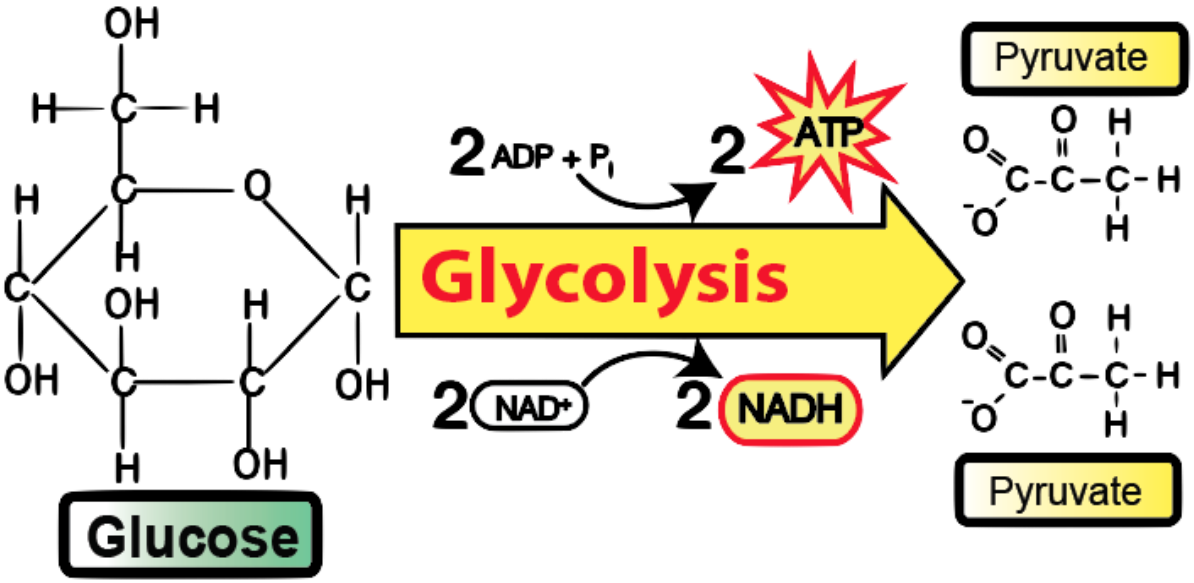
# Glycolysis
# Reactions and Regulation

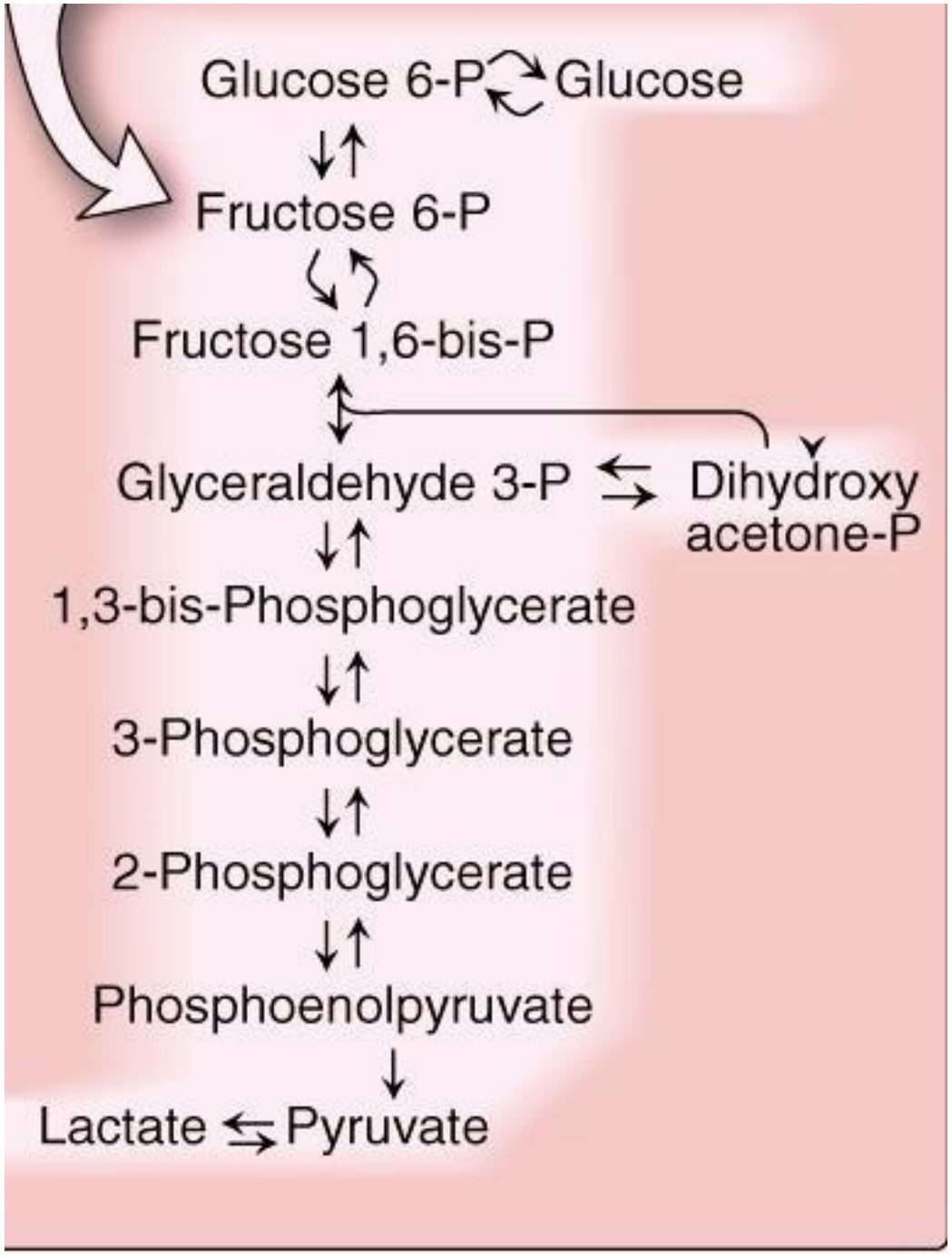



Dr. Diala Abu-Hassan

Suggested Reading:

Lippincott's Illustrated reviews: Biochemistry

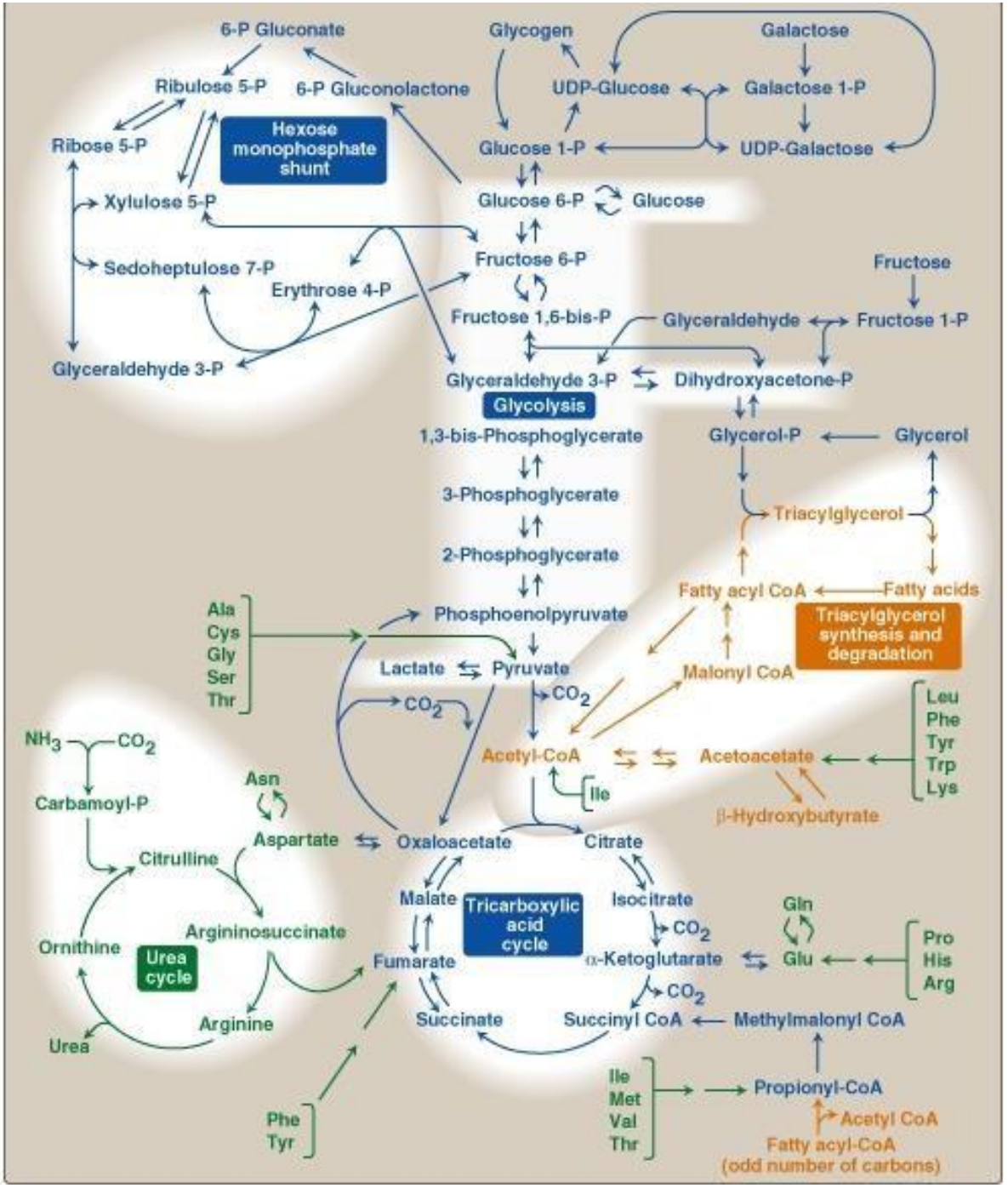
sciencemusicvideos



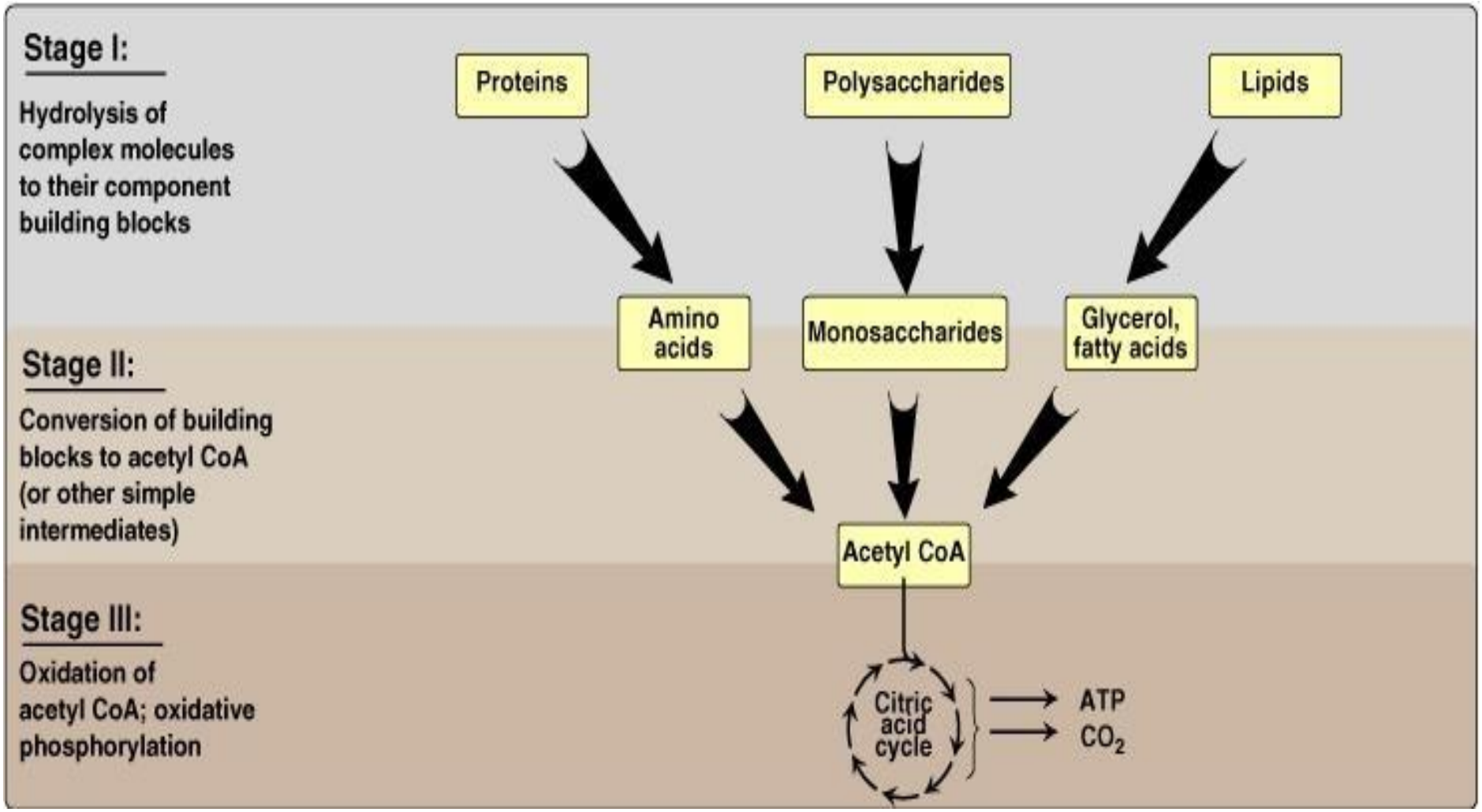

Glycolysis is an example of metabolic pathway

The product of one reaction is the substrate of the next reaction

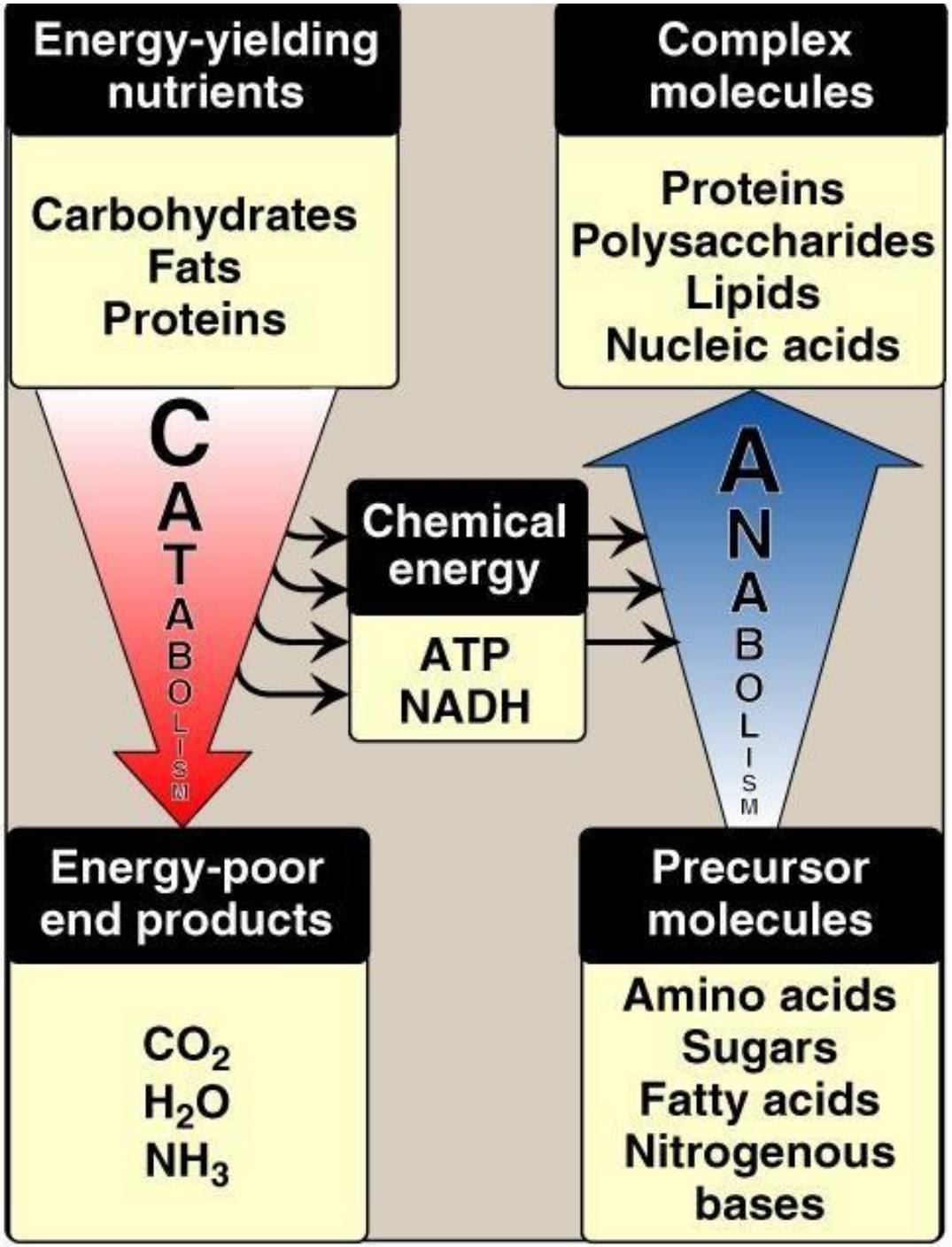
Metabolic pathways intersect to form network of chemical reactions



