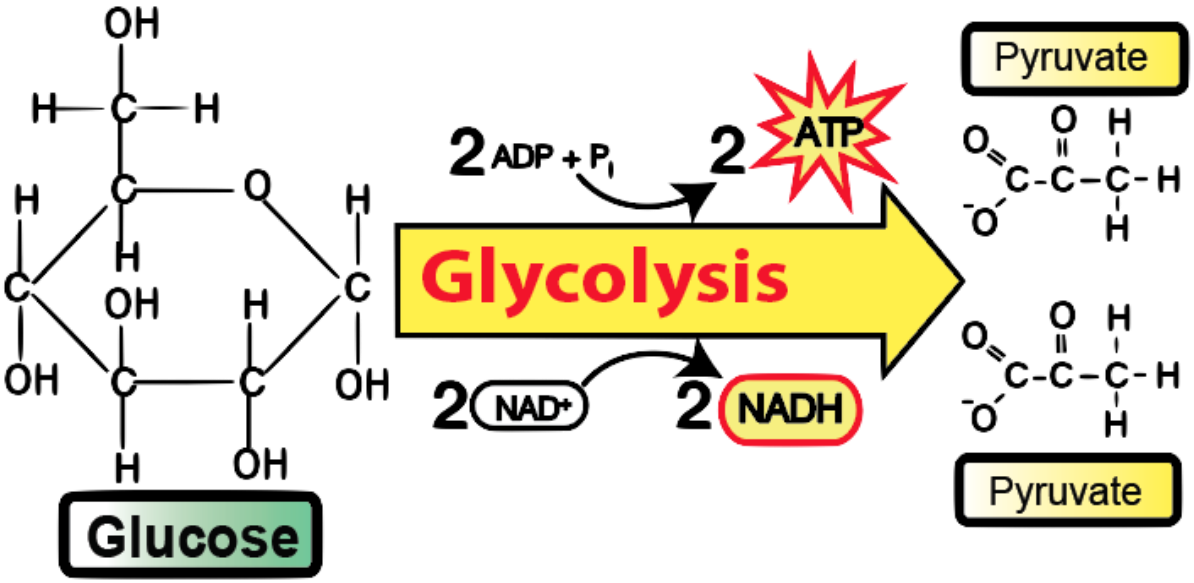
Glycolysis
Reactions and Regulation

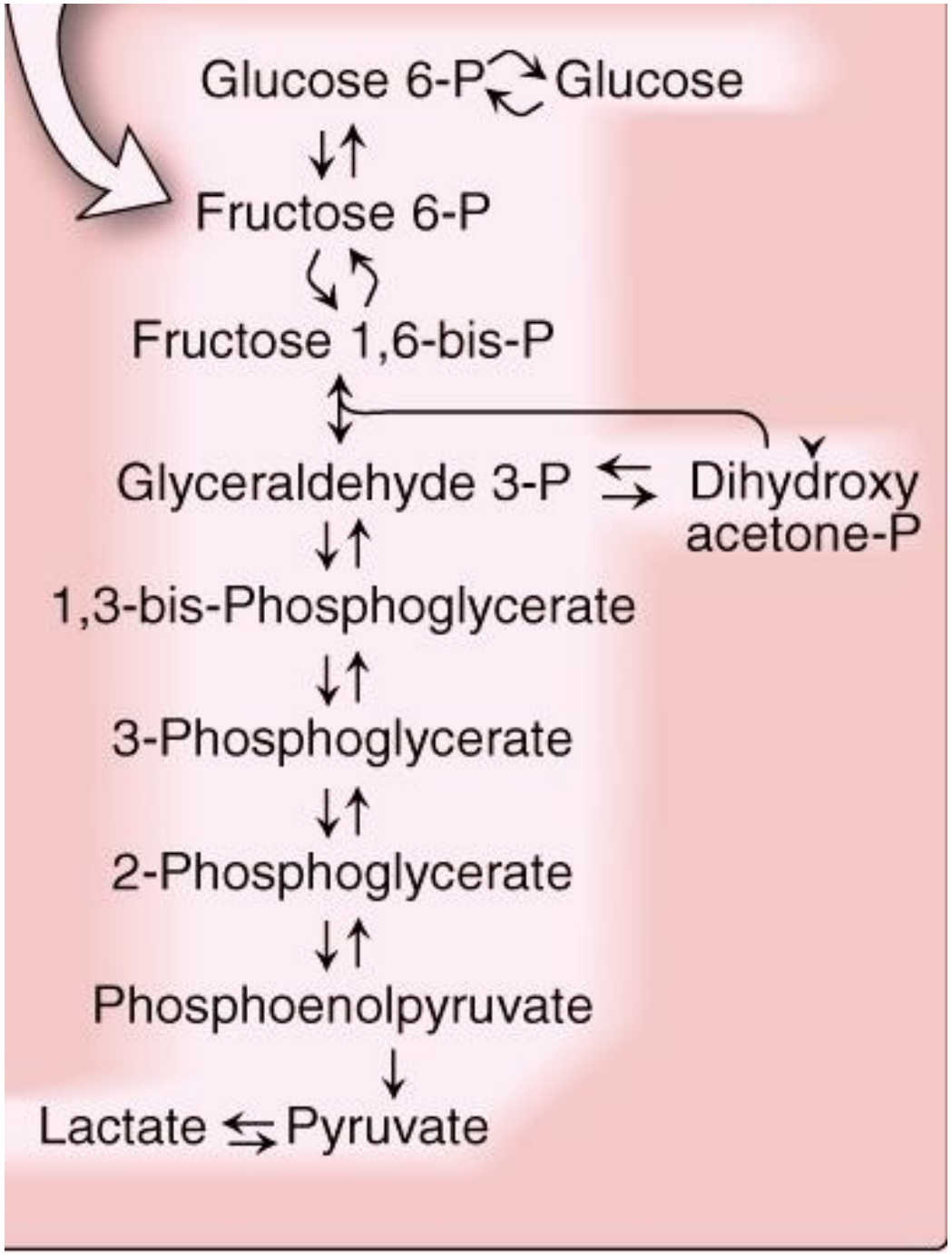


Dr. Diala Abu-Hassan

Suggested Reading:

