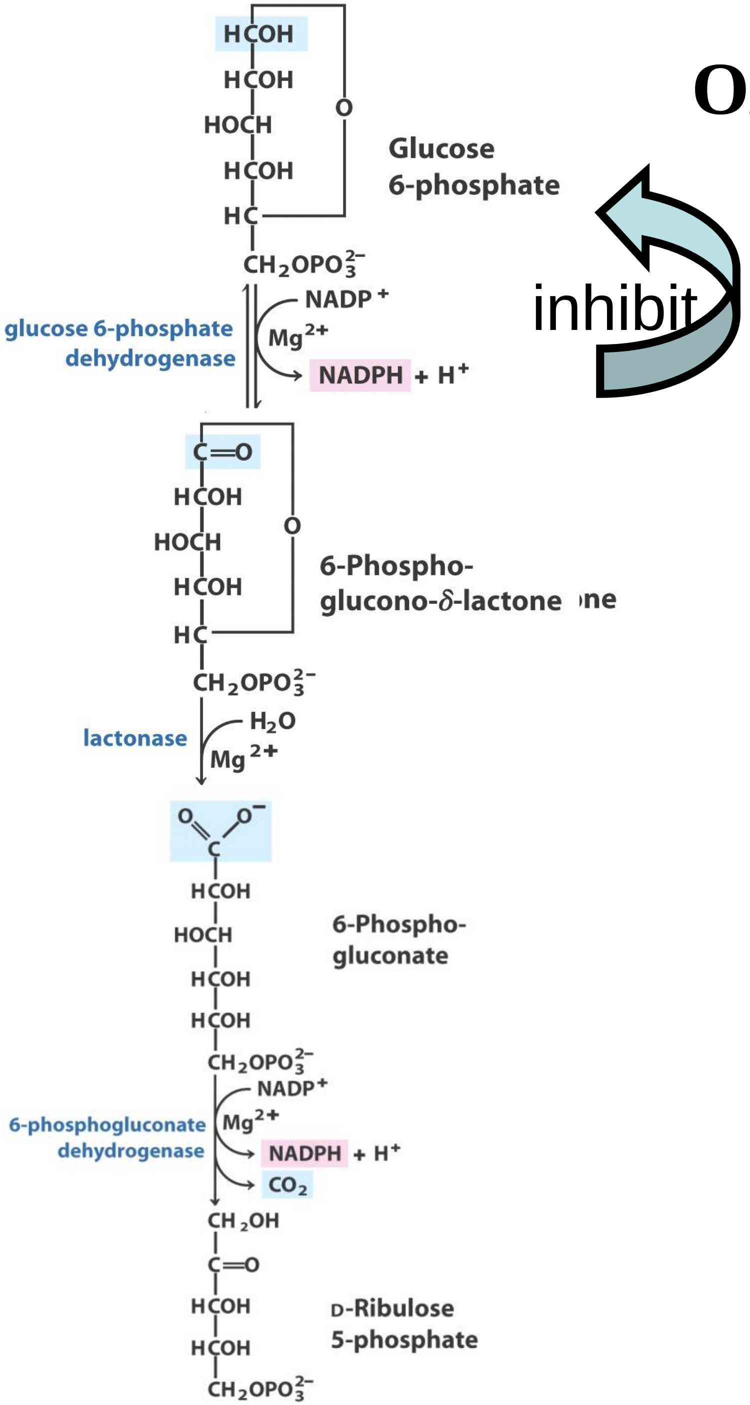
- RNA
- DNA
- NTP
- NADH/NA
- $FADH_2$
- CoA