# General Stages of Metabolism

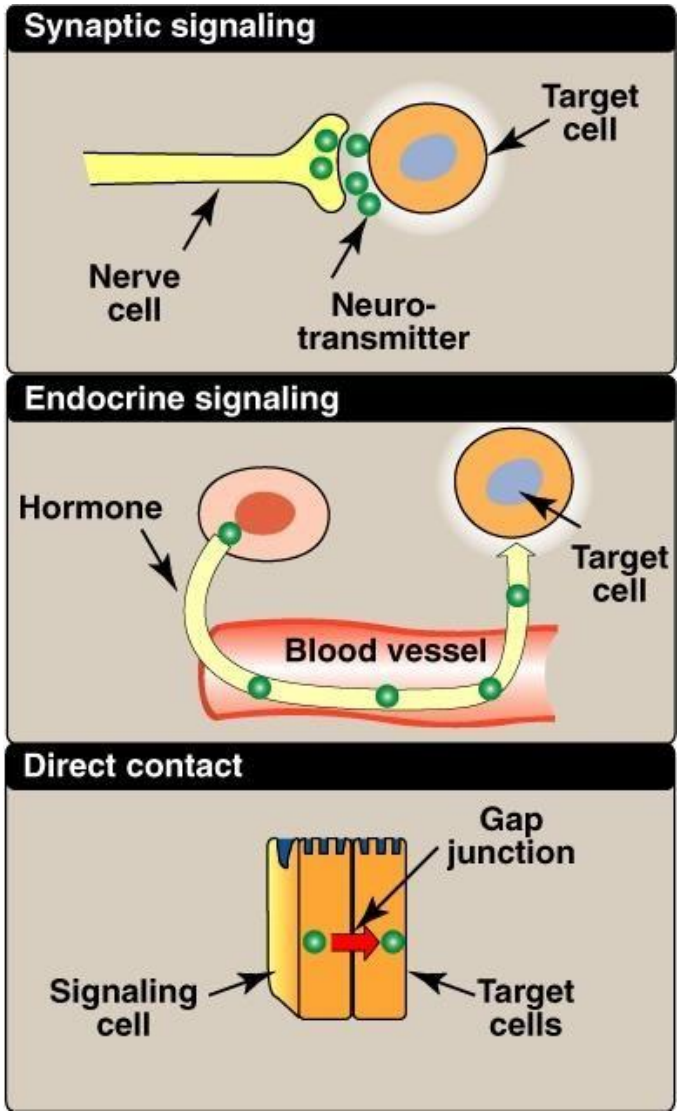


# Types of Metabolic Pathways



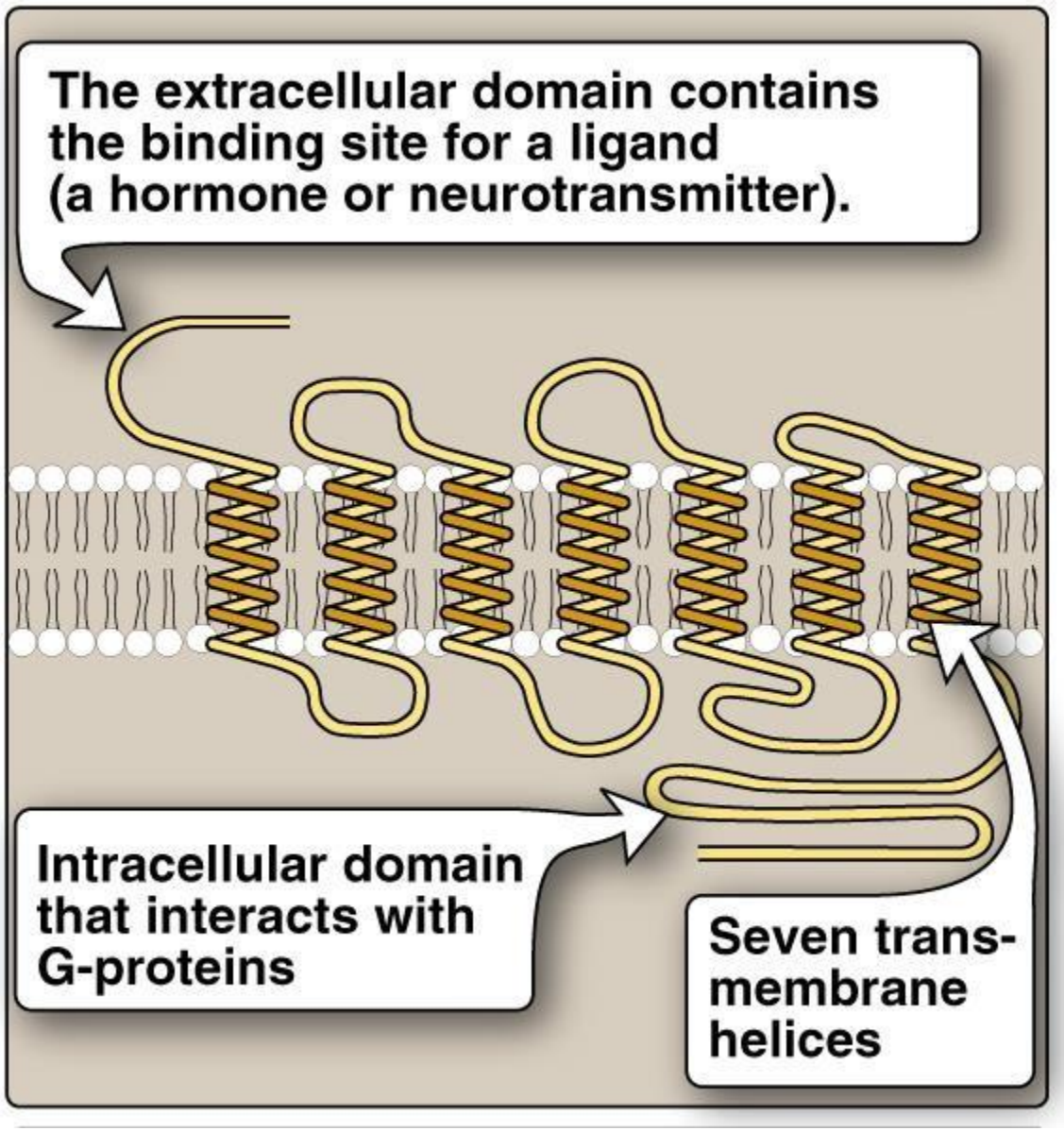
# Regulation of Metabolism

- Signals from within the cell
  - Substrate availability, product inhibition, allosteric
  - Rapid response, moment to moment
- Communication between cells (intercellular)
  - Slower response, longer range integration
- Second messenger
  - $Ca^{2+}$ / phosphatidylinositol system
  - Adenylcyclase system