Lippincott's Illustrated reviews: Biochemistry

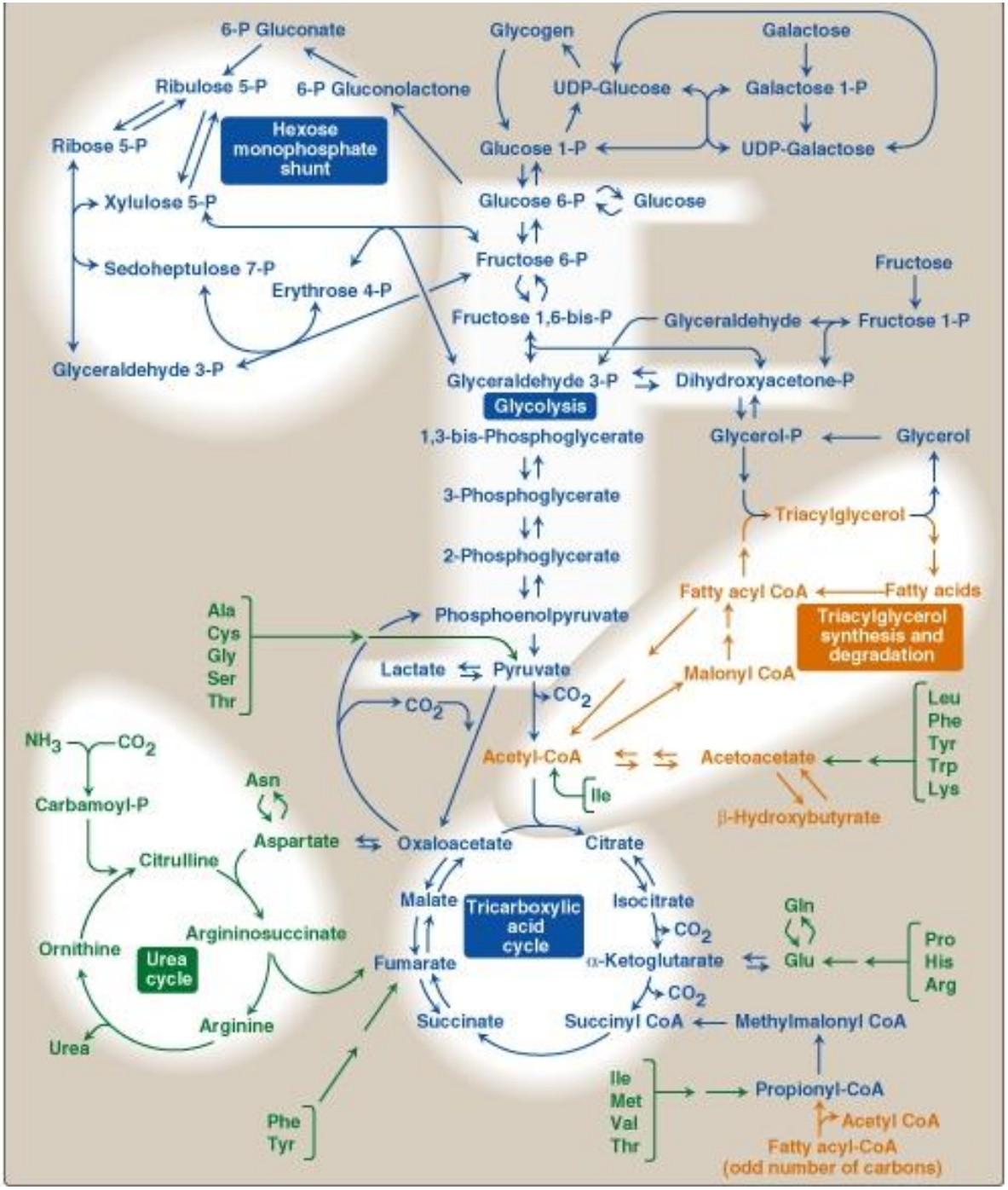
sciencemusicvideos



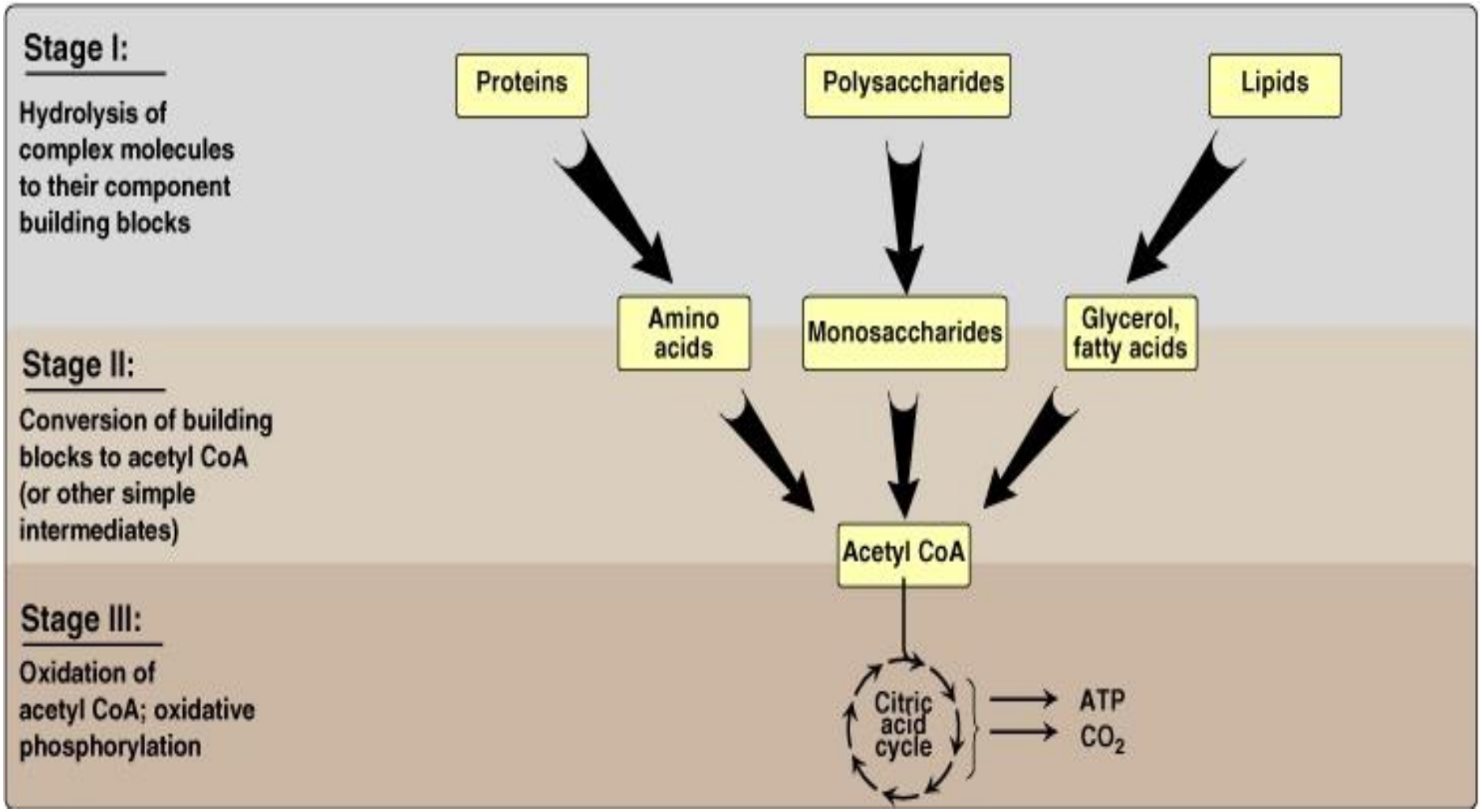
Glycolysis is an example of metabolic pathway

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

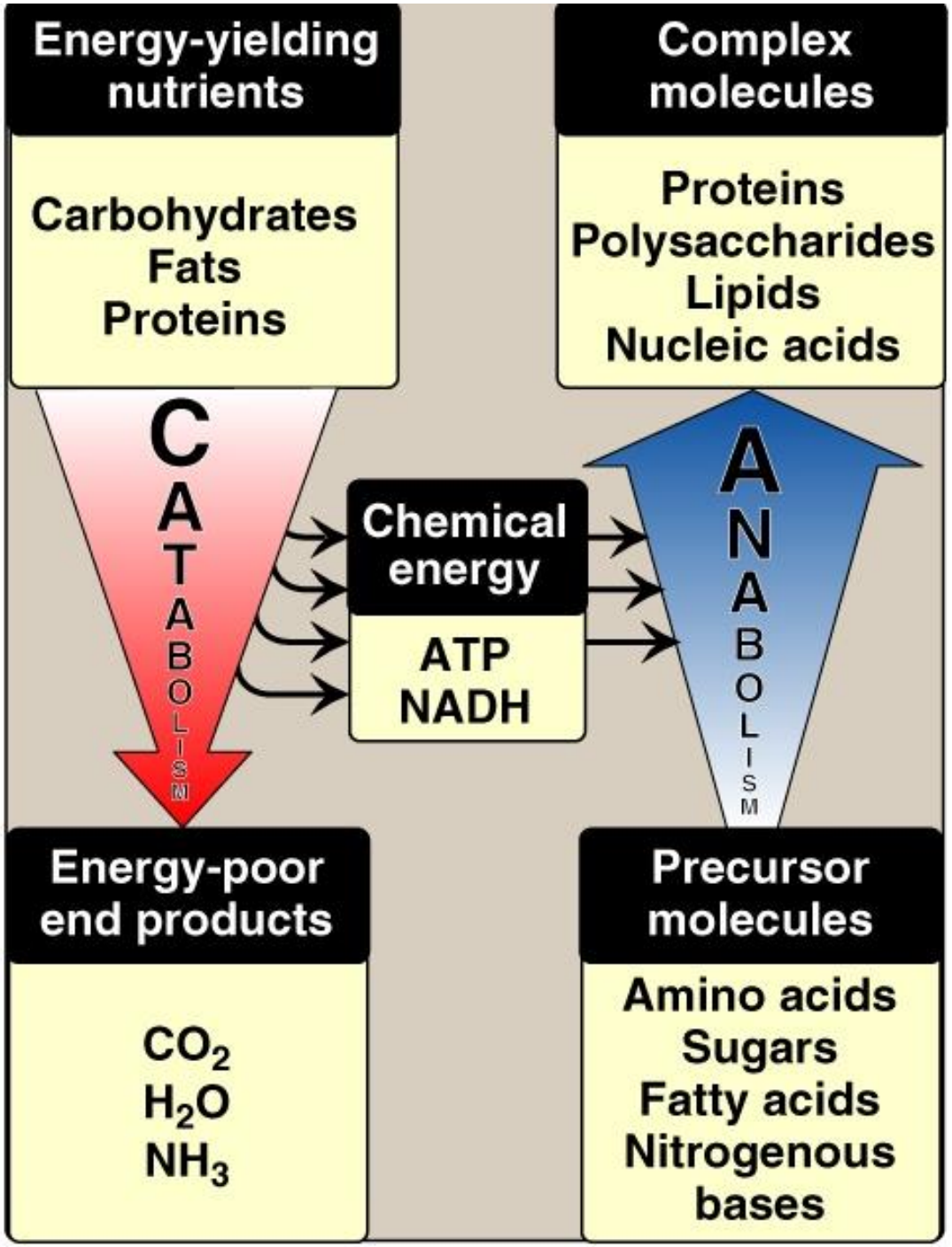
Metabolic pathways intersect to form network of chemical reactions