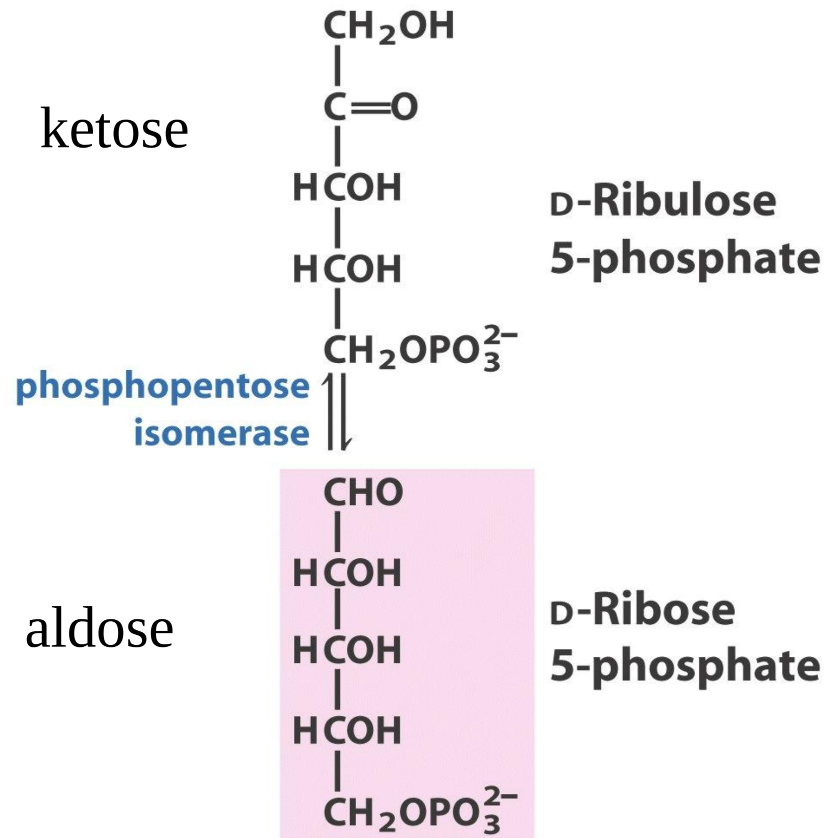






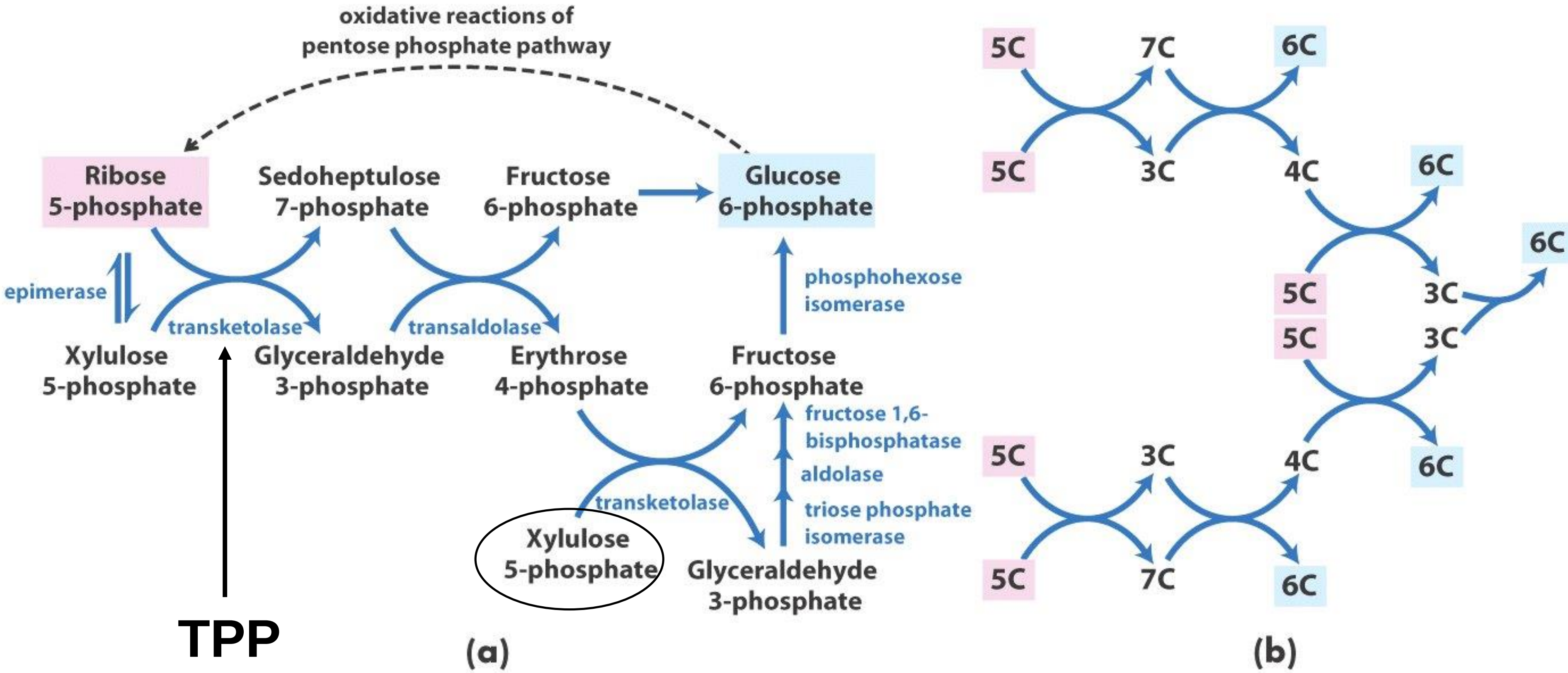
Oxidative phase



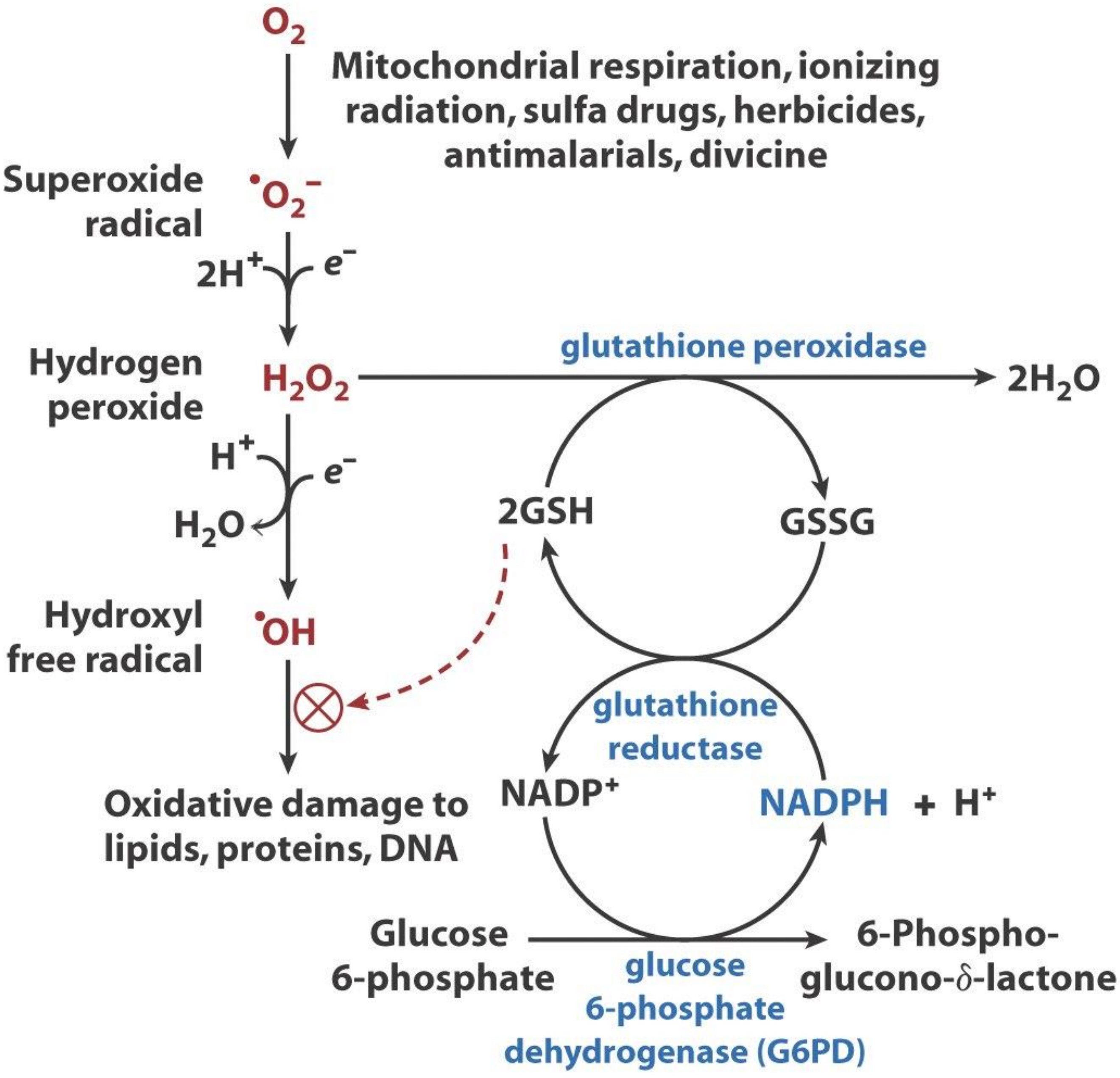


