Biochemistry

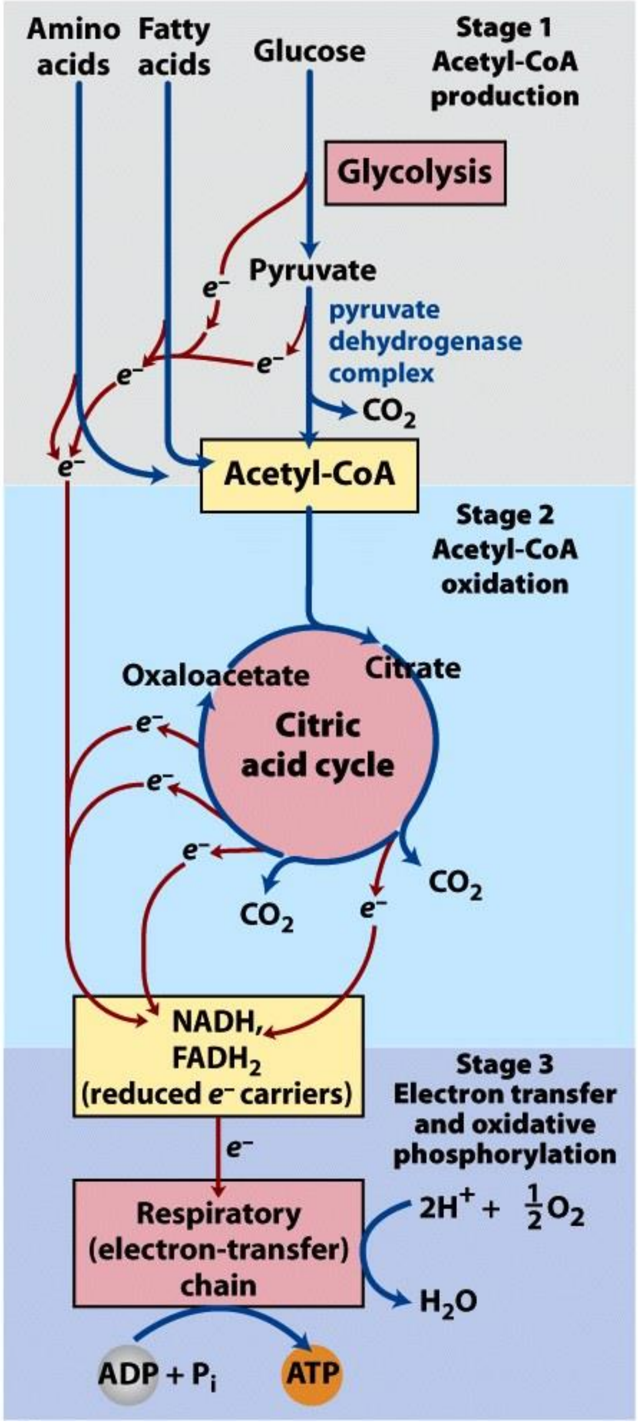
Carbohydrate metabolism I.

General scheme of biological oxidation

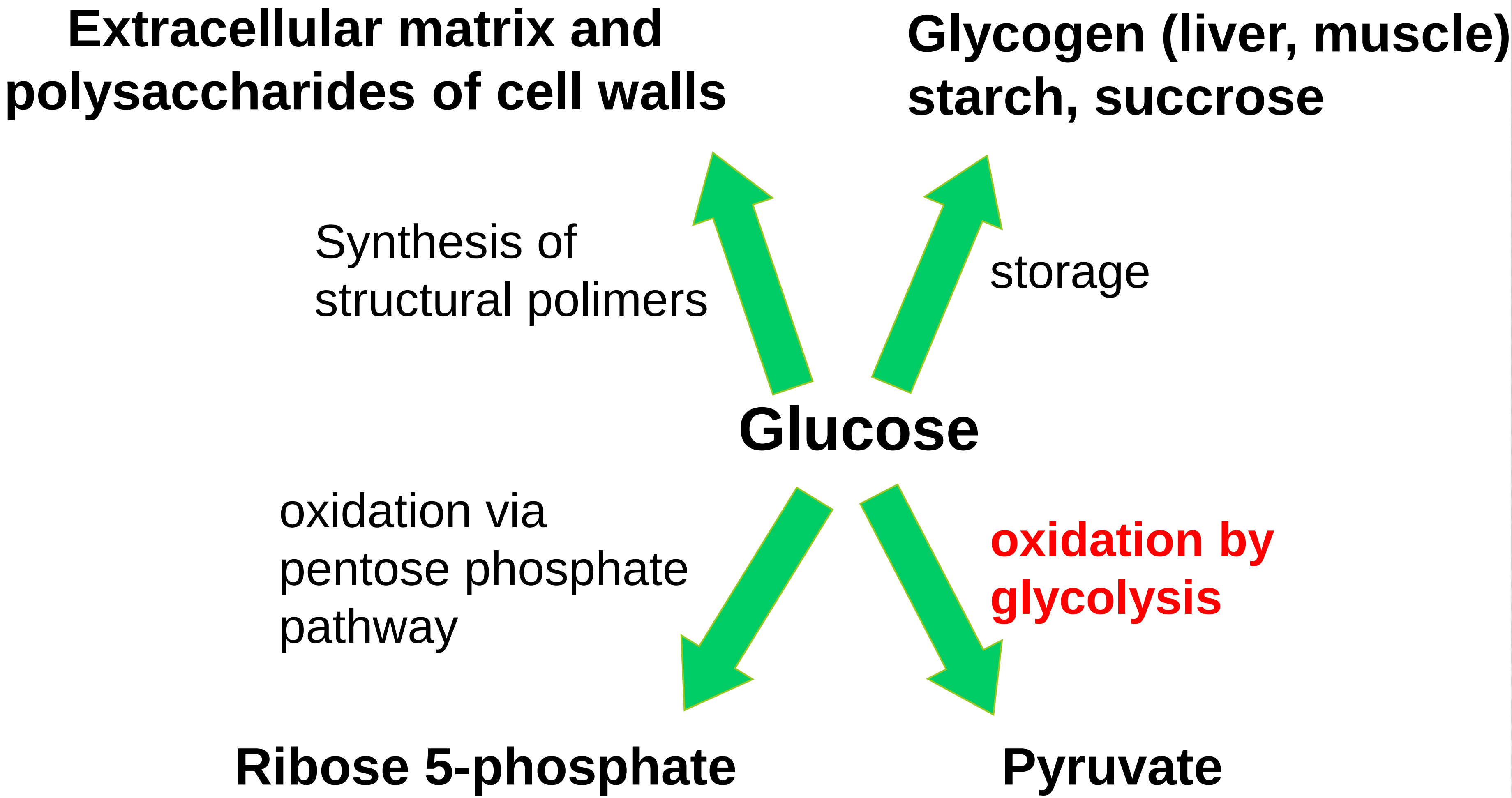
1. Glycolysis

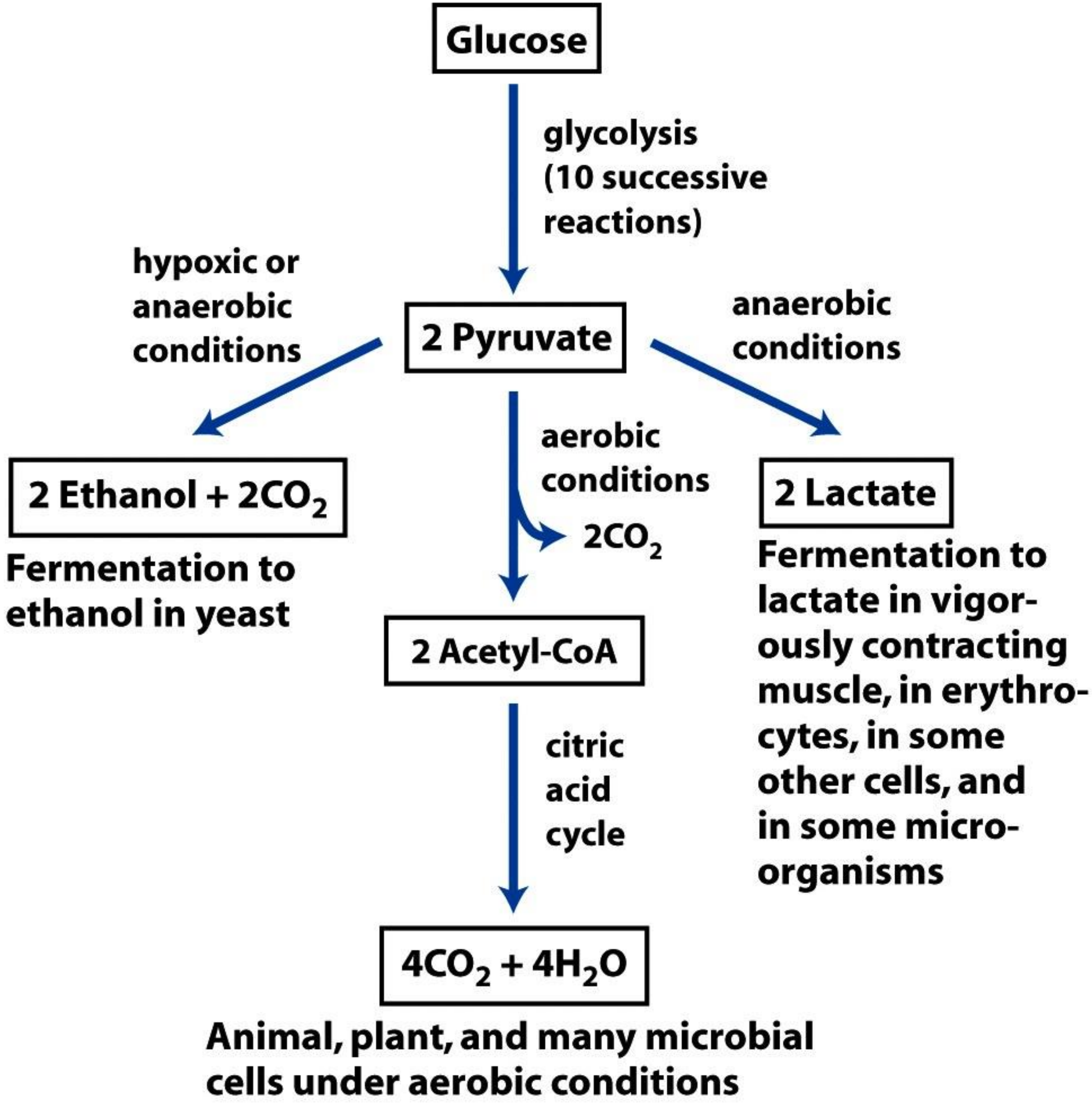
2. Citric acid cycle

3. Oxidative phosphorylation



Major pathways of glucose utilization




Glucose
glycolysis
(10 successive
reactions)
hypoxic or
anaerobic
conditions
2 Pyruvate
anaerobic
conditions
aerobic
conditions
2 Ethanol + $2CO_2$
$2CO_2$
2 Lactate
Fermentation to
ethanol in yeast
2 Acetyl-CoA
Fermentation to
lactate in vigor-
ously contracting
muscle, in erythro-
cytes, in some
other cells, and
in some micro-
organisms
citric
acid
cycle
$4CO_2 + 4H_2O$
Animal, plant, and many microbial
cells under aerobic conditions

GLYCOLYSIS

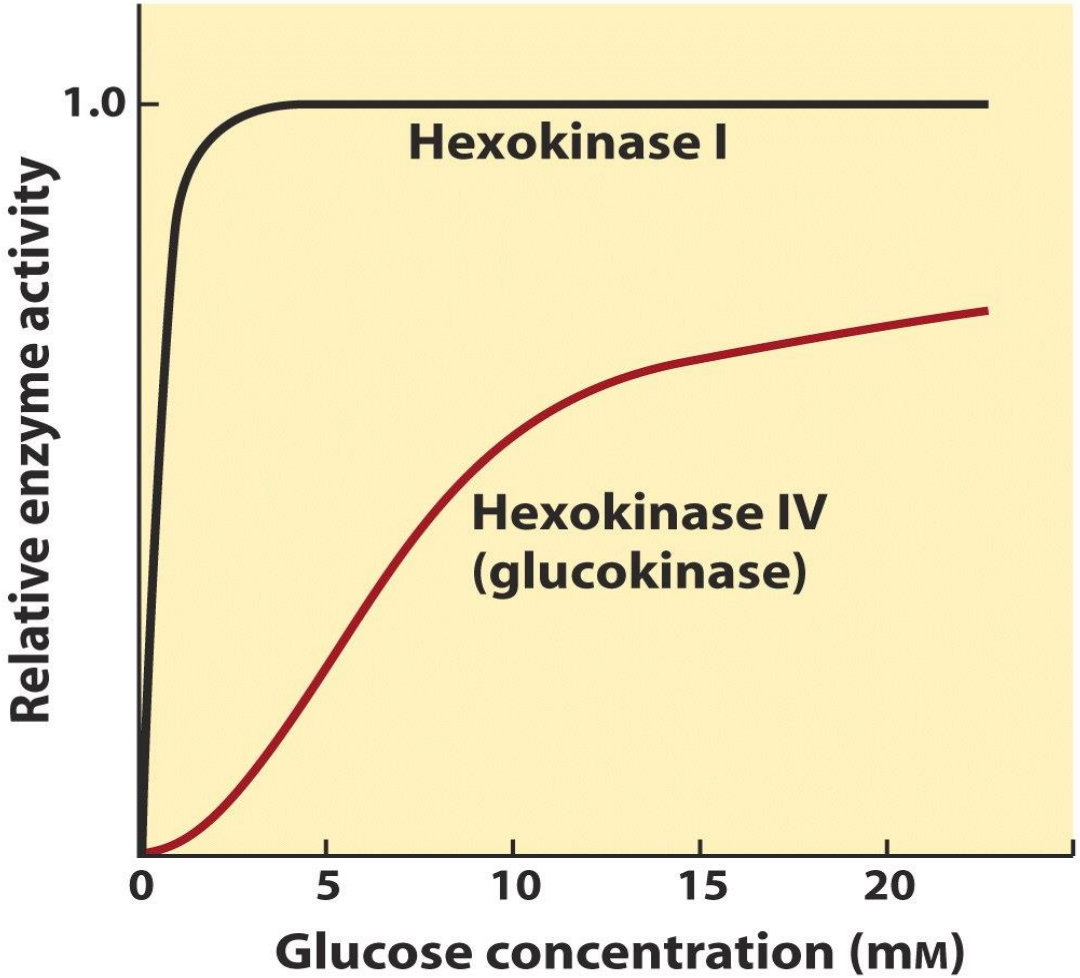
- Glycolysis is an almost universal central pathway of glucose catabolism, the pathway with the largest flux of carbon in most cells.
- Glycolysis takes place inside the cytoplasm of the cell.
- It is the most important or the only energy production pathway of several cell types (e.g. *erythrocytes, cornea, brain, partially the cells of retina, kidney medulla, sperm*).
- It produces ATP even under anaerobic conditions.
- The glycolytic enzymes are almost identical in every organism (from yeast to human).
- Glycolytic intermediates are phosphorylated (glycolytic intermediates can’t leave the cells: negative charge, lack of transporters, concentration gradient)
- Most glycolytic enzymes require Mg^{2+} for activity.

