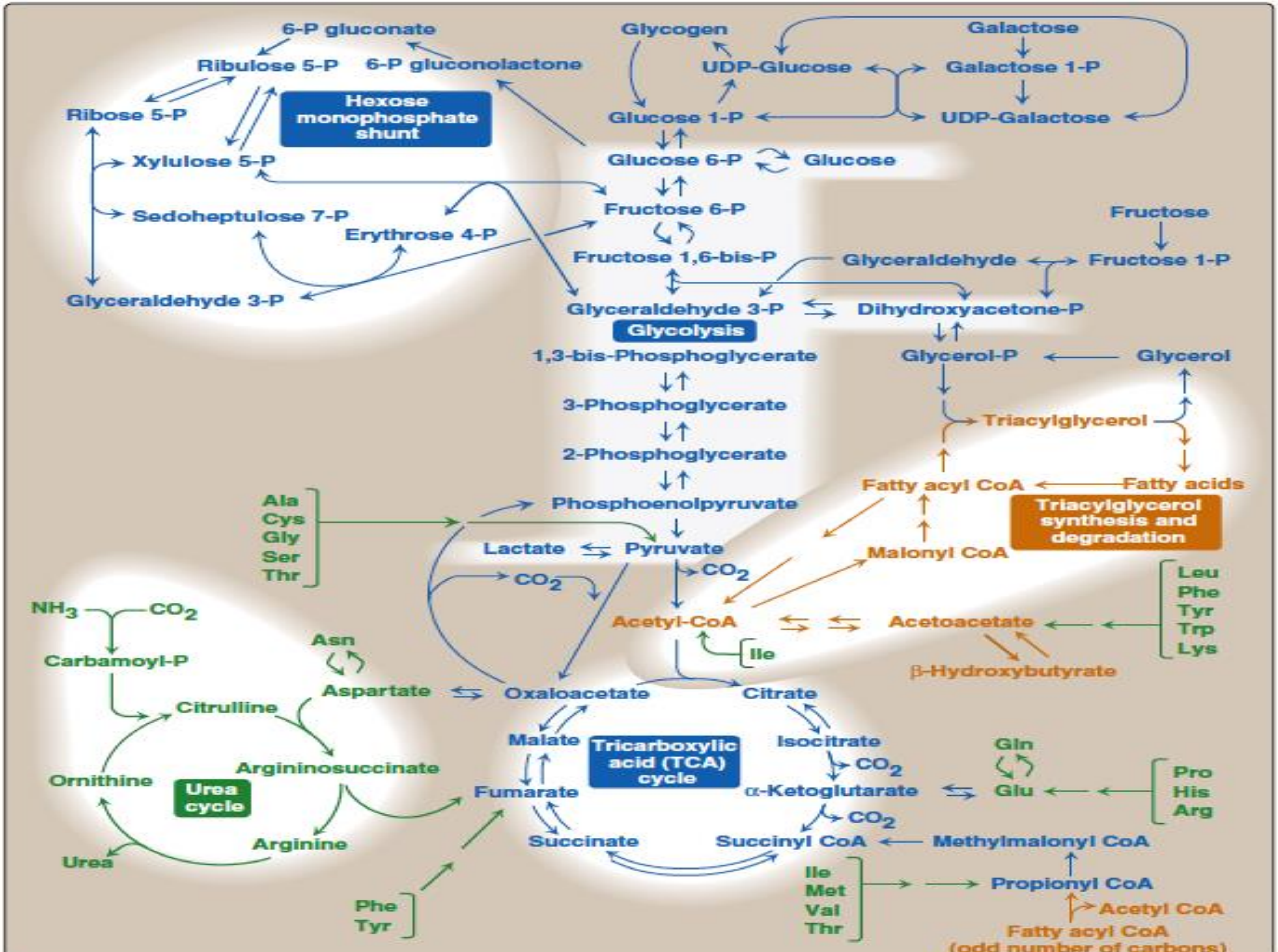
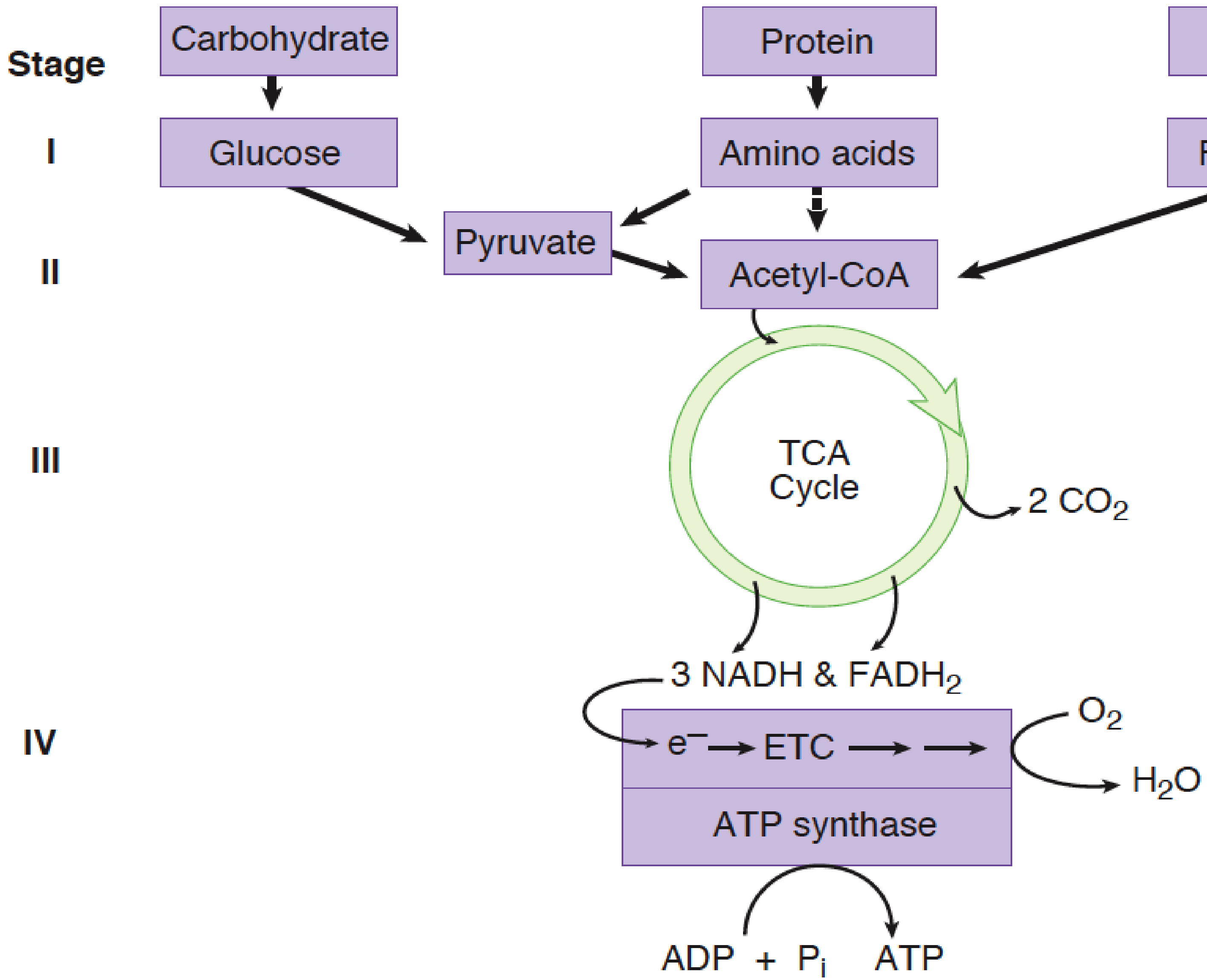
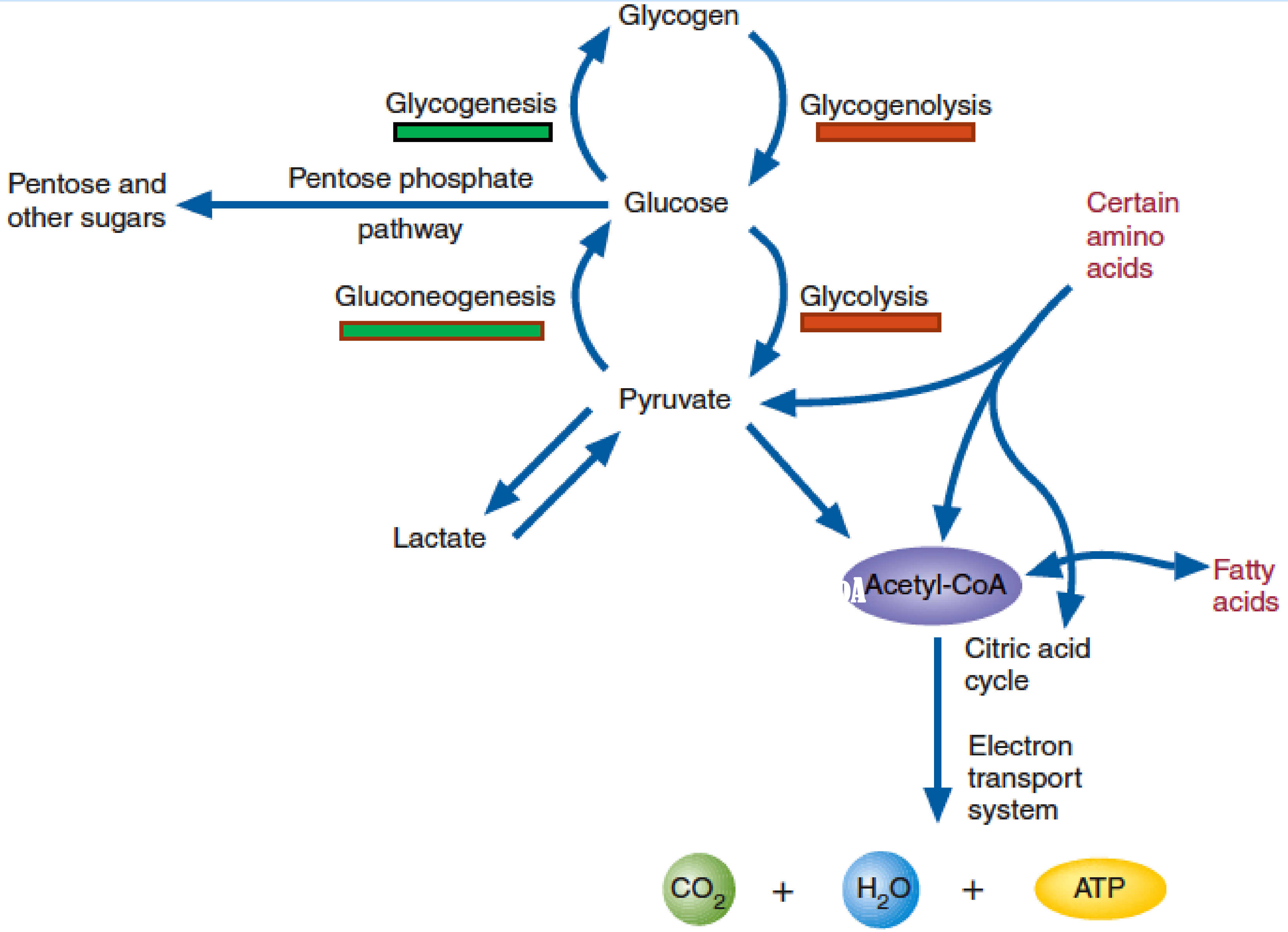
METABOLISM OF CARBOHYDREATES

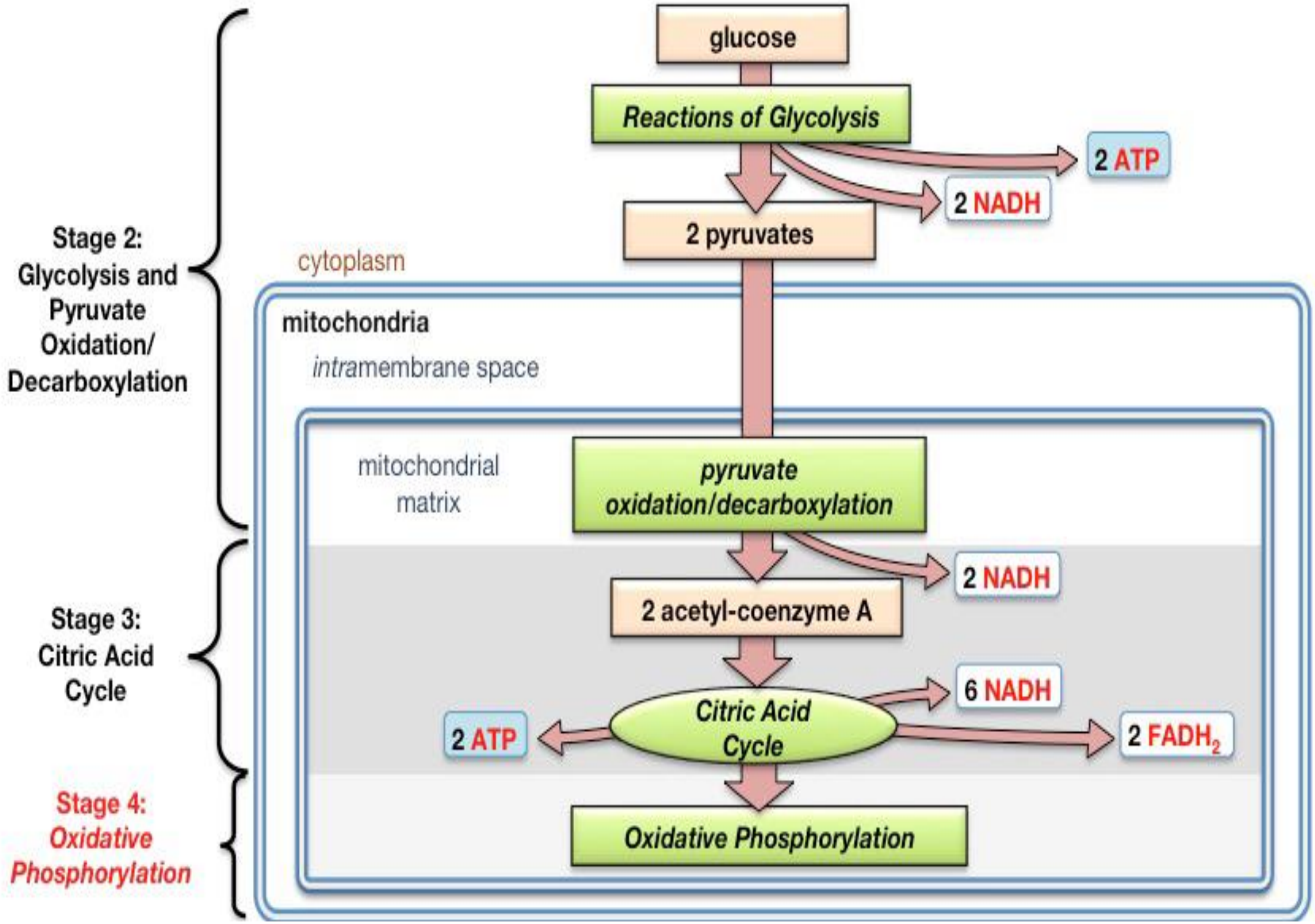

6-P gluconate
Ribulose 5-P
6-P gluconolactone
Hexose monophosphate shunt
Ribose 5-P
Xylulose 5-P
Sedoheptulose 7-P
Erythrose 4-P
Glyceraldehyde 3-P
Glycogen
UDP-Glucose
Galactose
Galactose 1-P
UDP-Galactose
Glucose 1-P
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Fructose
Glyceraldehyde
Fructose 1-P
Glyceraldehyde 3-P
Dihydroxyacetone-P
Glycolysis
1,3-bis-Phosphoglycerate
Glycerol-P
Glycerol
3-Phosphoglycerate
Triacylglycerol
2-Phosphoglycerate
Fatty acyl CoA
Fatty acids
Phosphoenolpyruvate
Triacylglycerol synthesis and degradation
Ala
Cys
Gly
Ser
Thr
Lactate
Pyruvate
Malonyl CoA
CO_2
CO_2
NH_3
CO_2
Leu
Phe
Tyr
Trp
Lys
Acetyl-CoA
Acetoacetate
Carbamoyl-P
Asn
Ile
β-Hydroxybutyrate
Aspartate
Oxaloacetate
Citrate
Citrulline
Malate
Tricarboxylic acid (TCA) cycle
Isocitrate
Gln
CO_2
Ornithine
Argininosuccinate
Pro
Urea cycle
Fumarate
α-Ketoglutarate
Glu
His
Arg
CO_2
Arginine
Succinate
Succinyl CoA
Methylmalonyl CoA
Urea
Ile
Met
Val
Thr
Propionyl CoA
Phe
Tyr
Acetyl CoA
Fatty acyl CoA (odd number of carbons)