Non-oxidative phase

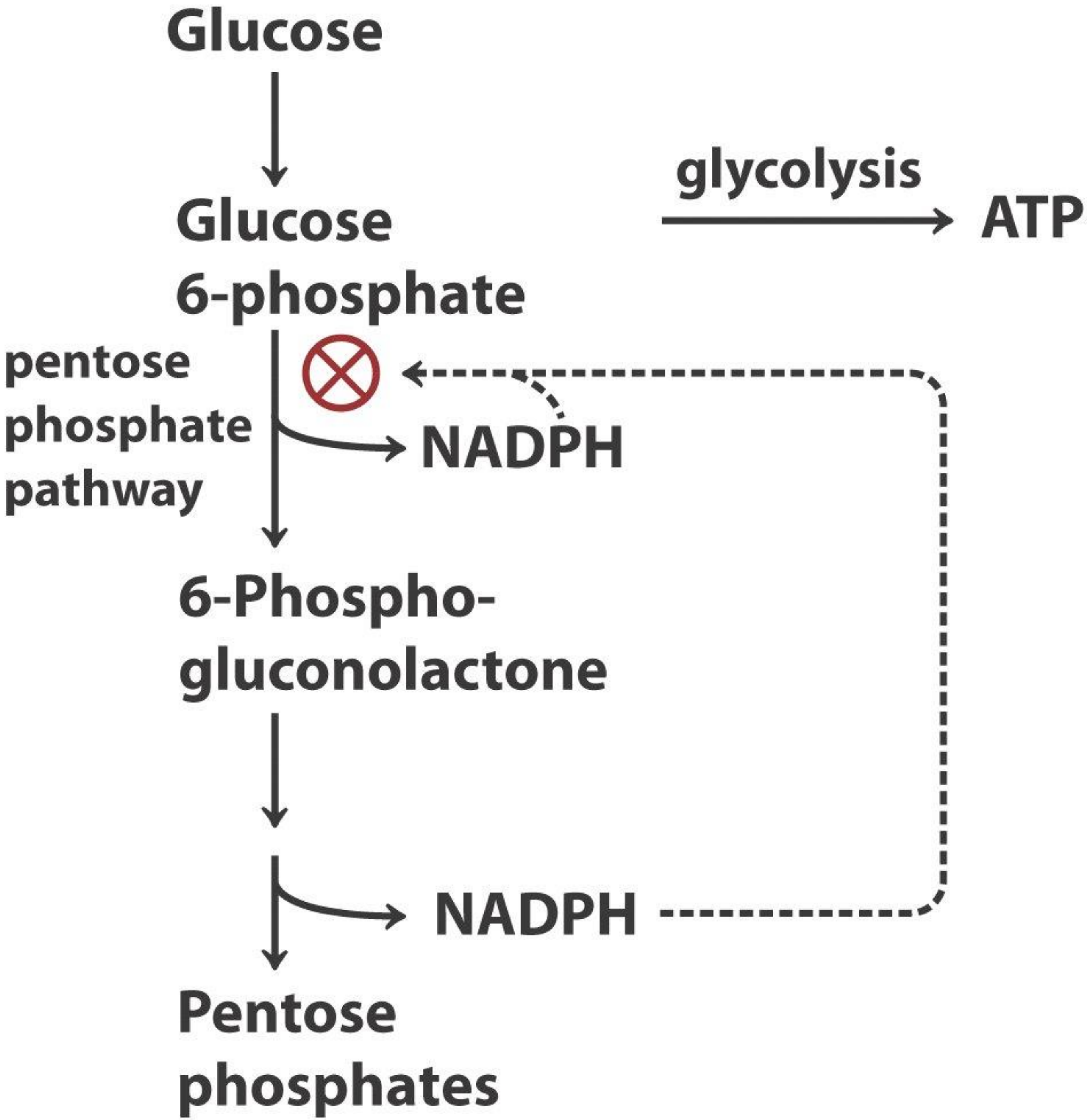
6 pentoses → 5 hexoses



Role of NADPH+H$^+$ and glutathione in protecting cells against ROS



B 14-4


Glucose
glycolysis
ATP
Glucose 6-phosphate
pentose phosphate pathway
NADPH
6-Phosphogluconolactone
NADPH
Pentose phosphates