Glucose transporter

Name	Present	Insulin
GLUT 1	Erythrocytes, brain - neurons, muscle, adipocyte	independent
GLUT 2	Renal tubular, pancreatic β cells, liver, small intestinal epithelial cells	independent
GLUT 3	Brain - neurons	independent
GLUT 4	Muscle, adipocytes	dependent
GLUT 5	Small intestinal, testis, kidney (<u>fructose</u>)	independent

Hexokinase I, II, III – general distribution, e.g. muscle (not specific for glucose; it is inhibited by G-6-P)

Hexokinase IV = glucokinase – in parenchyma cells of liver (specific for glucose; it is not affected by G-6-P)



Regulation of hexokinase IV/glucokinase

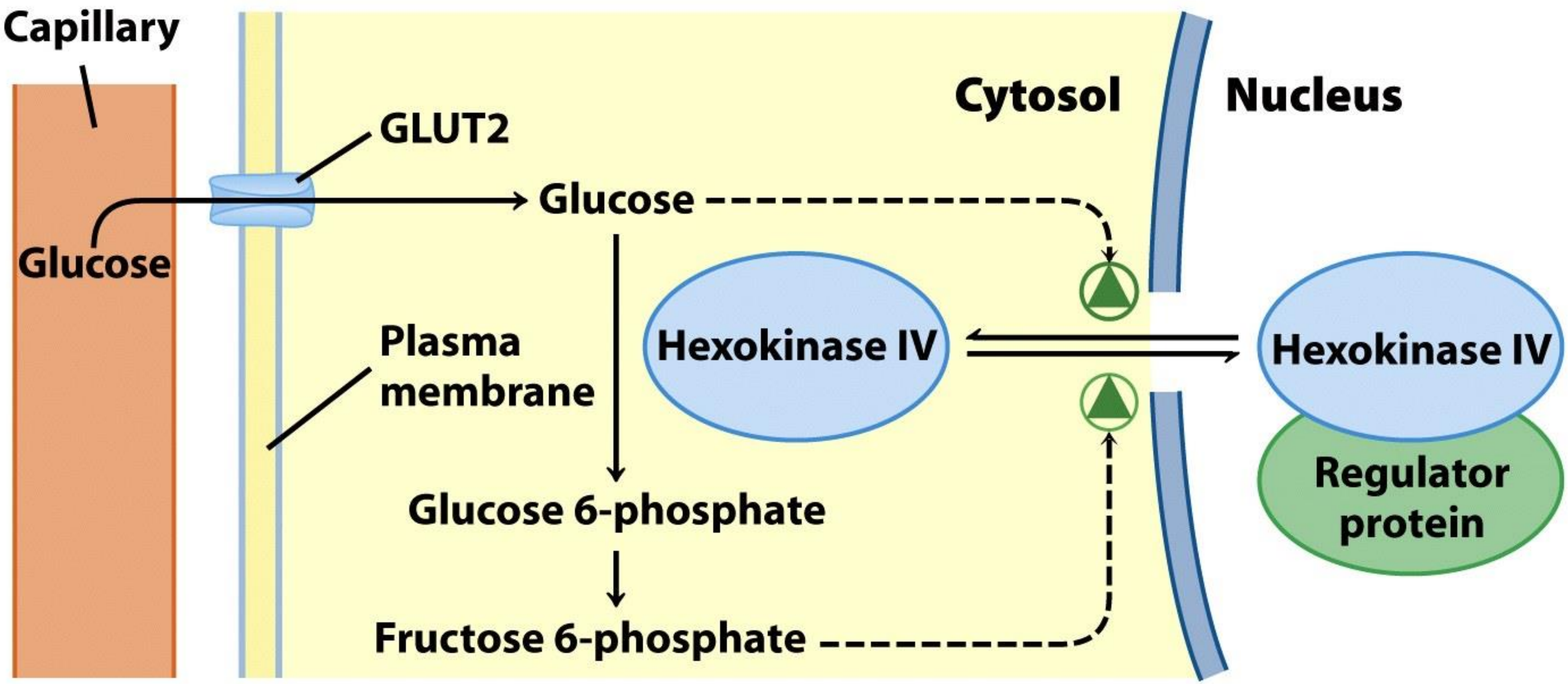
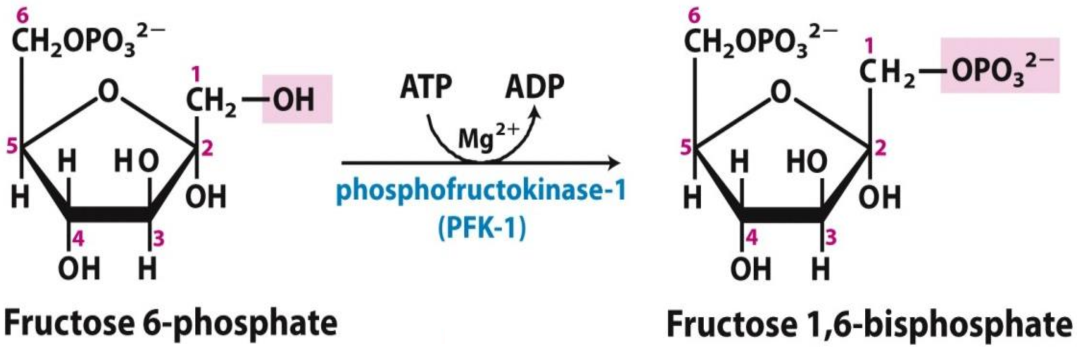
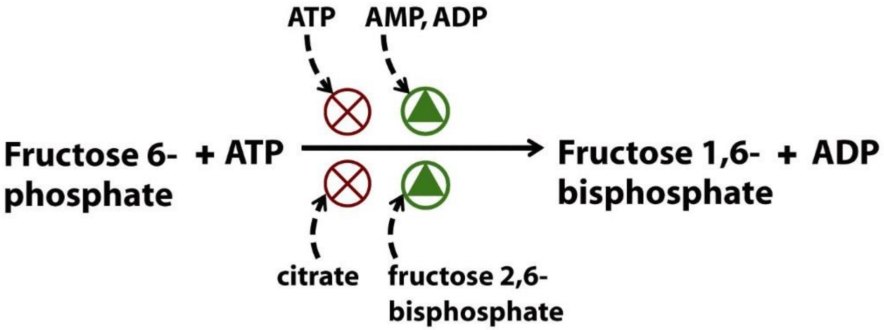


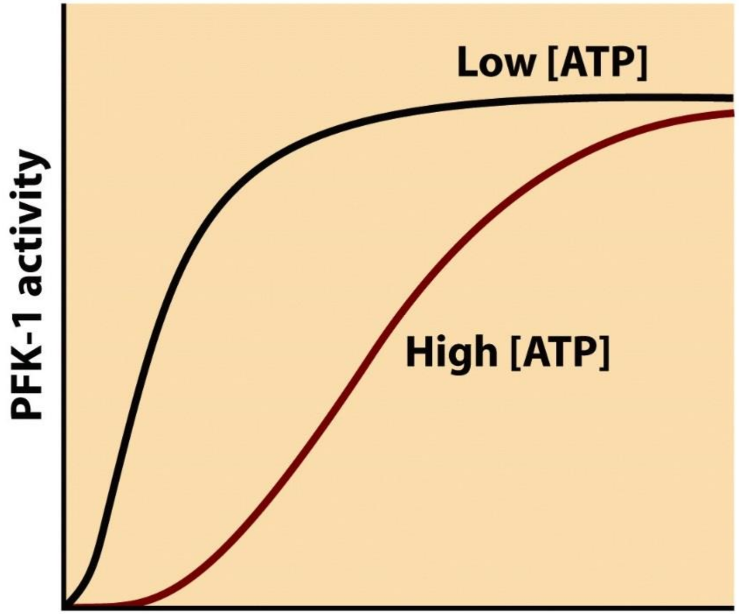
Figure 15-13
Lehninger Principles of Biochemistry, Fifth Edition

PFK-1 is a regulated step

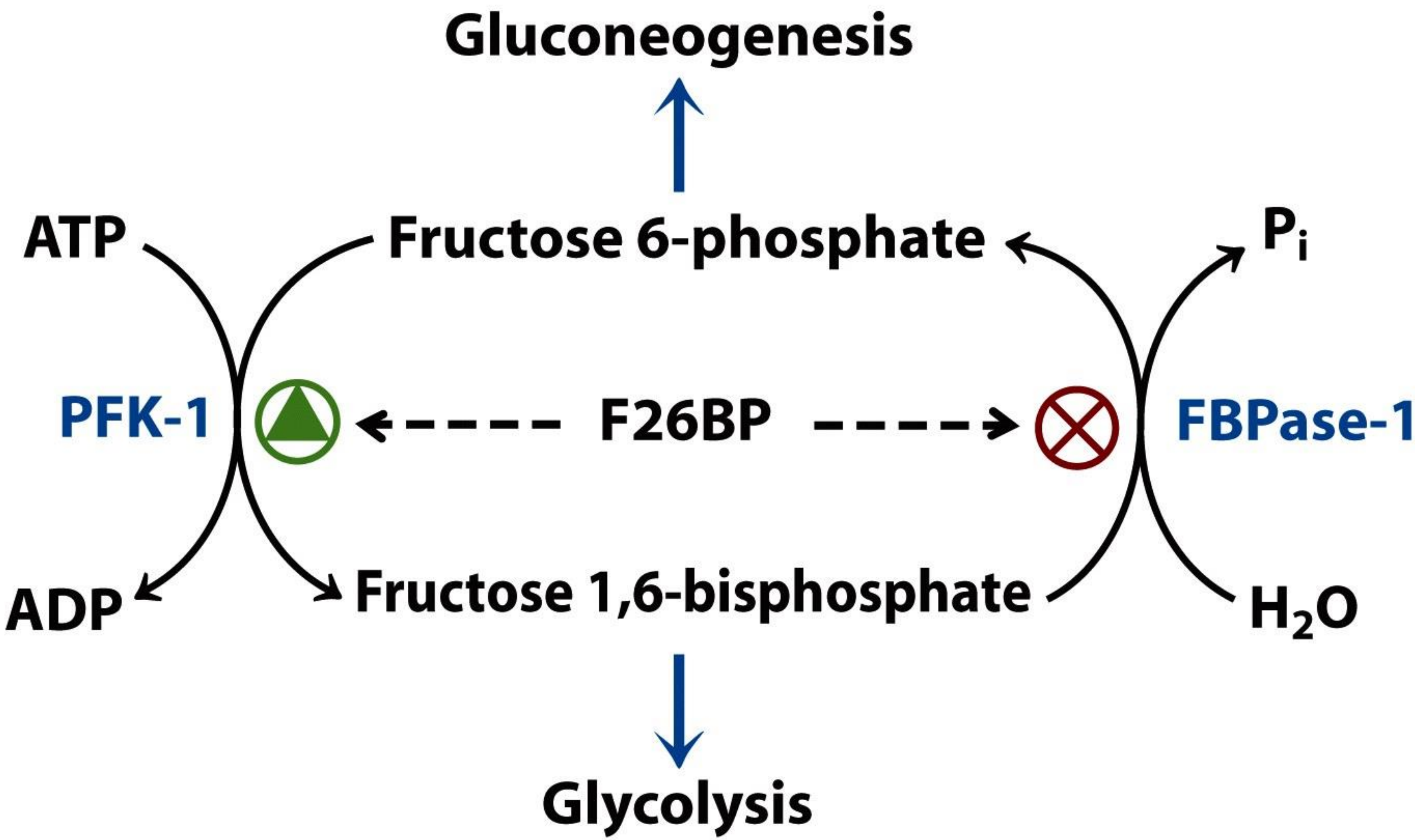


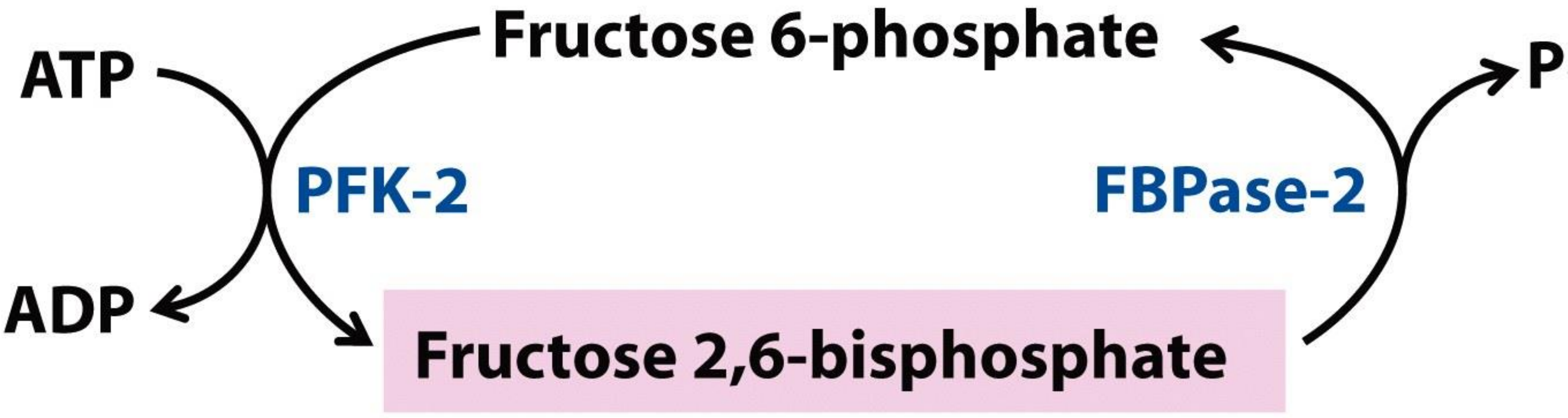
$$\Delta G'^{\circ} = -14.2 \text{ kJ/mol}$$