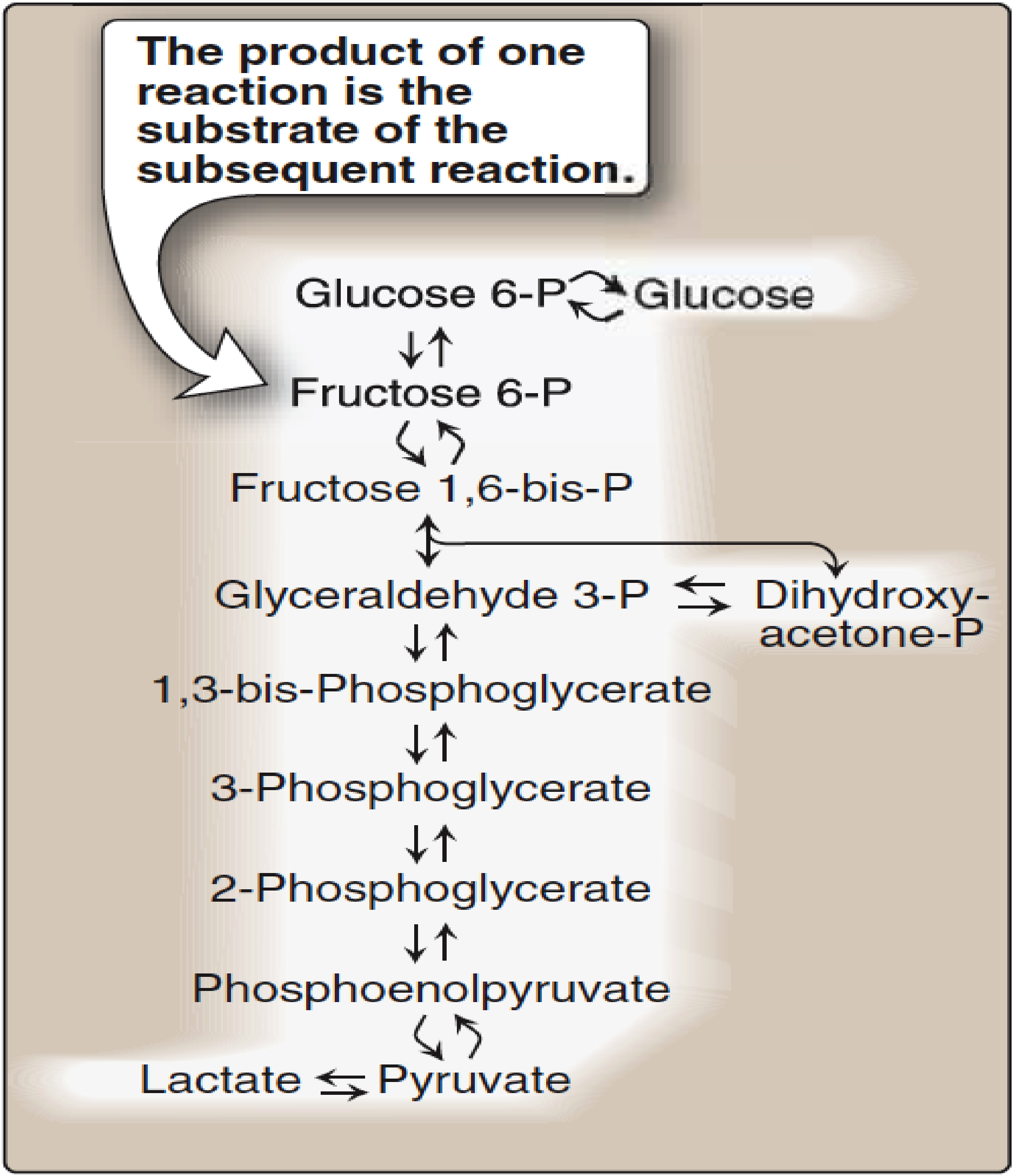
Stages of Metabolism – 4 stages

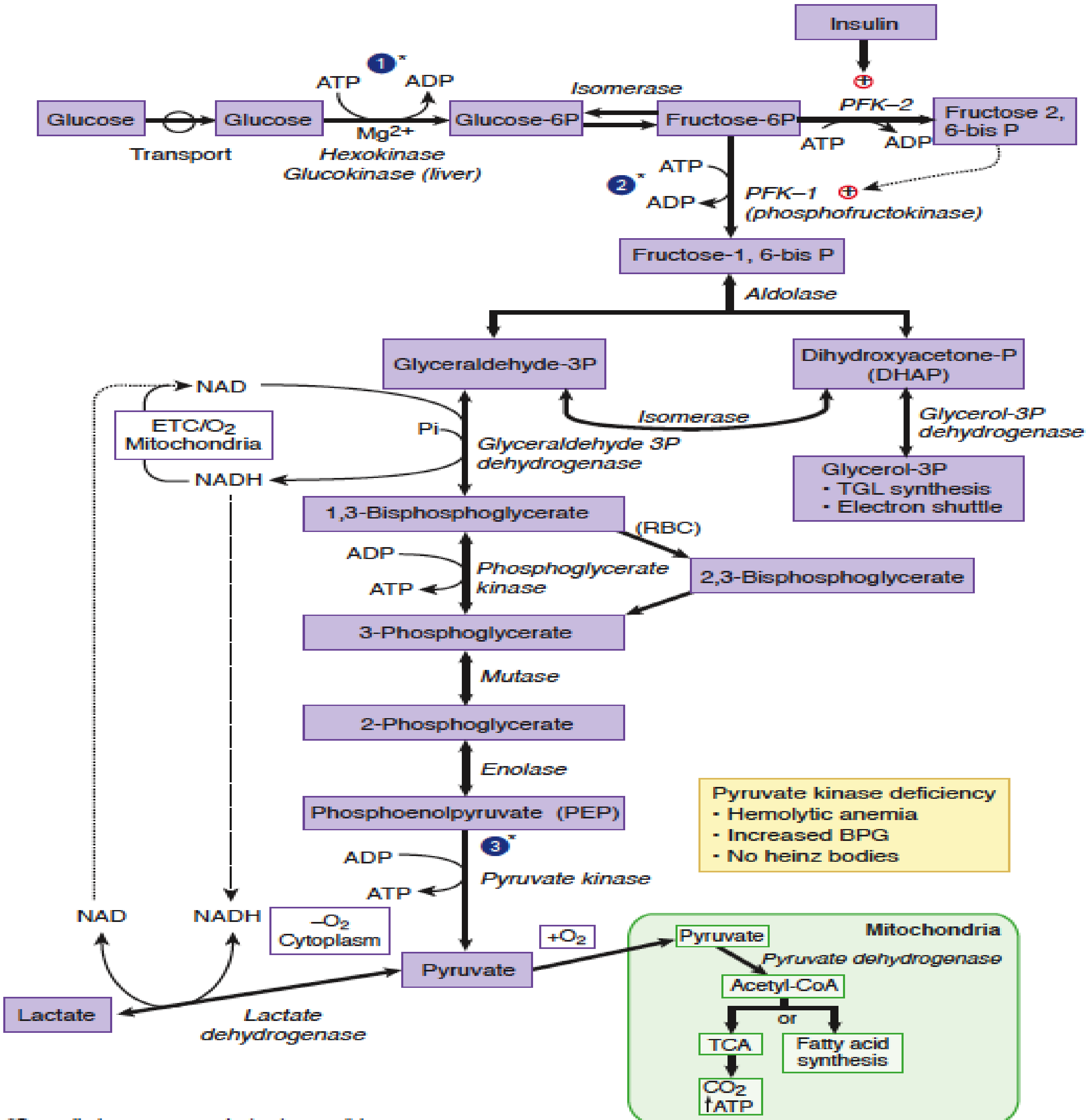


Carbohydrate Metabolism




Stage 2:
Glycolysis and
Pyruvate
Oxidation/
Decarboxylation
Stage 3:
Citric Acid
Cycle
Stage 4:
Oxidative
Phosphorylation
glucose
Reactions of Glycolysis
2 ATP
2 NADH
2 pyruvates
cytoplasm
mitochondria
intramembrane space
mitochondrial
matrix
pyruvate
oxidation/decarboxylation
2 NADH
2 acetyl-coenzyme A
6 NADH
Citric Acid
Cycle
2 ATP
2 $FADH_2$
Oxidative Phosphorylation


The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate



*Controlled enzymes catalyzing irreversible steps

Definition: **Glycolysis**

- Glycolysis means oxidation of glucose to give pyruvate (in the presence of oxygen) or lactate (in the absence of oxygen).
- **It is a cascade of reactions that converts glucose into two pyruvate molecules or into lactate aiming at production of ATP and other intermediates.**
- It is also utilized in its opposite direction in gluconeogenesis.

Intracellular site and tissue distribution:

- **It occurs in the cell cytosol of all tissues of the body.**

But it is of physiological importance in:

- Tissues with no mitochondria: mature RBCs, cornea and lens.
- Tissues with few mitochondria: Testis, leucocytes, medulla of the kidney, retina, skin and gastrointestinal tract.
- Tissues undergo frequent oxygen lack: skeletal muscles especially during exercise.

Biological importance (Functions) of glycolysis:

- Glucose oxidation producing ATP.
  - a) anaerobic glycolysis gives 2 ATP.
  - b) aerobic glycolysis gives 8 ATP.
- It is the major source of energy in certain tissues, e.g., RBCs and skeletal muscles.
- Production of 2,3-DPG that is important in tissue oxygenation.

Biological importance (Functions) of glycolysis:

- It provides pyruvic acid for Krebs' cycle.
- Provides important intermediates:

a) Dihydroxyacetone phosphate: can give glycerol-3phosphate, which is used for synthesis of triacylglycerols and phospholipids (lipogenesis).

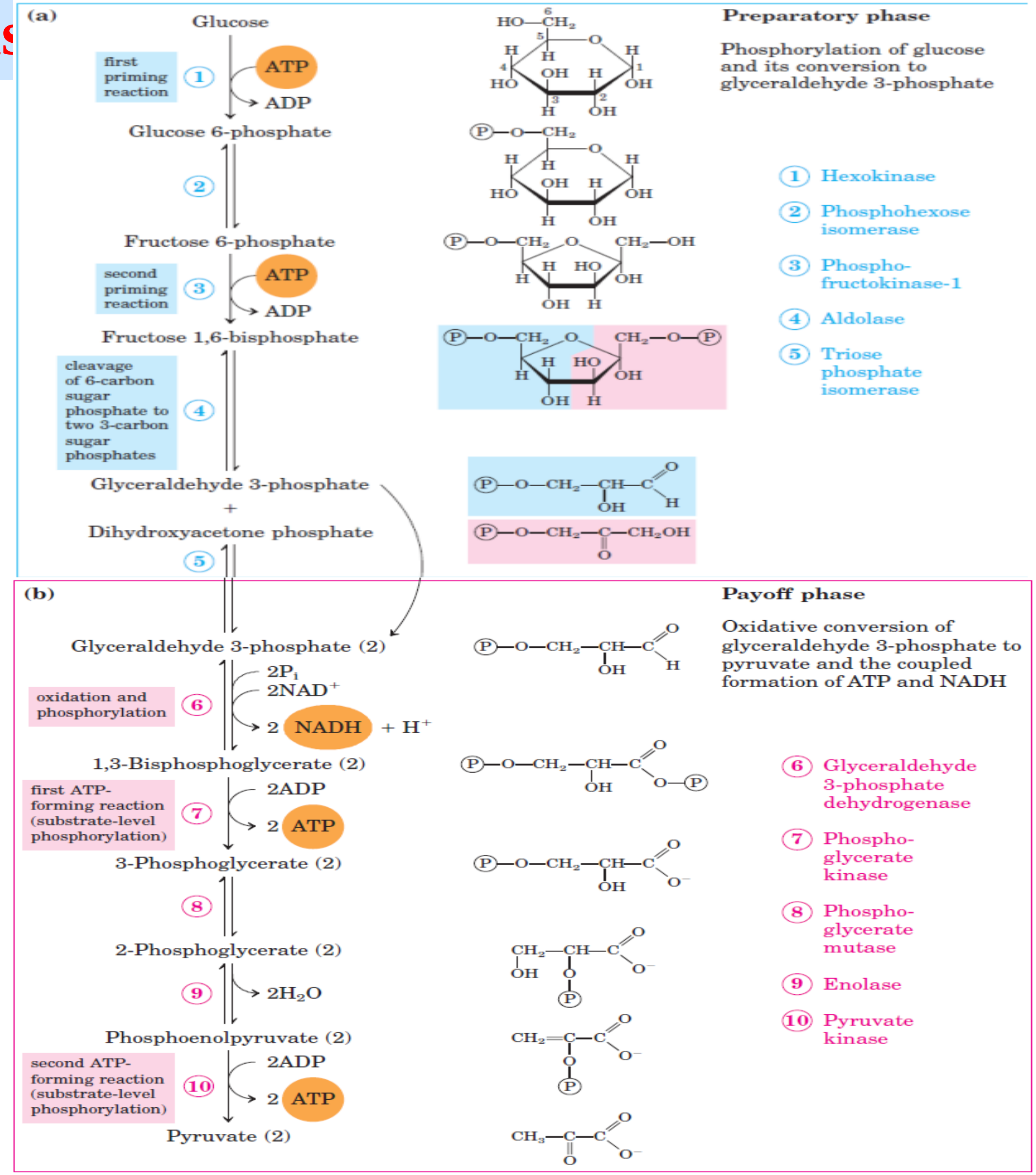
b) 3 Phosphoglycerate: which can be used for synthesis of amino acid serine.

c) Pyruvate: which can be used in synthesis of amino acid alanine.