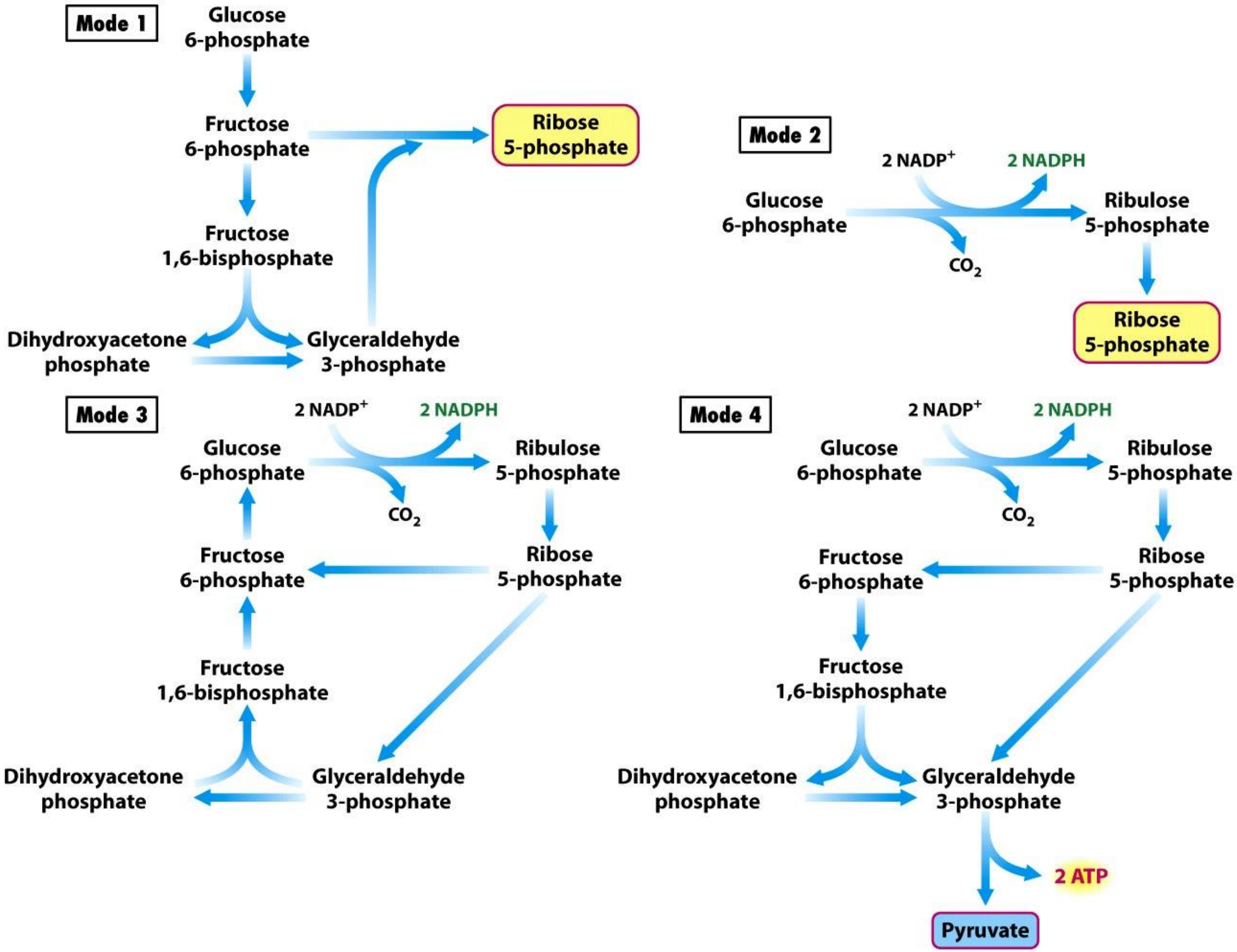
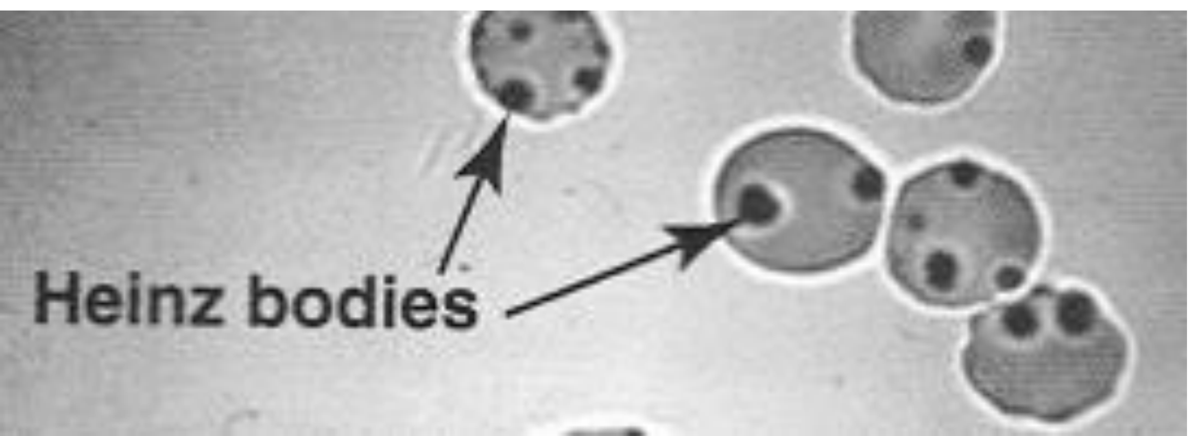