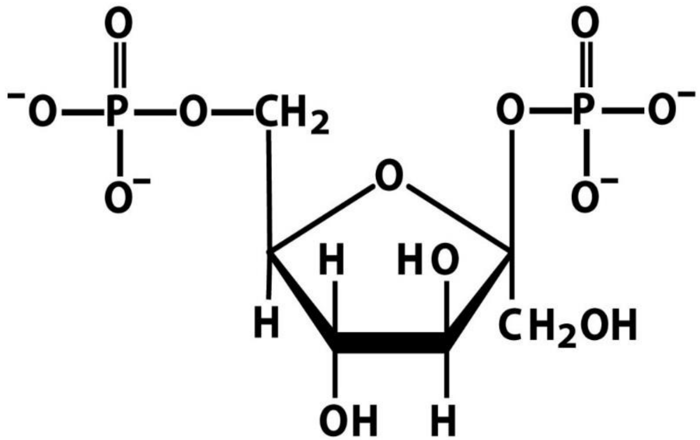




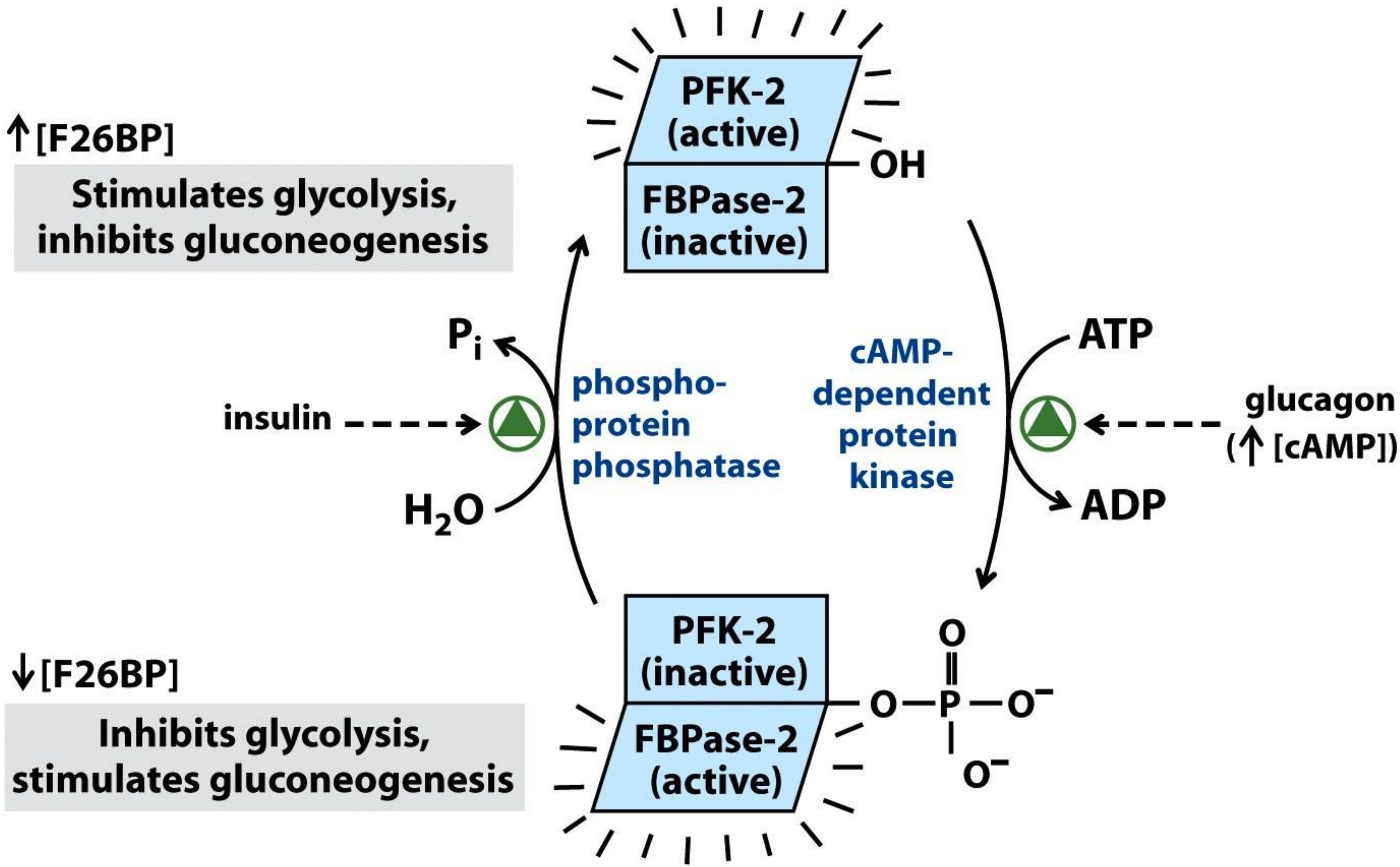
PFK-1 is a regulated step





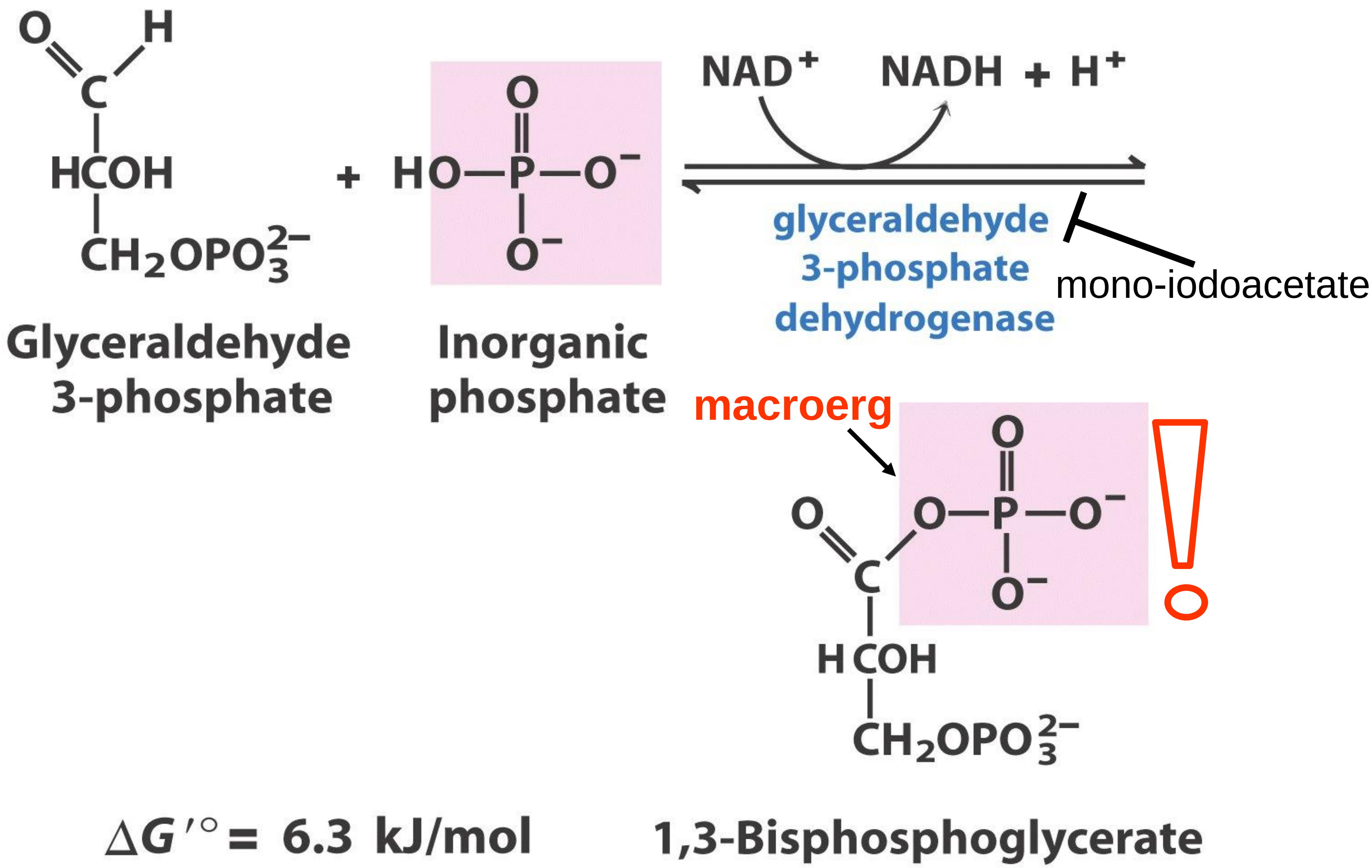


Fructose 2,6-bisphosphate
(F26BP)

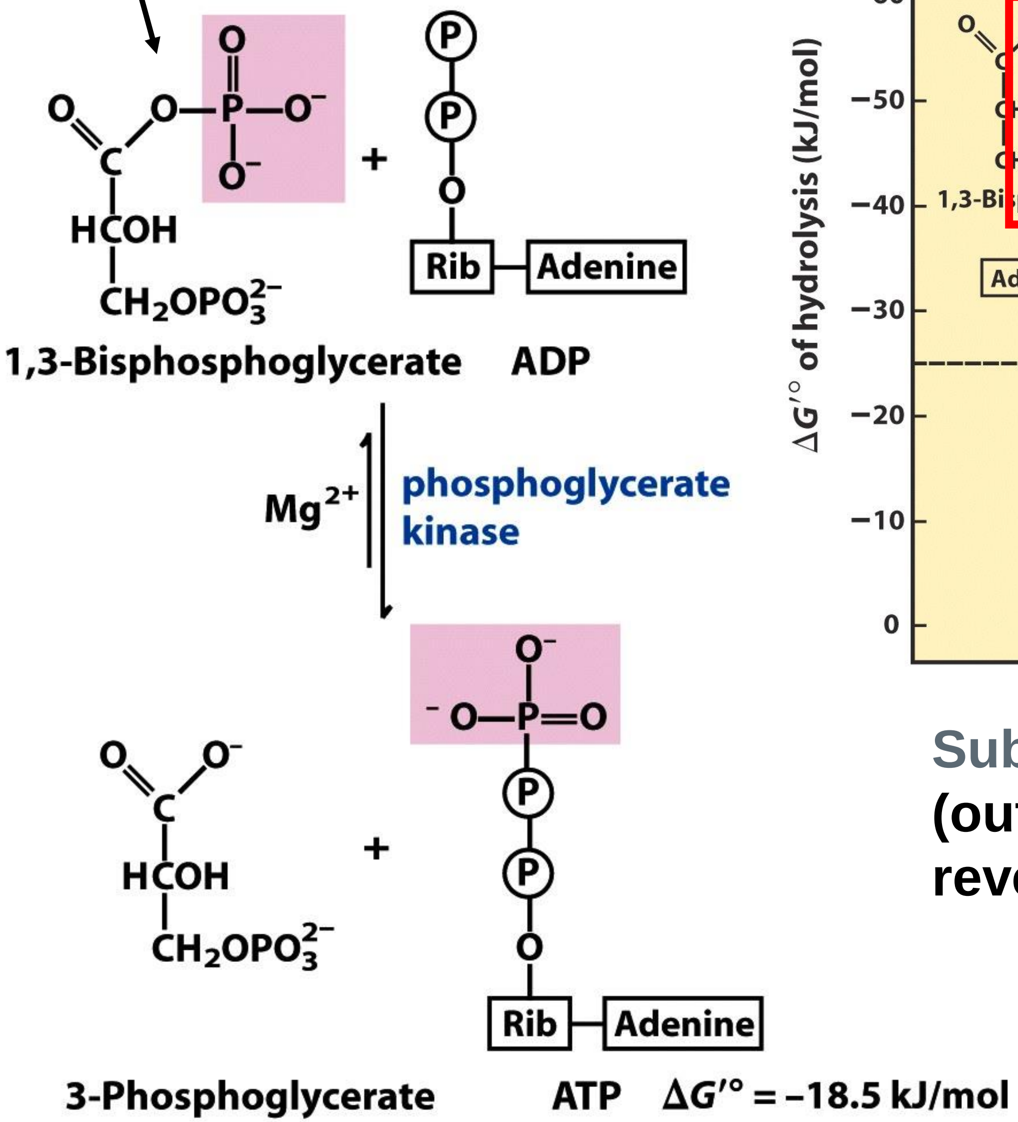


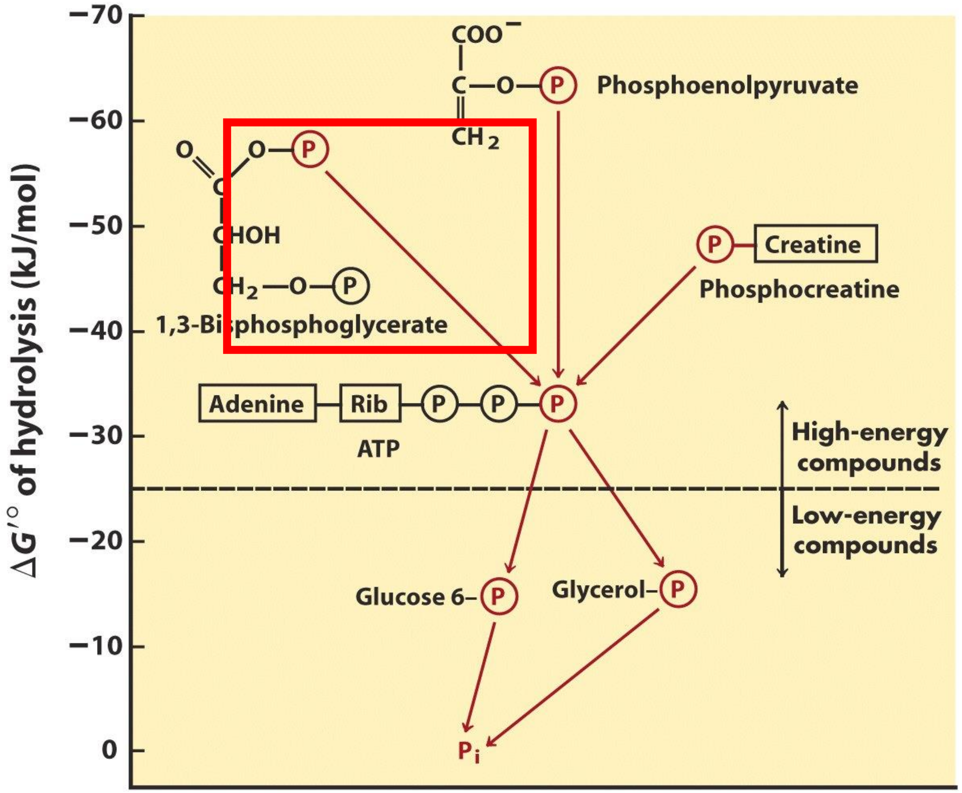
↑[F26BP]
Stimulates glycolysis, inhibits gluconeogenesis
PFK-2 (active)
FBPase-2 (inactive)
OH
P_i
insulin
H_2O
phospho-protein phosphatase
cAMP-dependent protein kinase
ATP
glucagon (↑ [cAMP])
ADP
↓[F26BP]
Inhibits glycolysis, stimulates gluconeogenesis
PFK-2 (inactive)
FBPase-2 (active)
O
O
P
O^-
O^-