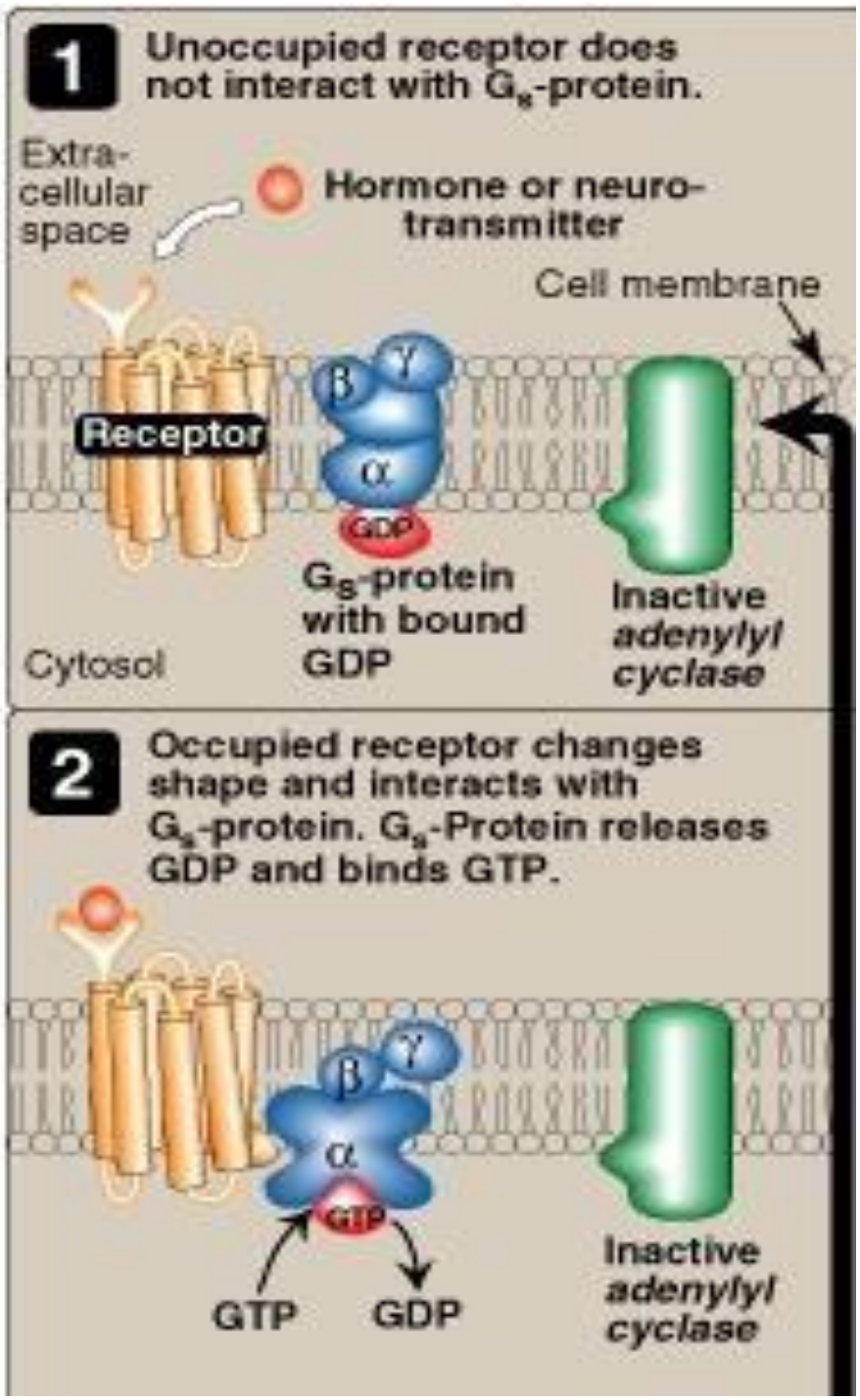


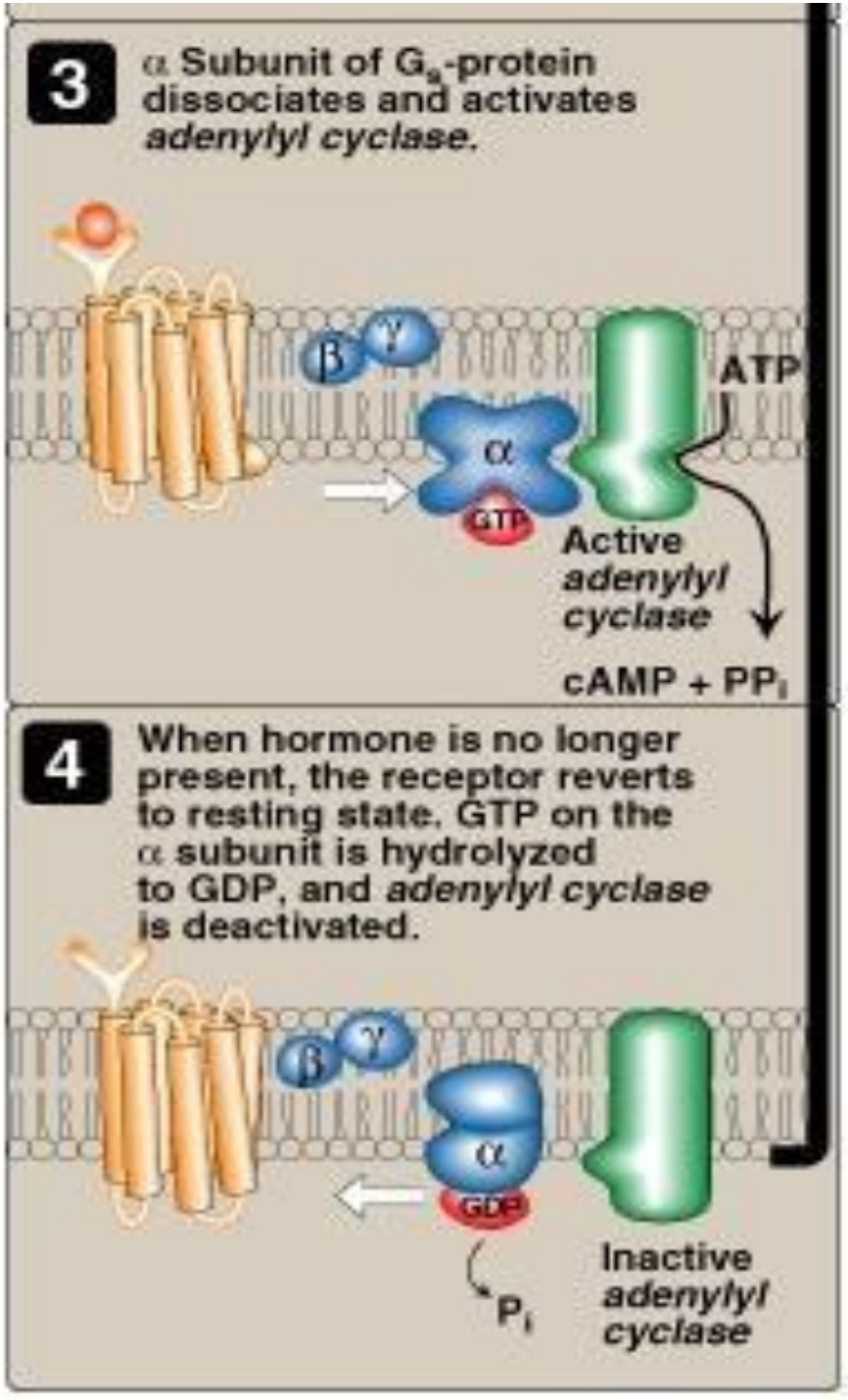

Commonly used mechanisms of communication between cells

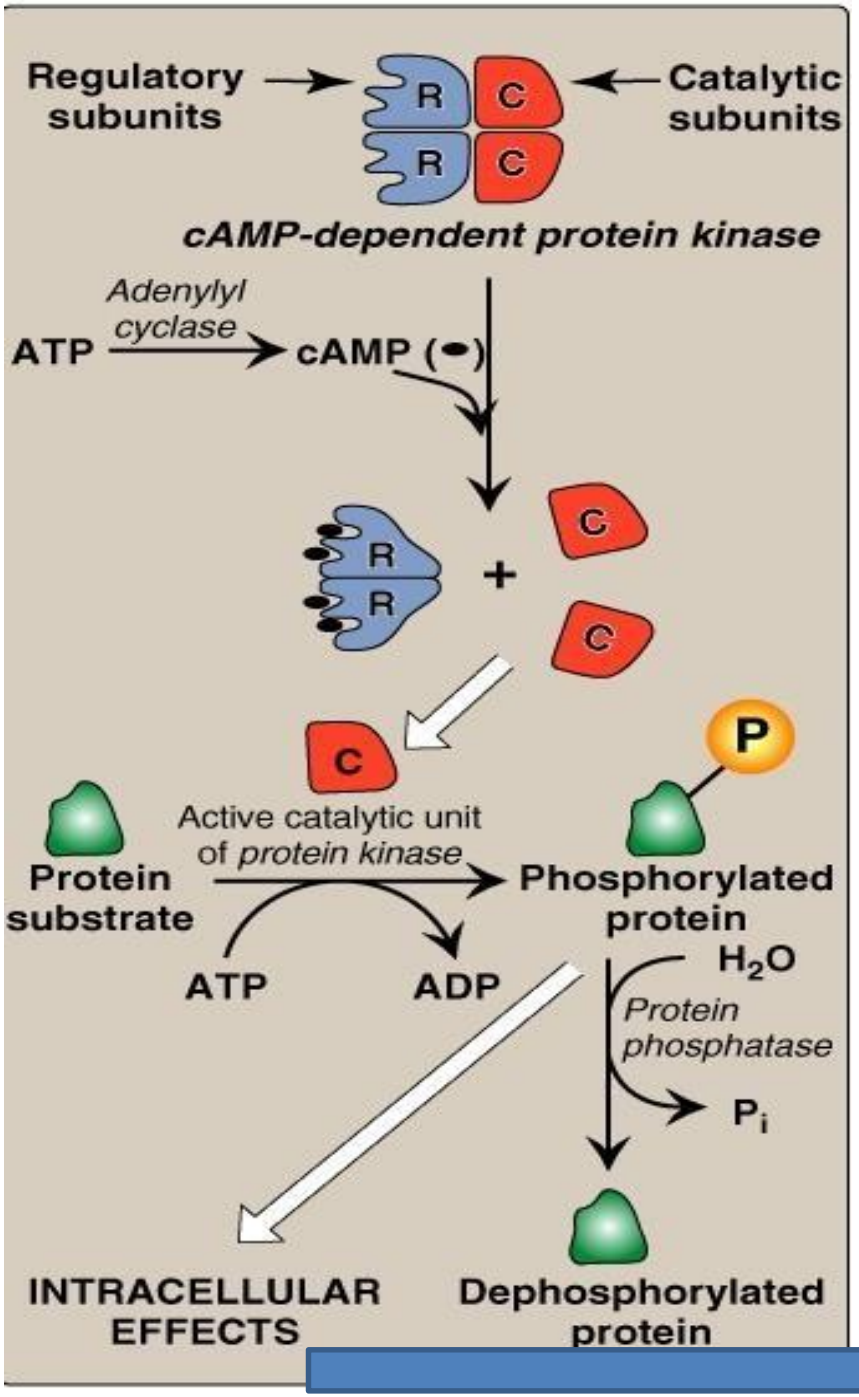
# Communication between Cells through Receptors- GPCR




G protein-coupled receptor of plasma membrane


1
Unoccupied receptor does not interact with $G_s$-protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
$G_s$-protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with $G_s$-protein. $G_s$-Protein releases GDP and binds GTP.
GTP
GTP
GDP
Inactive adenylyl cyclase


3
α Subunit of $G_s$-protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + $PP_i$
4
When hormone is no longer present, the receptor reverts to resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
$P_i$
Inactive adenylyl cyclase




# INTRACELLULAR EFEECTS

- ✓ Activated enzymes
- ✓ Inhibited Enzymes
- ✓ Cell's ion channels
- ✓ Bind to promoter

# GLYCOLYSIS

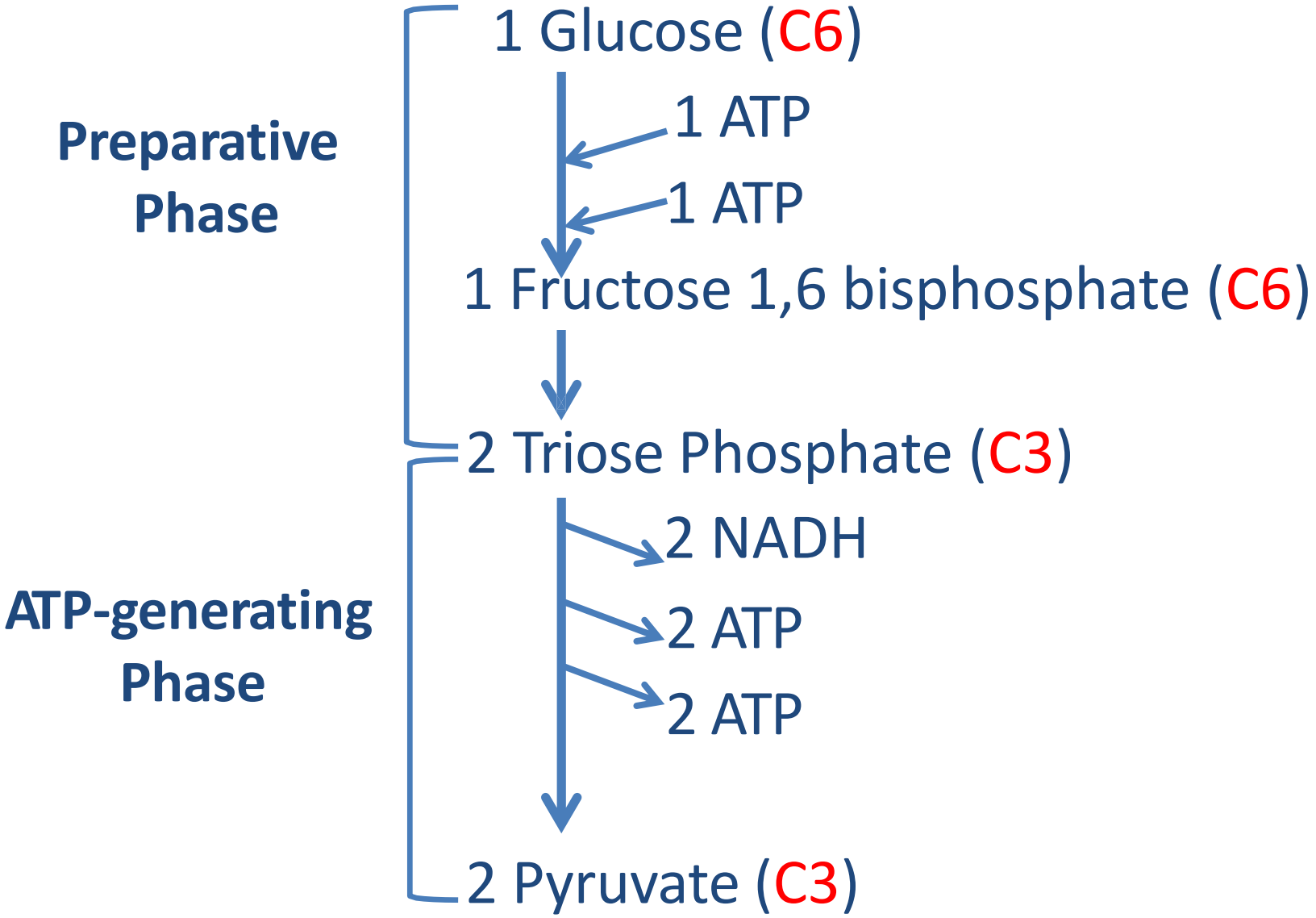
✓Breakdown of glucose to pyruvate

Pathway characteristics

- Universal Pathway: In all cell types
- Generation of ATP
- With or without $O_2$
- Anabolic Pathway:

→ biosynthetic precursors

# The Two Phases of the glycolytic Pathway

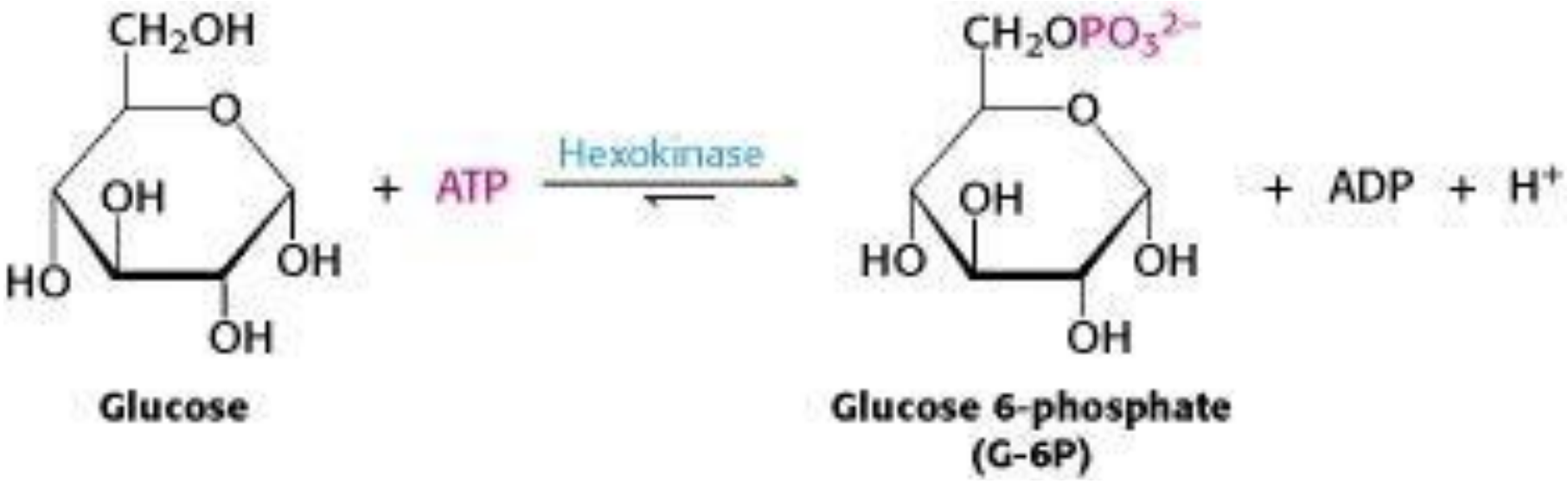


# Types of Glycolytic Reactions

- Phosphoryl transfer
- Isomerization
- Cleavage
- Oxidation reduction
- Phosphoryl shift
- Dehydration

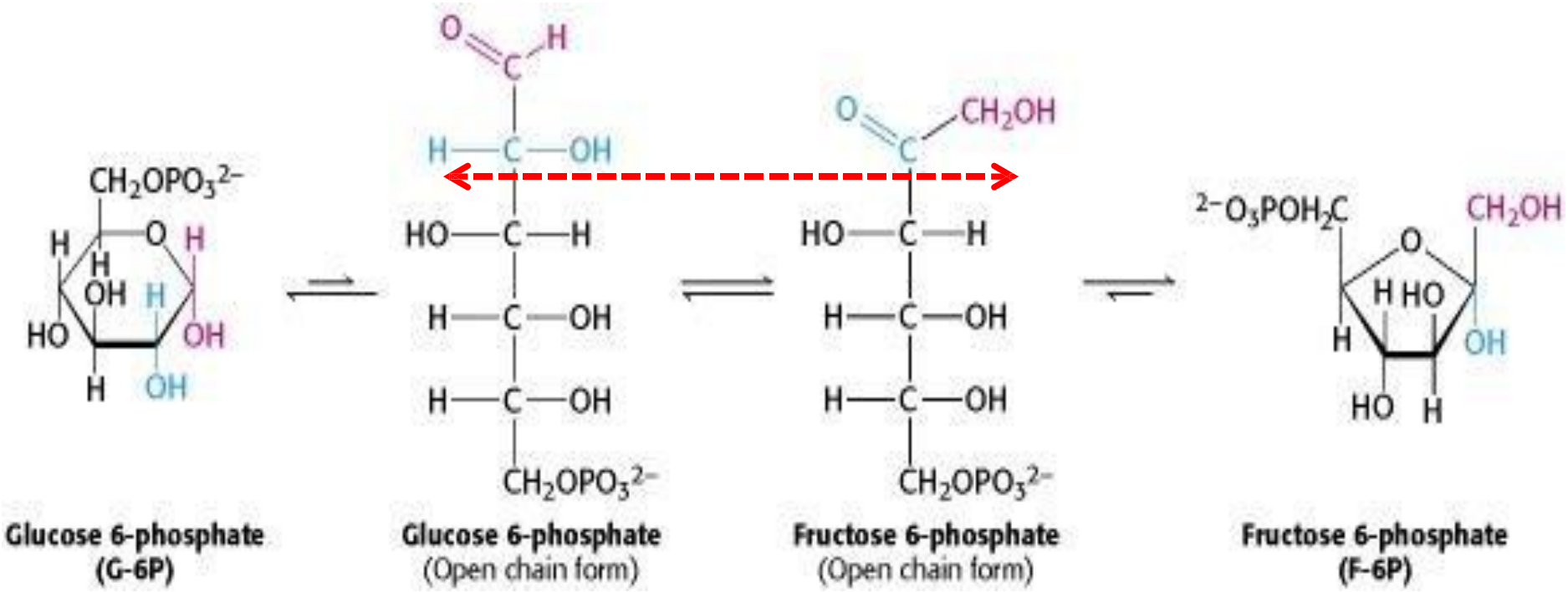
# Steps of Glycolysis

## Step 1



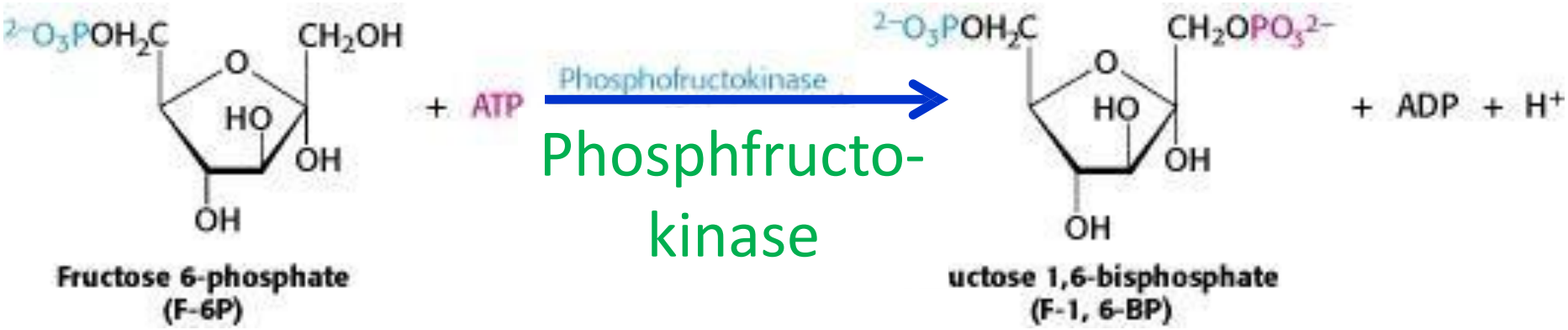

| | Hexokinase | Glucokinase |
|---|---|---|
| Occurrence | In all tissues | In liver |
| Km | < 0.02 mM | 10-20 mM |
| Specificity | Glc., Fruc, Man, Gal | Glc. |
| induction | Not induced | ↑ insulin, Glc |
| Function | At any glucose level | Only > 100 mg/dl |