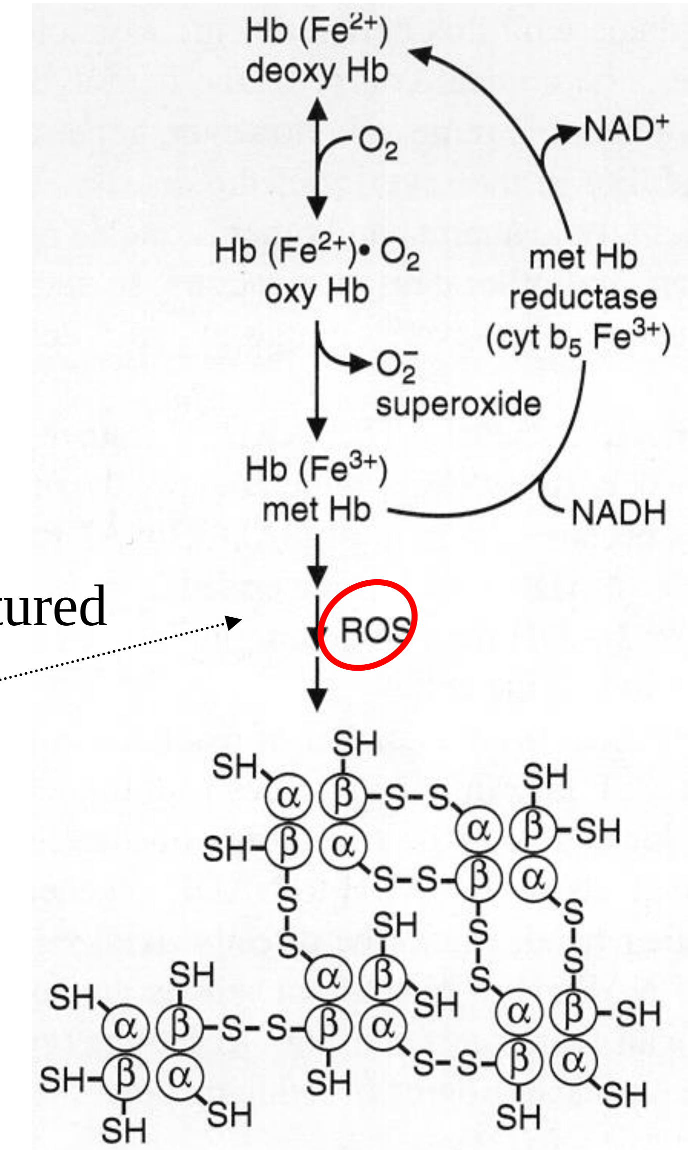
Figure 20-24
Biochemistry, Sixth Edition

Red blood cells with Heinz-bodies in G6PDH deficiency

Heinz-bodies

(haemoglobin denatured by oxidative stress)





Cross-linked hemoglobin in Heinz bodies

Wernicke-Korsakoff Syndrome

- mutation in the transketolase gene
- decreased affinity to **TPP**
- Thiamine deficiency results in - severe memory loss
  - mental confusion
  - partial paralysis

Malaria vs. falafel

Unnumbered figure pg 586b
Biochemistry, Sixth Edition

Fava beans (falafel)