The essential role of inorganic phosphate (P_i)



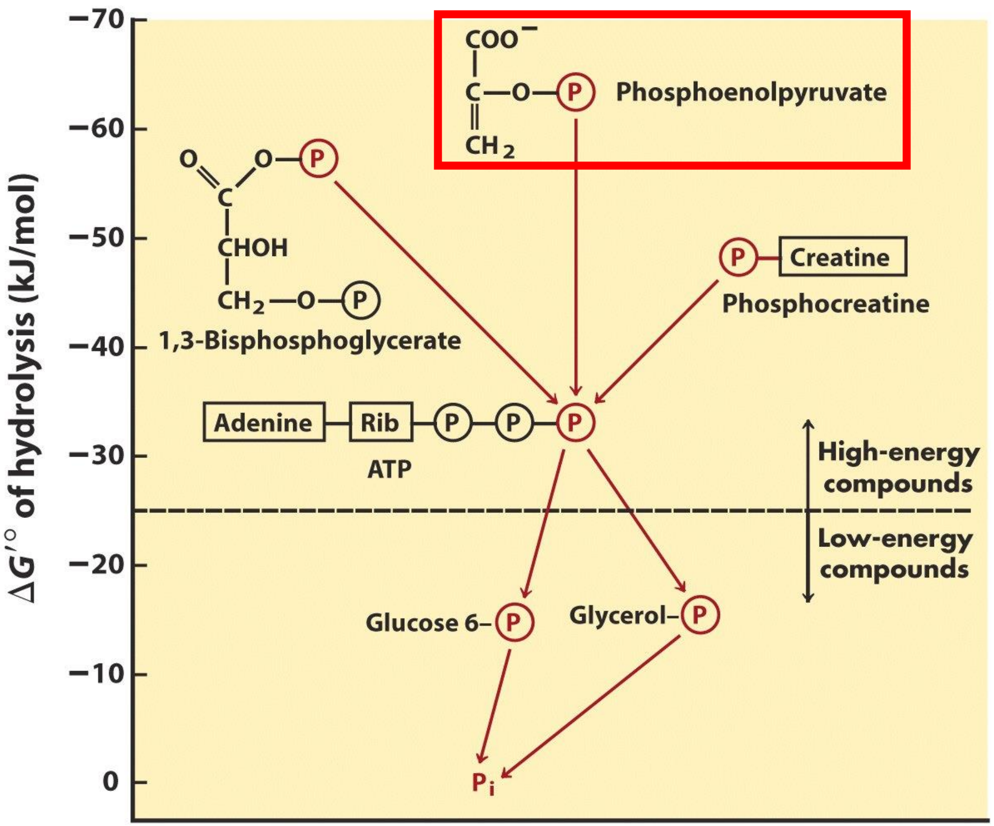
macroerg

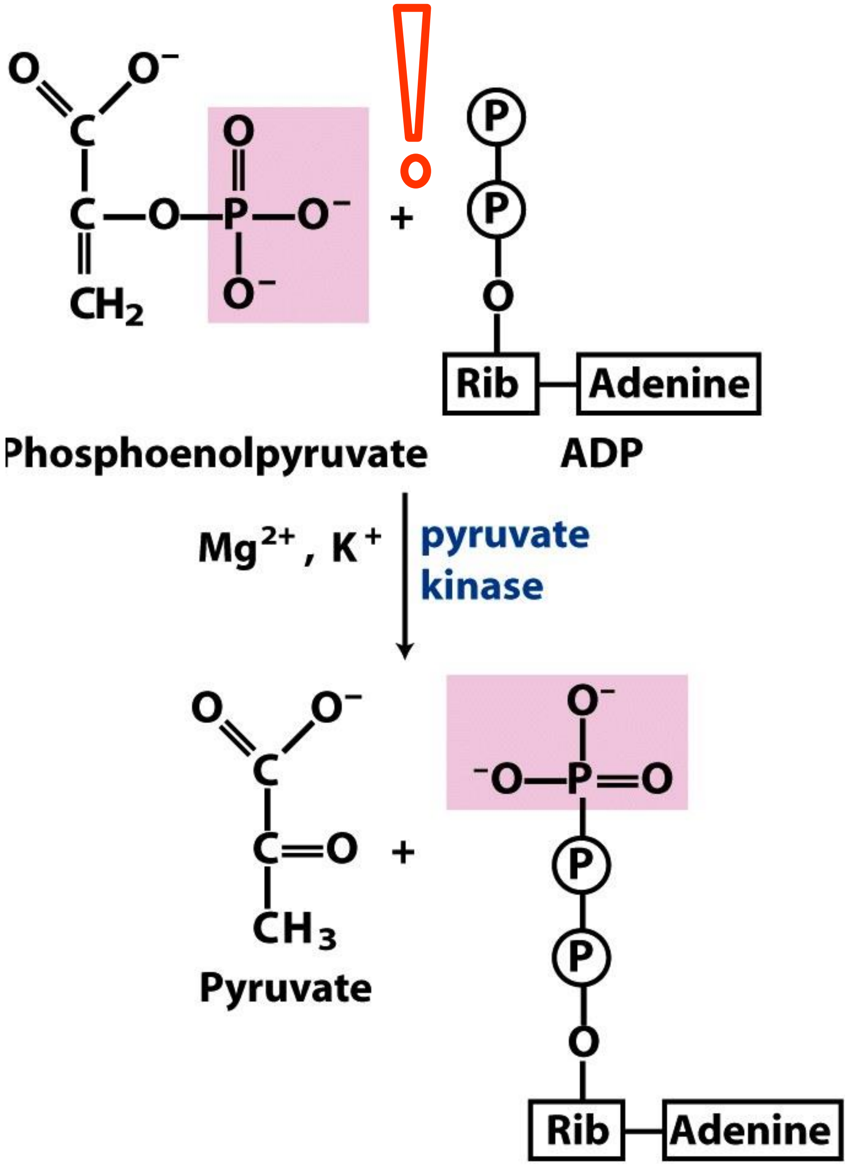




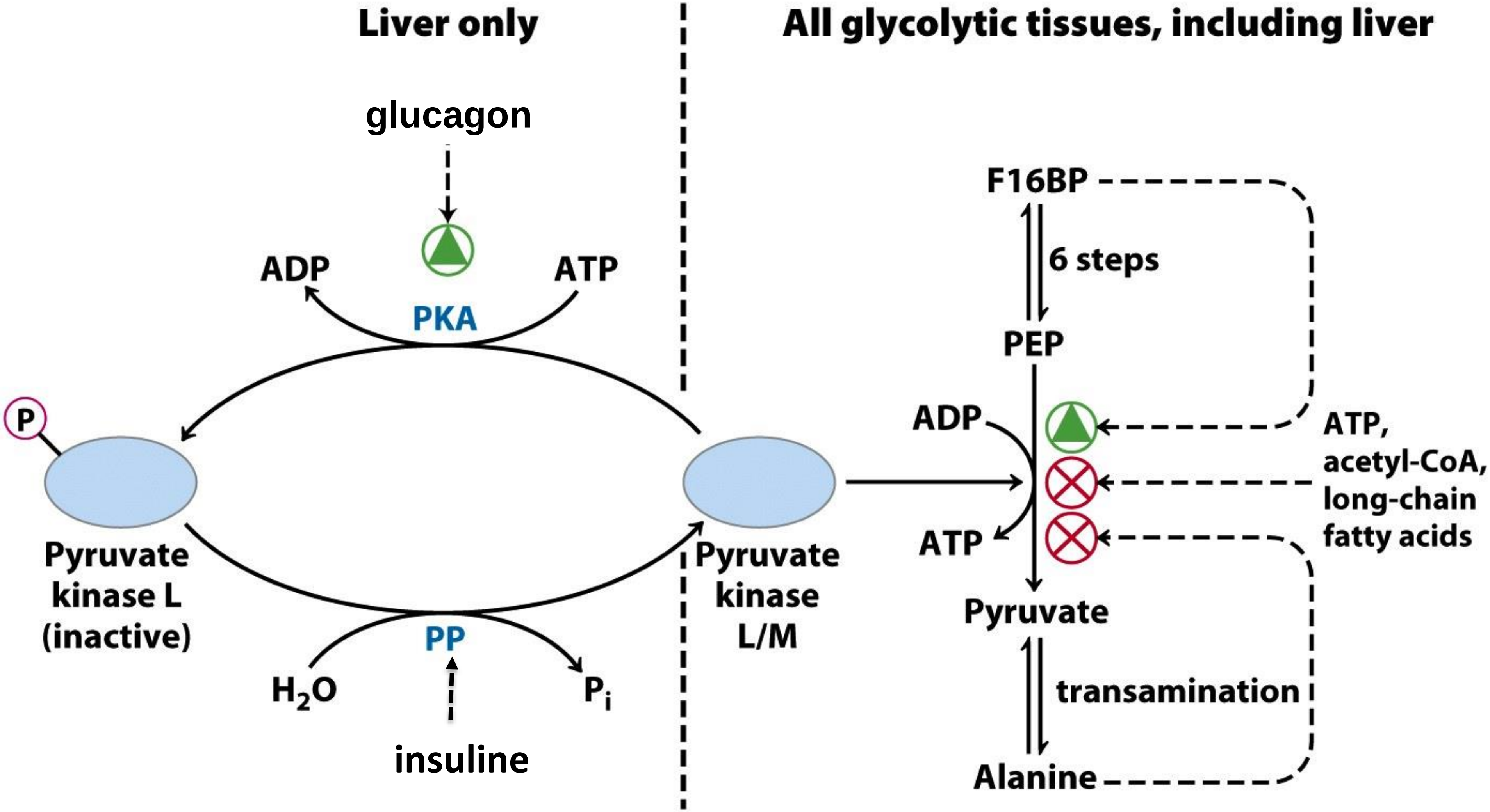
Substrate-level phosphorylation
(outside of the mitochondrion), reversible

Irreversible and regulated:





$\Delta G'° = -31.4$ kJ/mol


Liver only
All glycolytic tissues, including liver
glucagon
ADP
ATP
PKA
P
Pyruvate kinase L (inactive)
PP
H_2O
P_i
insuline
Pyruvate kinase L/M
F16BP
6 steps
PEP
ADP
ATP
Pyruvate
transamination
Alanine
ATP, acetyl-CoA, long-chain fatty acids

The energy balance of glycolysis

$\text{Glucose} + 2\ \text{NAD}^+ \rightarrow 2\ \text{pyruvate} + 2\ \text{NADH} + 2\ \text{H}^+$ $\Delta g'^\circ = -146$ kJ/mol

$2\ \text{ADP} + 2\ \text{P}_i \rightarrow 2\ \text{ATP} + 2\ \text{H}_2\text{O}$ $\Delta G'^\circ = +61$ kJ/mol

Overall equation for aerob conditions:

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

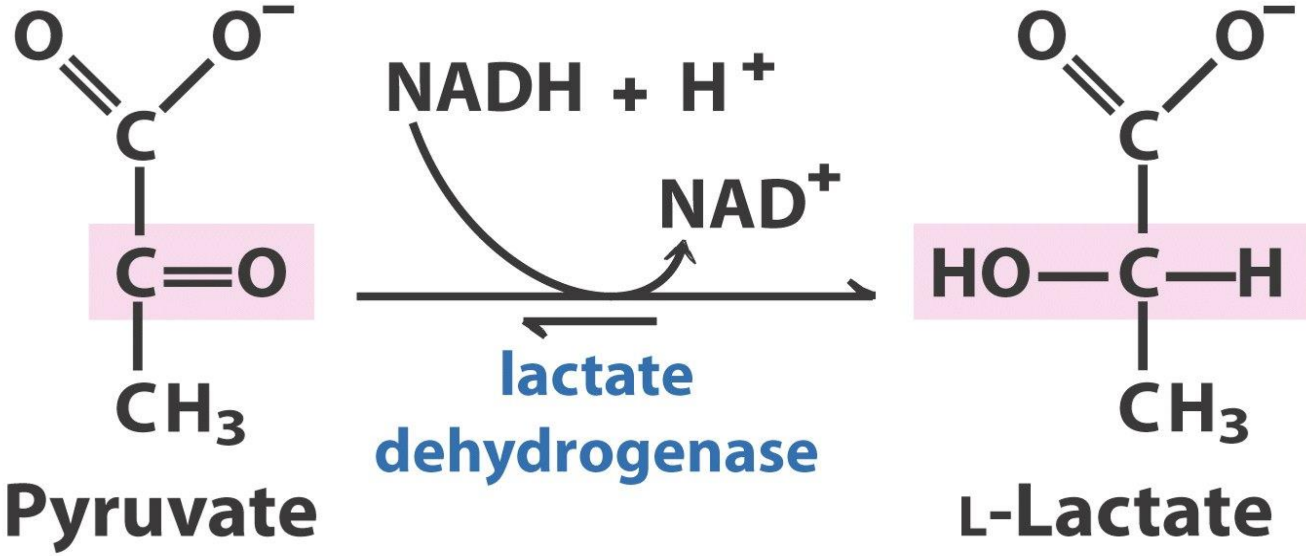
$\Delta g'^\circ = -146$ kJ/mol + 61 kJ/mol = -85 kJ/mol

This is only a small part of energy that can be gained from a glucose molecule (see the TCA-cycle).