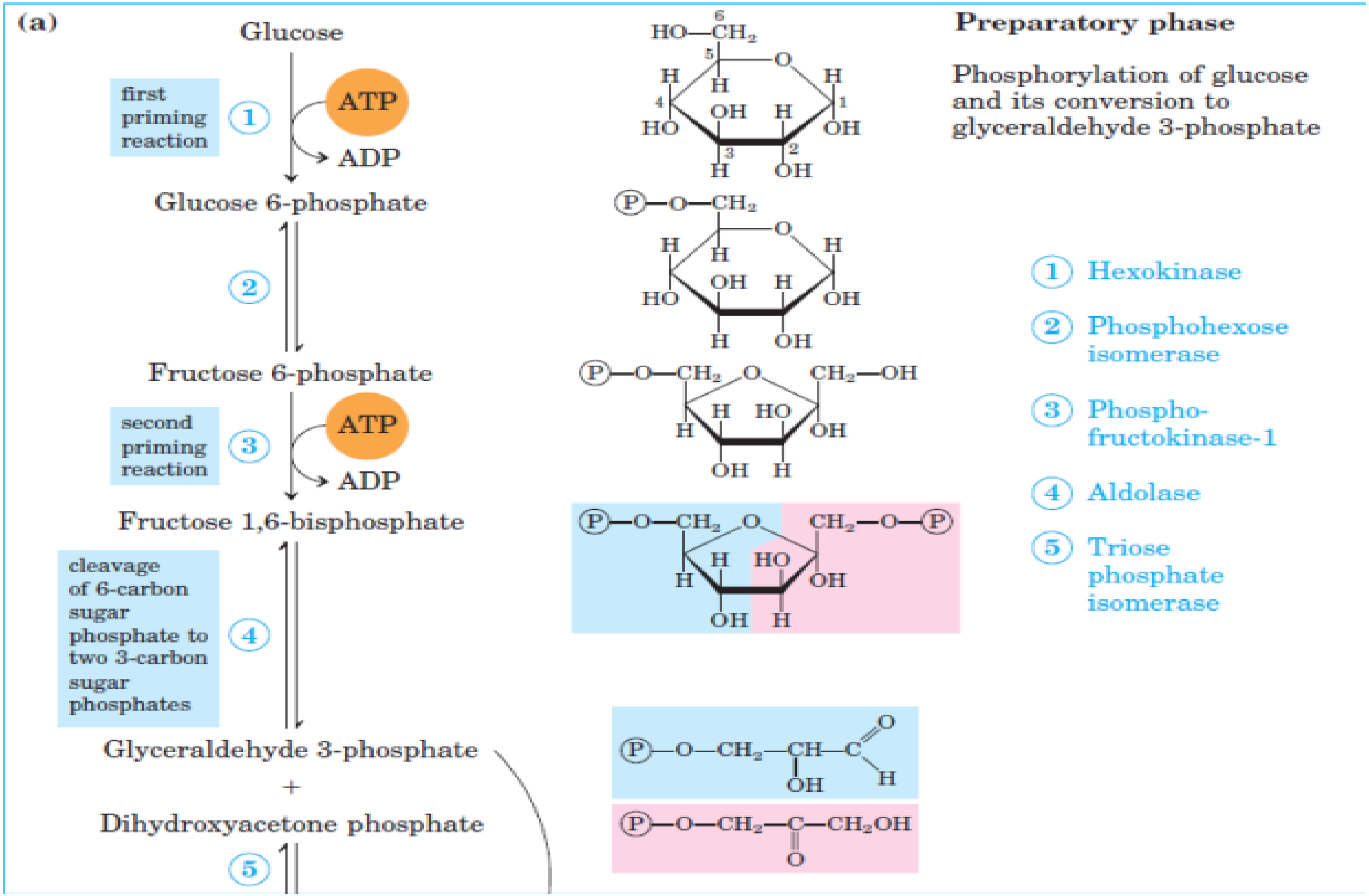
Biological importance (Functions) of glycolysis:

- It is the major source of lactic acid that is gluconeogenic.
- Reversal of glycolysis is gluconeogenesis, an important source of glucose.
- Main pathway of metabolism of fructose from the diet.
- Genetic diseases (a small number) occur due to deficiency in activity of enzymes of glycolysis –mainly manifested as hemolytic anemia.
- Cancer cells are glycolytic – producing large amount of lactate, favoring a relatively acidic local pH in the tumor.

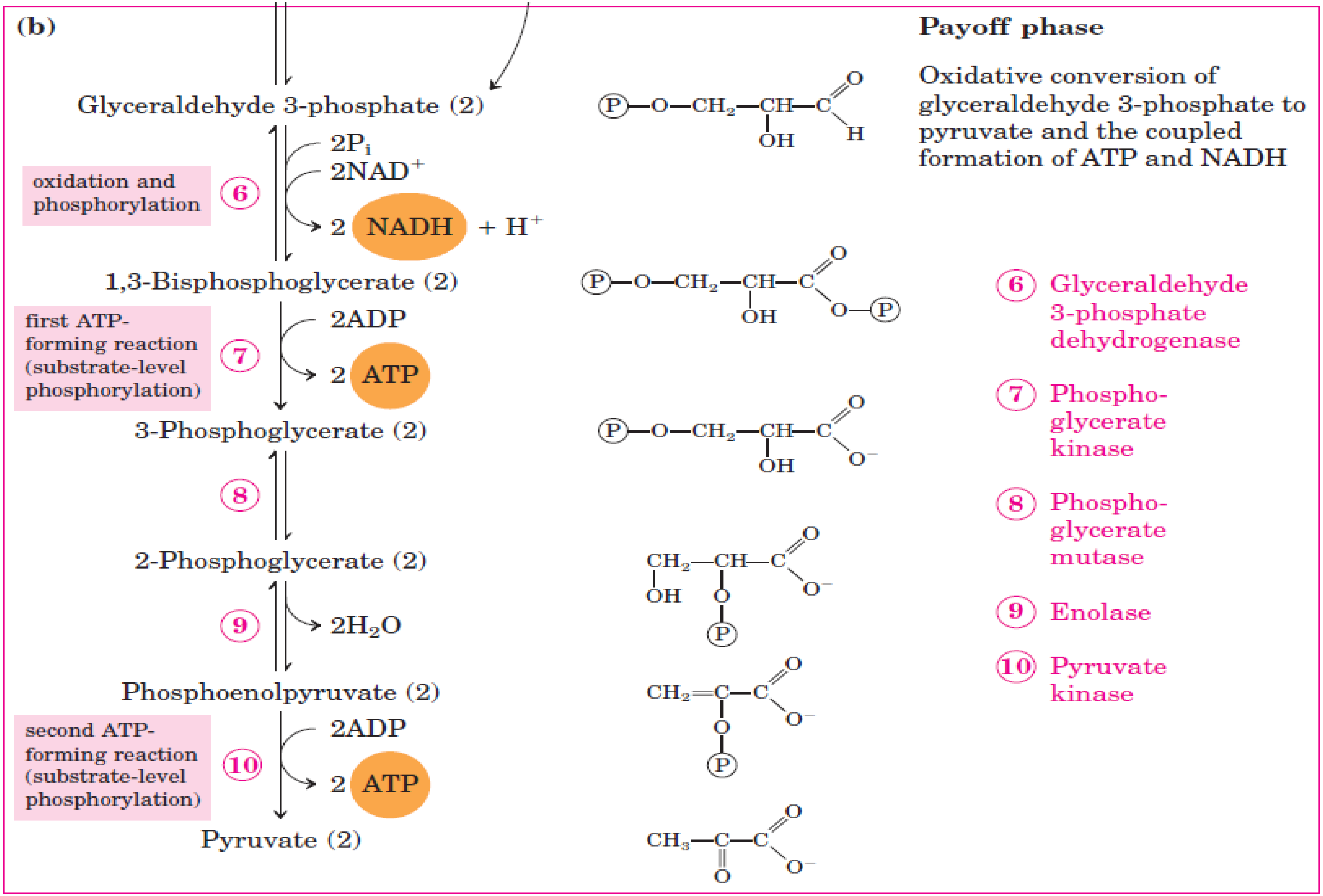
Steps of Glycolysis



Steps of Glycolysis (a)



Steps of Glycolysis (b)



Major Glucose Transporters in Human Cells

Name	Tissues	K_m, Glucose	Functions
GLUT 1	Most tissues (brain, red cells)	~1 mM	Basal uptake of glucose
GLUT 2	Liver Pancreatic β-cells	~15 mM	Uptake and release of glucose by the liver β-cell glucose sensor
GLUT 3	Most tissues	~1 mM	Basal uptake
GLUT 4	Skeletal muscle Adipose tissue	~5 mM	Insulin-stimulated glucose uptake; stimulated by exercise in skeletal muscle

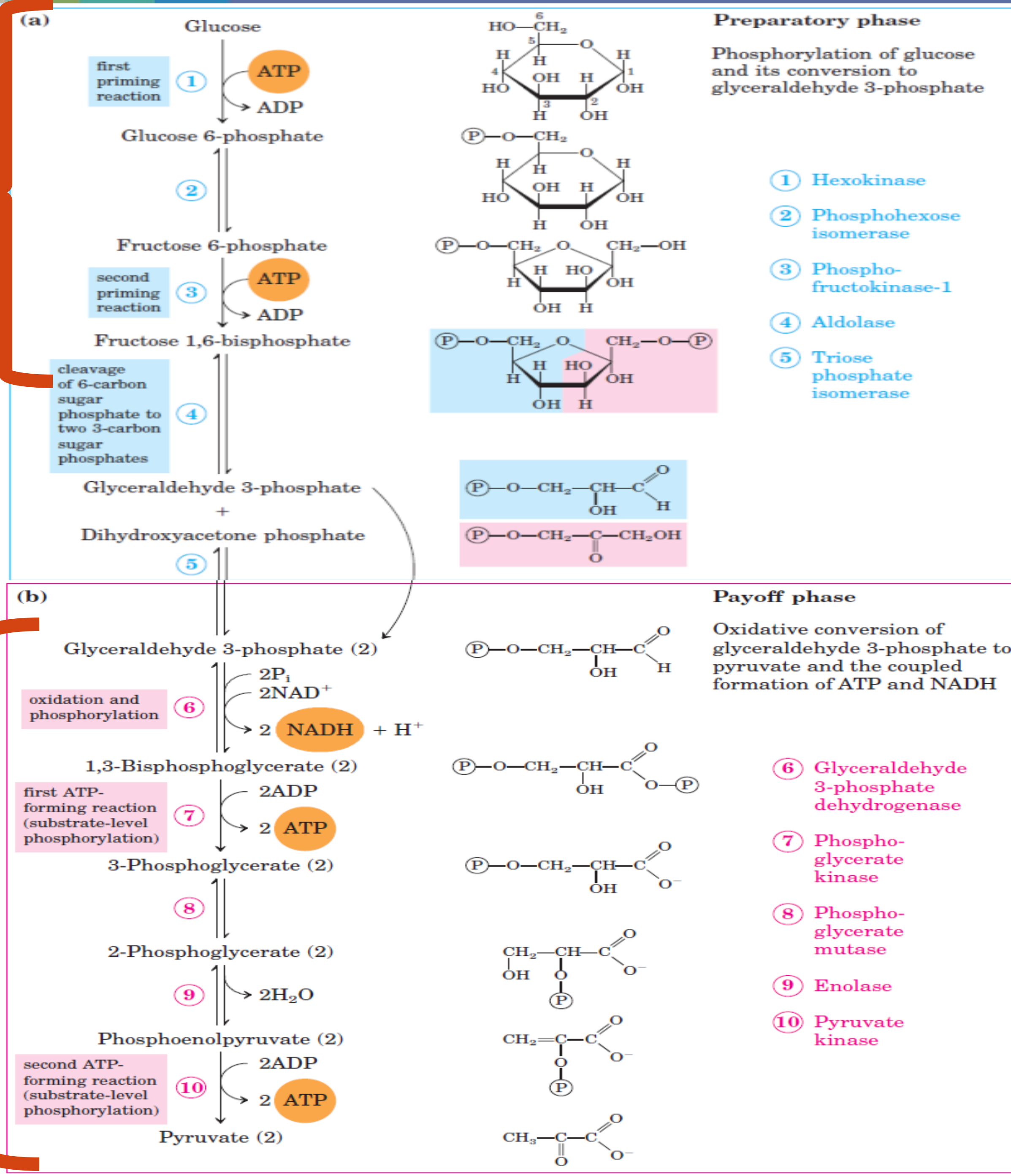
Normal blood glucose concentration is 4–6 mM (72–110 mg/dL).

Steps of Glycolysis

Priming stage

Splitting stage

Oxidoreduction – Phosphorylation stage



Stages of Glycolysis

Stages on the basis of energy consumption

1. **Stage one (the energy requiring stage):**

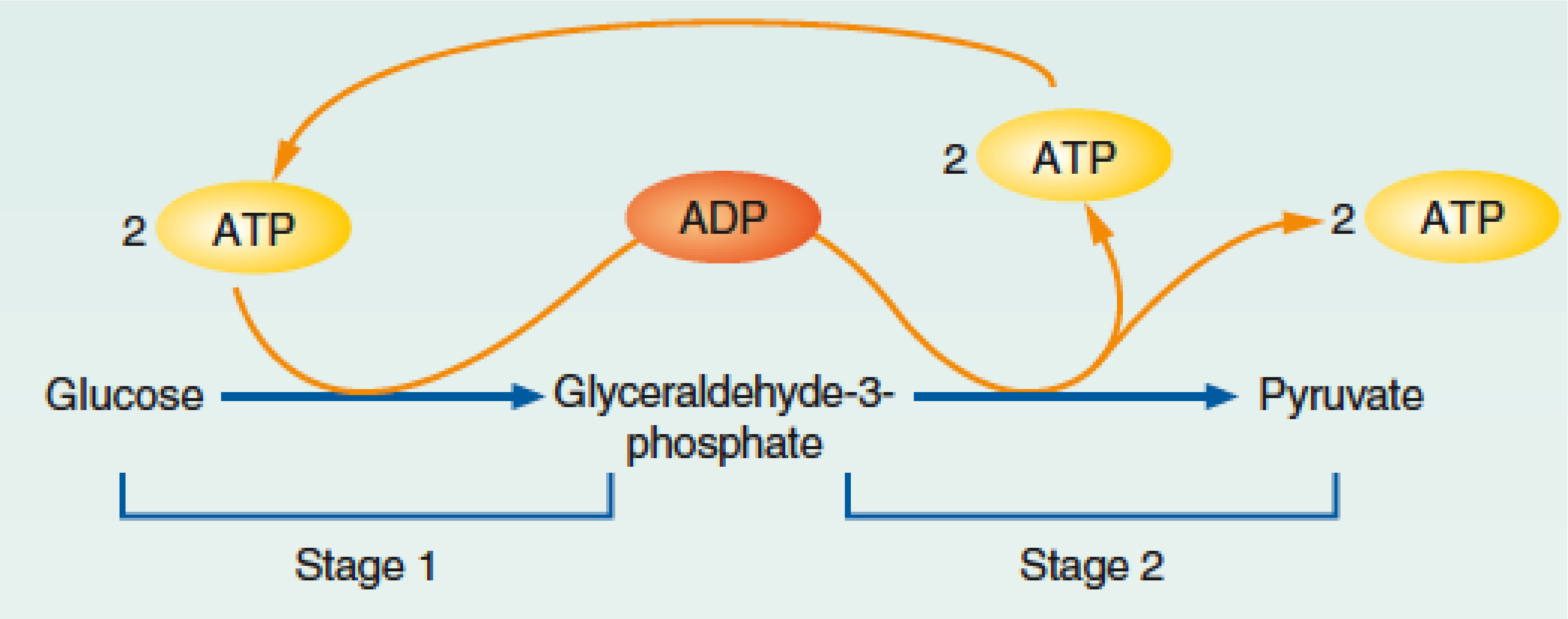
a) One molecule of glucose is converted into two molecules of glycerosldhyde-3-phosphate.

b) These steps requires 2 molecules of ATP (energy loss)

2. Stage two (the energy producing stage):

a) The 2 molecules of glyceroaldehyde-3-phosphate are converted into pyruvate (aerobic glycolysis) or lactate (anaerobic glycolysis).

b) These steps produce ATP molecules (energy production).