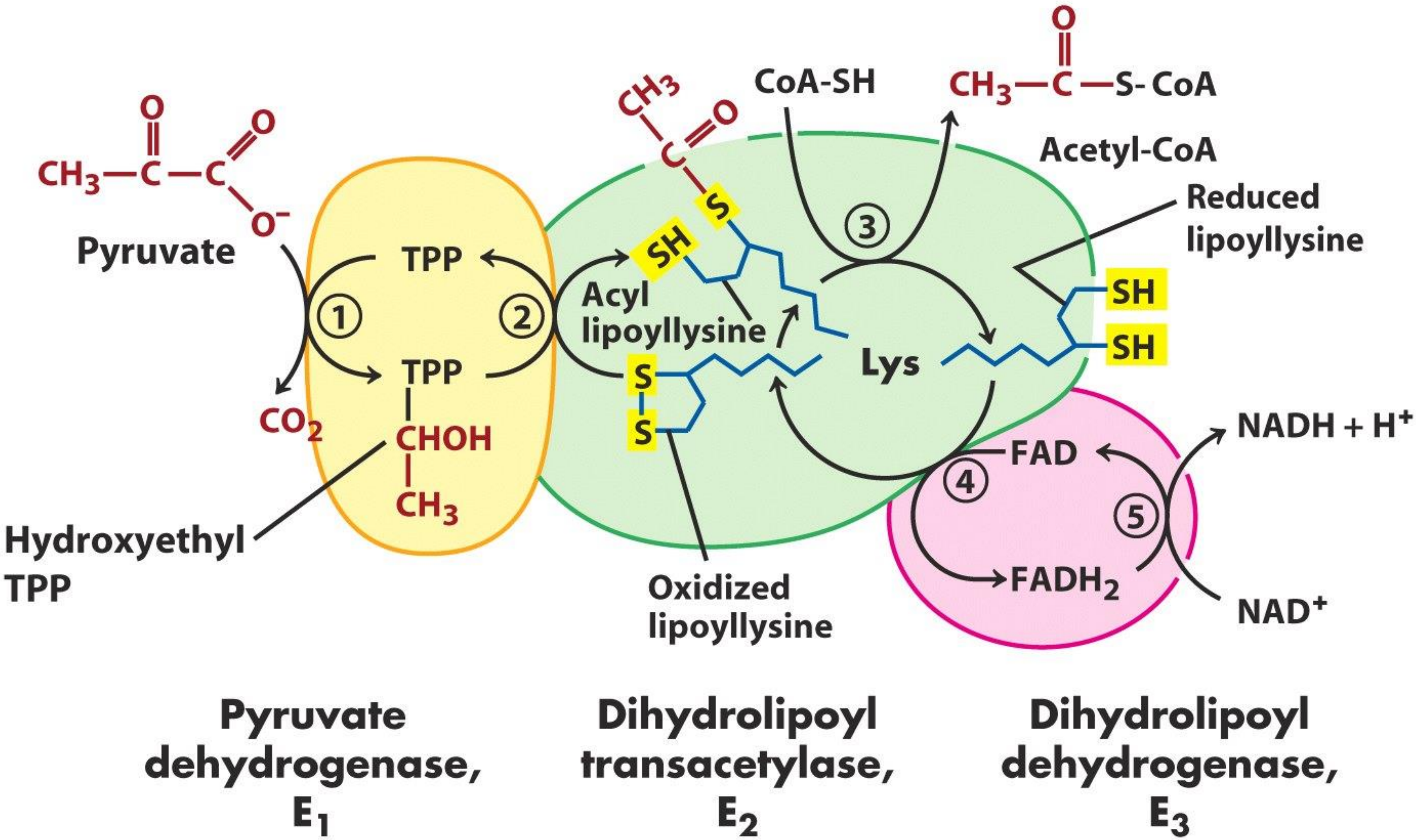
antimalarial drug

ROS

GSH
NADPH

PYRUVATE METABOLISM

Pyruvate Dehydorgenase



REGULATION of PDH

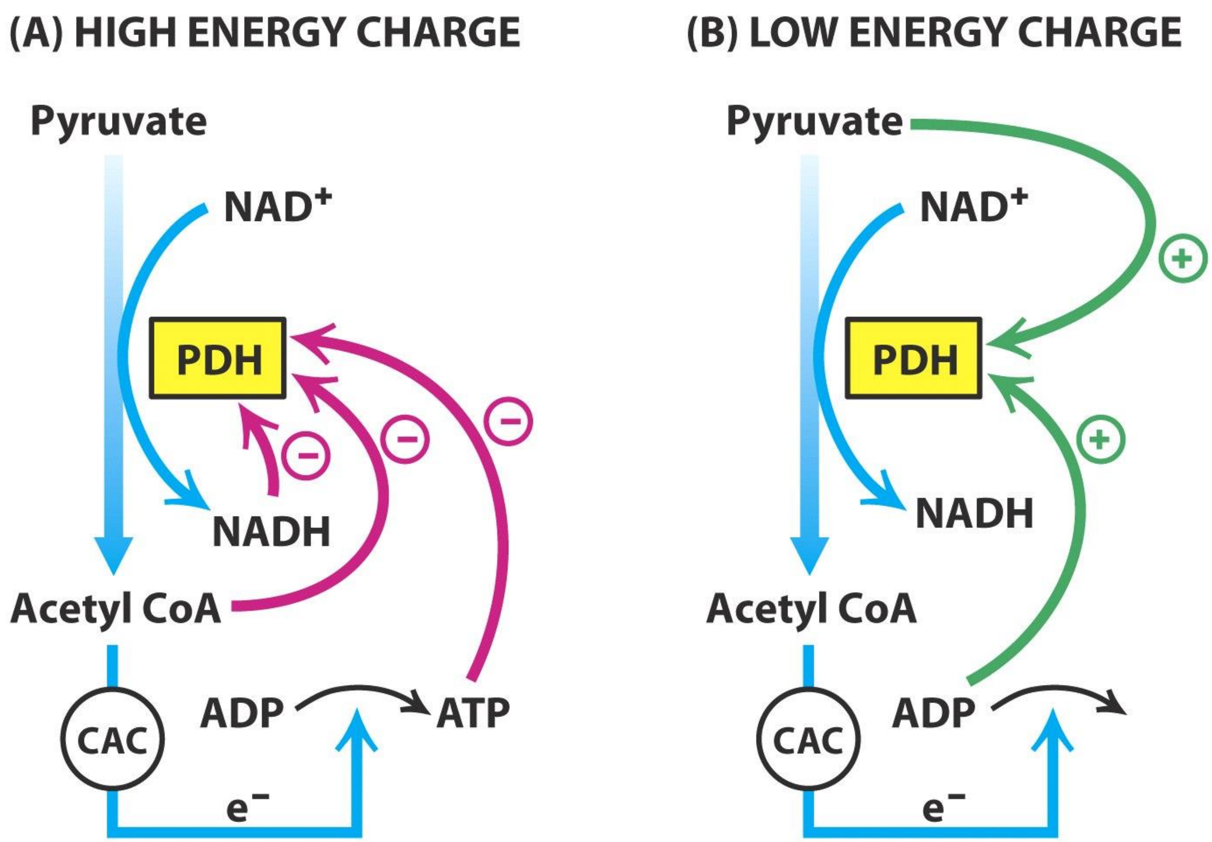


Figure 17-18

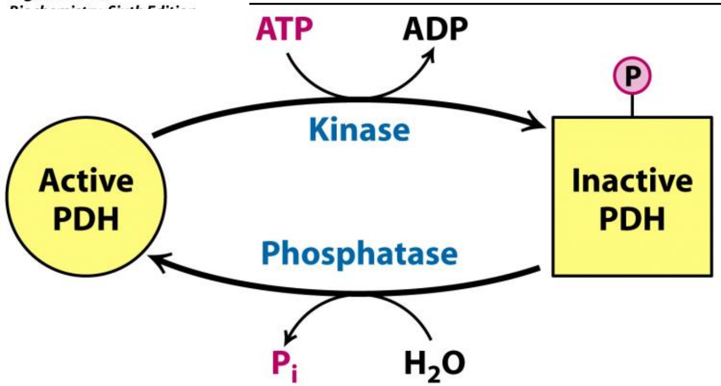
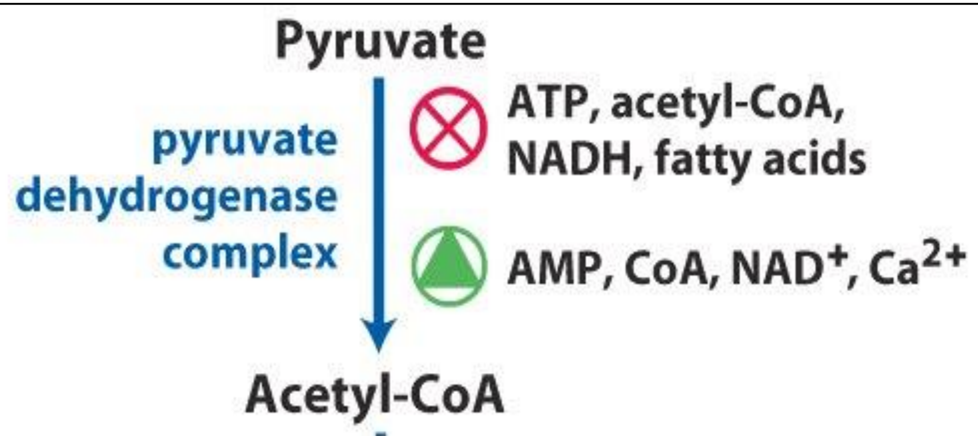


Figure 17-17
Biochemistry, Sixth Edition



Pyruvate dehydrogenase complex deficiency:

- follows X-linked inheritance pattern, **incidence 1:1.000.000**