# Step 2

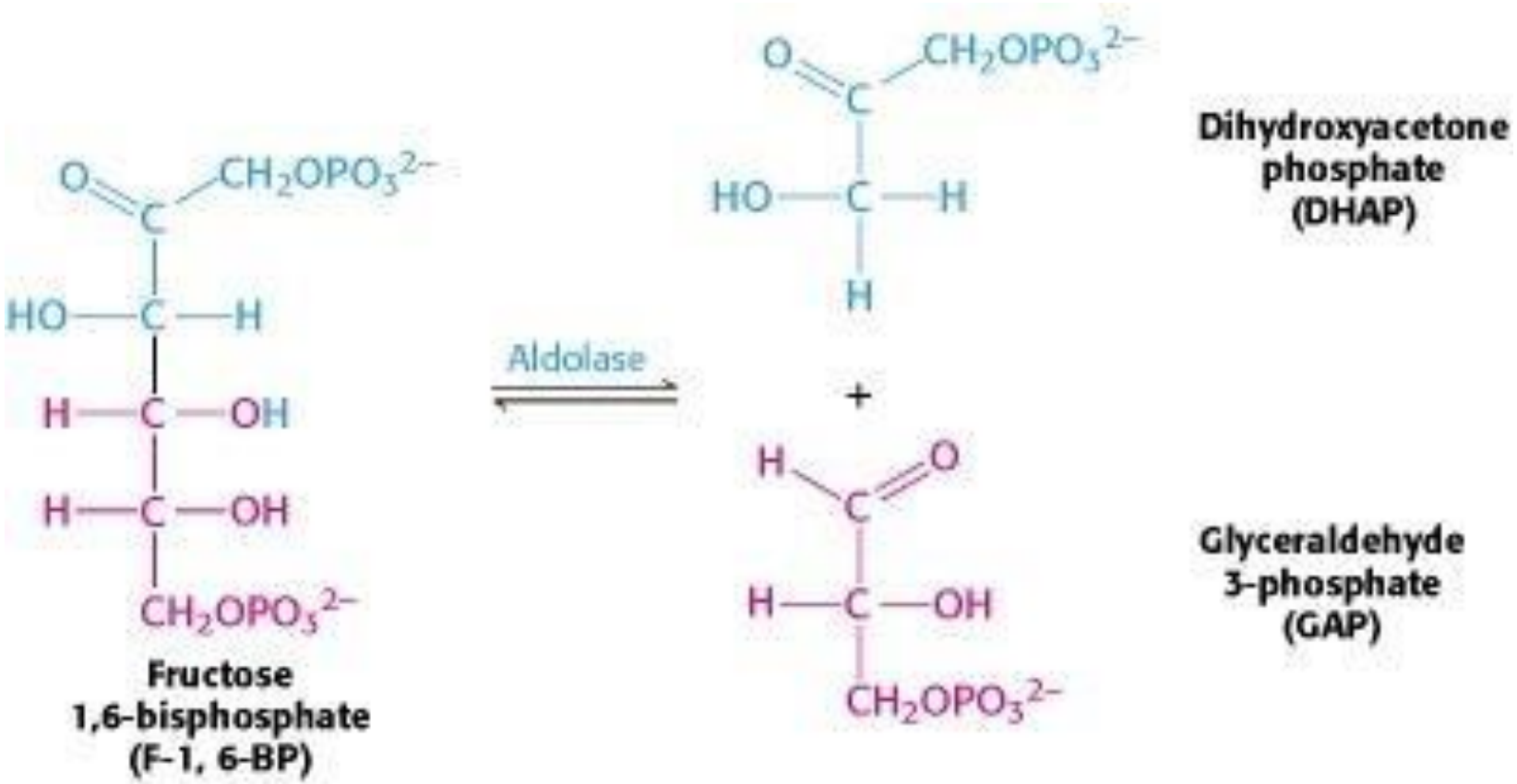



Phosphoglucose Isomerase

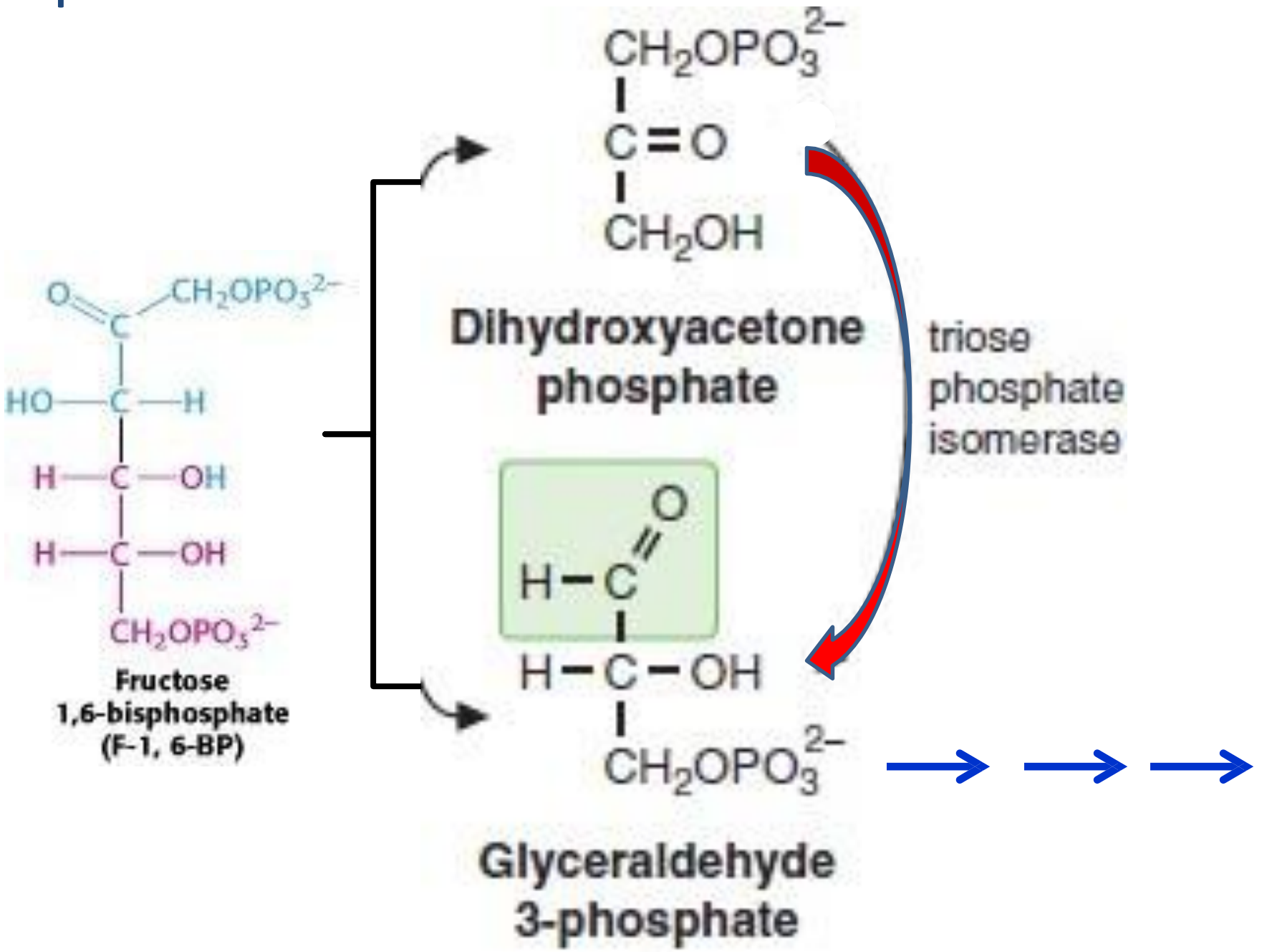
# Step 3


$^{2-}O_3POH_2C$
$CH_2OH$
O
HO
OH
OH
Fructose 6-phosphate
(F-6P)
+ ATP
Phosphofructokinase
Phosphfructo-
kinase
$^{2-}O_3POH_2C$
$CH_2OPO_3^{2-}$
O
HO
OH
OH
uctose 1,6-bisphosphate
(F-1, 6-BP)
+ ADP + $H^+$

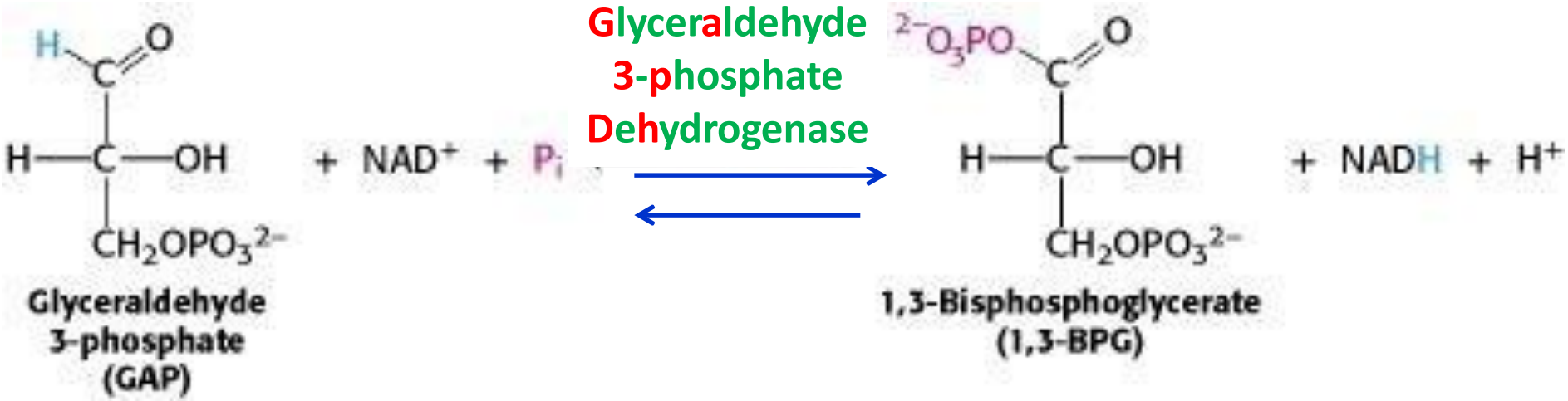
# Step 4


Fructose
1,6-bisphosphate
(F-1, 6-BP)
Aldolase
Dihydroxyacetone
phosphate
(DHAP)
Glyceraldehyde
3-phosphate
(GAP)

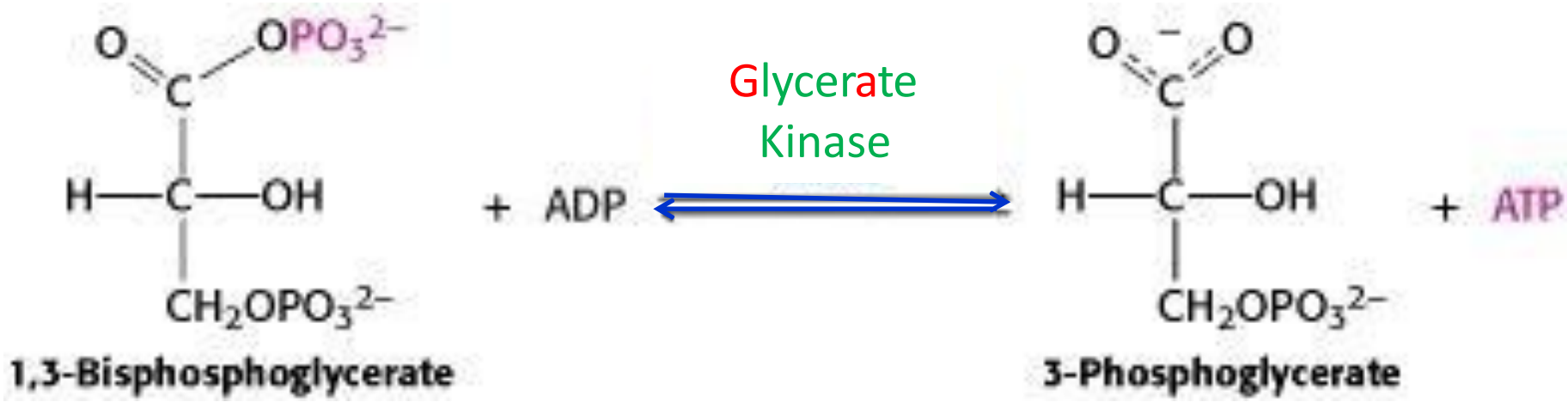
# Step 5


Fructose
1,6-bisphosphate
(F-1, 6-BP)
Dihydroxyacetone
phosphate
triose
phosphate
isomerase
Glyceraldehyde
3-phosphate

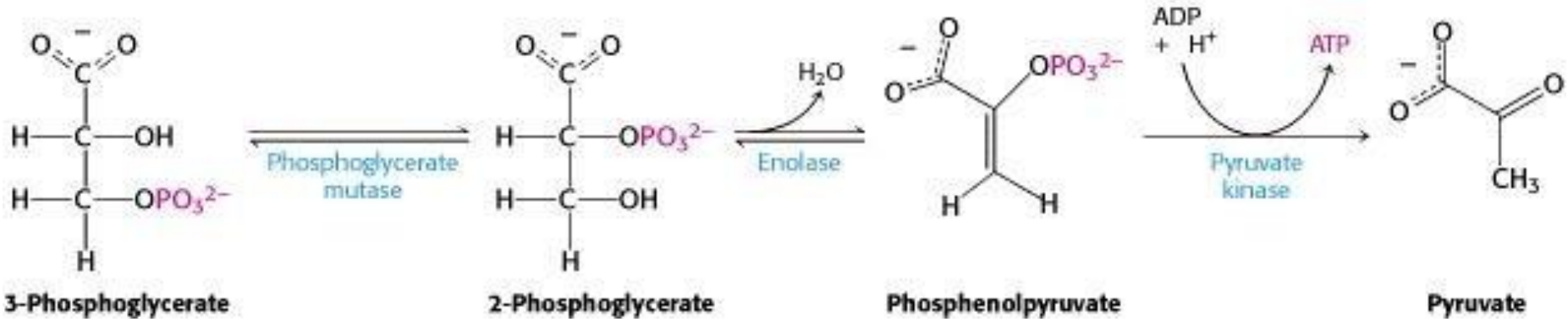
# Step 6


Glyceraldehyde
3-phosphate
Dehydrogenase
+ NAD+ + Pi
+ NADH + H+
Glyceraldehyde
3-phosphate
(GAP)
1,3-Bisphosphoglycerate
(1,3-BPG)