General Stages of Metabolism

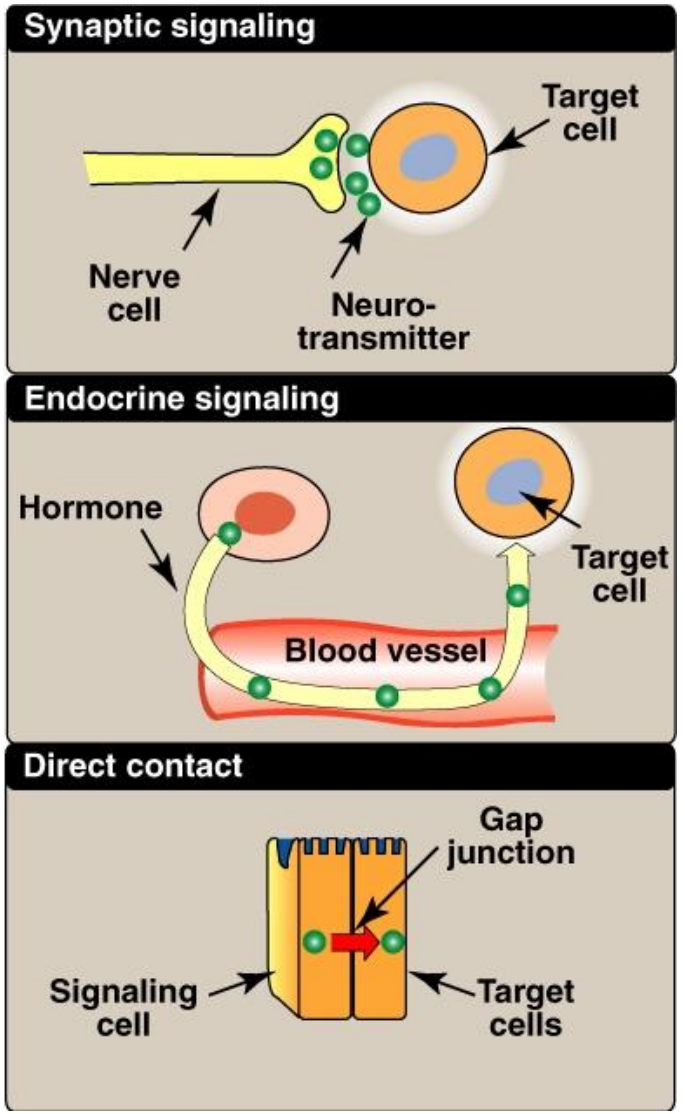


Types of Metabolic Pathways



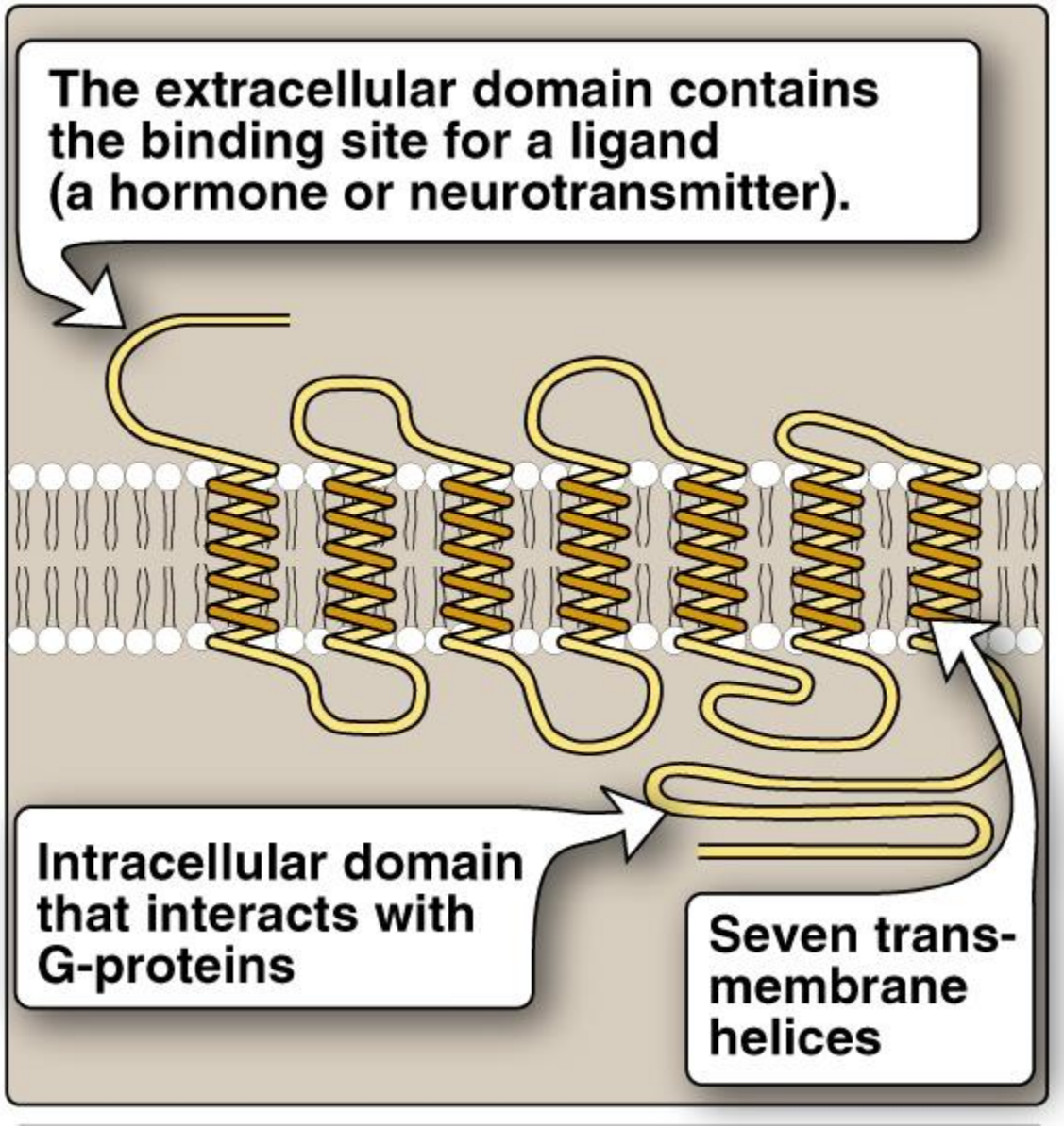
Regulation of Metabolism