-heterozygous females commonly manifest severe symptoms, equally
prevalent in both males and females

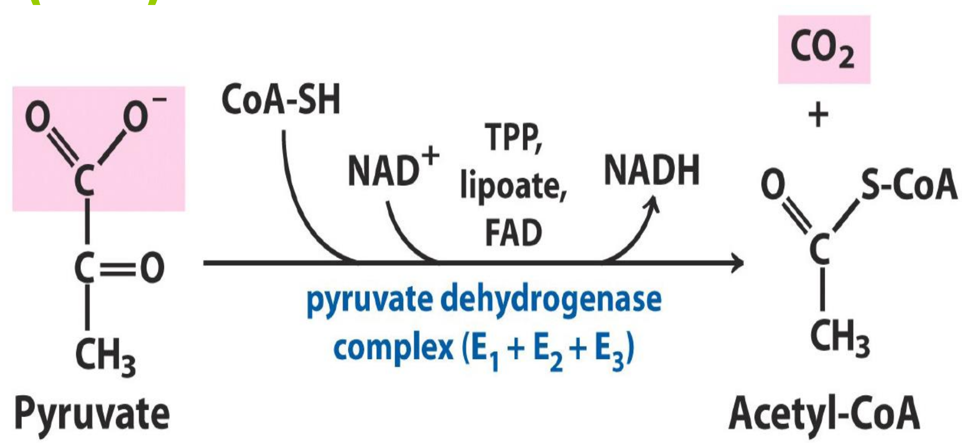
- several mutations can cause PDC deficiency leading to a broad range of
symptoms

→ lactic acidosis, central nervous system symptoms

- In case of decreased TPP affinity of PDC → B_1 vitamine

-**Diagnosis:** enzyme activity assay

- **BERI-BERI lack of thyamine-PP (TPP)**



Thank you for your attention