# Step 7


Glycerate
Kinase
+ ADP
+ ATP
1,3-Bisphosphoglycerate
3-Phosphoglycerate

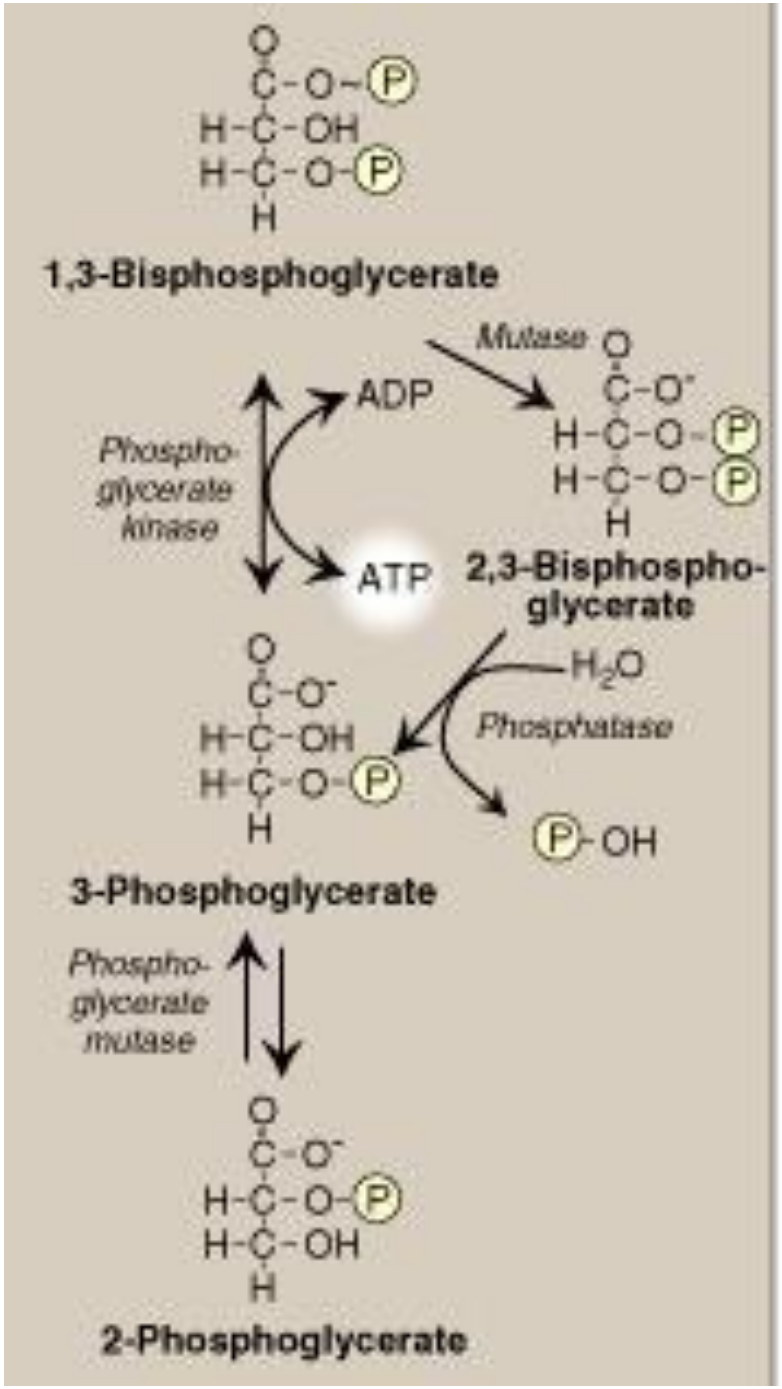
# Step 8-10

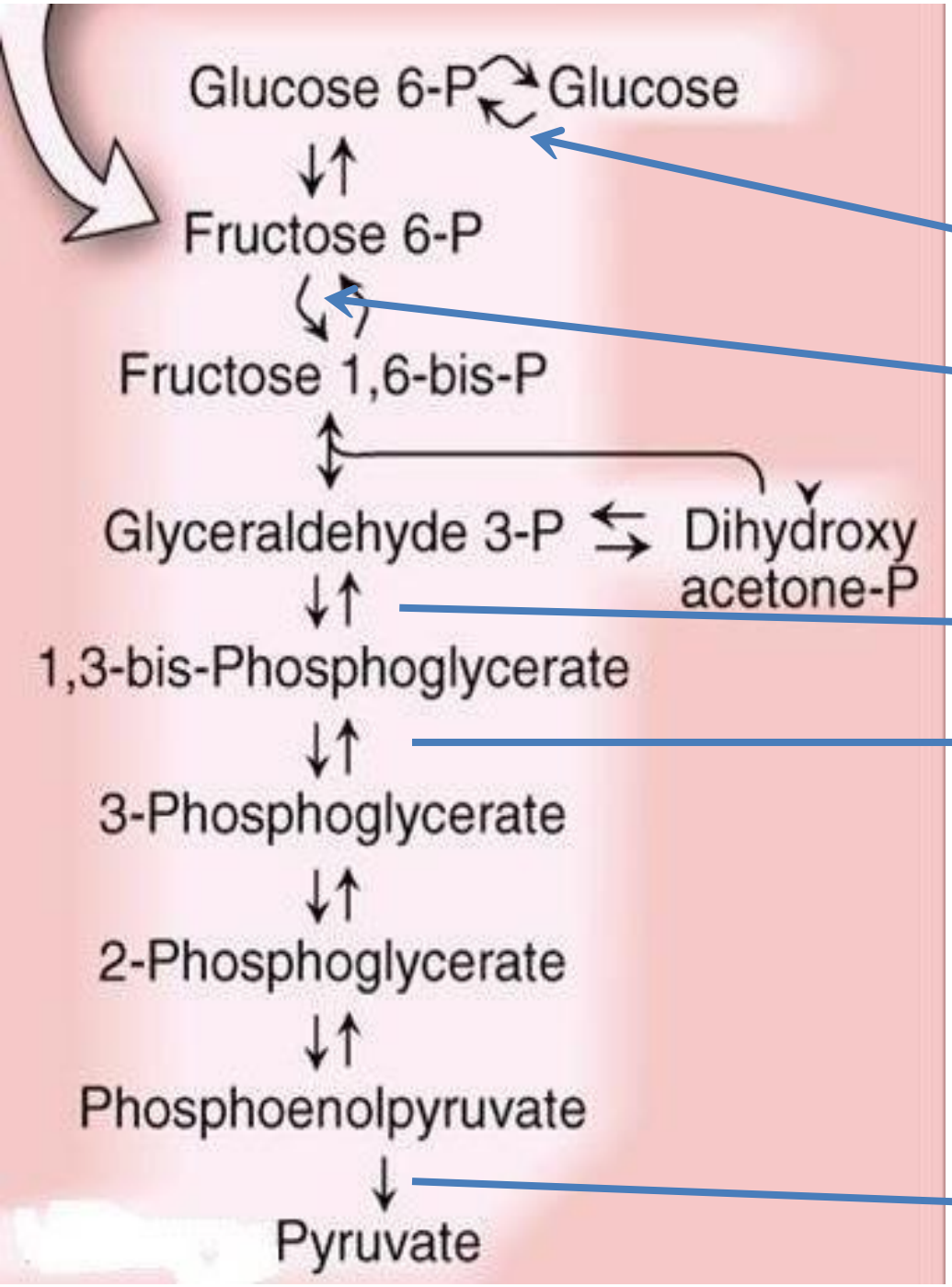

3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
$H_2O$
Enolase
Phosphenolpyruvate
ADP + $H^+$
ATP
Pyruvate kinase
Pyruvate

# Synthesis of 2,3 bisphosphoglycerate in RBC

↑↑Oxygen delivery to tissues

By binding to deoxyhemoglobin reducing its affinity to O2 and increasing O2 release to tissues






# Energy Need and Production

-ATP

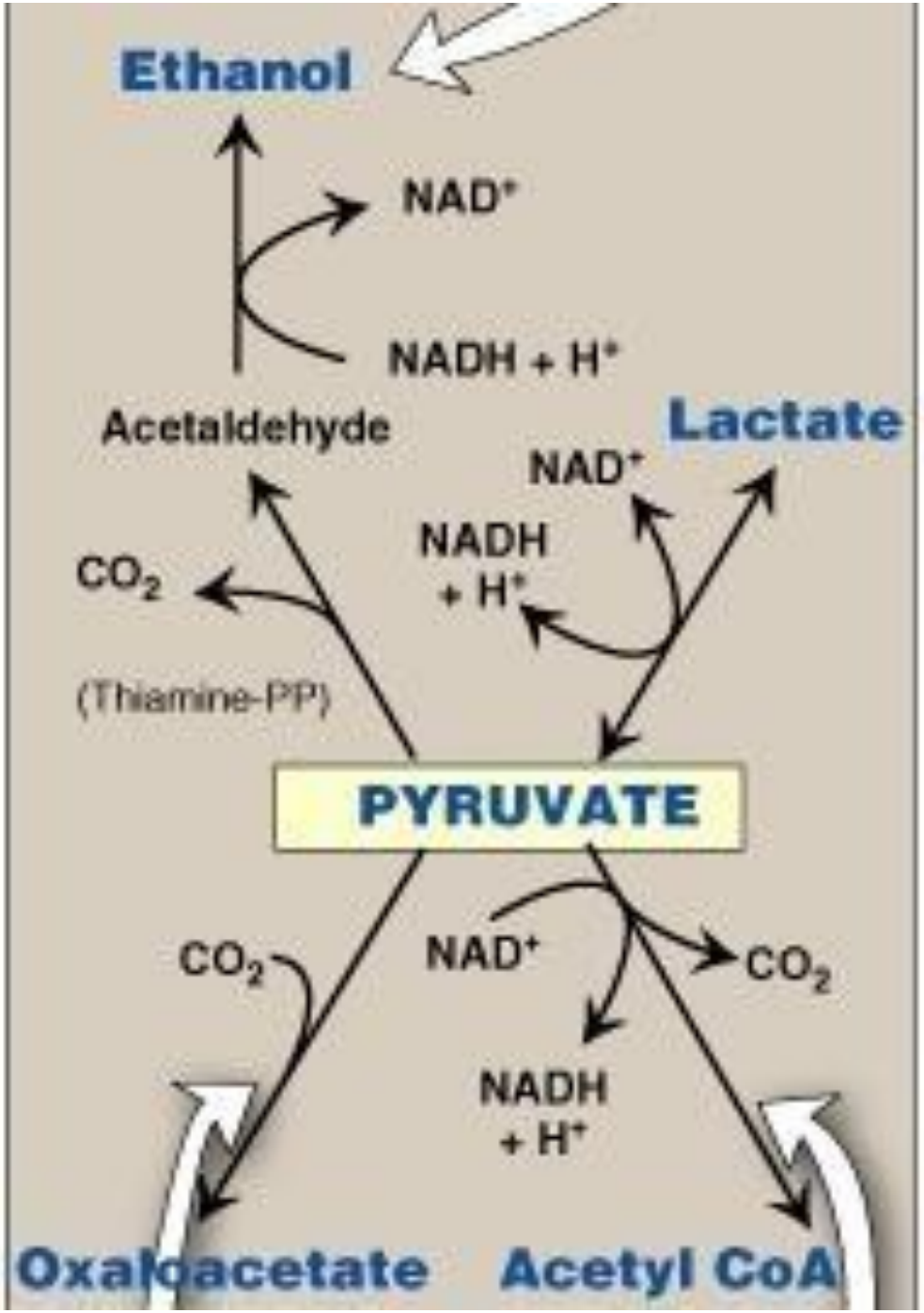
-ATP

2 NADH

2 ATP

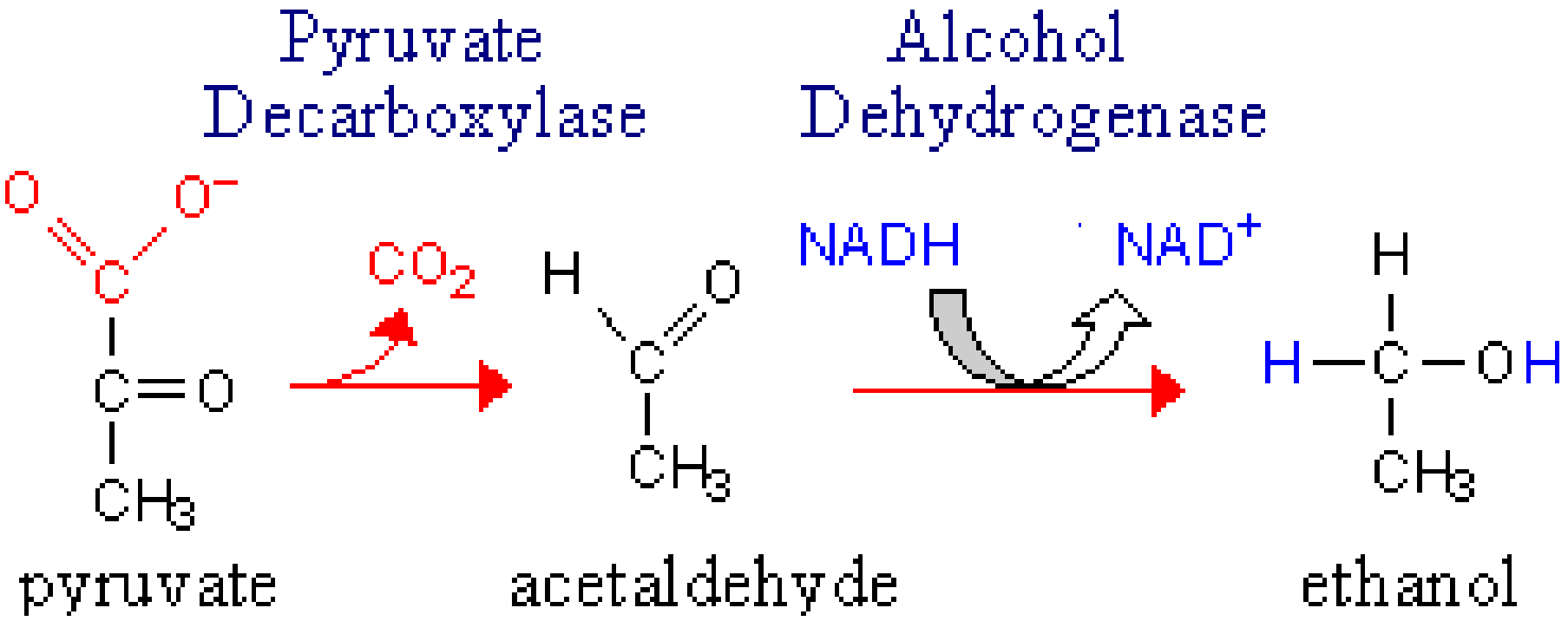
Is Oxygen needed?