- 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

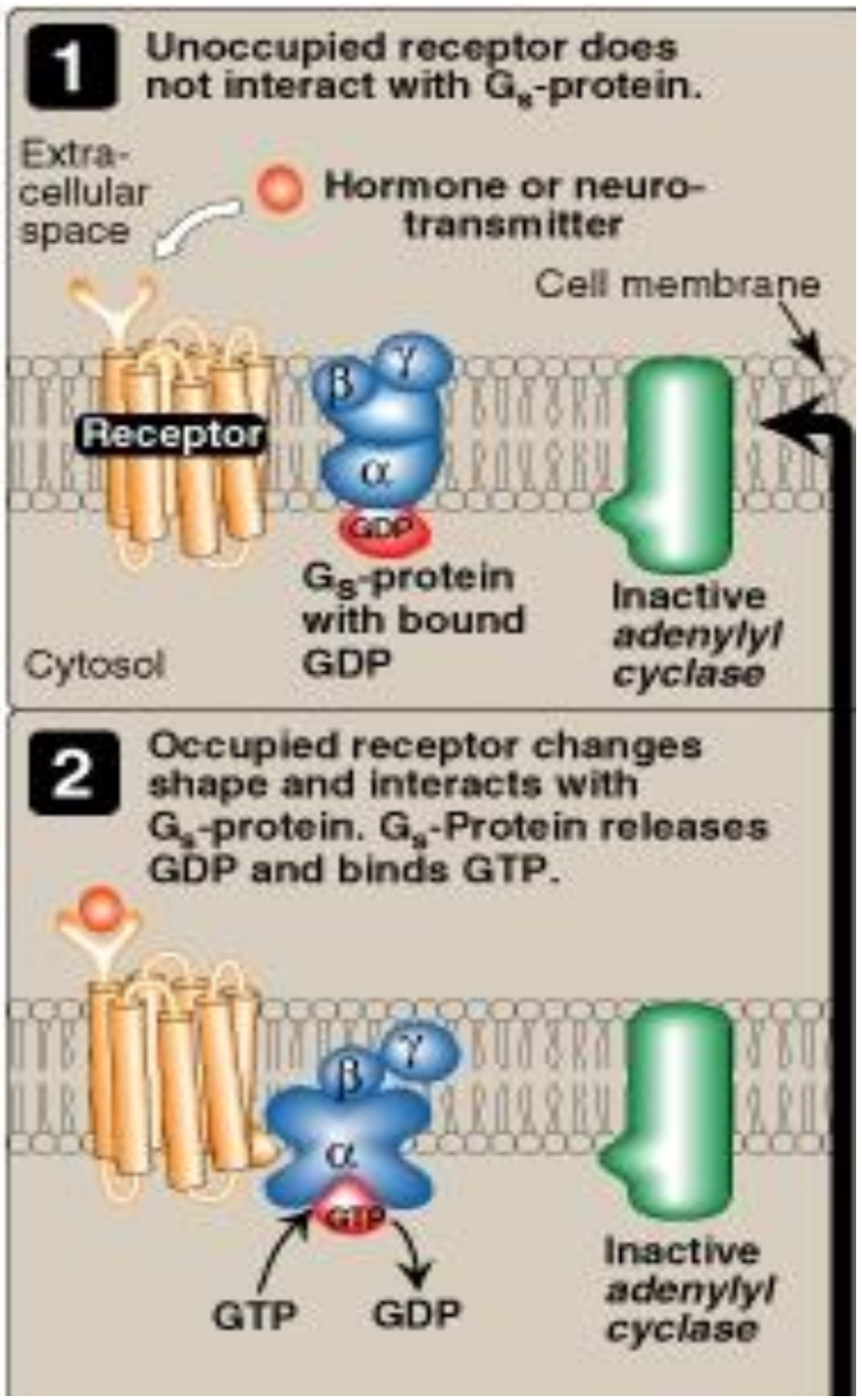


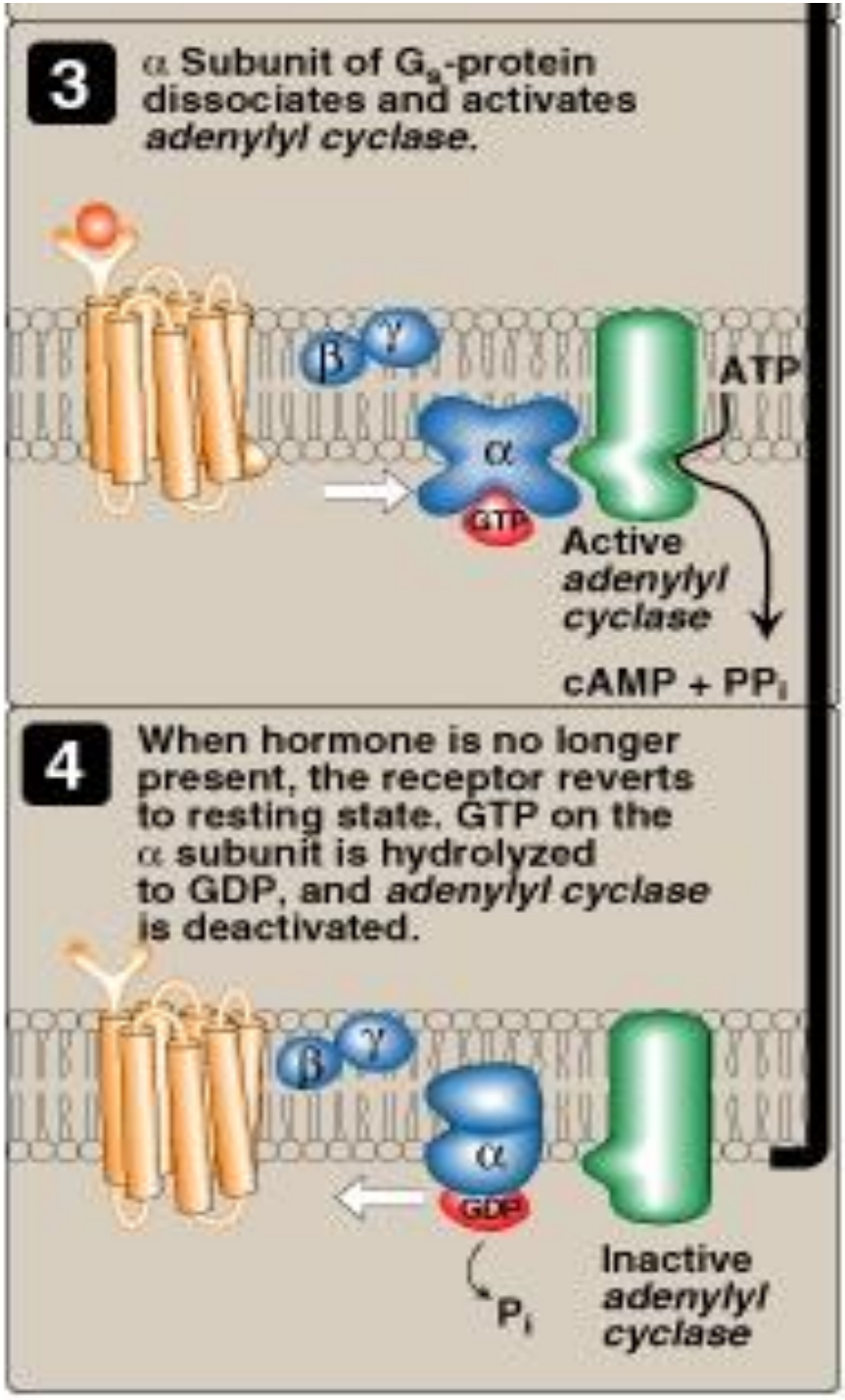
Commonly used mechanisms of communication between cells