Overall equation for anaerob conditions:

$$\text{Glucose} + 2\ \text{ADP} + 2\ \text{Pi} \rightarrow 2\ \text{lactate} + 2\ \text{ATP} + 2\ \text{H}_2\text{O}$$

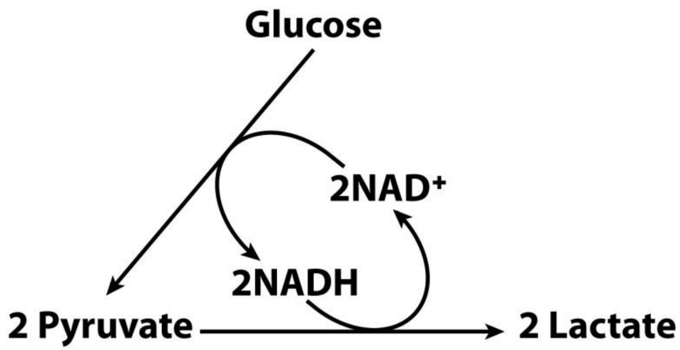
Anaerob conditions

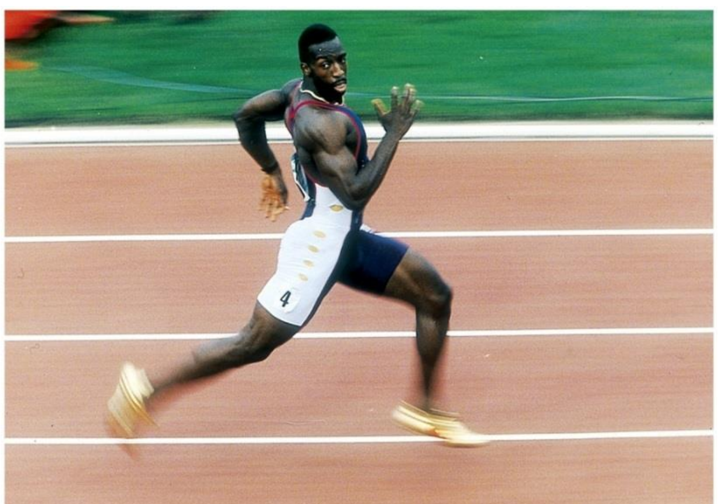


$\Delta G'^{\circ} = -25.1$ kJ/mol

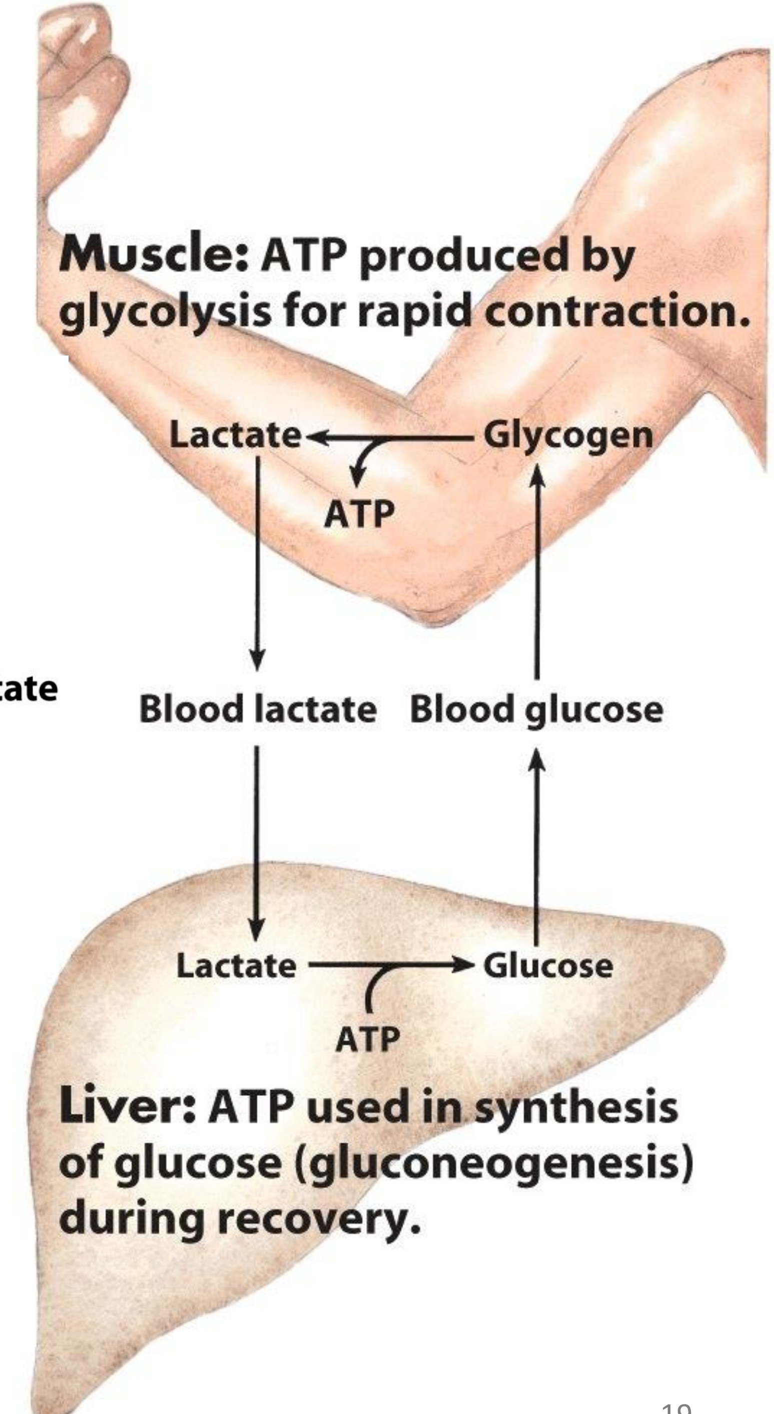
Cori-cycle

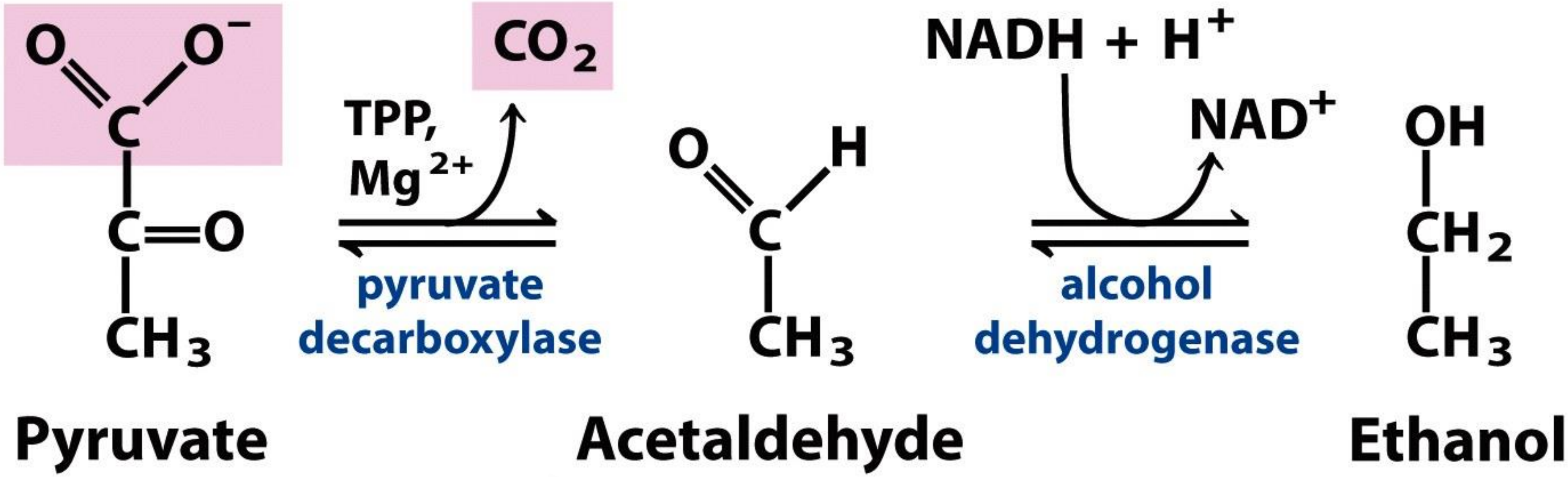
Gerty Cori and Carl Cori

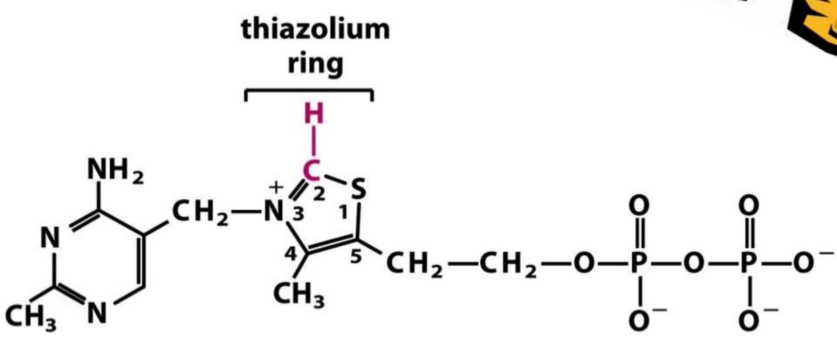




Chapter 16 Opener part 1
Biochemistry, Sixth Edition







Thiamine pyrophosphate (TPP)

Box 14-3 figure 1
Lehninger Principles of Biochemistry, Fifth Edition

The irreversible steps of glycolysis

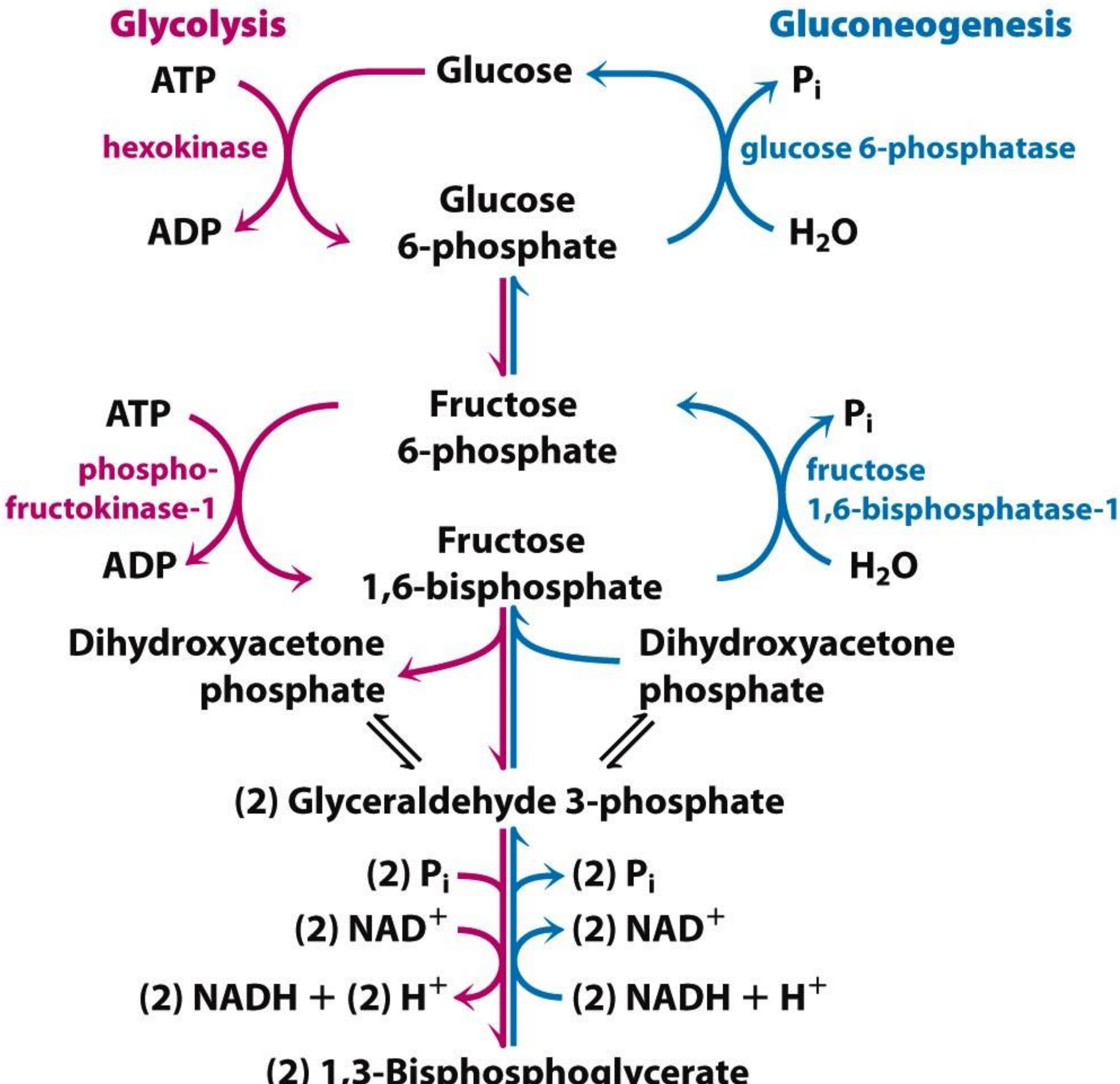
$\Delta G = \Delta G° + RT \ln Q$

TABLE 14–2 Free-Energy Changes of Glycolytic Reactions in Erythrocytes

Glycolytic reaction step		$\Delta G'°$ (kJ/mol)	ΔG (kJ/mol)
1 Glucose + ATP ⟶ glucose 6-phosphate + ADP	hexokinase	−16.7	−33.4
2 Glucose 6-phosphate ⇌ fructose 6-phosphate		1.7	0 to 25
3 Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP	phosphofructo-kinase 1	−14.2	−22.2
4 Fructose 1,6-bisphosphate ⇌ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate		23.8	−6 to 0
5 Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate		7.5	0 to 4
6 Glyceraldehyde 3-phosphate + P_i + NAD^+ ⇌ 1,3-bisphosphoglycerate + NADH + H^+		6.3	−2 to 2
7 1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP		−18.8	0 to 2
8 3-Phosphoglycerate ⇌ 2-phosphoglycerate		4.4	0 to 0.8
9 2-Phosphoglycerate ⇌ phosphoenolpyruvate + H_2O		7.5	0 to 3.3
10 Phosphoenolpyruvate + ADP ⟶ pyruvate + ATP	pyruvate kinase	−31.4	−16.7