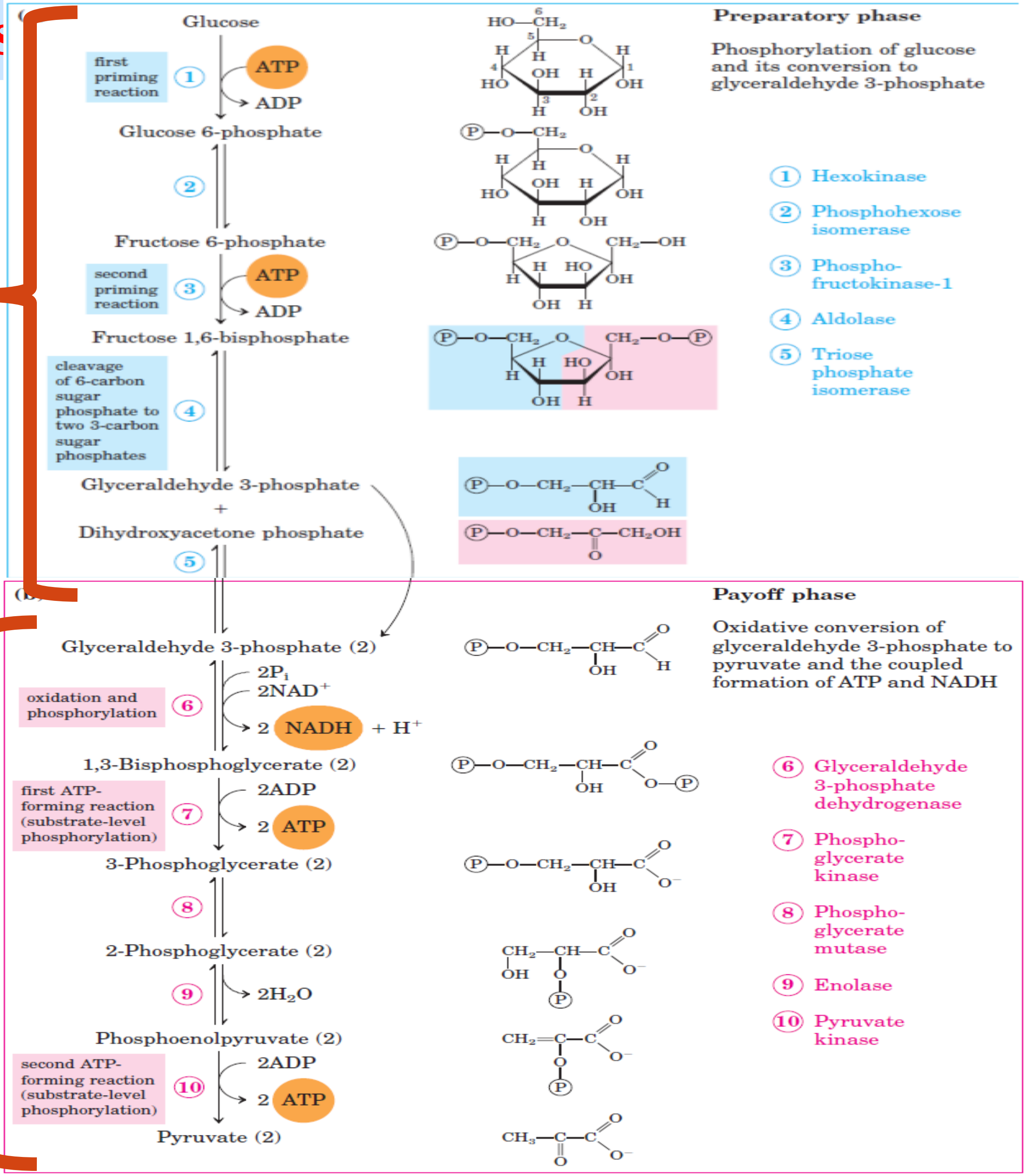


2 ATP
ADP
2 ATP
2 ATP
Glucose
Glyceraldehyde-3-phosphate
Pyruvate
Stage 1
Stage 2

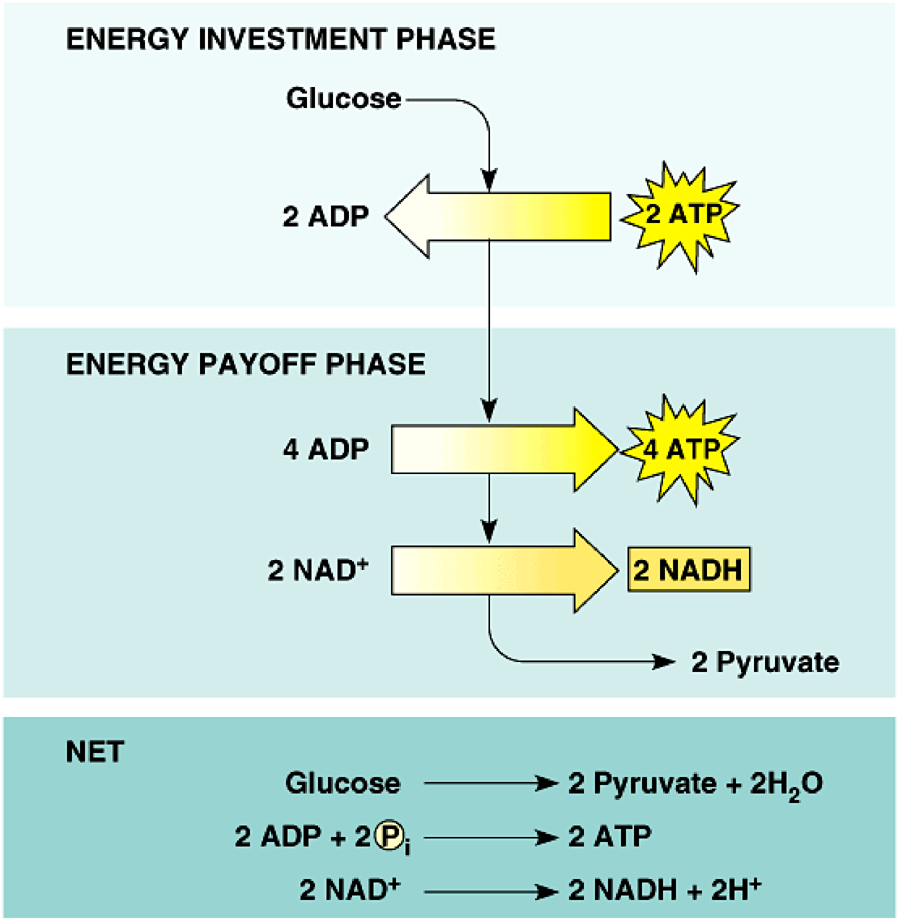
Steps of Glycolysis

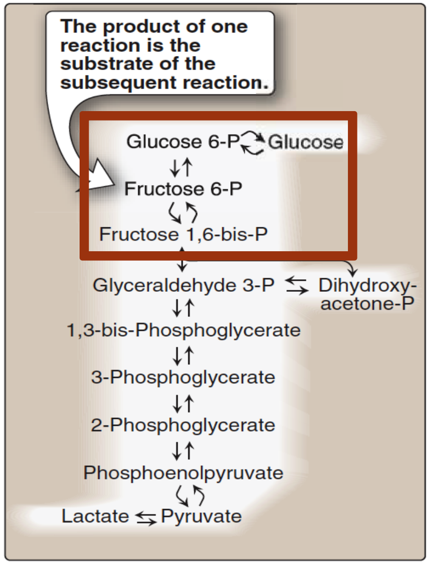
Energy requiring stage

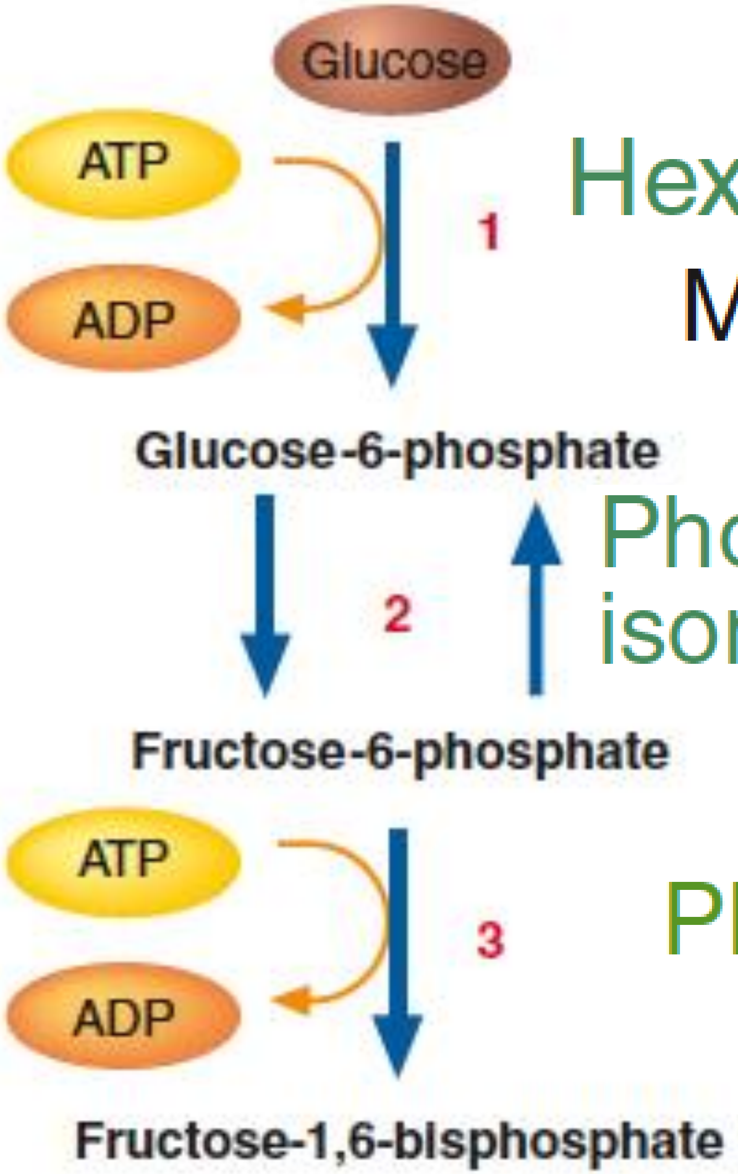
Energy producing stage



- In the energy investment phase, ATP provides activation energy by phosphorylating glucose.
  - This requires 2 ATP per glucose.
- In the energy payoff phase, ATP is produced by substrate-level phosphorylation and NAD^+ is reduced to NADH.
- 2 ATP (net) and 2 NADH are produced per glucose.