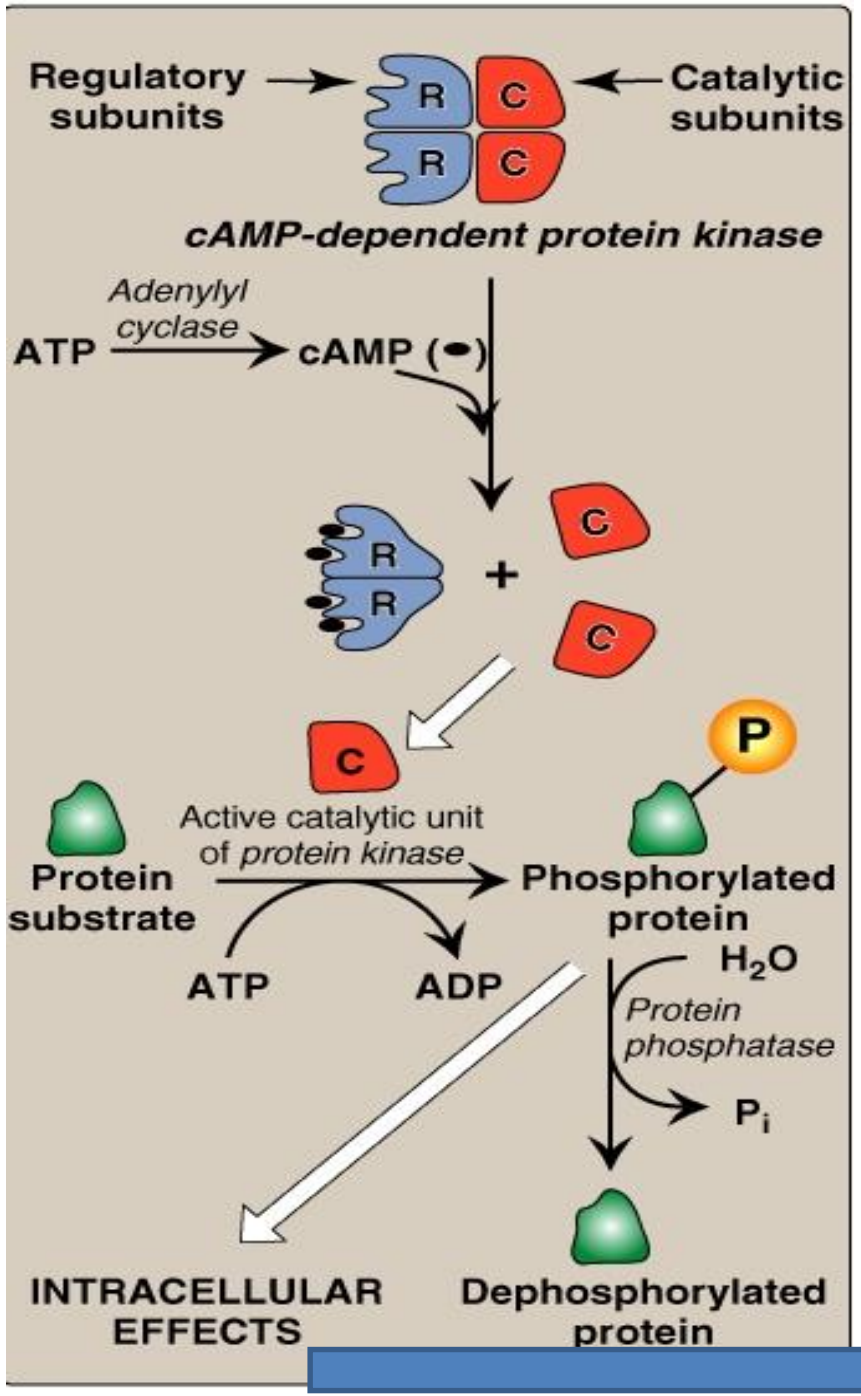
Communication between Cells through Receptors- GPCR



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
GDP
GTP
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