2ATP

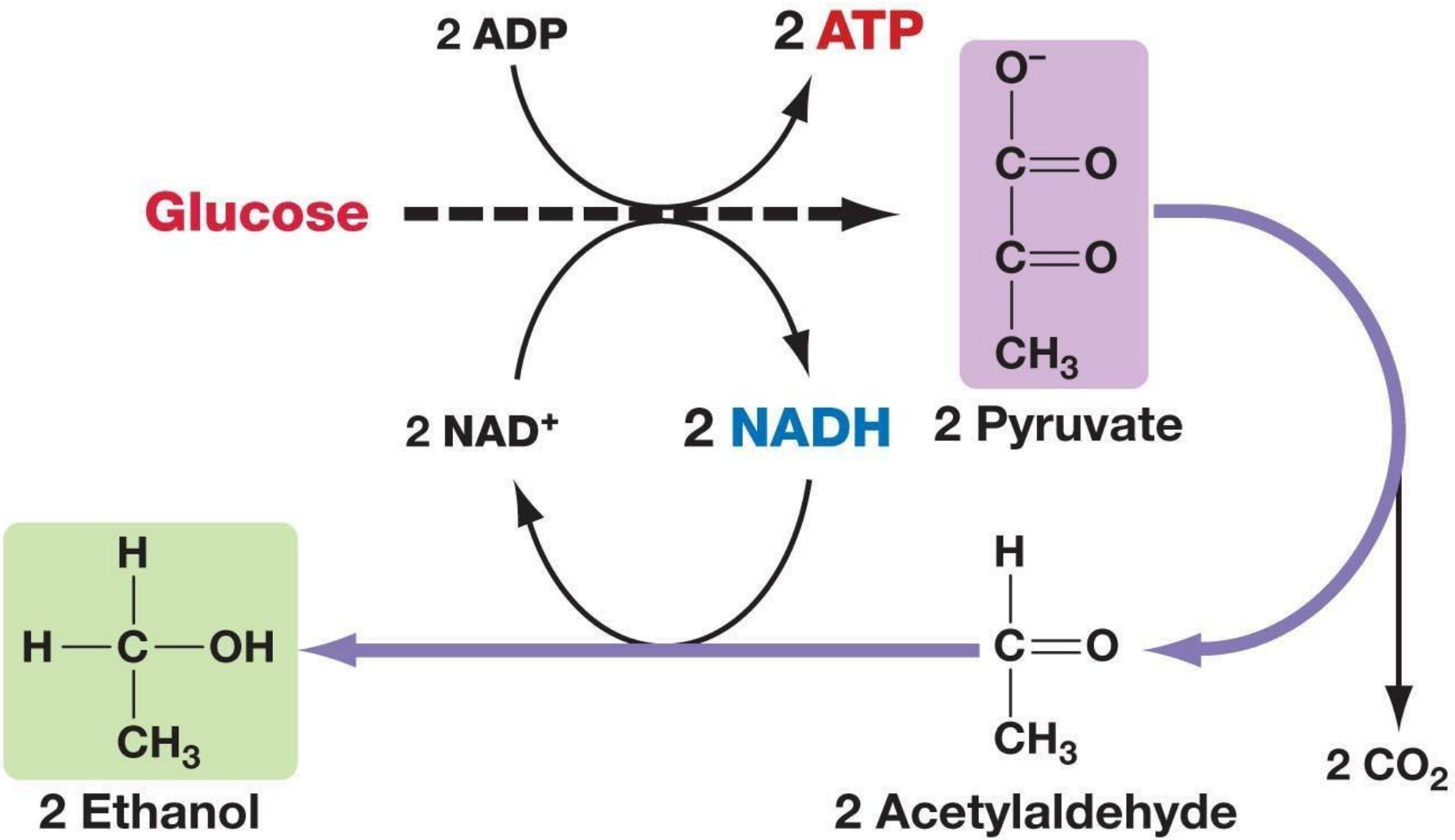



# Pyruvate Fates

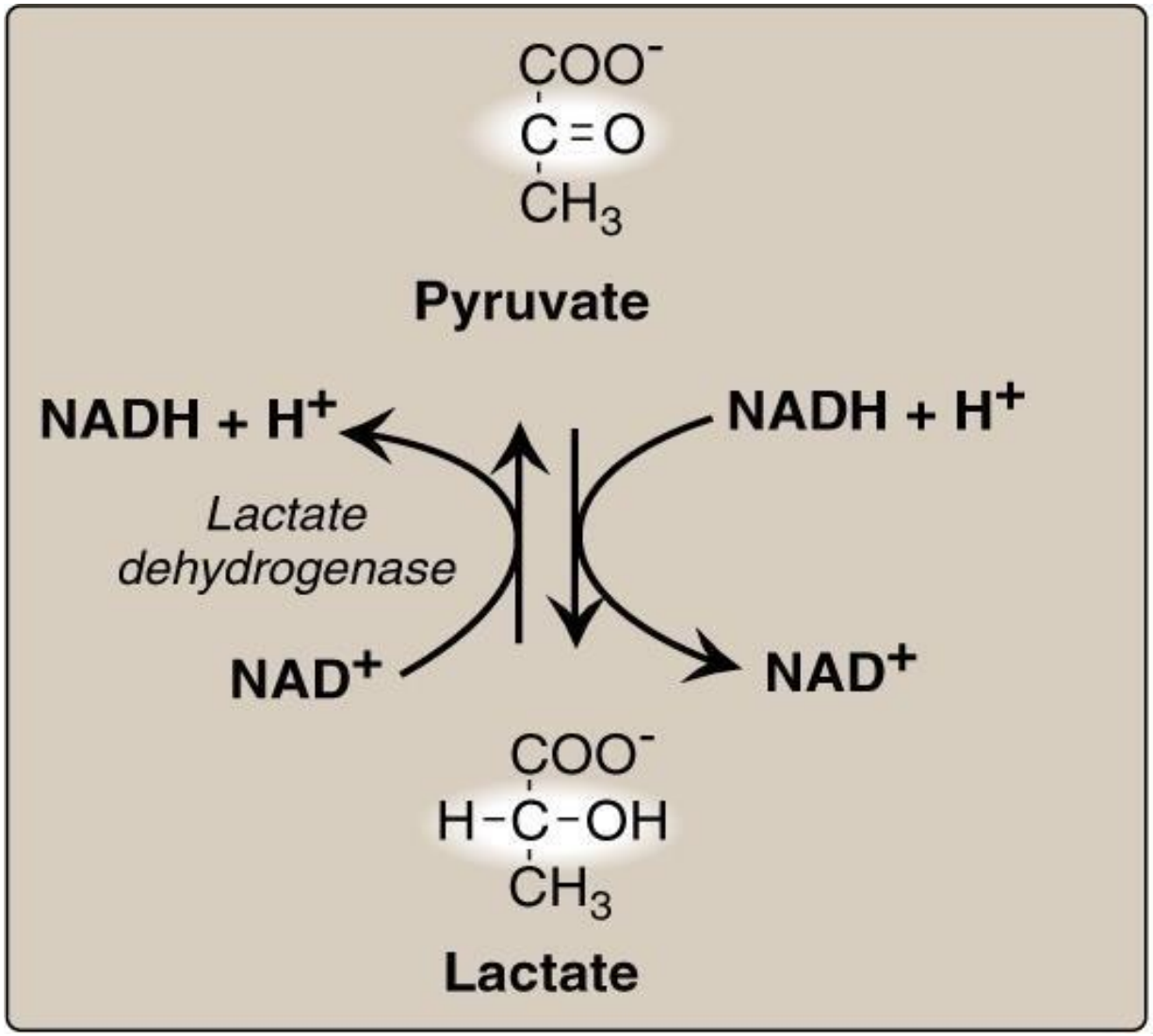
# From Pyruvate to Ethanol



# (b) Alcohol fermentation occurs in yeast.



# From Pyruvate to Lactate




Pyruvate + NADH ⇌ Lactate + $NAD^+$

# When is Lactate Produced?

- Cells with low energy demand
- To cope with increased energy demand in rigorously exercising muscle, lactate level is increased 5 to 10 folds
- Hypoxia

  to survive brief episodes of hypoxia

# Clinical Hint: Lactic Acidosis

- ↓ pH of the plasma
- The most common cause of metabolic acidosis
  - ↑ Production of lactic acid
  - ↓ utilization of lactic acid

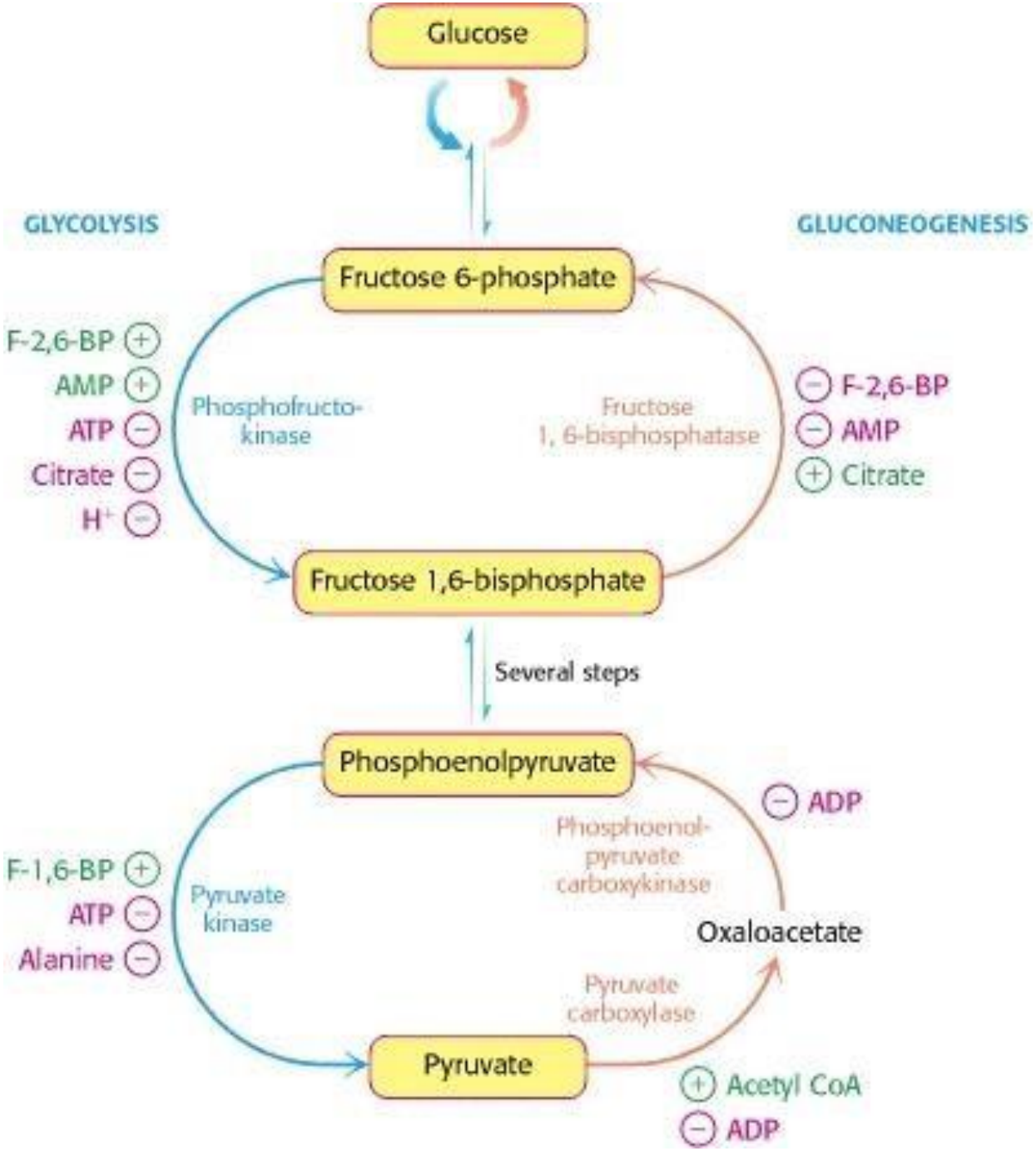

- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired $O_2$ transport
  - Respiratory failure
  - Uncontrolled hemorrhage

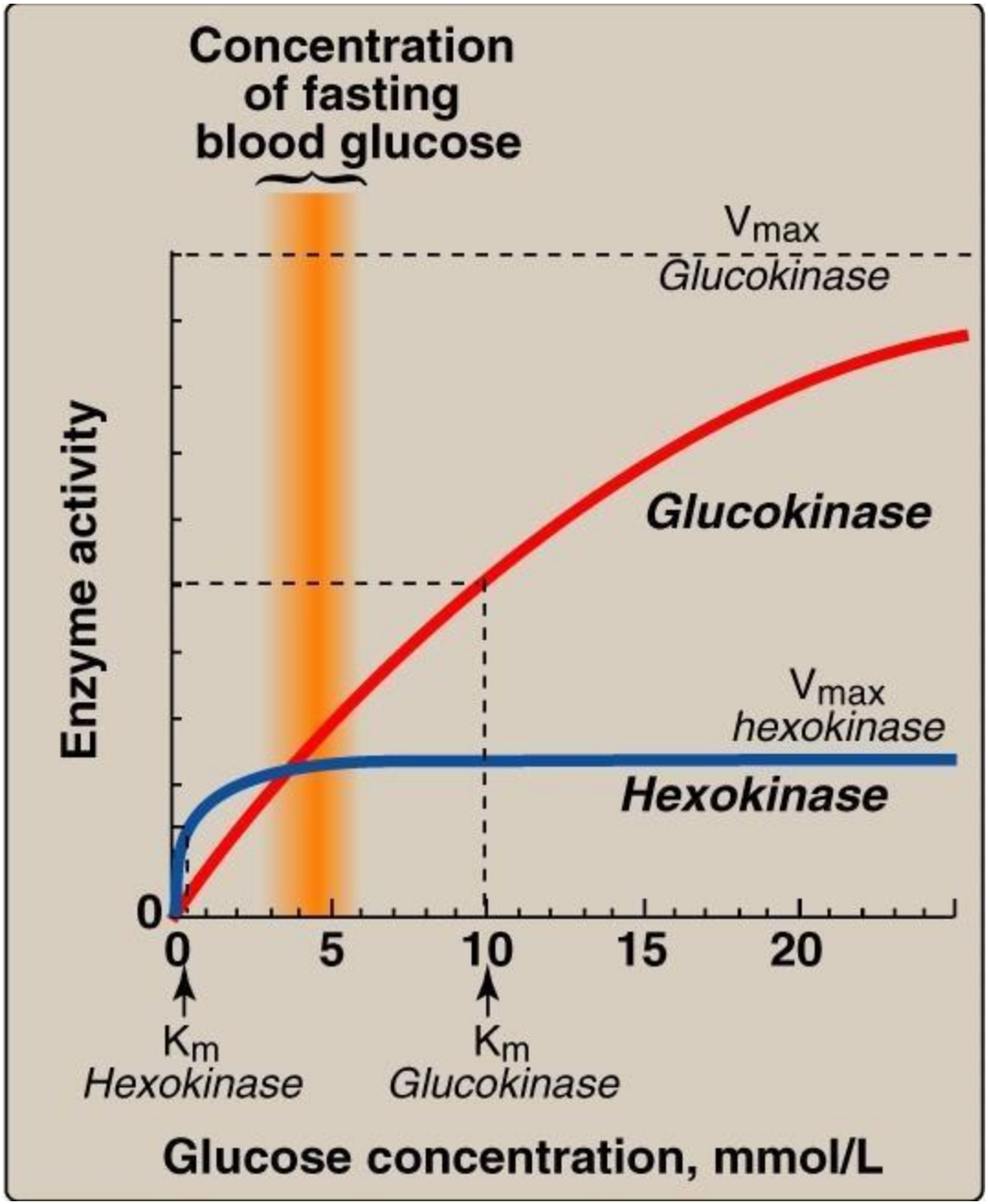
# Clinical Hint: Lactic Acidosis

- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissue
- Alcohol intoxication ( high NADH/ NAD+ )
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydrogenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase

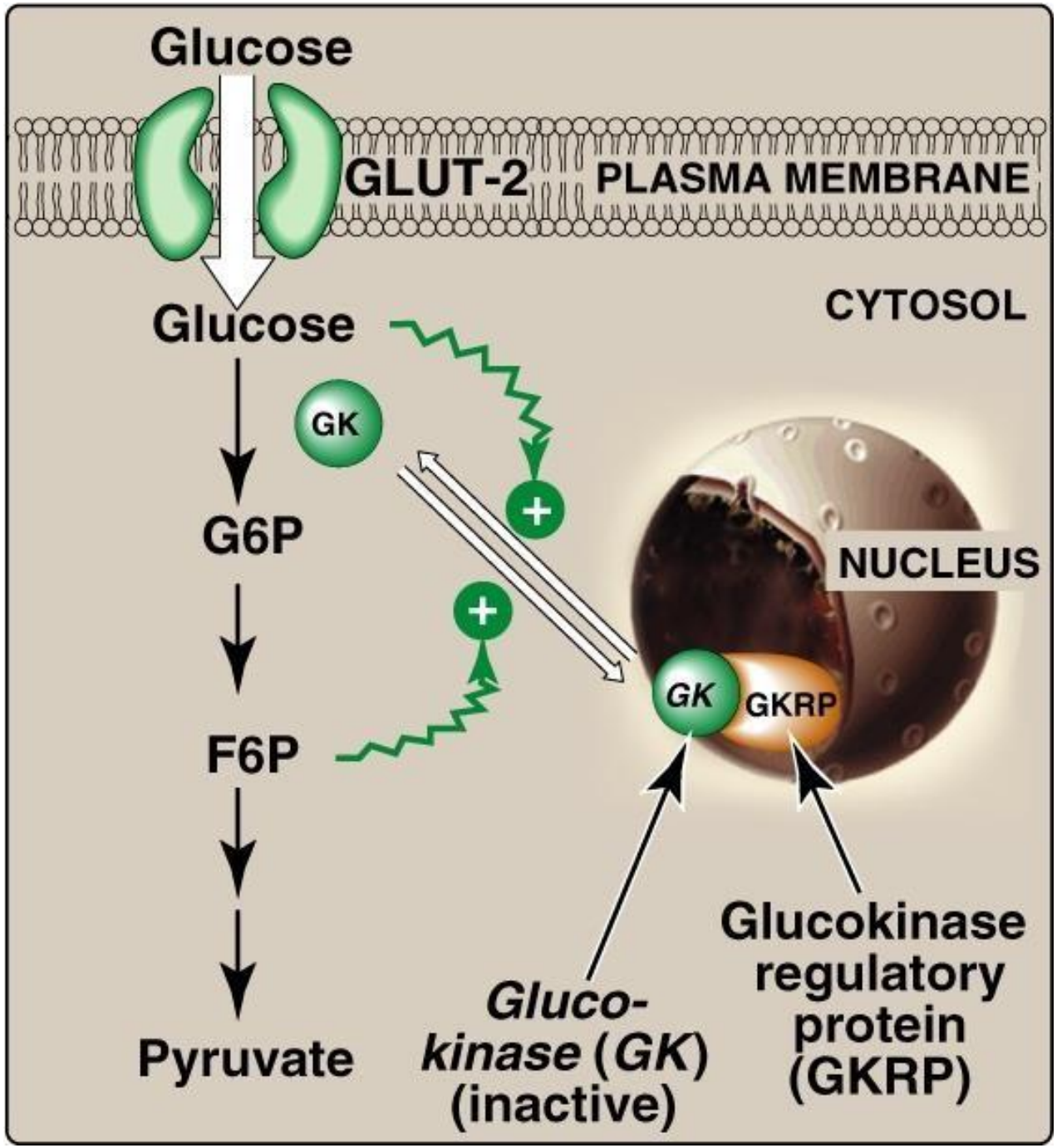
# Regulation of Glycolysis

# Regulators of PFK and PK

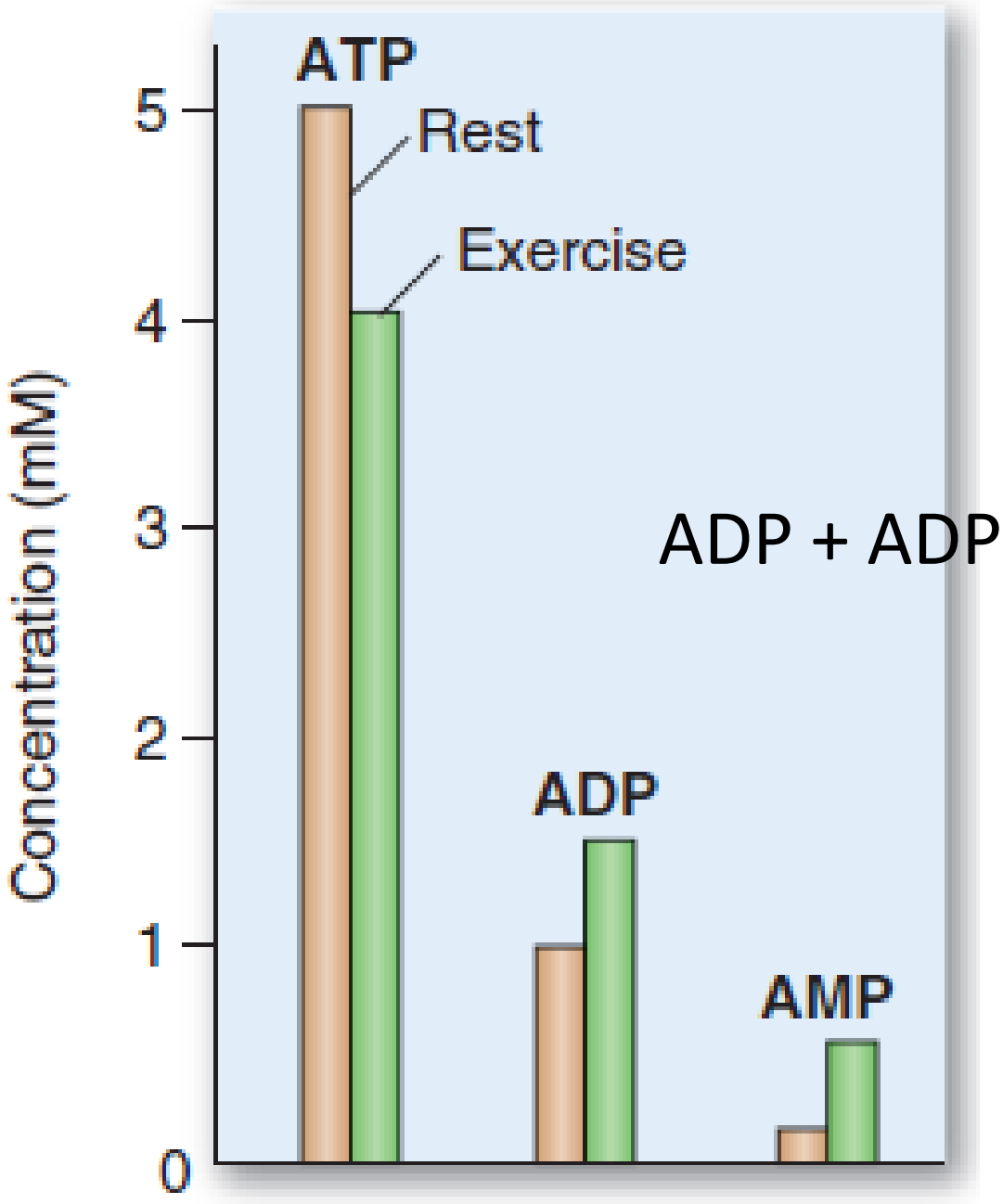





# Glucokinase and Hexokinase Activity



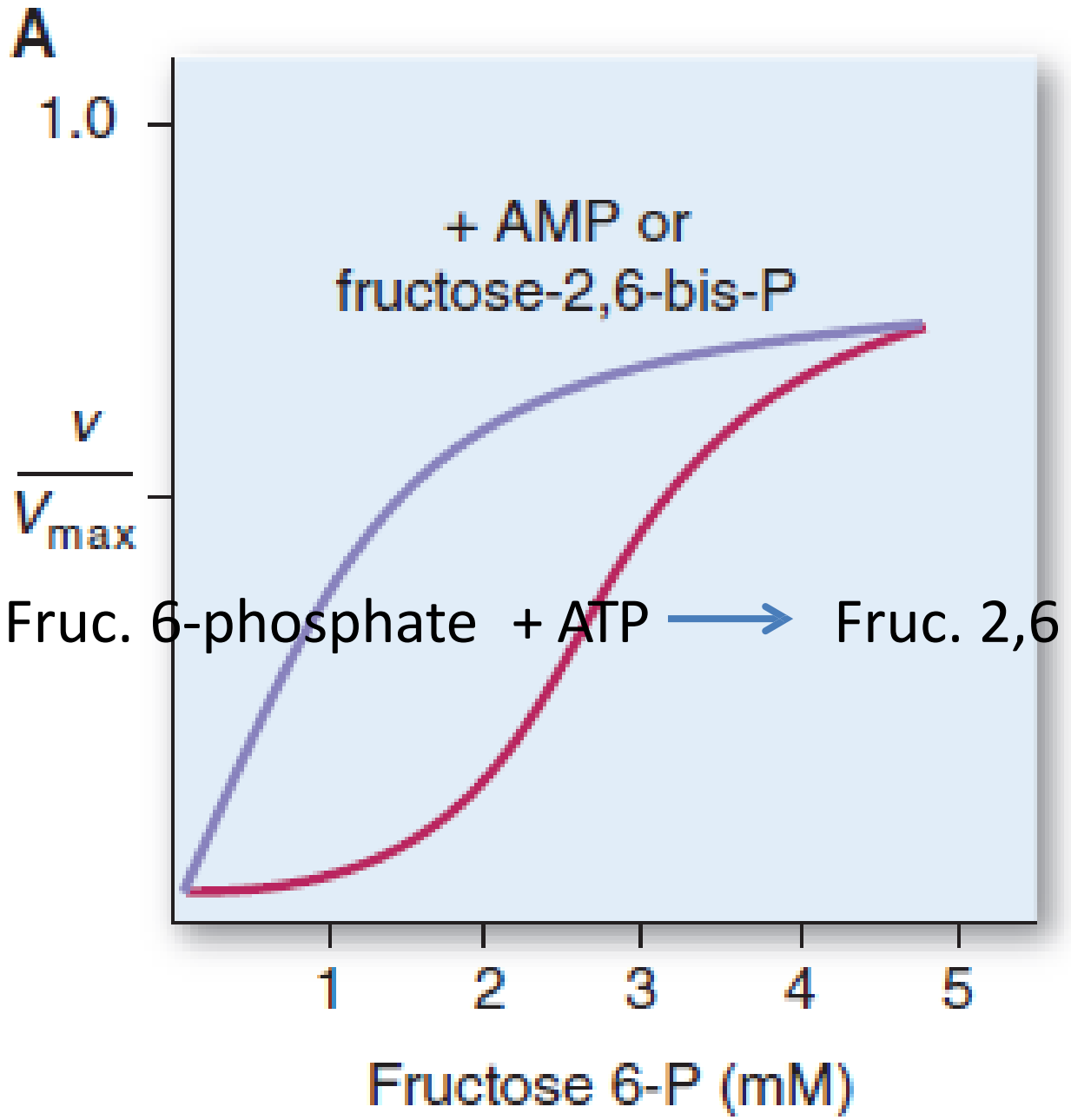

# Glucokinase Regulation




# Regulation by ATP and AMP

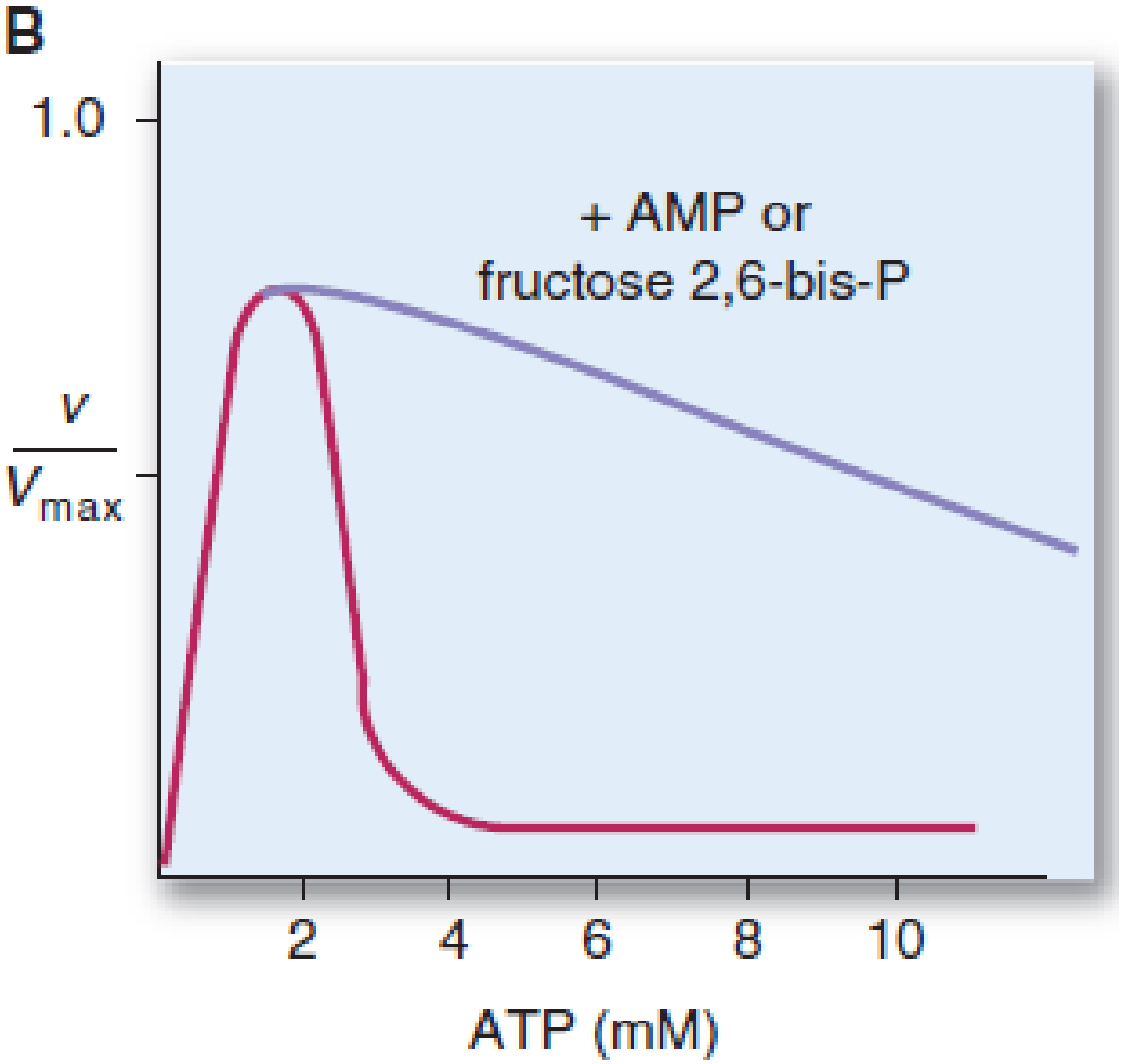
ADP + ADP ⇌ ATP + AMP

# Regulation of PFK by Fructose 2,6-bisphosphate

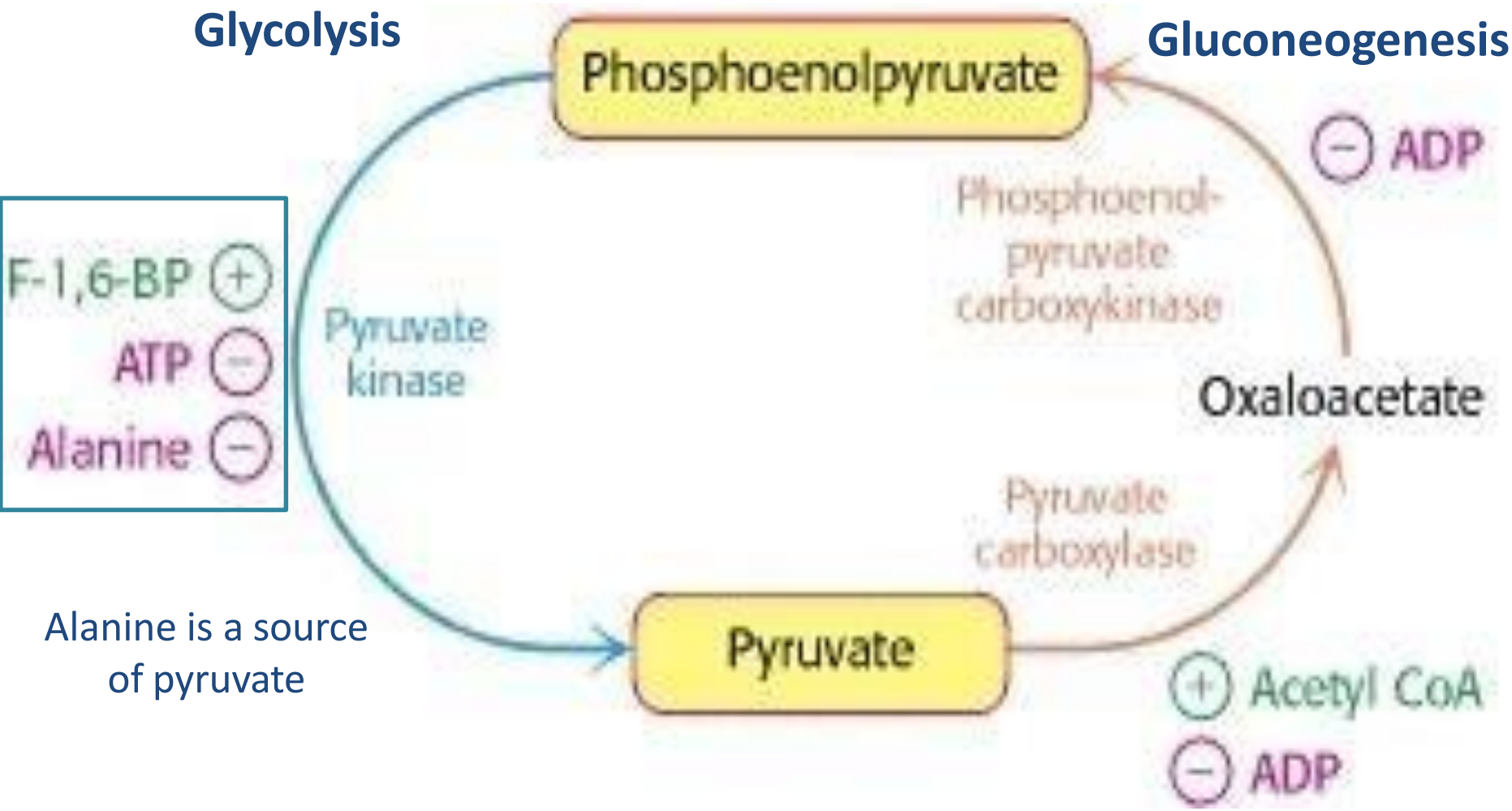



Fruc. 6-phosphate + ATP → Fruc. 2,6 bisphosphate + ADP

# How about the other substrate?

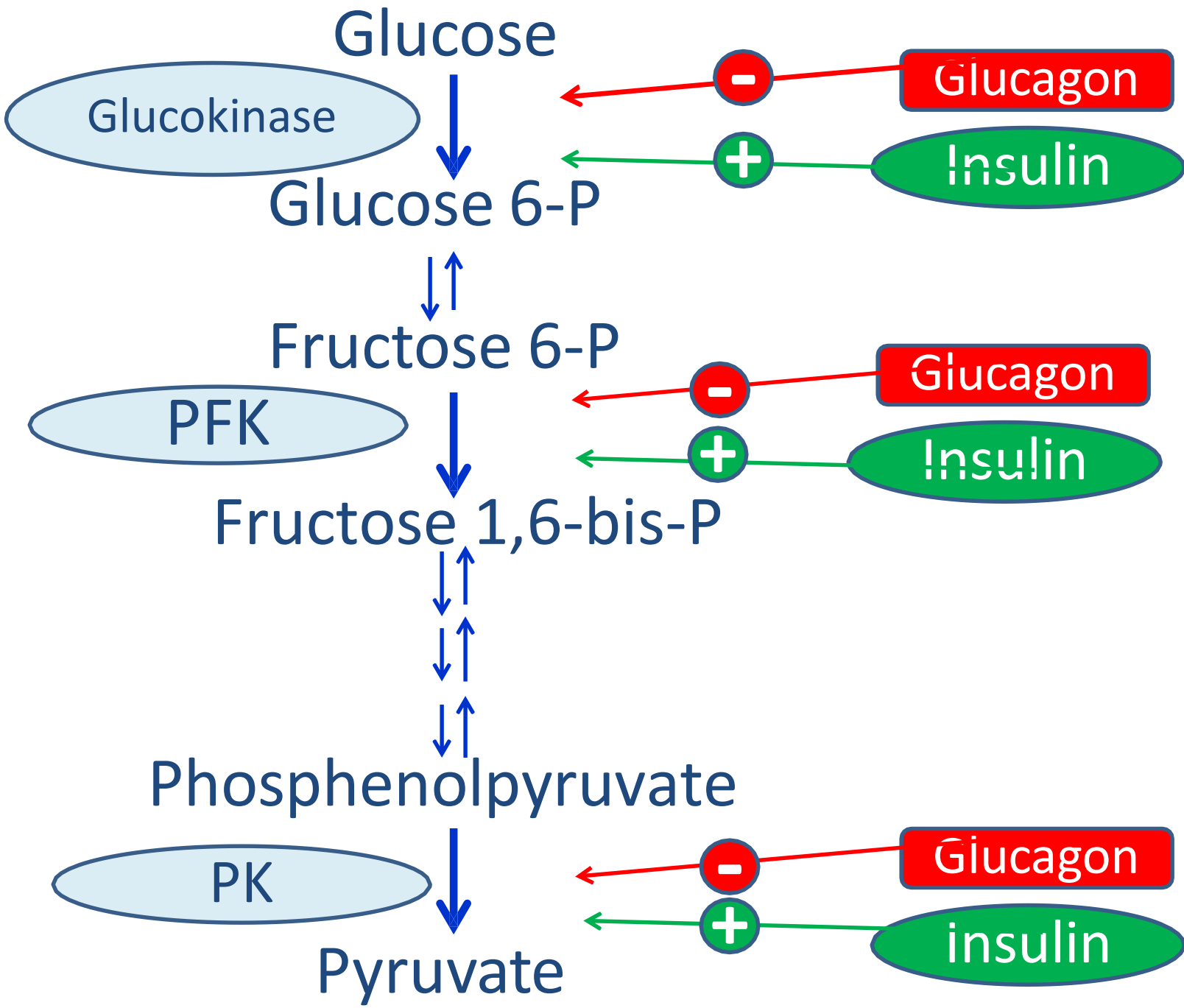


# Regulation of Pyruvate Kinase

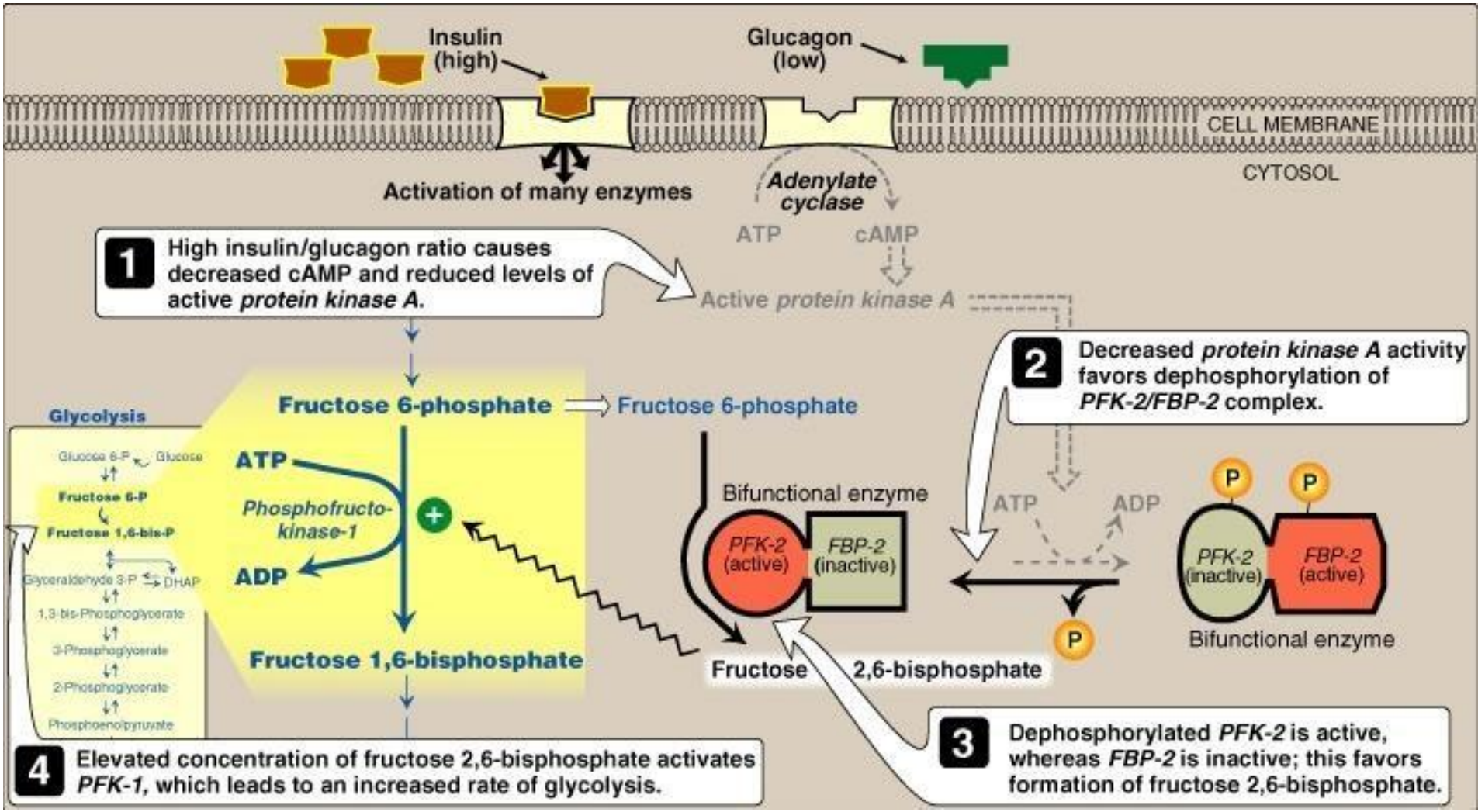


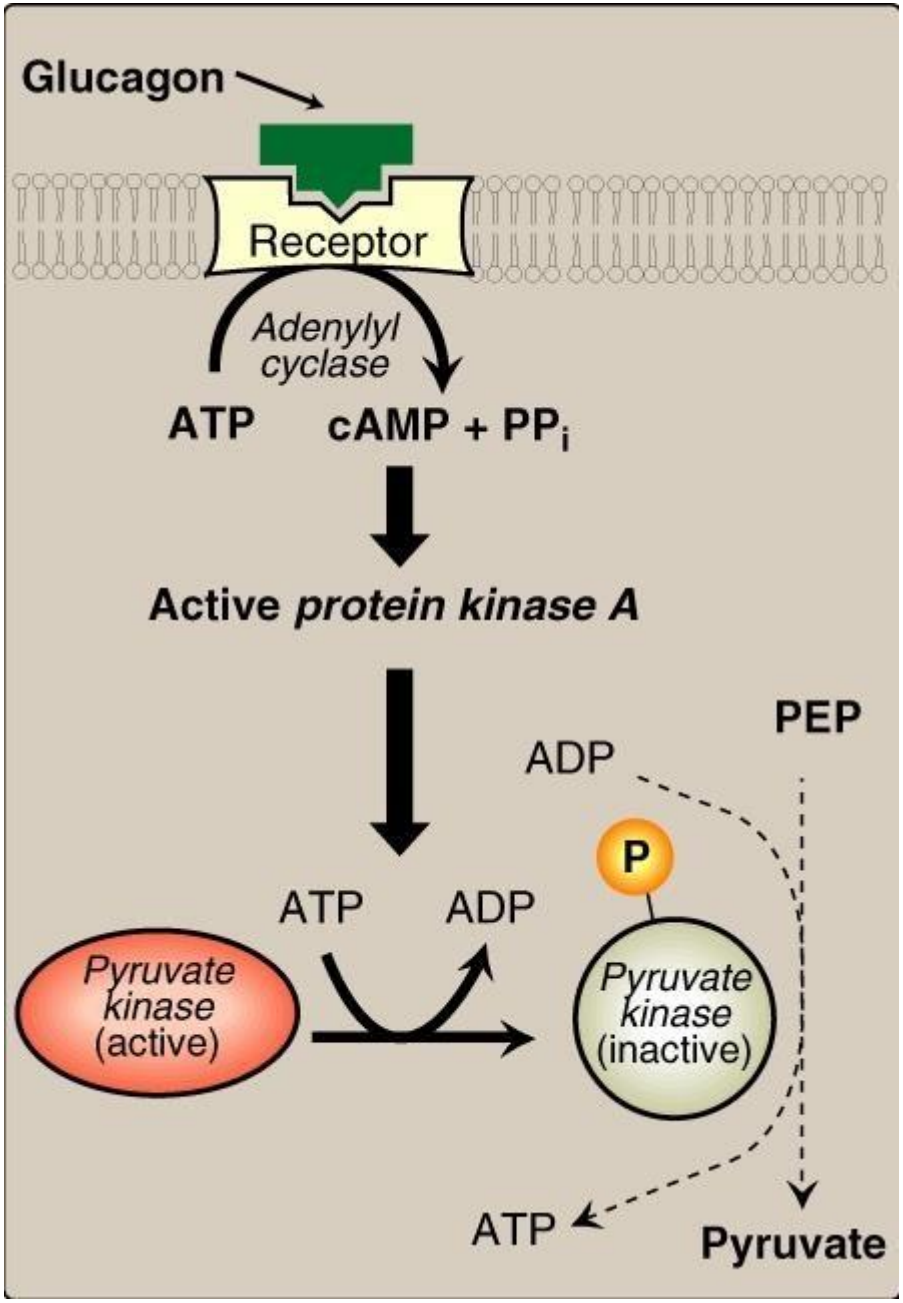

Alanine is a source of pyruvate

Hormonal Regulation



# Hormonal Regulation of Phosphofructokinase

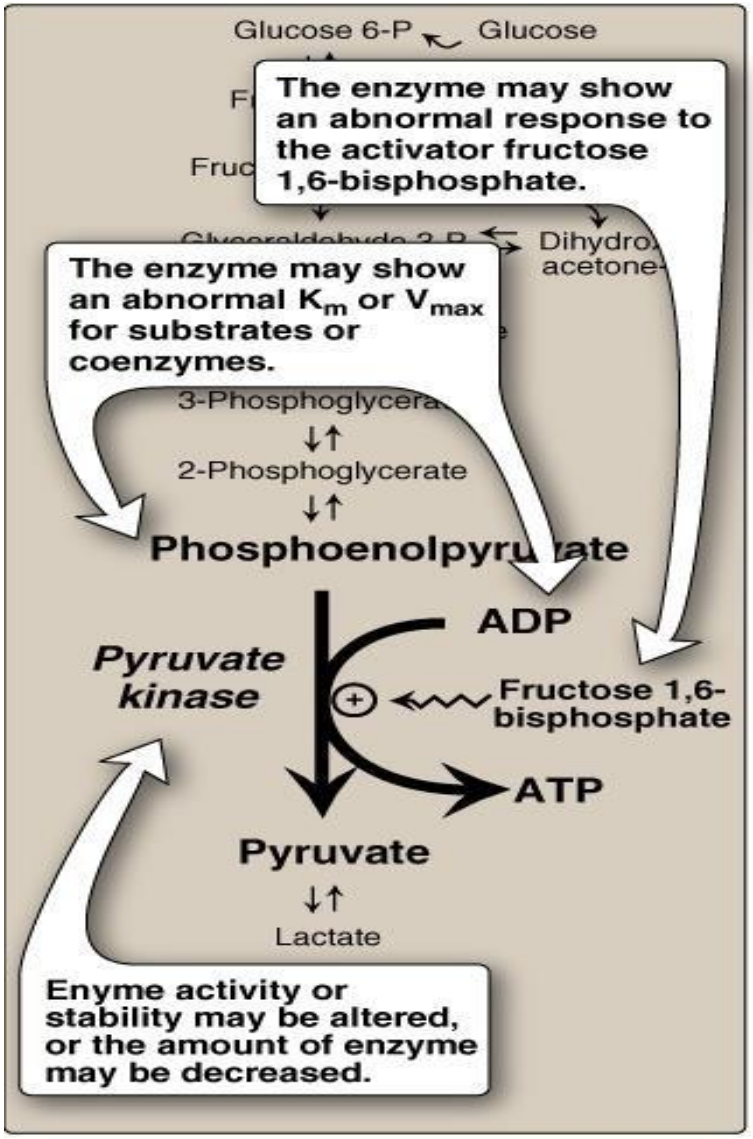





# Hormonal Regulation of Pyruvate Kinase

# Clinical Hint: Pyruvate Kinase Deficiency

- The most common among glycolytic enzyme deficiencies