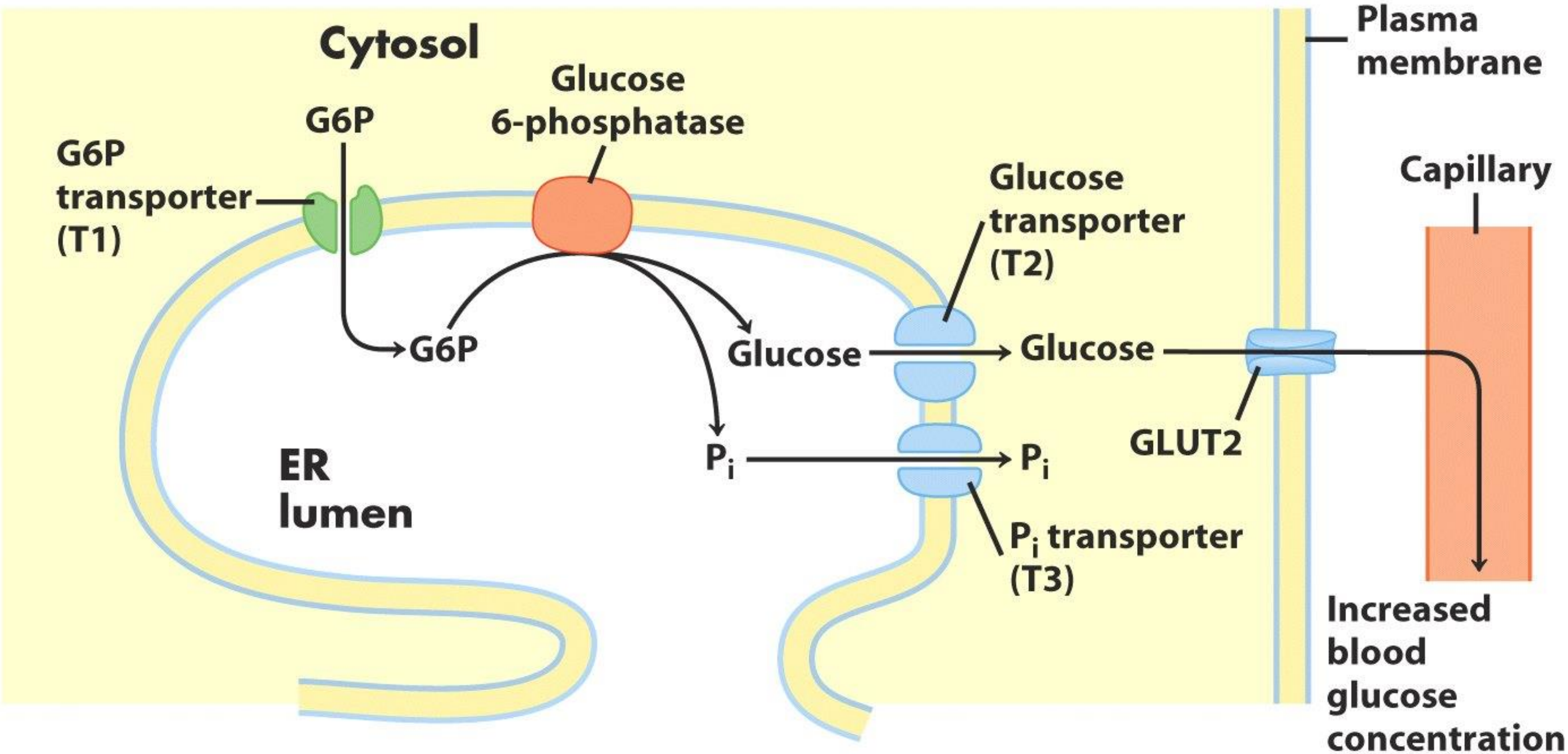
Note: $\Delta G'°$ is the standard free-energy change, as defined in Chapter 13 (pp. 491–492). ΔG is the free-energy change calculated from the actual concentrations of glycolytic intermediates present under physiological conditions in erythrocytes, at pH 7. The glycolytic reactions bypassed in gluconeogenesis are shown in red. Biochemical equations are not necessarily balanced for H or charge (p. 501).

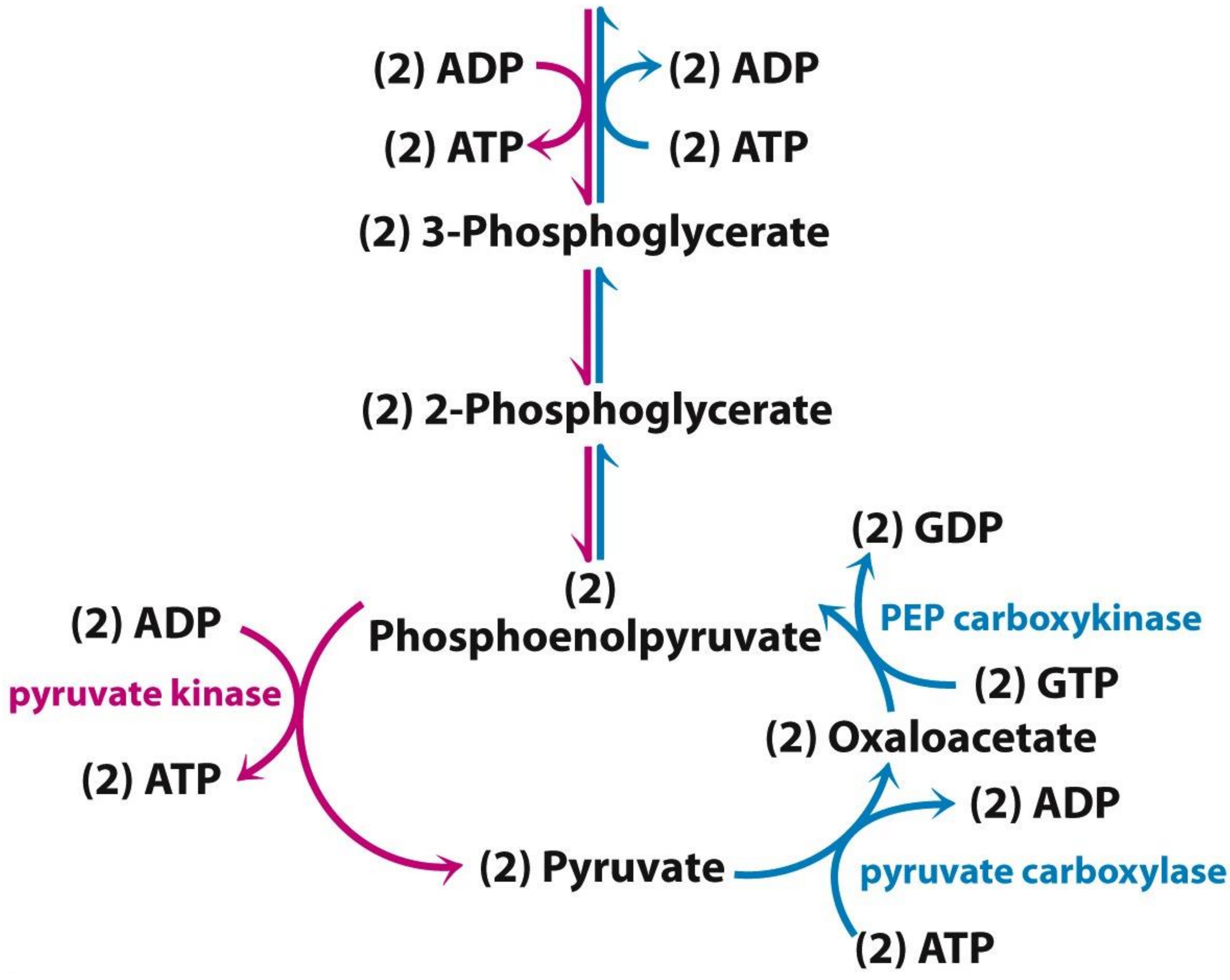
Table 14-2
Lehninger Principles of Biochemistry, Fifth Edition



Glycolysis
Gluconeogenesis
Glucose
ATP
hexokinase
ADP
Glucose 6-phosphate
P_i
glucose 6-phosphatase
H_2O
ATP
phospho-fructokinase-1
ADP
Fructose 6-phosphate
Fructose 1,6-bisphosphate
P_i
fructose 1,6-bisphosphatase-1
H_2O
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

Glucose-6-phosphatase





(2) ADP
(2) ADP
(2) ATP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) GDP
(2)
Phosphoenolpyruvate
(2) ADP
PEP carboxykinase
pyruvate kinase
(2) GTP
(2) Oxaloacetate
(2) ATP
(2) ADP
(2) Pyruvate
pyruvate carboxylase
(2) ATP

First Gluconeogenic Steps

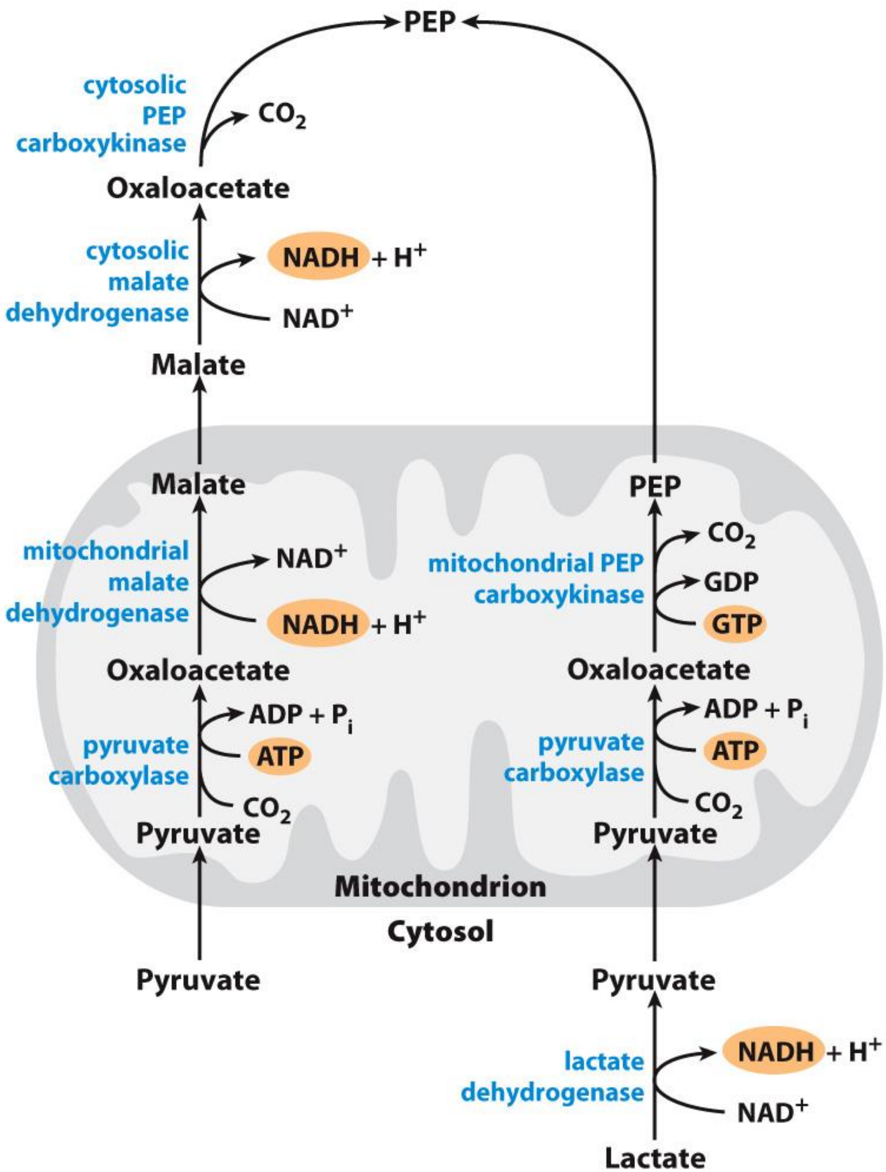
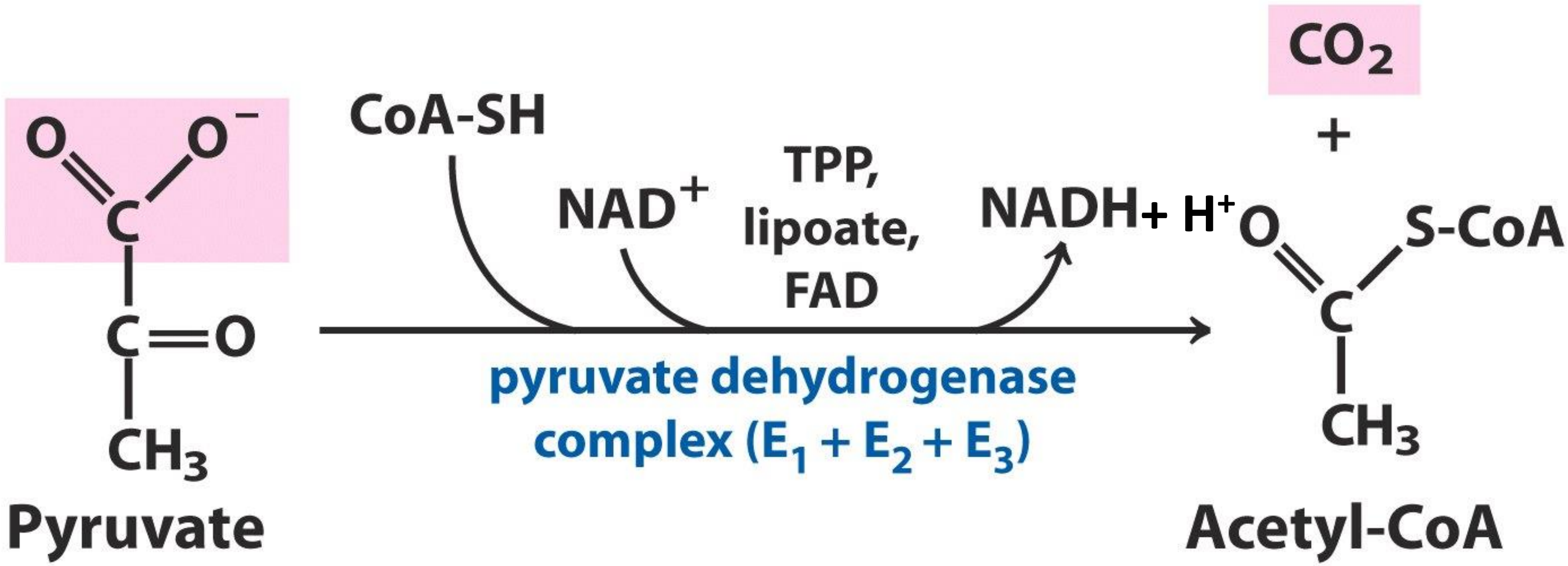