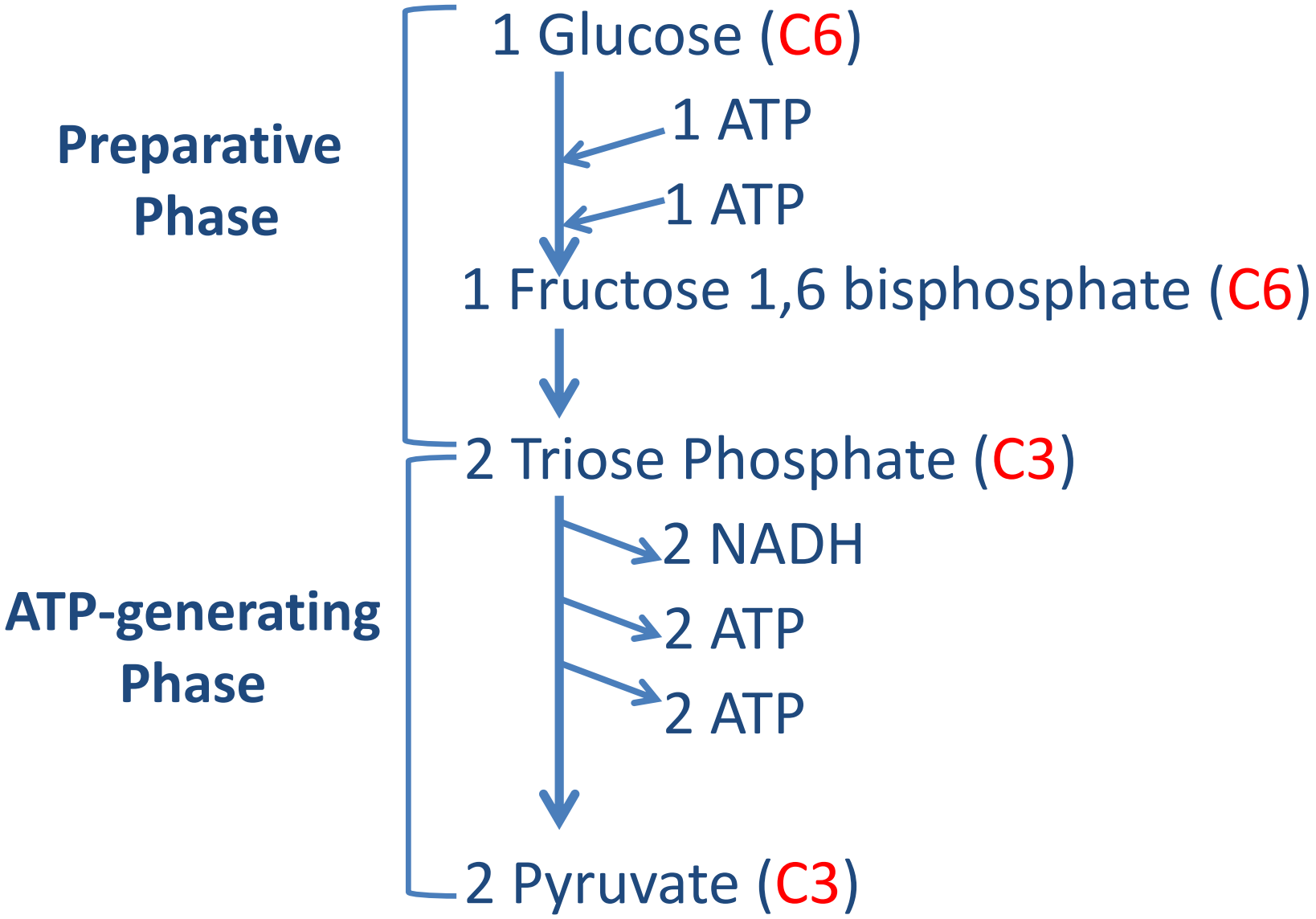
✓ Breakdown of glucose to pyruvate

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

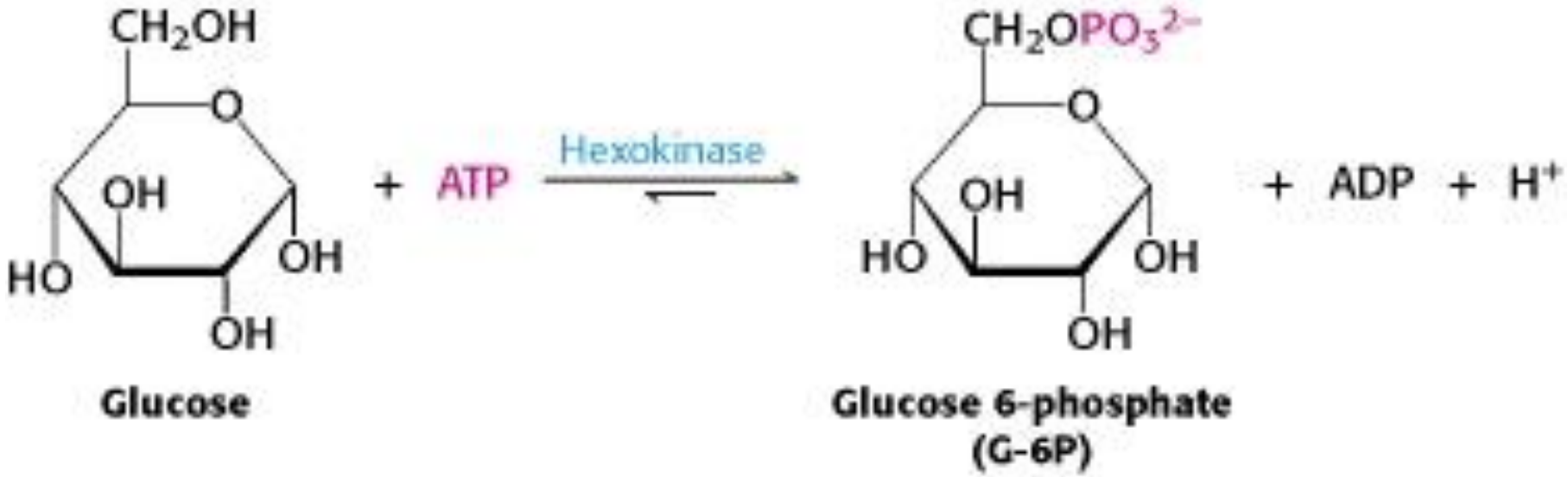


Types of Glycolytic Reactions

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

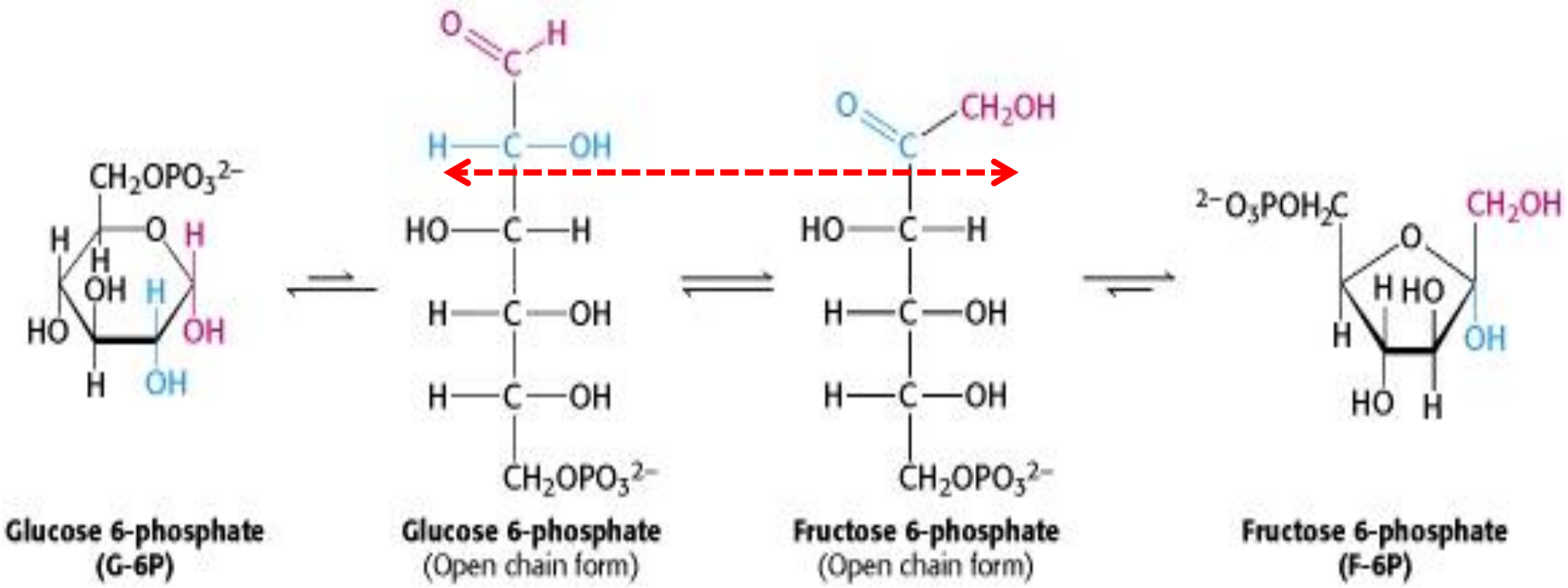
Steps of Glycolysis

Step 1



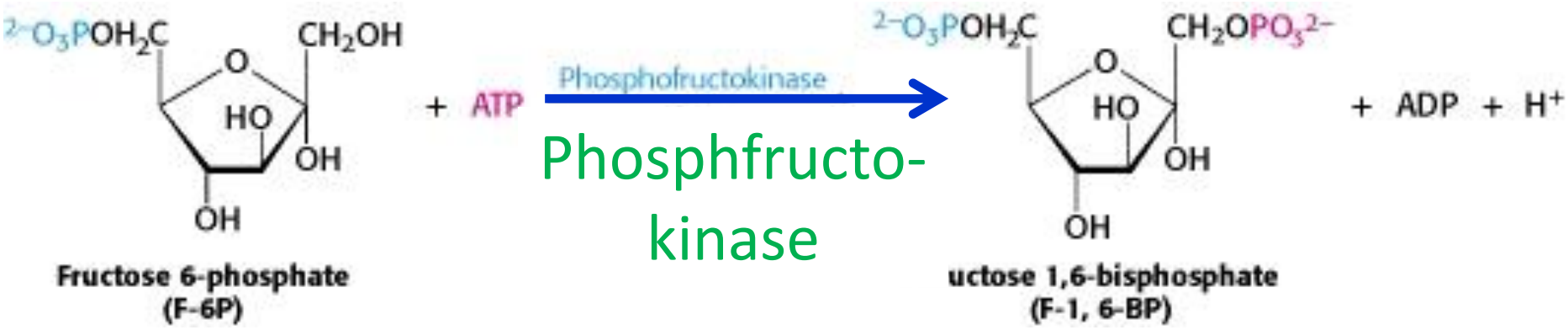
	Hexokinase	Glucokinase
Occurrence	In all tissues	In liver
Km	< 0.02 mM	10-20 mM
Specificity	Glc., Fruc, Man, Gal	Glc.
induction	Not induced	↑ insulin, Glc
Function	At any glucose level	Only > 100 mg/dl