- RBCs are affected
- Mild to severe chronic hemolytic anemia
- ATP is needed for Na+/K+ pump➔ maintain the flexible shape of the cell
- Low ATP ➔ premature death of RBC
- Abnormal enzyme; mostly altered kinetic properties

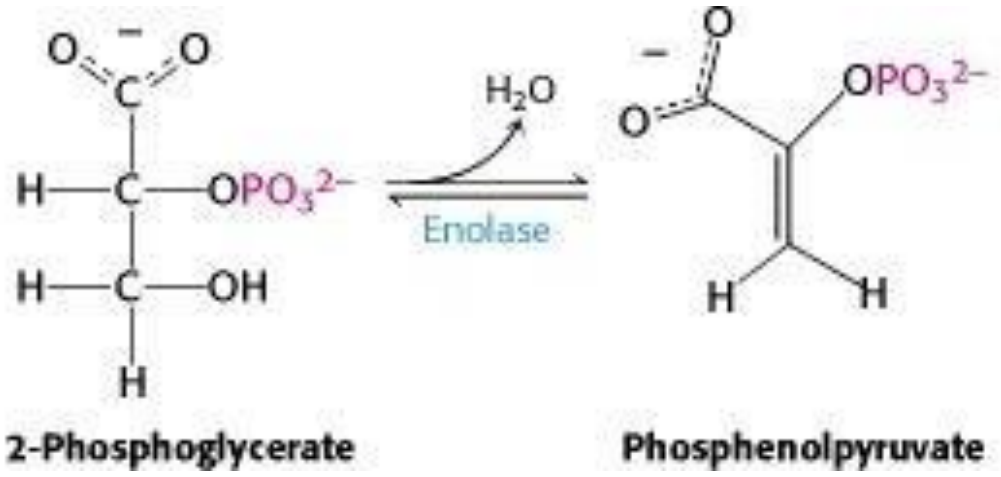



**Alterations observed with various mutant forms of pyruvate kinase**

# External Inhibitors of Glycolysis

# Inorganic Inhibitors of Glycolysis Fluoride

- Fluoride inhibits Enolase




Fluoridated water ➔ ↓ bacterial enolase ➔

Prevention of Dental Carries

# Inorganic Inhibitors of Glycolysis

## Arsenic Poisoning

–Pentavalent Arsenic (Arsenate) competes with phosphate as as a substrate for GA3PDH

↓ ATP synthesis

–Trivalent Arsenic (Arsenite) Forms stable complex with -SH of lipoic acid

↓ Pyruvate Dehydrogenase

↓ α ketoglutarate Dehydrogenase

➔ Neurological disturbances…….**DEATH**