Hexokinase

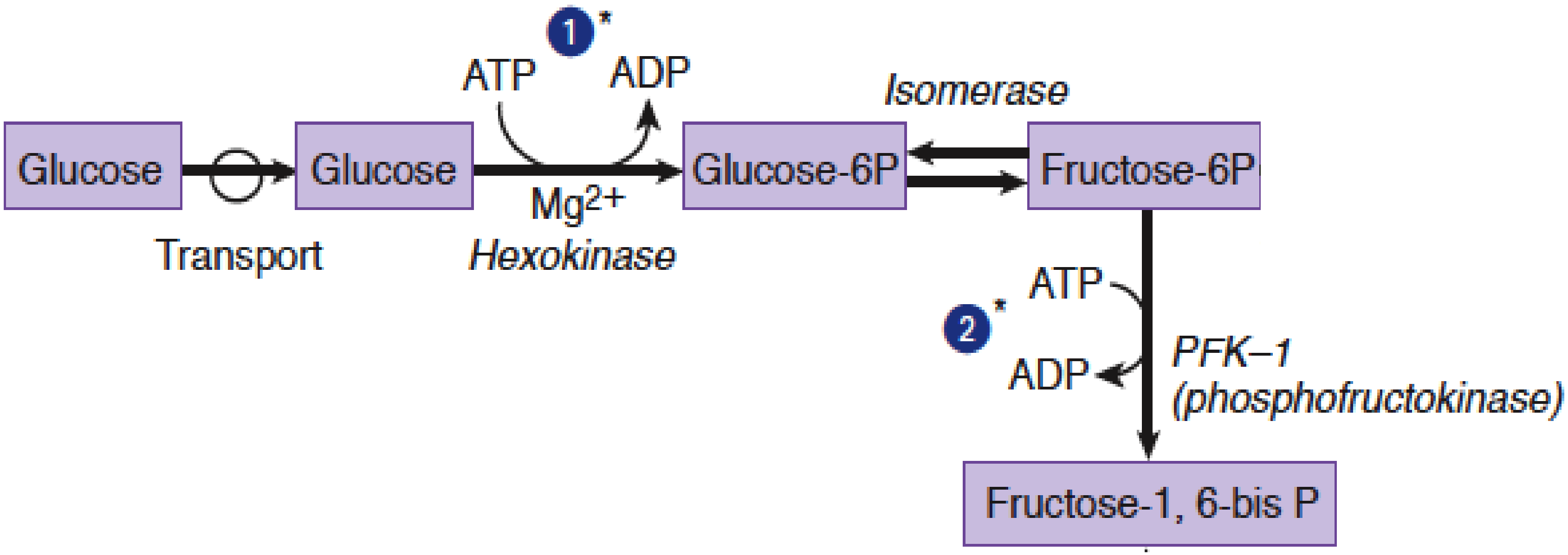
Mg^{2+}

Phosphoglucose isomerase

PFK-1

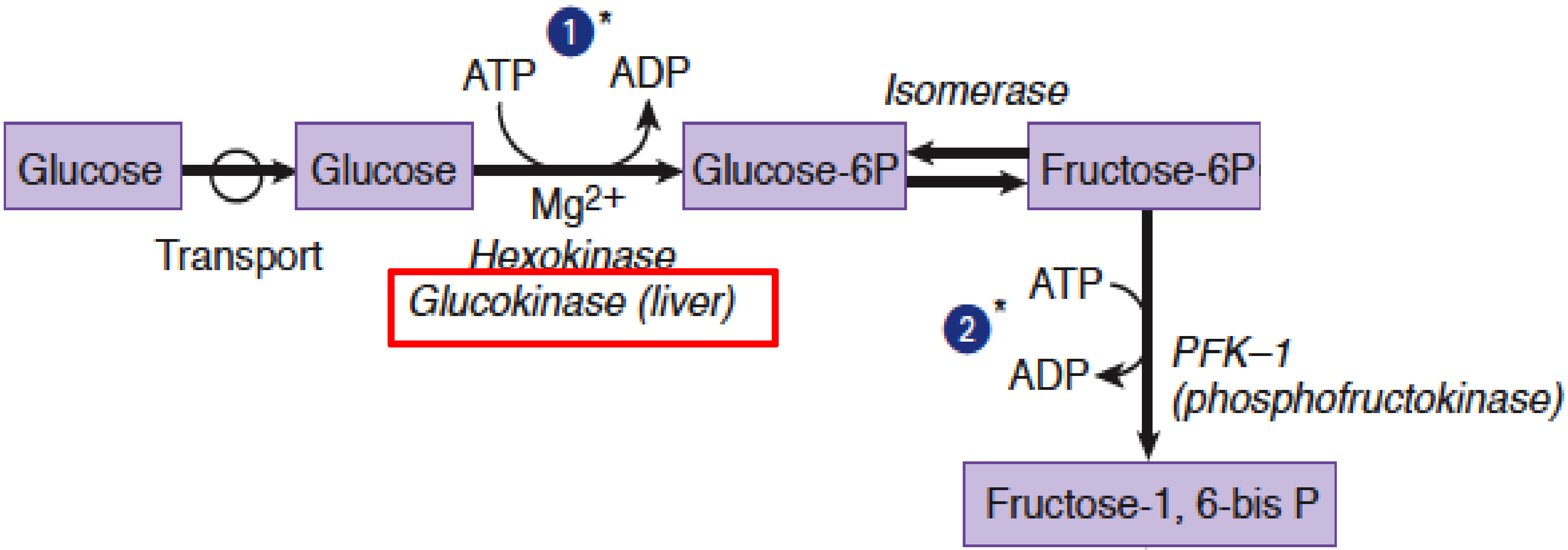
Mg^{2+}

All cells



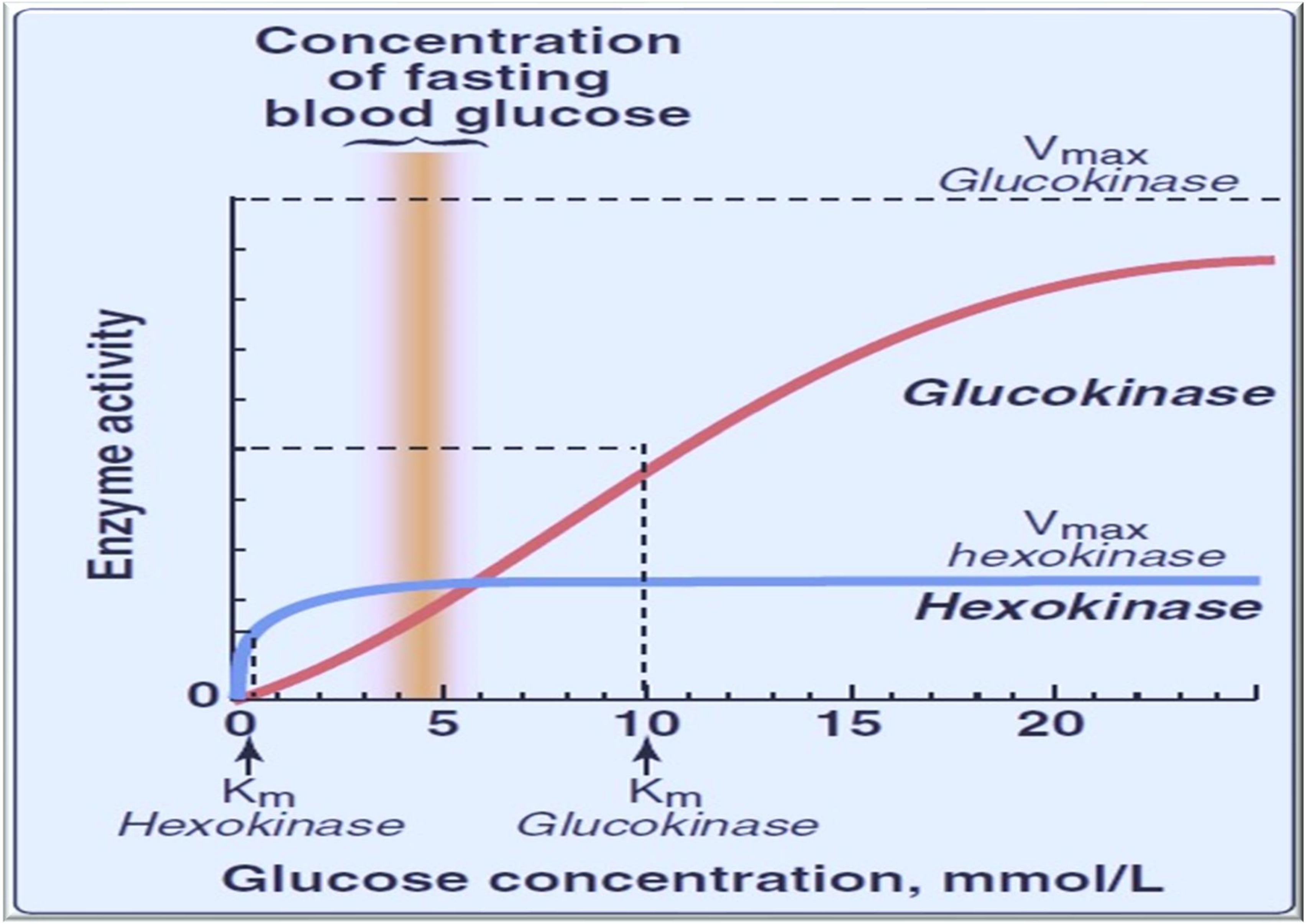
Glucose
Transport
Glucose
ATP
1 *
ADP
Mg2+
Hexokinase
Glucose-6P
Isomerase
Fructose-6P
ATP
2 *
ADP
PFK–1
(phosphofructokinase)
Fructose-1, 6-bis P

LIVER

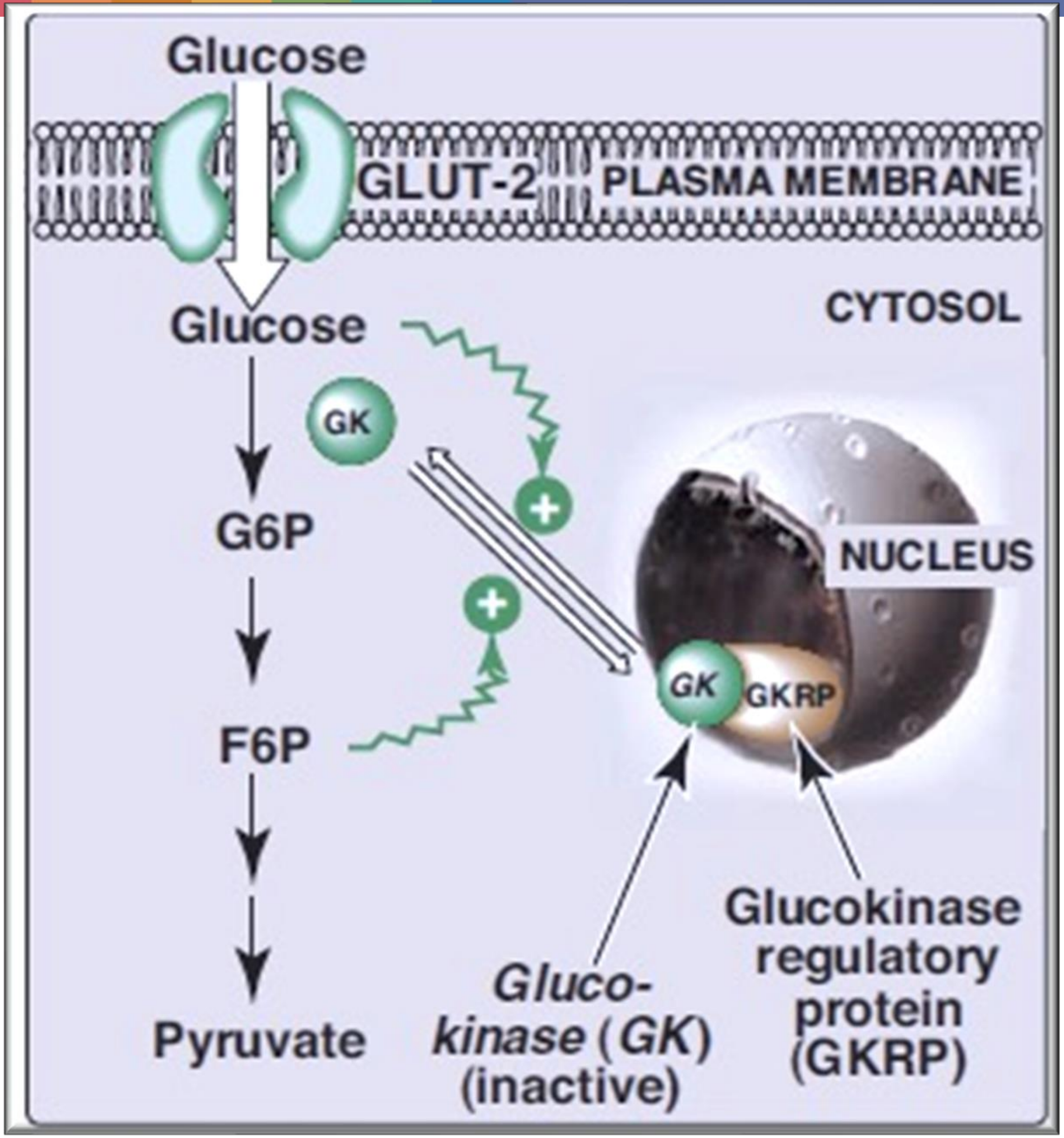


Glucose
Transport
Glucose
ATP
1 *
ADP
Mg2+
Hexokinase
Glucokinase (liver)
Glucose-6P
Isomerase
Fructose-6P
ATP
2 *
ADP
PFK–1
(phosphofructokinase)
Fructose-1, 6-bis P

	Glucokinase	**Hexokinase**
Km	High (10mM)	Low (<0.1mM)
Affinity	Low affinity	High affinity
Vmax	High	Low
Tissue distribution	Liver, pancreas	muscle and other tissues
Glu6PO4	Is not inhibited	Inhibited
Insulin	Is regulated by insulin	Is not regulated by insulin

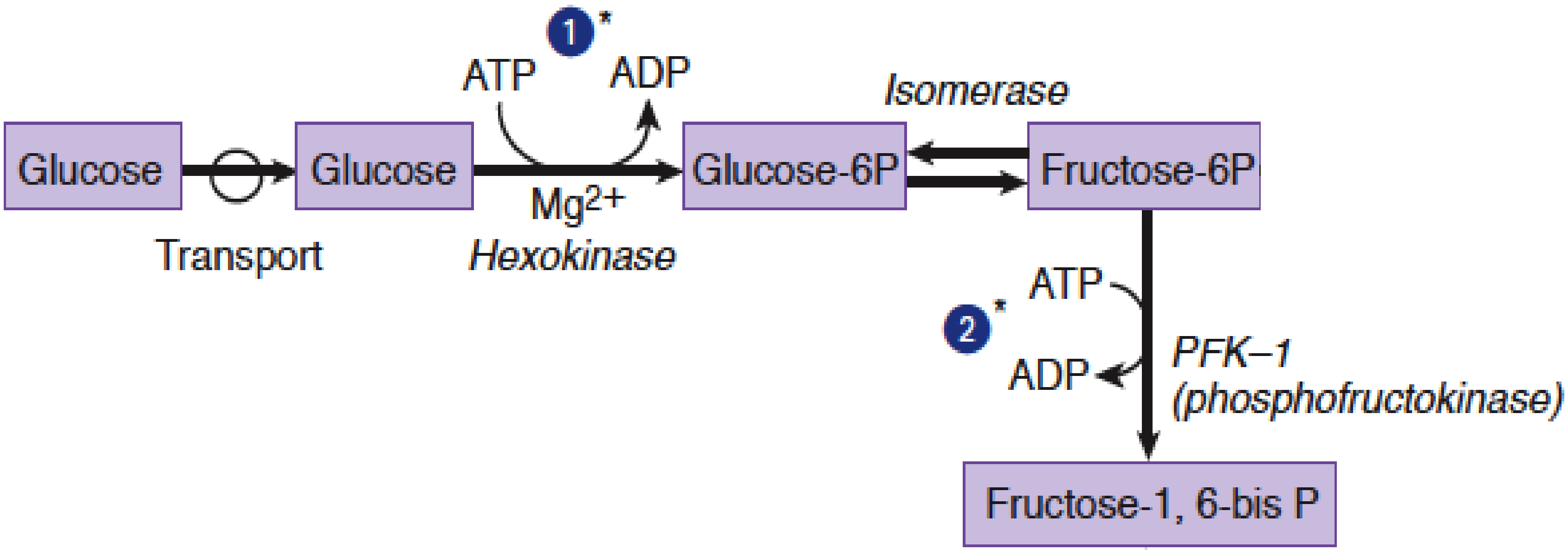


Concentration of fasting blood glucose
Vmax Glucokinase
Enzyme activity
Glucokinase
Vmax hexokinase
Hexokinase
0
0
5
10
15
20
Km Hexokinase
Km Glucokinase
Glucose concentration, mmol/L