Step 2

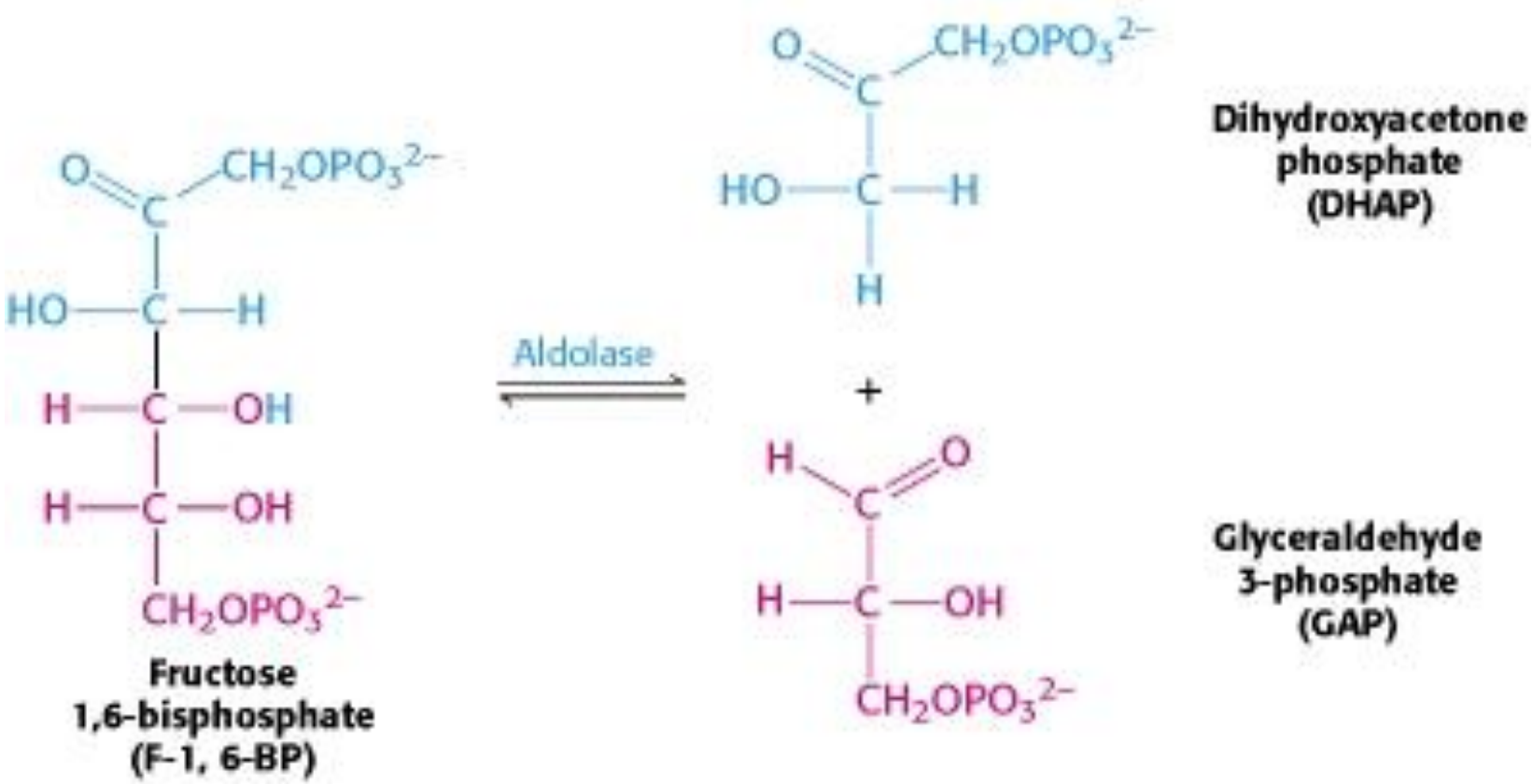


Phosphoglucose Isomerase

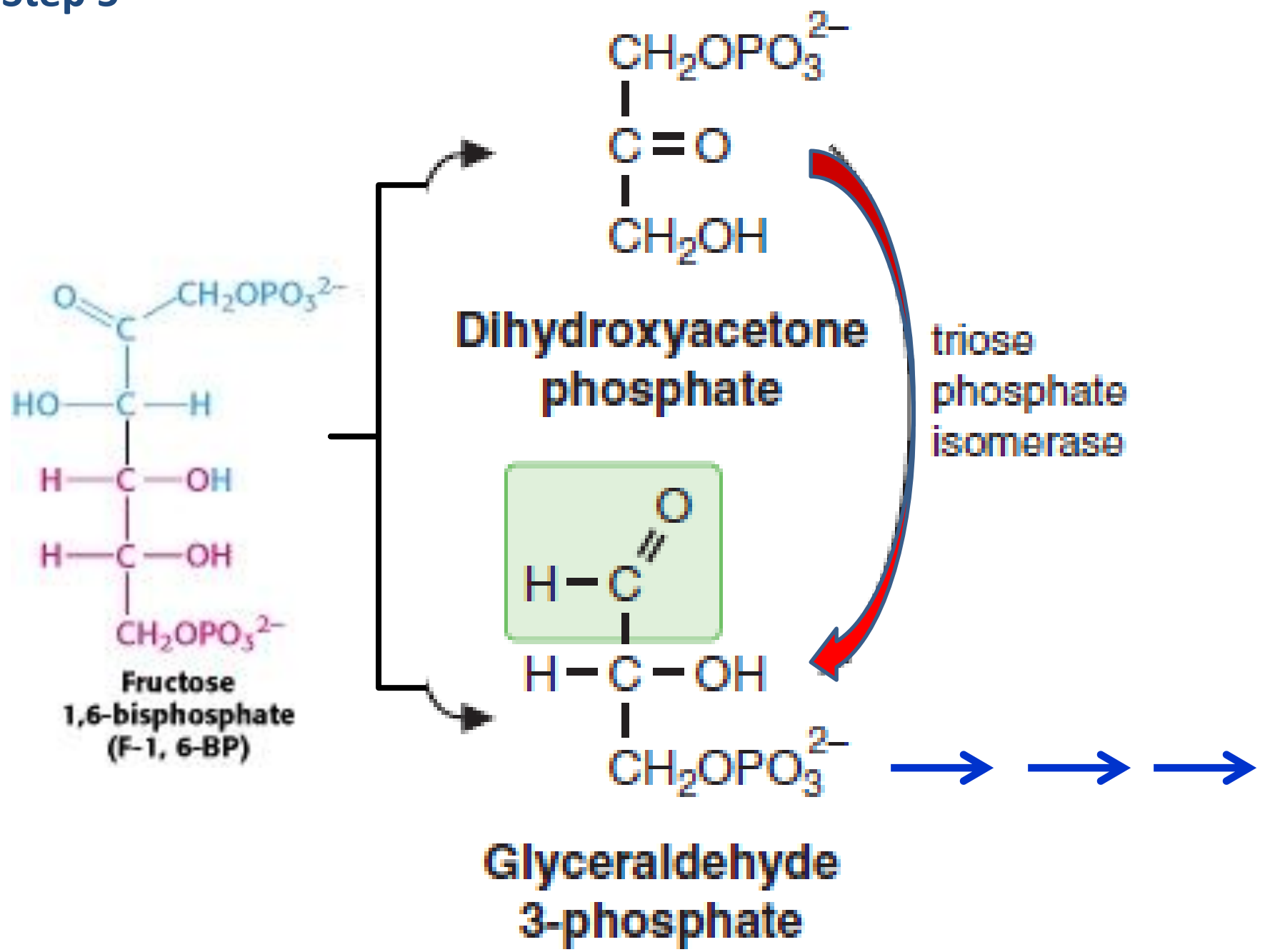
Step 3


$^{2-}O_3POH_2C$
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^+

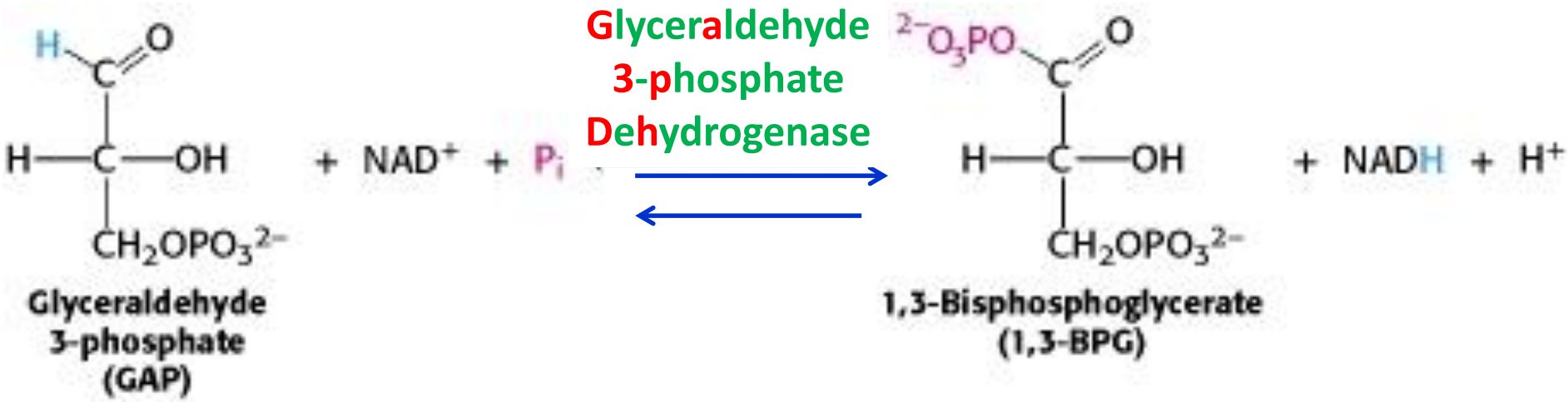
Step 4


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