Figure 14-20
Lehninger Principles of Biochemistry, Seventh Edition

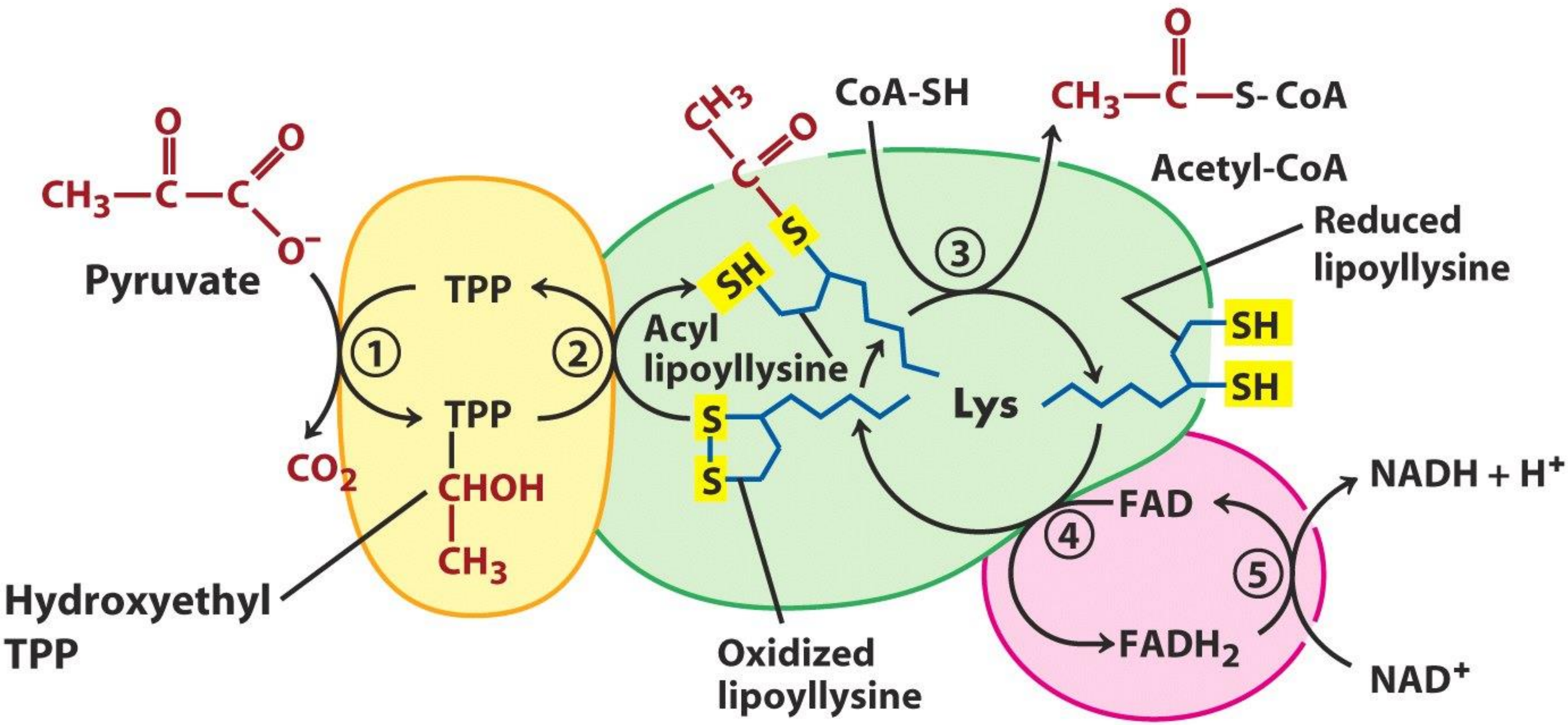
- The inner mitochondrial membrane is selectively permeable: for malate, PEP, and pyruvate it is permeable, while oxaloacetate cannot escape.
- Oxaloacetate can be utilized in the citric acid cycle (Kreb's cycle) if needed.
- Oxaloacetate can be converted to PEP or malate to allow transport to cytosol for gluconeogenesis.

The overall reaction catalysed by pyruvate dehydrogenase complex



$$\Delta G'^{\circ} = -33.4 \text{ kJ/mol}$$

Oxidative decarboxylation of pyruvate

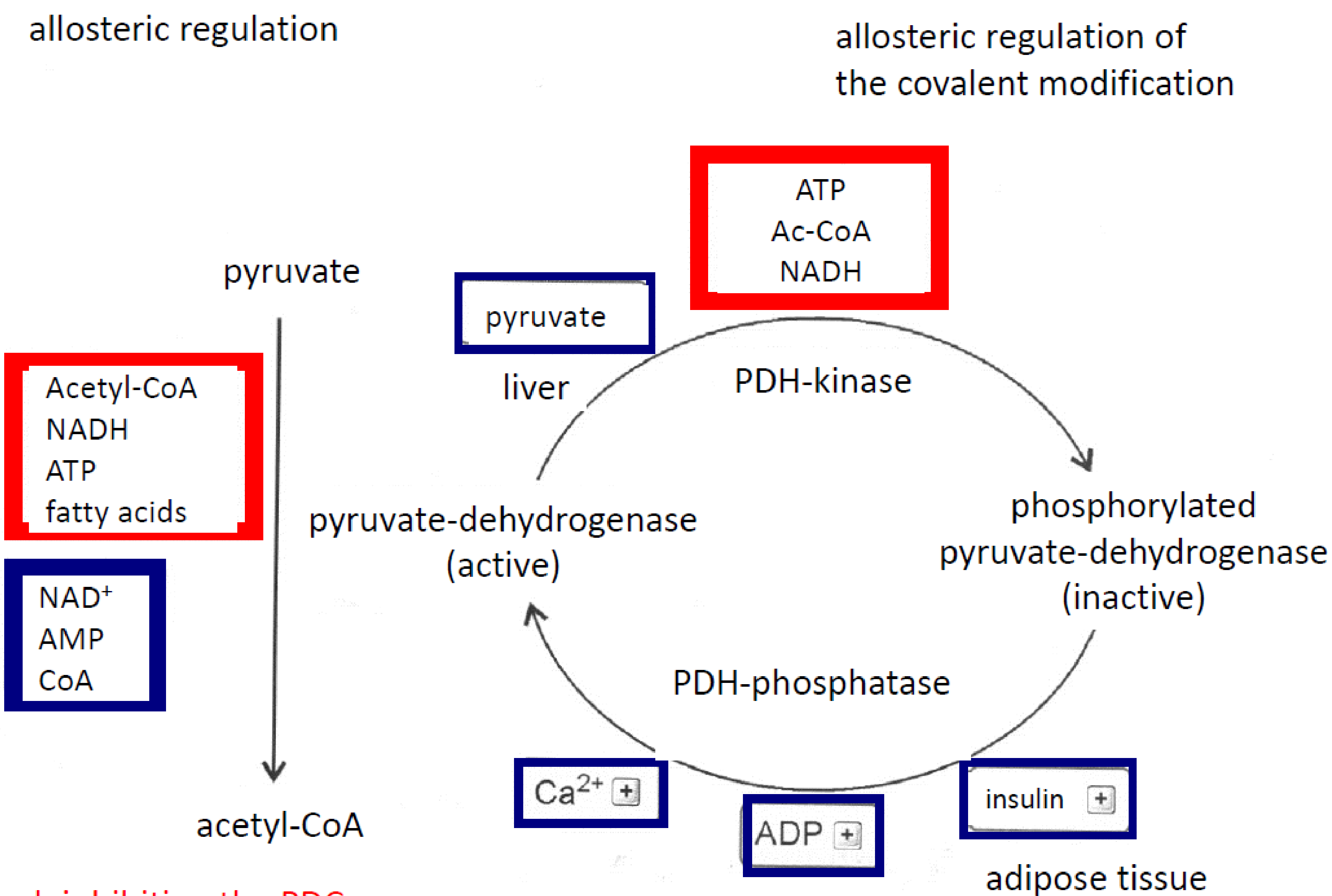


Pyruvate dehydrogenase E_1

Dihydrolipoyl transacetylase E_2

Dihydrolipoyl dehydrogenase E_3

The complex regulation of pyruvate dehydrogenase complex (PDH)



red: inhibiting the PDC
blue: activating the PDC

Crucial contribution

by A. Szent-Györgyi, Franz Knoop

and Carl Martius in 1935

Postulation of

TCA cycle by H.A.Krebs

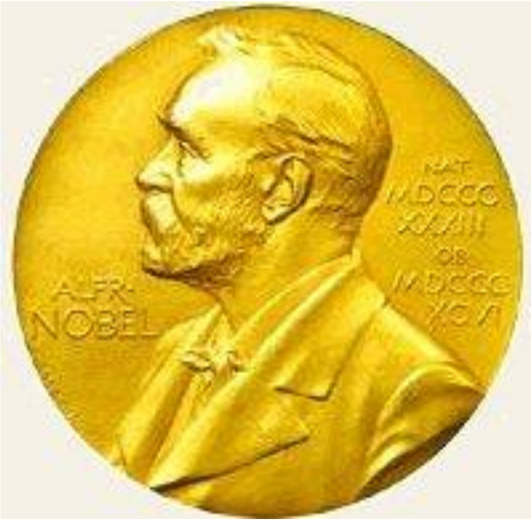
in 1937

Albert **Szent-Györgyi**

1893-1986

University of Szeged,

Hungary, Prize in 1937

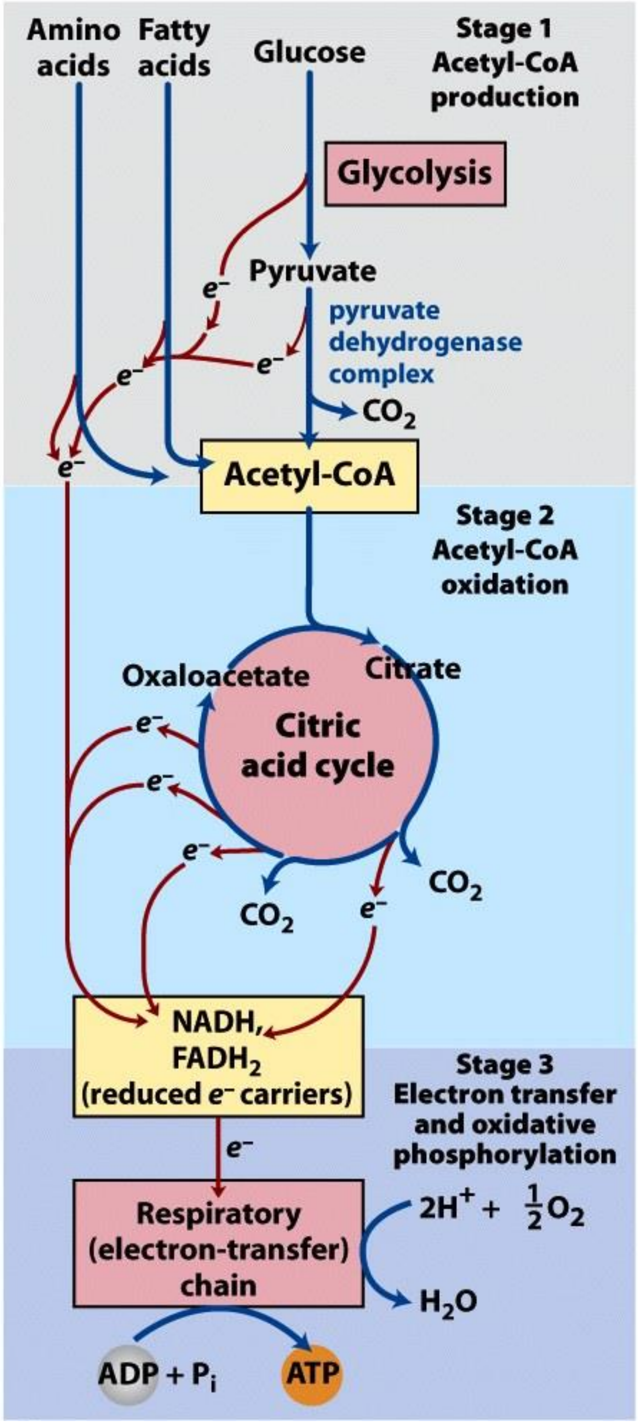
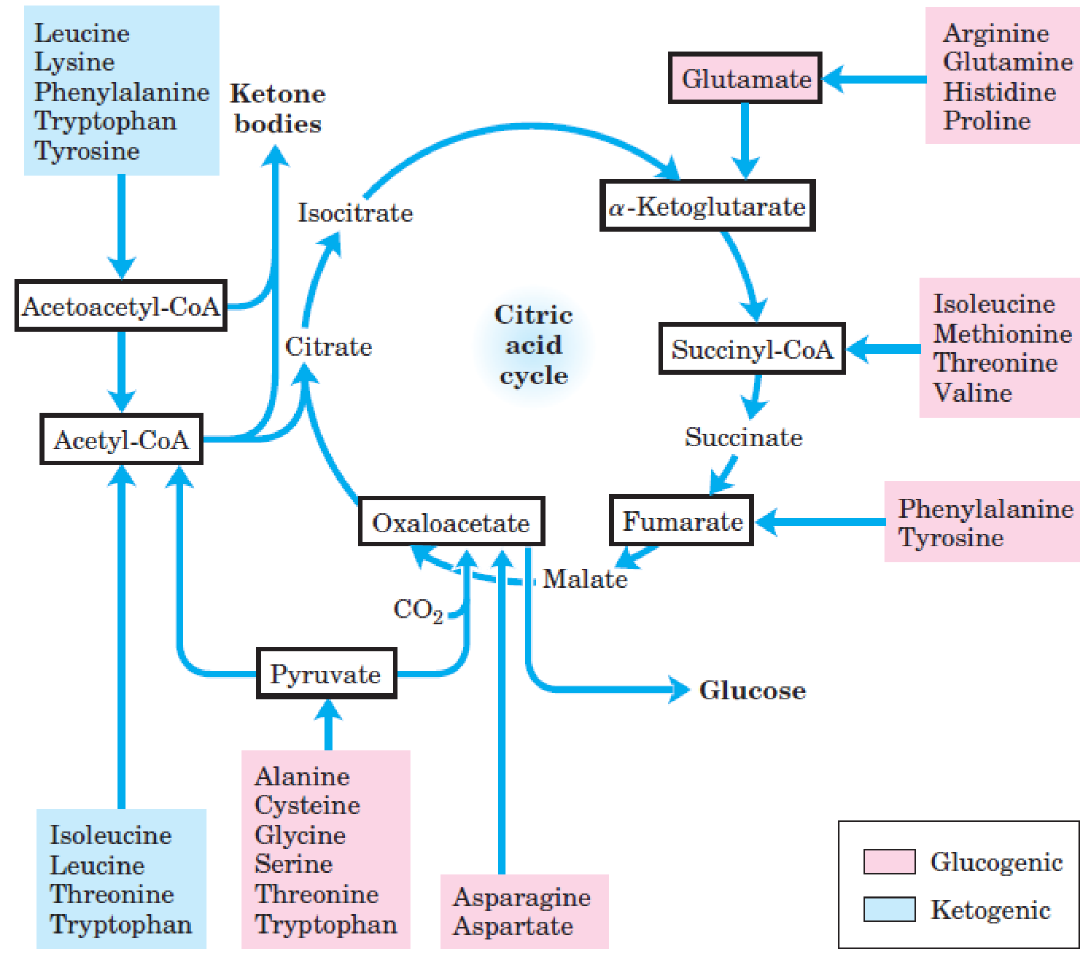