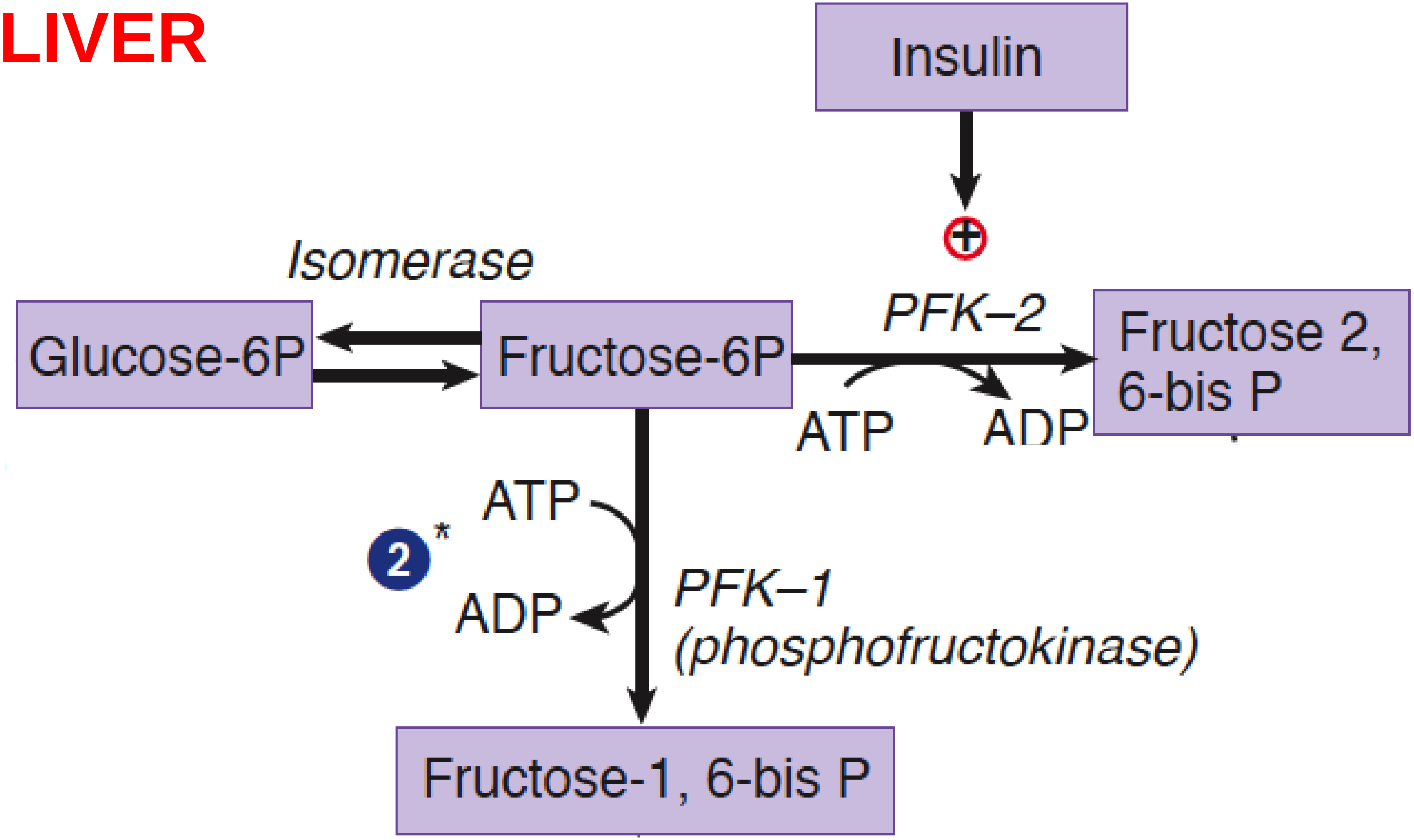
INSULIN DEPENDENT

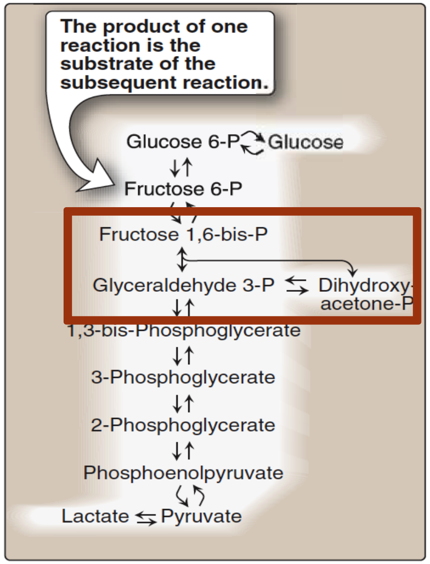
All cells

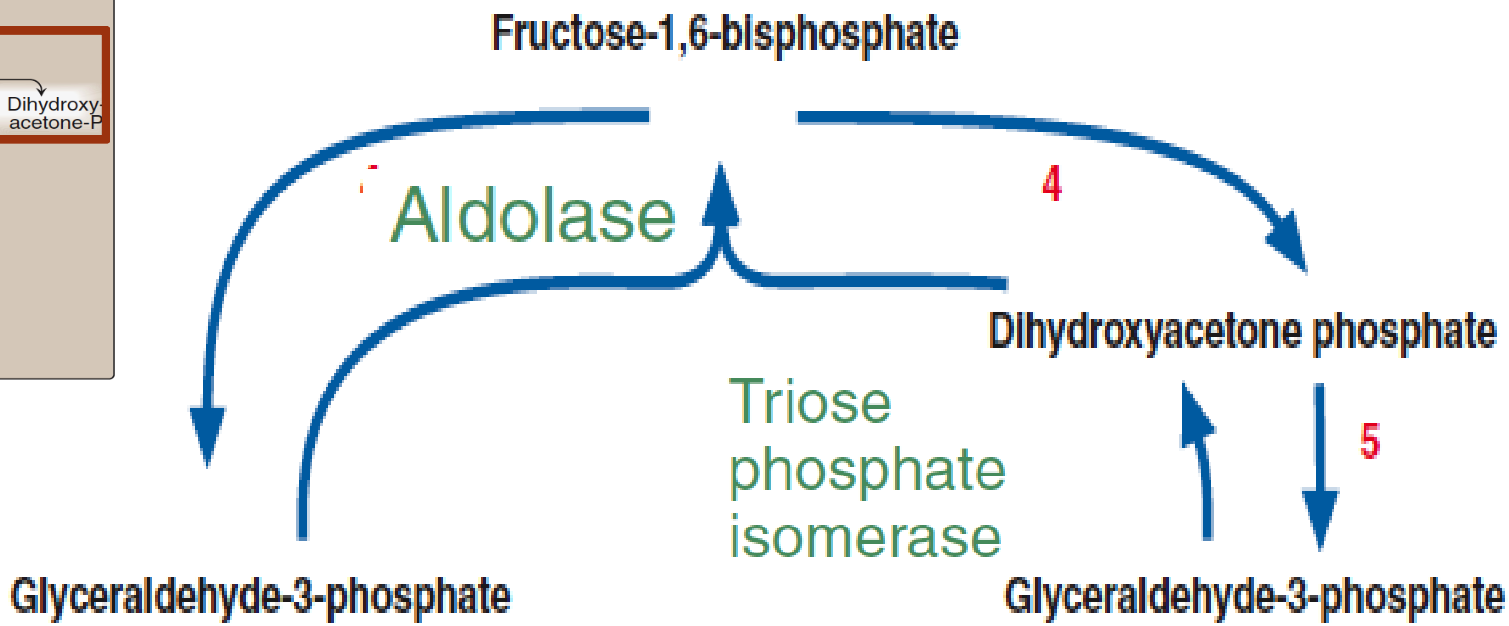


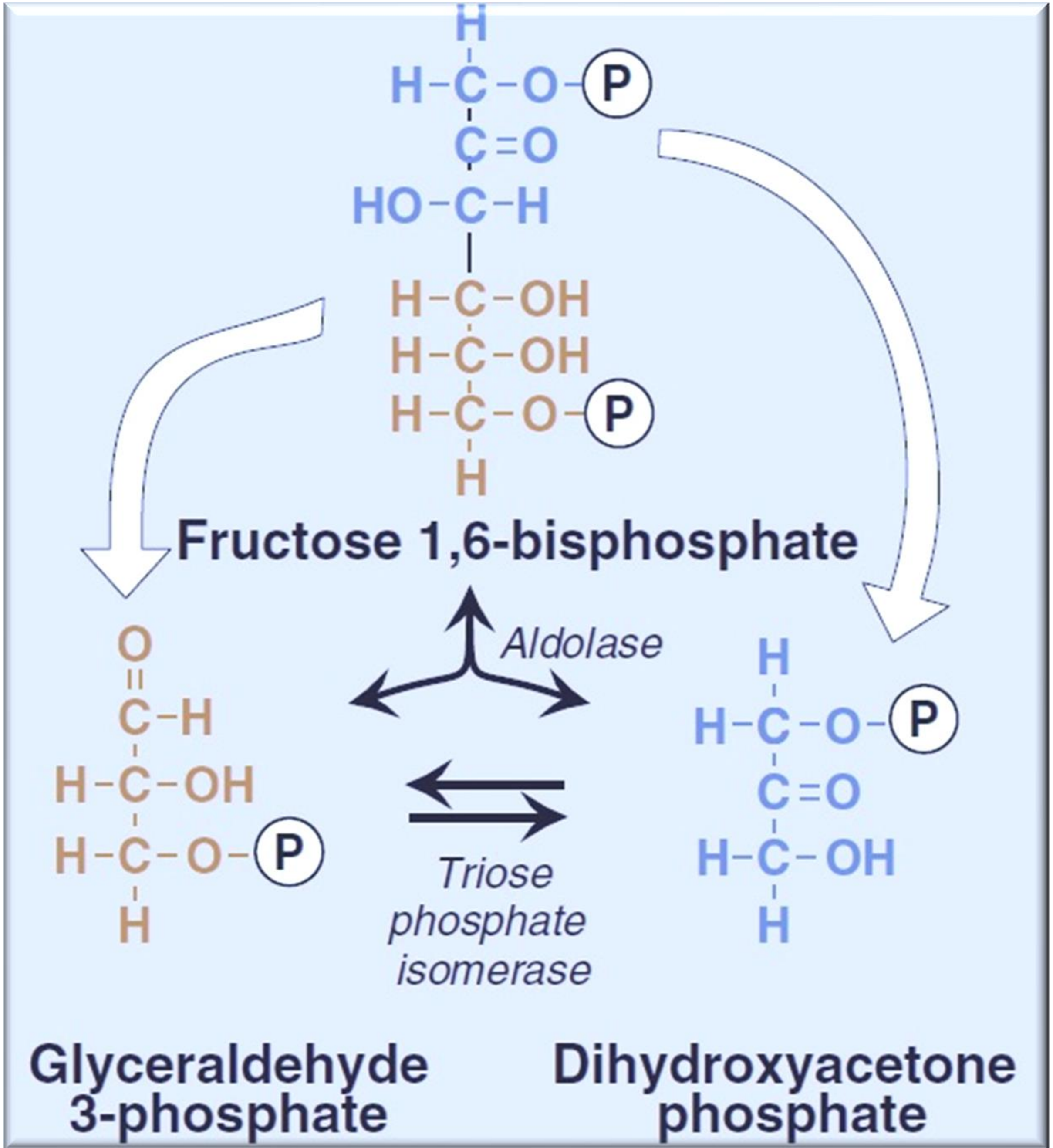
1*
ATP
ADP
Isomerase
Glucose
Glucose
Glucose-6P
Fructose-6P
Mg2+
Transport
Hexokinase
ATP
2*
ADP
PFK–1
(phosphofructokinase)
Fructose-1, 6-bis P

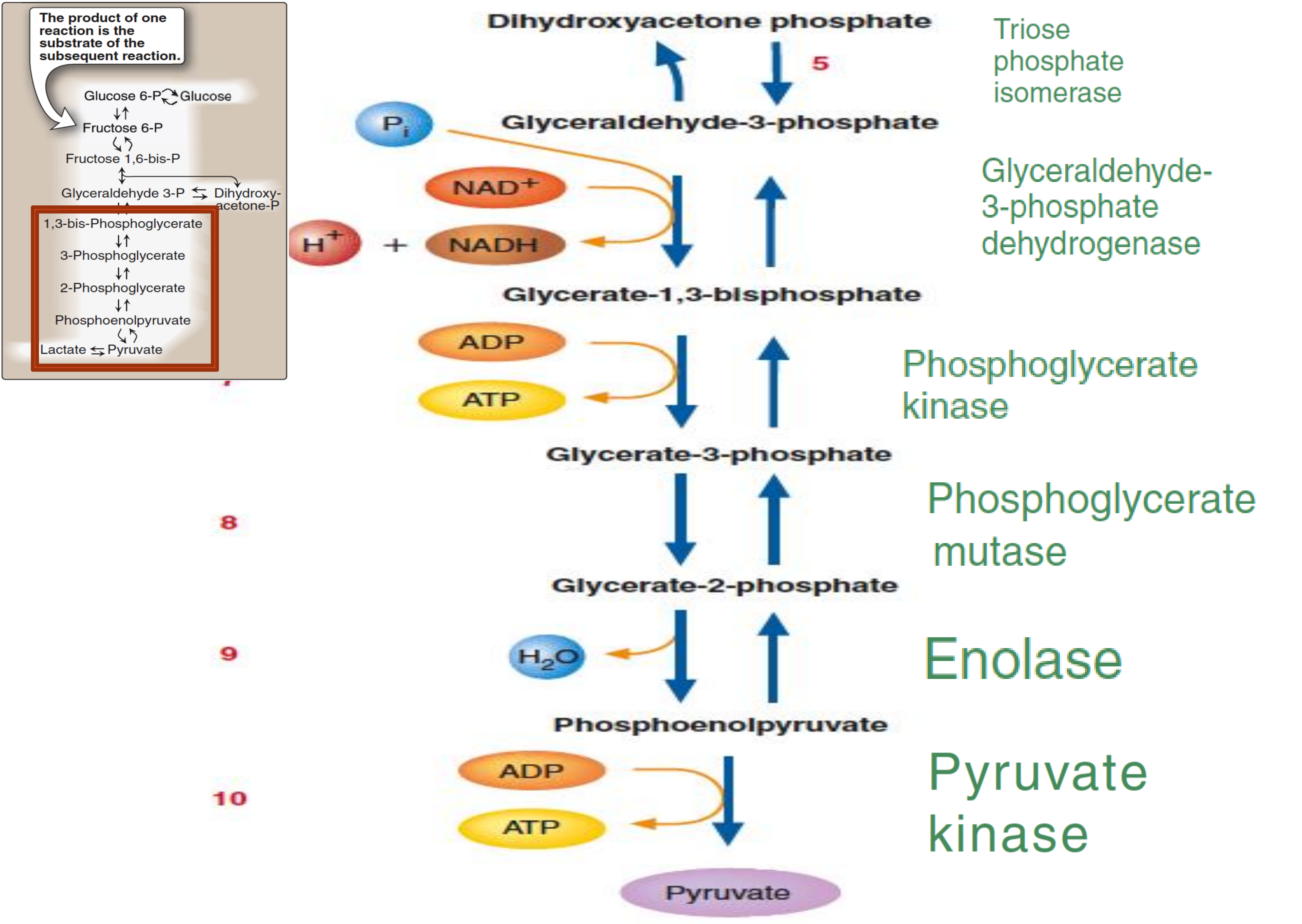
LIVER


Insulin
+
Isomerase
Glucose-6P
Fructose-6P
PFK–2
Fructose 2, 6-bis P
ATP
ADP
ATP
2 *
ADP
PFK–1 (phosphofructokinase)
Fructose-1, 6-bis P


The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate


Fructose-1,6-bisphosphate
Aldolase
4
Dihydroxyacetone phosphate
Triose phosphate isomerase
5
Glyceraldehyde-3-phosphate
Glyceraldehyde-3-phosphate


H
H–C–O–P
C=O
HO–C–H
H–C–OH
H–C–OH
H–C–O–P
H
Fructose 1,6-bisphosphate
Aldolase
O
C–H
H–C–OH
H–C–O–P
H
Triose
phosphate
isomerase
H
H–C–O–P
C=O
H–C–OH
H
Glyceraldehyde
3-phosphate
Dihydroxyacetone
phosphate



The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate
Dihydroxyacetone phosphate
5
Triose phosphate isomerase
P_i
Glyceraldehyde-3-phosphate
NAD^+
H^+ + NADH
Glyceraldehyde-3-phosphate dehydrogenase
Glycerate-1,3-bisphosphate
ADP
ATP
Phosphoglycerate kinase
Glycerate-3-phosphate
8
Phosphoglycerate mutase
Glycerate-2-phosphate
9
H_2O
Enolase
Phosphoenolpyruvate
10
ADP
ATP
Pyruvate kinase
Pyruvate

Covalent modulation of PK:

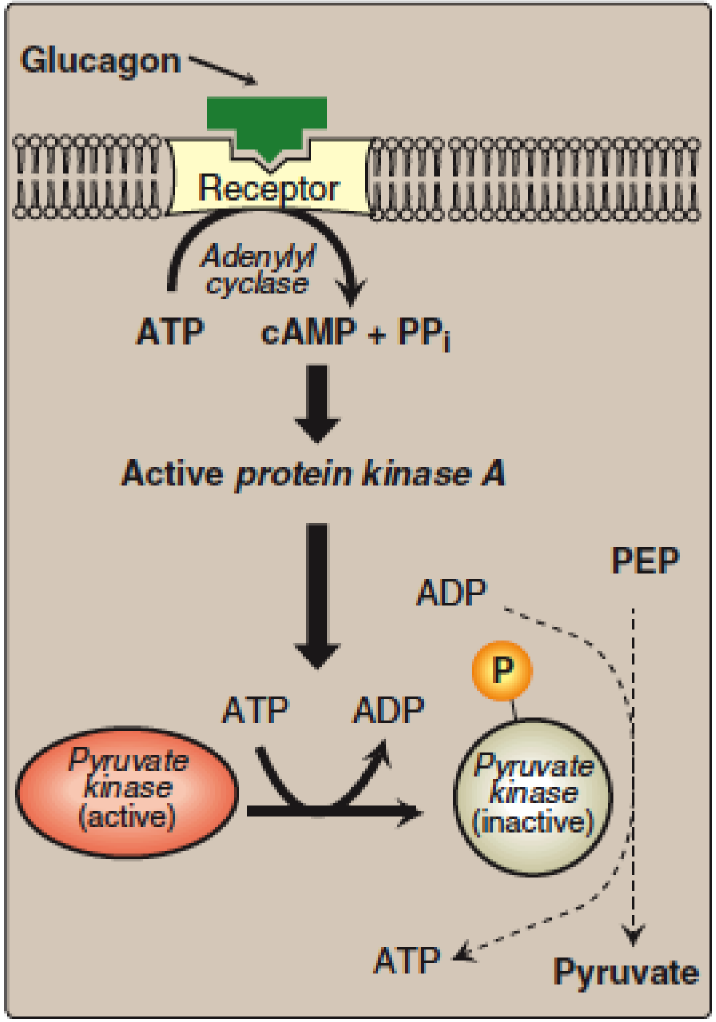
Elevated glucagon ->

increase cAMP ->

phosphorylation/inactivation PK ->

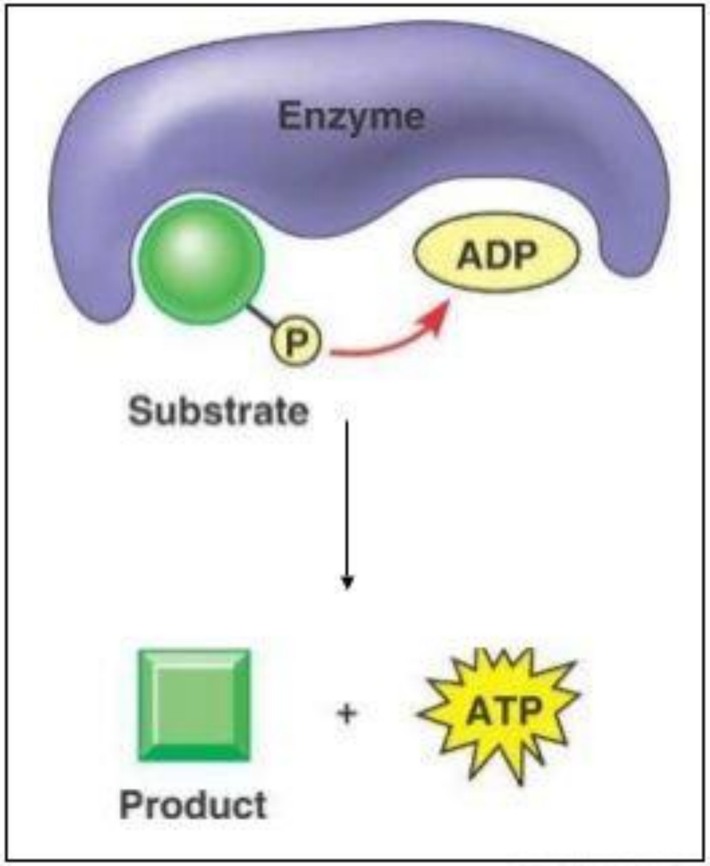
No glycolysis + gluconeogenesis

Dephosphorylation of PK -> Re-activation of the enzyme.

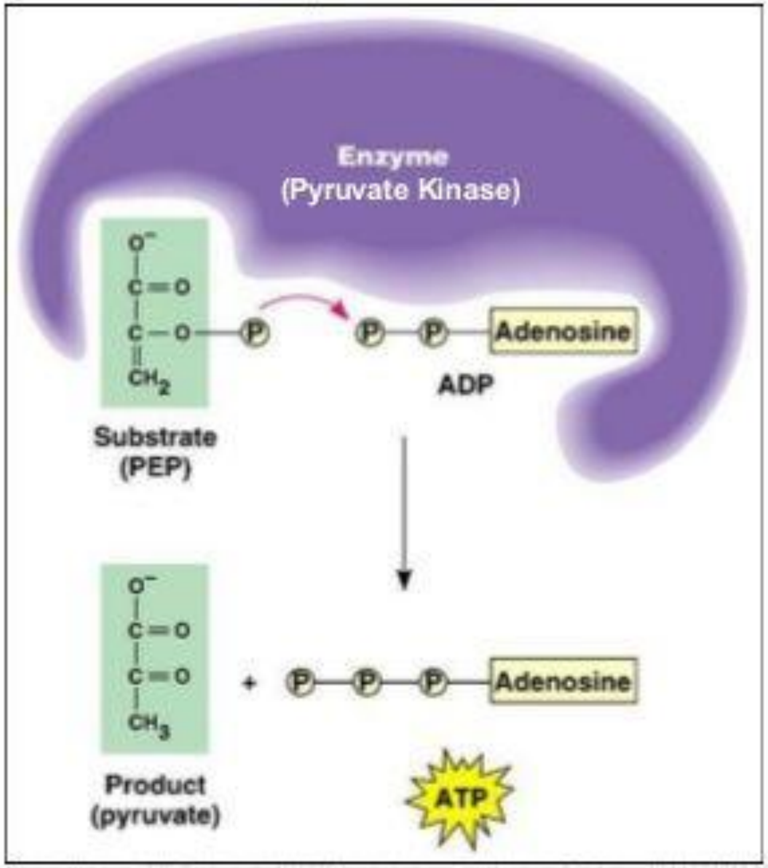


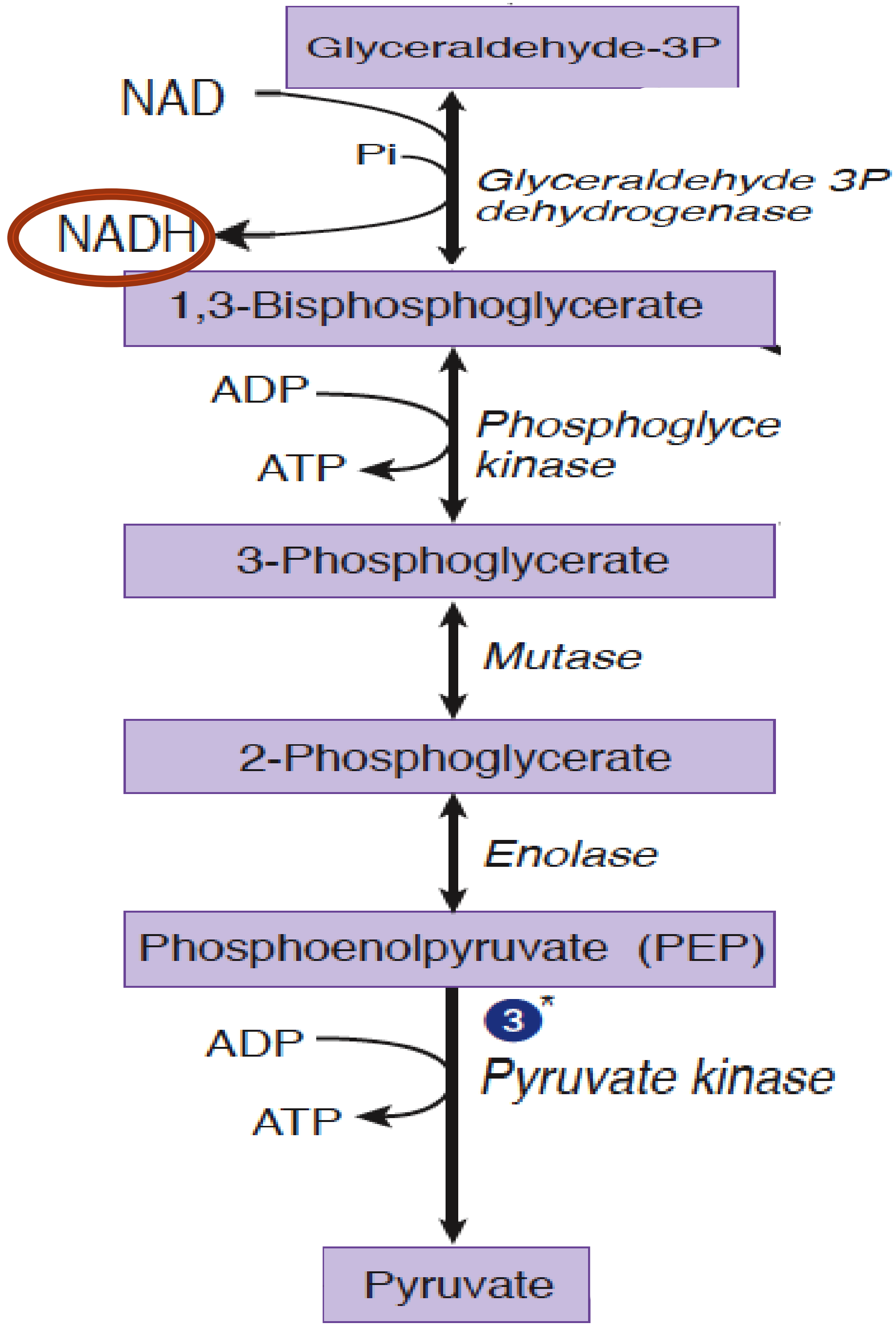
Substrate-level Phosphorylation

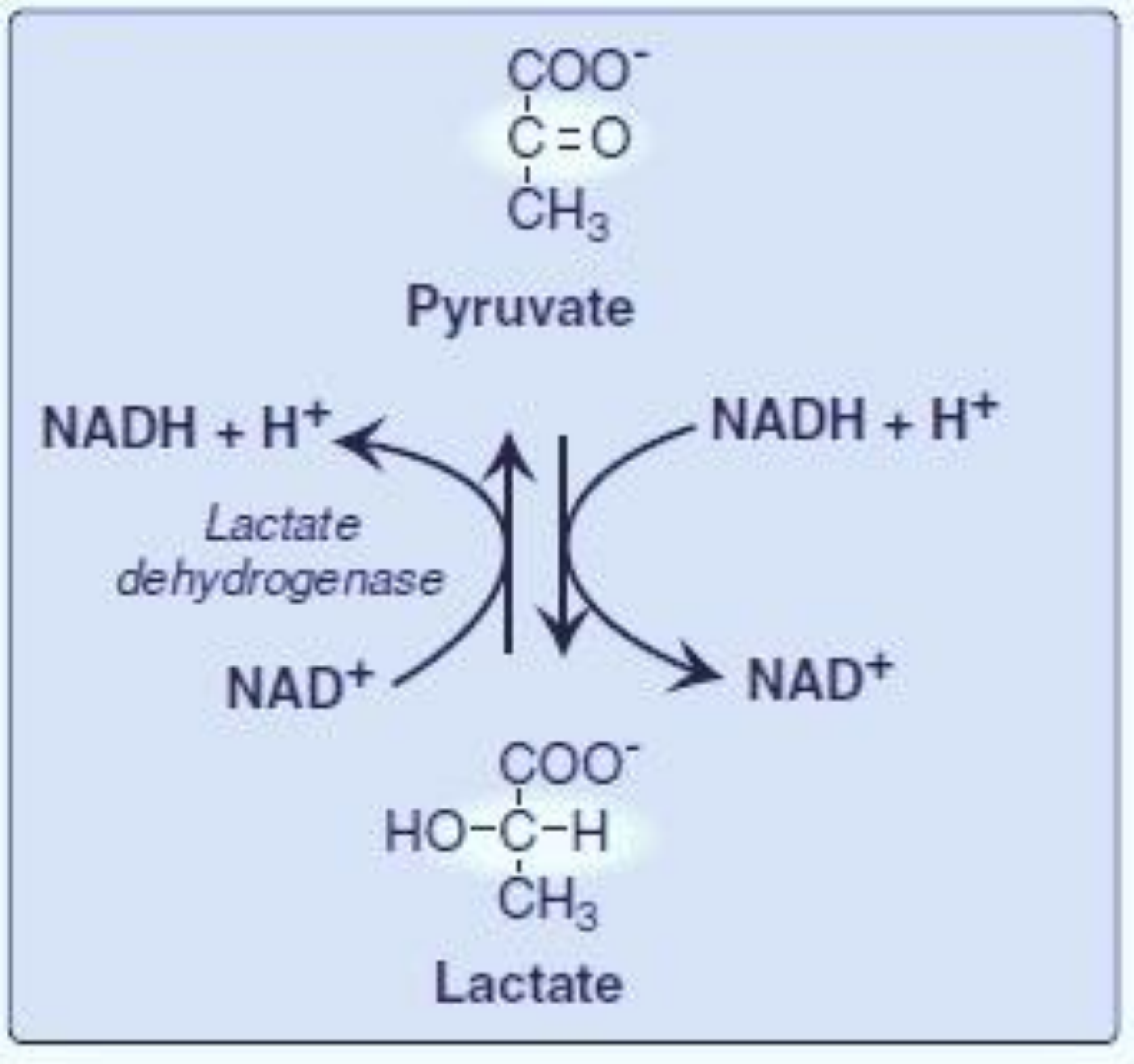
- An enzyme transfers phosphate from substrate to ADP