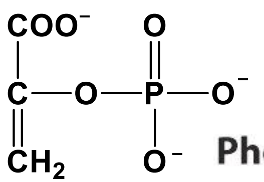
Hans Adolf **Krebs**

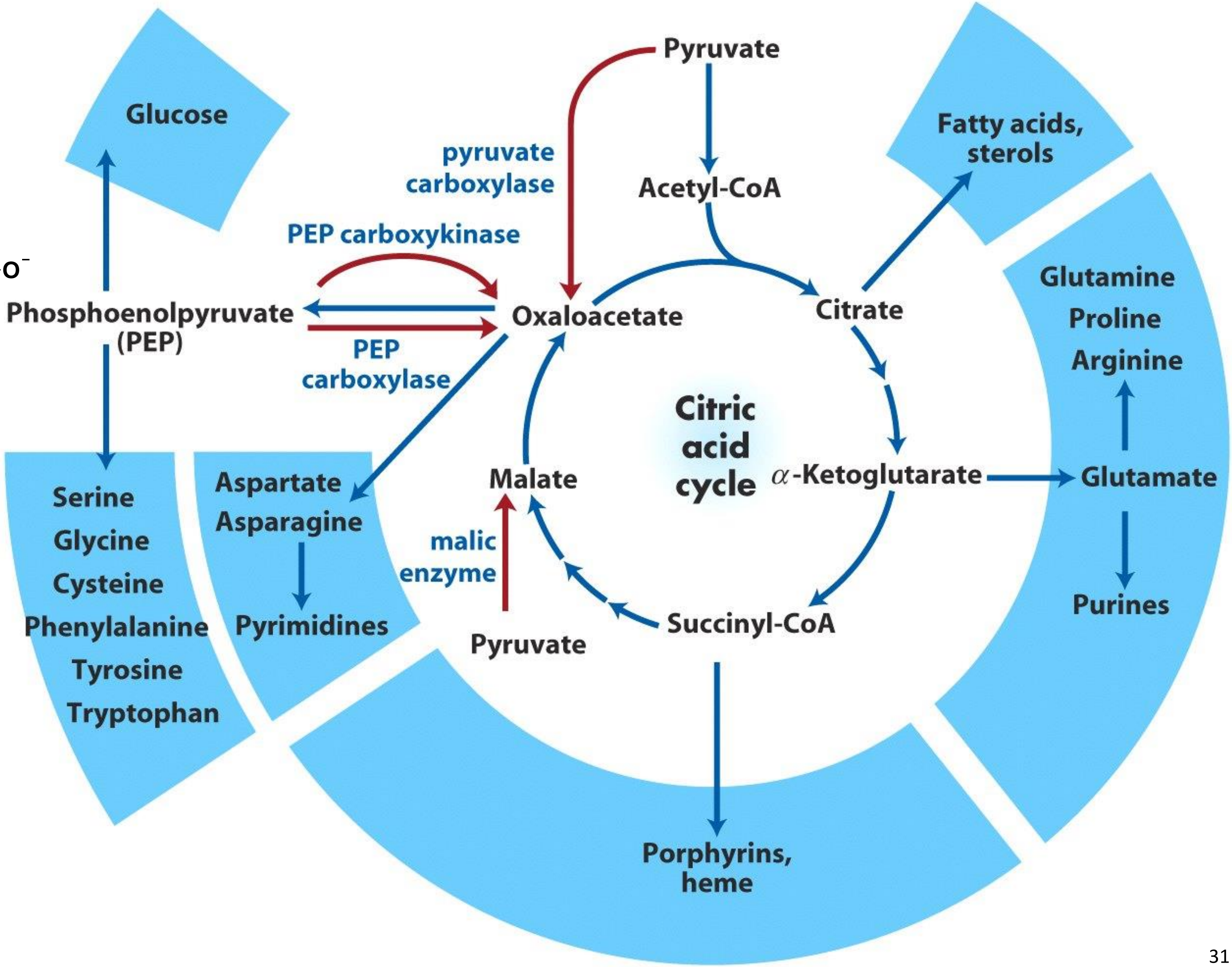
1900-1981

University of Sheffield,

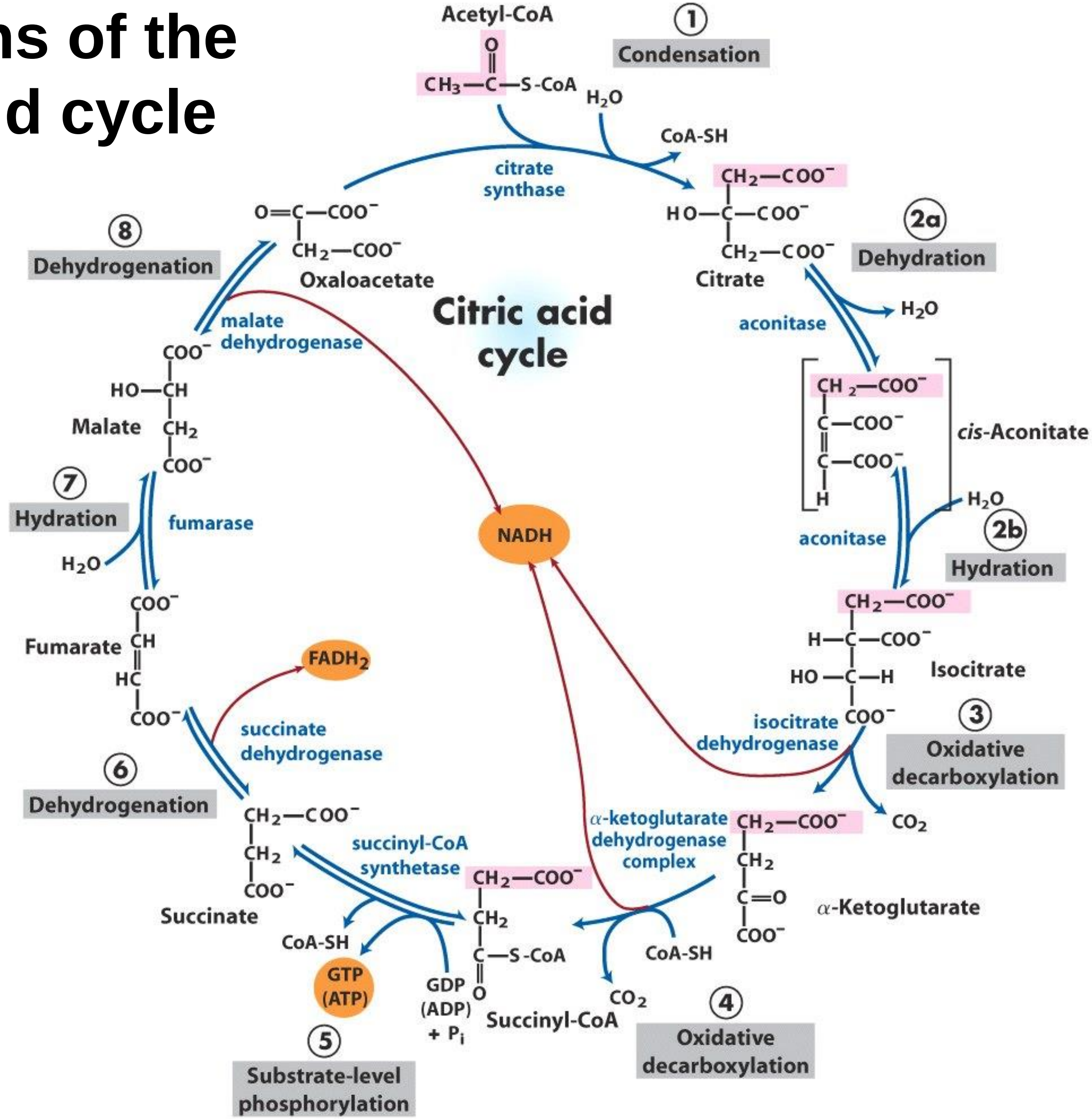
England, Prize in 1953


Amino acids
Fatty acids
Glucose
Stage 1
Acetyl-CoA production
Glycolysis
Pyruvate
pyruvate dehydrogenase complex
CO_2
e^-
Acetyl-CoA
Stage 2
Acetyl-CoA oxidation
Oxaloacetate
Citrate
Citric acid cycle
CO_2
NADH, $FADH_2$
(reduced e^- carriers)
Stage 3
Electron transfer and oxidative phosphorylation
Respiratory (electron-transfer) chain
$2H^+ + \frac{1}{2}O_2$
H_2O
$ADP + P_i$
ATP

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Acetoacetyl-CoA
Acetyl-CoA
Isocitrate
Citrate
Citric acid cycle
Glutamate
Arginine
Glutamine
Histidine
Proline
α-Ketoglutarate
Succinyl-CoA
Isoleucine
Methionine
Threonine
Valine
Succinate
Fumarate
Phenylalanine
Tyrosine
Oxaloacetate
Malate
CO_2
Pyruvate
Glucose
Isoleucine
Leucine
Threonine
Tryptophan
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Asparagine
Aspartate
Glucogenic
Ketogenic

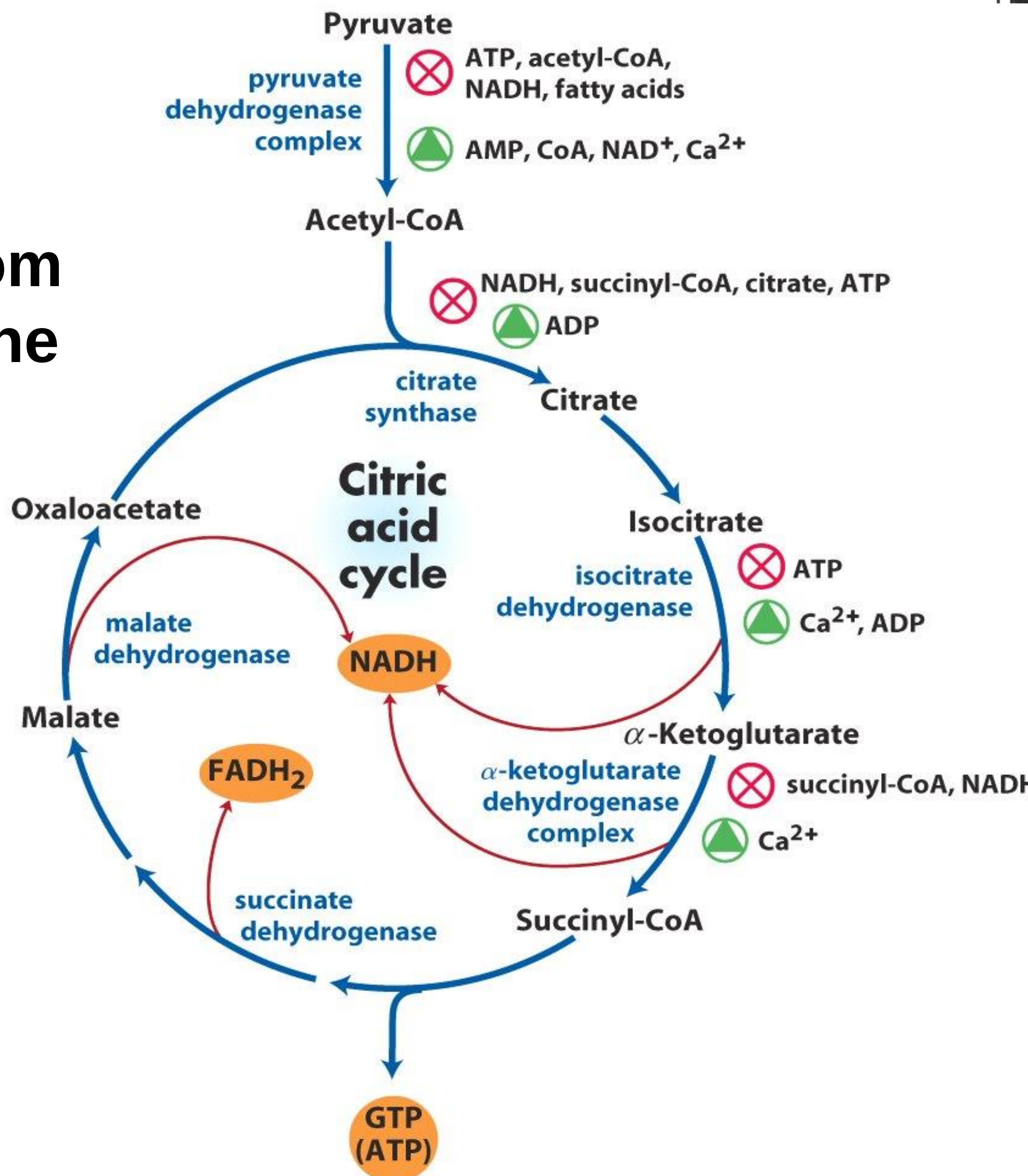

COO⁻
C—O—P—O⁻
CH2
O
O⁻


Glucose
Pyruvate
pyruvate carboxylase
Acetyl-CoA
Fatty acids, sterols
PEP carboxykinase
Phosphoenolpyruvate (PEP)
Oxaloacetate
Citrate
PEP carboxylase
Citric acid cycle
Glutamine
Proline
Arginine
Glutamate
Purines
α-Ketoglutarate
Malate
malic enzyme
Pyruvate
Succinyl-CoA
Serine
Glycine
Cysteine
Phenylalanine
Tyrosine
Tryptophan
Aspartate
Asparagine
Pyrimidines
Porphyrins, heme

Reactions of the citric acid cycle



Regulation of metabolite flow from the PDC through the citric acid cycle



General scheme of biological oxidation

1. Glycolysis

2. Citric acid cycle

3. Oxidative phosphorylation