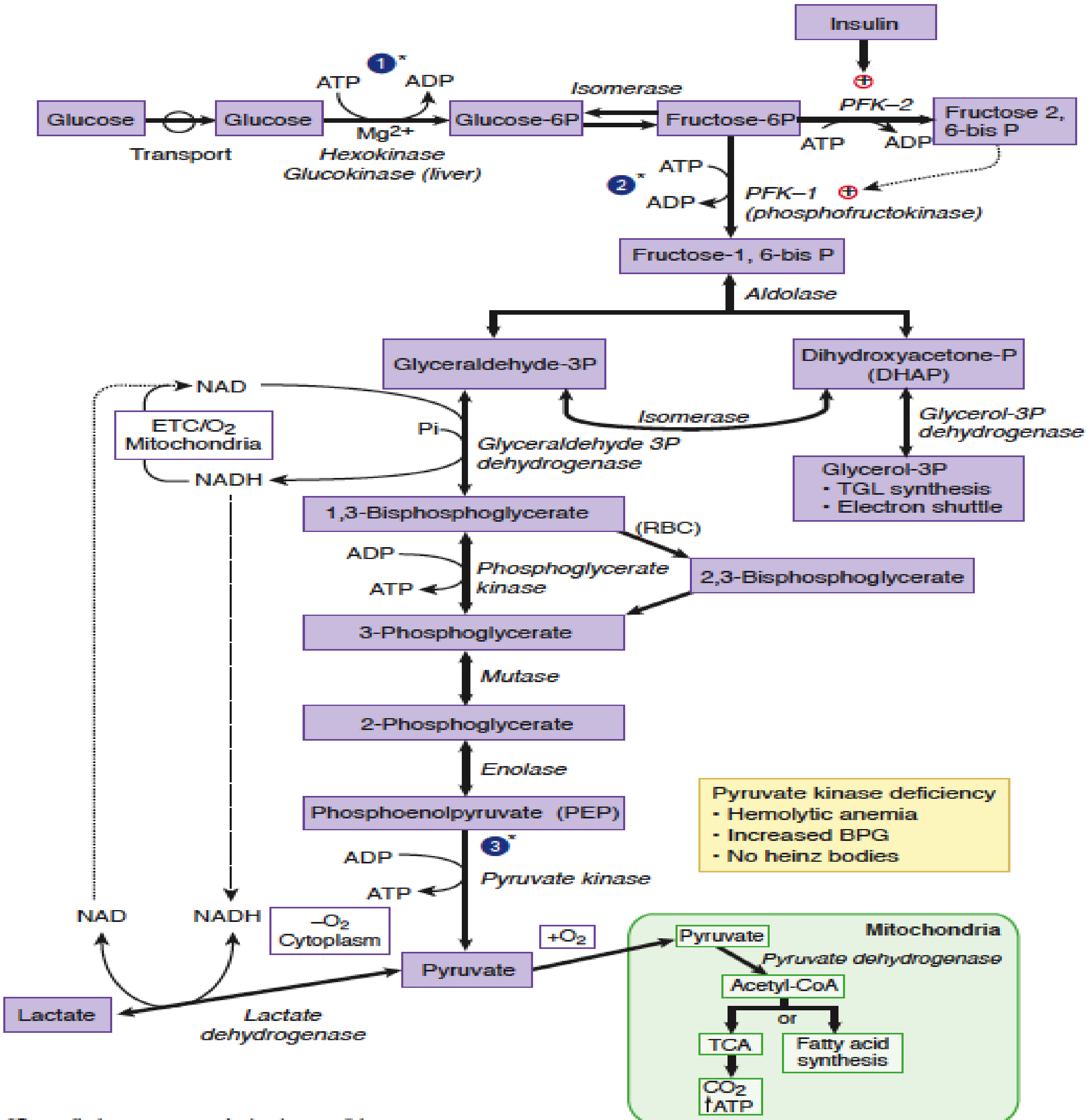


- Example from glycolysis in cellular respiration

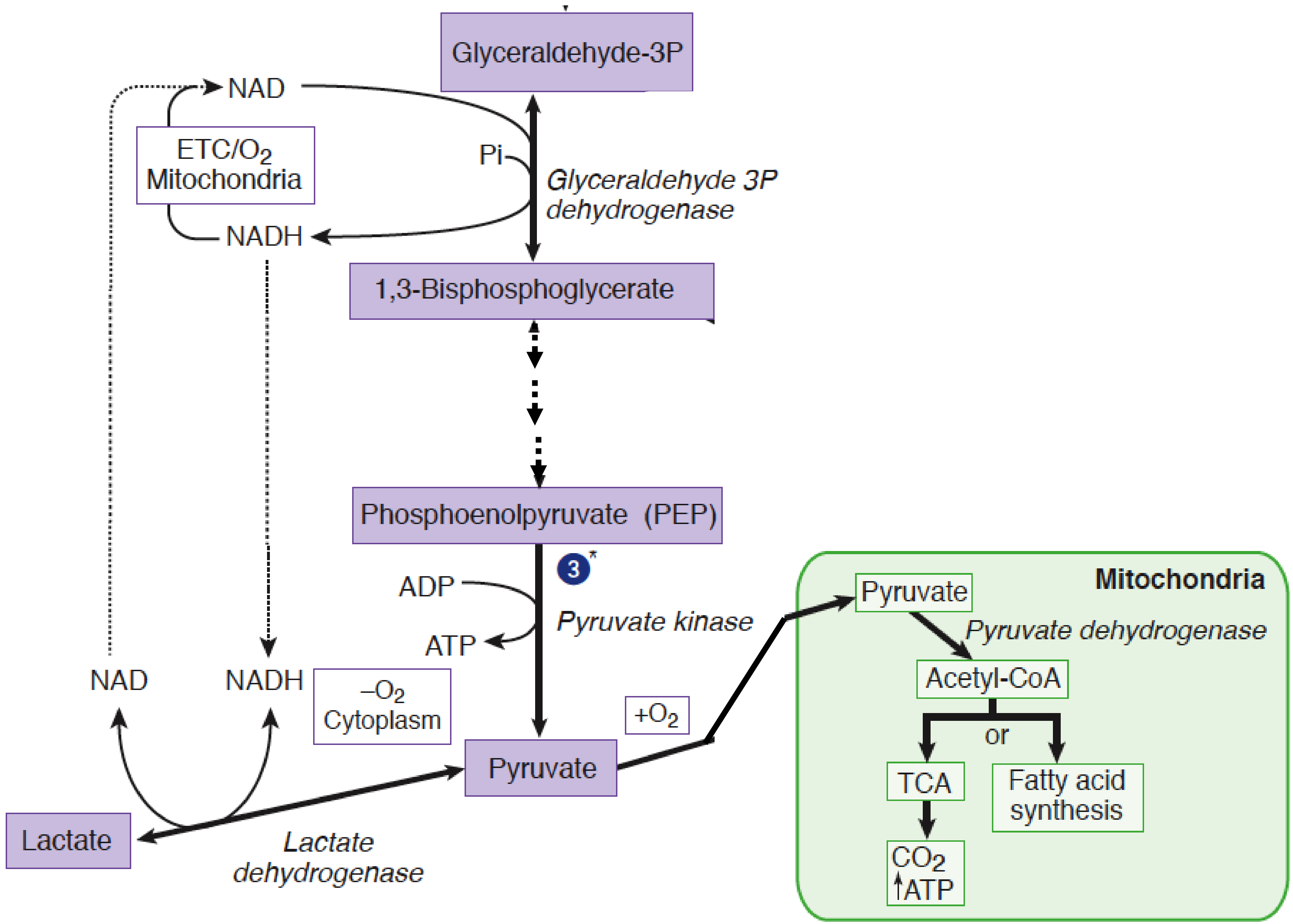



Glyceraldehyde-3P
NAD
Pi
NADH
Glyceraldehyde 3P dehydrogenase
1,3-Bisphosphoglycerate
ADP
ATP
Phosphoglyce kinase
3-Phosphoglycerate
Mutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate (PEP)
3
ADP
ATP
Pyruvate kinase
Pyruvate


COO⁻
C=O
CH3
Pyruvate
NADH + H+
NADH + H+
Lactate
dehydrogenase
NAD+
NAD+
COO⁻
HO–C–H
CH3
Lactate

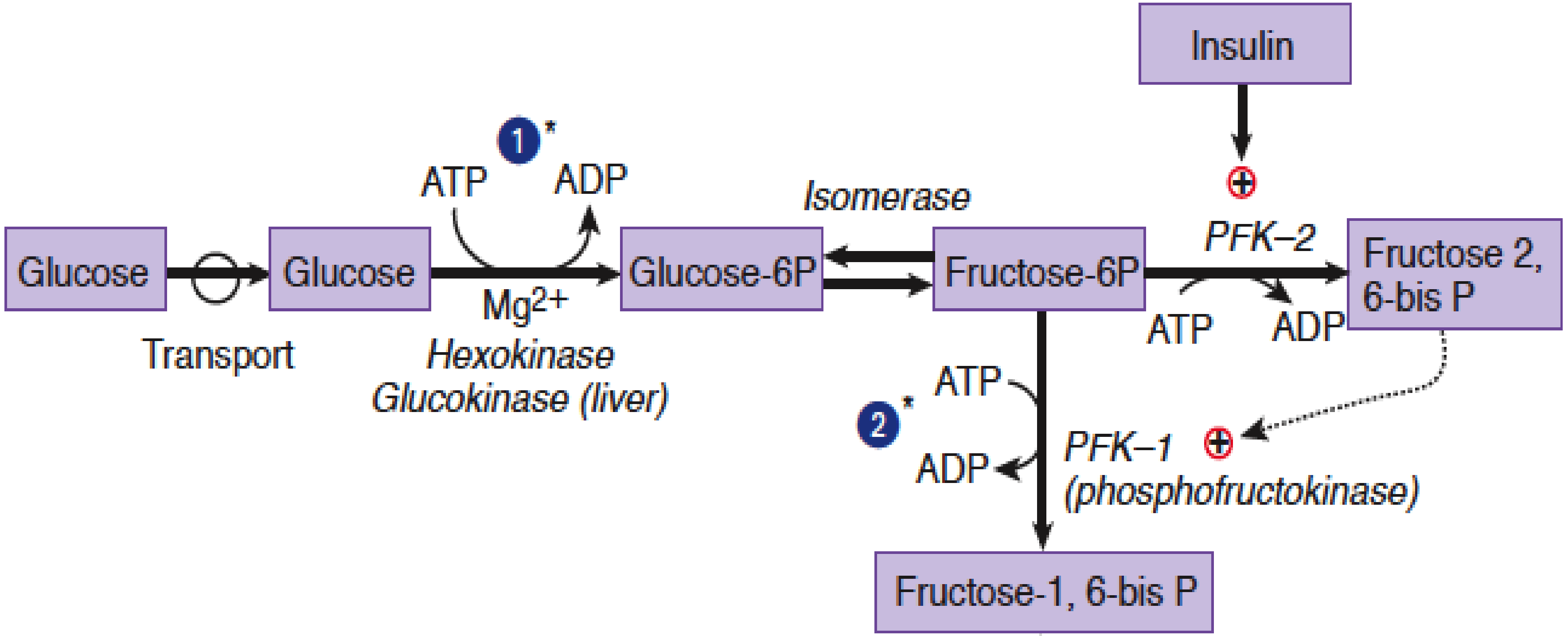


*Controlled enzymes catalyzing irreversible steps



Glyceraldehyde-3P
NAD
ETC/O_2
Mitochondria
NADH
Pi
Glyceraldehyde 3P dehydrogenase
1,3-Bisphosphoglycerate
Phosphoenolpyruvate (PEP)
3*
ADP
ATP
Pyruvate kinase
NAD
NADH
–O_2
Cytoplasm
+O_2
Pyruvate
Lactate
Lactate dehydrogenase
Mitochondria
Pyruvate
Pyruvate dehydrogenase
Acetyl-CoA
or
TCA
Fatty acid synthesis
CO_2
↑ATP

LIVER



<u>Effect of Diabetes:</u>

No Insulin → No PFK2 → PFK1 Inhibited → Glycolysis Inhibited

Incr. F6P → Incr. G6P → Hexokinase Inhibited

High Carb. Meal → more ATP in cells → Glycolysis Inhibited → Hyperglycemia

Regulation (or Control) of Glycolysis

- These pathways must be coordinated
- There is sophisticated communication system
- Regulatory signals
  - Hormones
  - Neurotransmitter
  - Product of the reaction

Regulation (or Control) of Glycolysis

A. Key regulatory enzymes:

are those enzymes that catalyze the irreversible steps of glycolysis that include three steps as follows:

1-Phosphofructokinase:

It is an allosteric enzyme stimulated by high levels of fructose-6- phosphate, fructose-2,6-diphosphate (in liver), ADP and AMP, Pi, and ammonia.

It is inhibited allosterically by ATP, AMP and citrate.

Regulation (or Control) of Glycolysis

2-Hexokinase:

Accumulation of glucose-6-phosphate and inhibition of phosphofructokinase results in accumulation of fructose-6-phosphate and glucose-6-phosphate that allosterically inhibit hexokinase.

3-Pyruvate kinase: It is inhibited also by excess ATP, fatty acids, and acetyl-CoA

and is stimulated by fructose-1,6-diphosphate, ADP and AMP

It is regulated by cAMP-dependent phosphorylation-dephosphorylation mechanism

Regulation (or Control) of Glycolysis

<u>B. Hormonal regulation:</u>

1. Insulin:

Stimulates synthesis of glucokinase, phosphofructokinase and pyruvate kinase, so it stimulates glycolysis.

It also induces glucose transporters to provide cells with glucose for glycolysis.

2-Adrenaline and glucagon

inhibitory by inhibiting pyruvate kinase.

TABLE 8.1 Allosteric Regulation of Glycolysis

Enzyme	Activator	Inhibitor
Hexokinase		Glucose-6-phosphate, ATP
PFK-1	Fructose-2,6-bisphosphate, AMP	Citrate, ATP
Pyruvate kinase	Fructose-1,6-bisphosphate, AMP	Acetyl-CoA, ATP

☺

Thanks for your attention!

☺