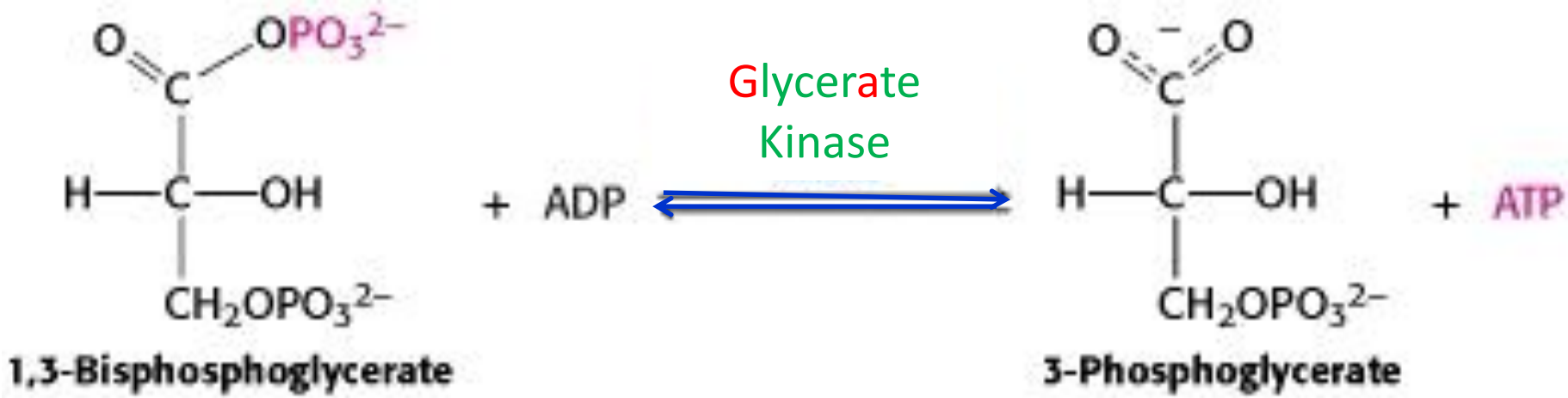
Step 5


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

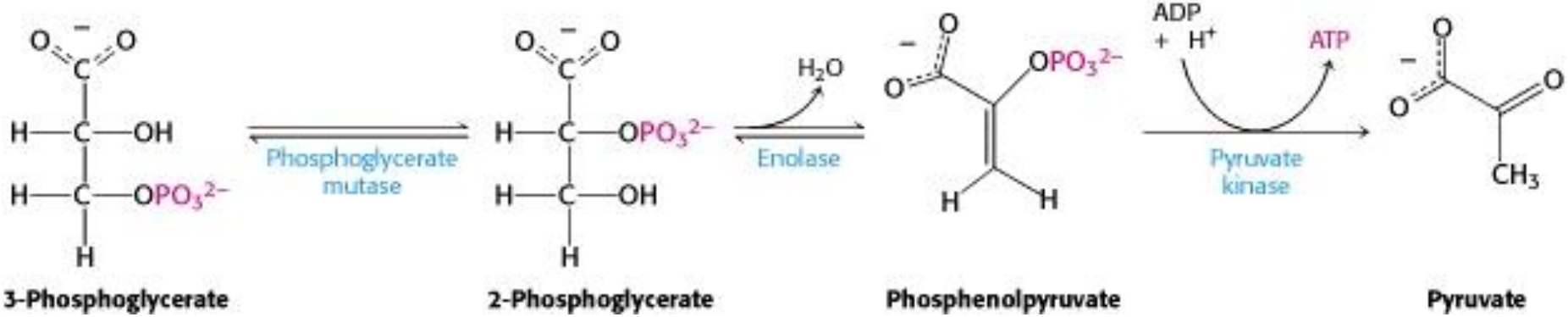
Step 6


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

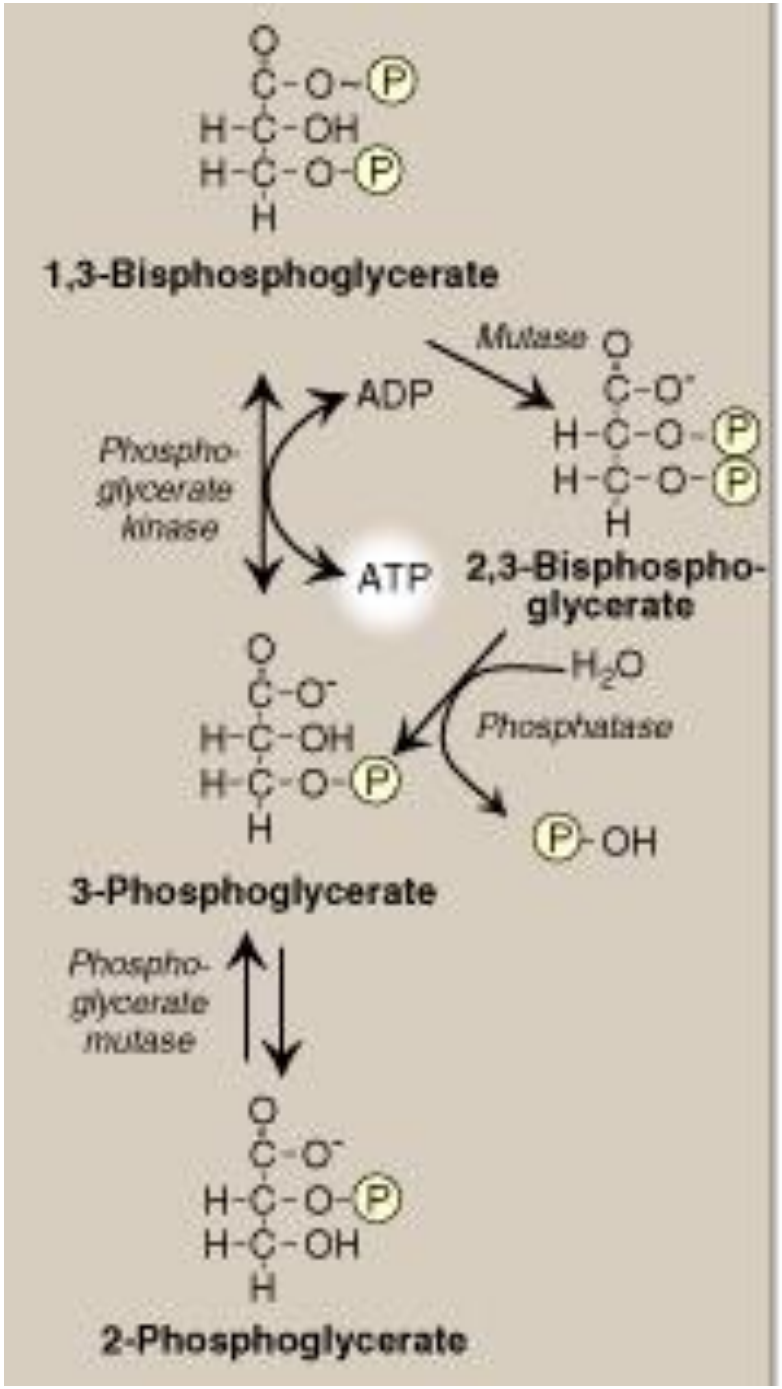
Step 8-10

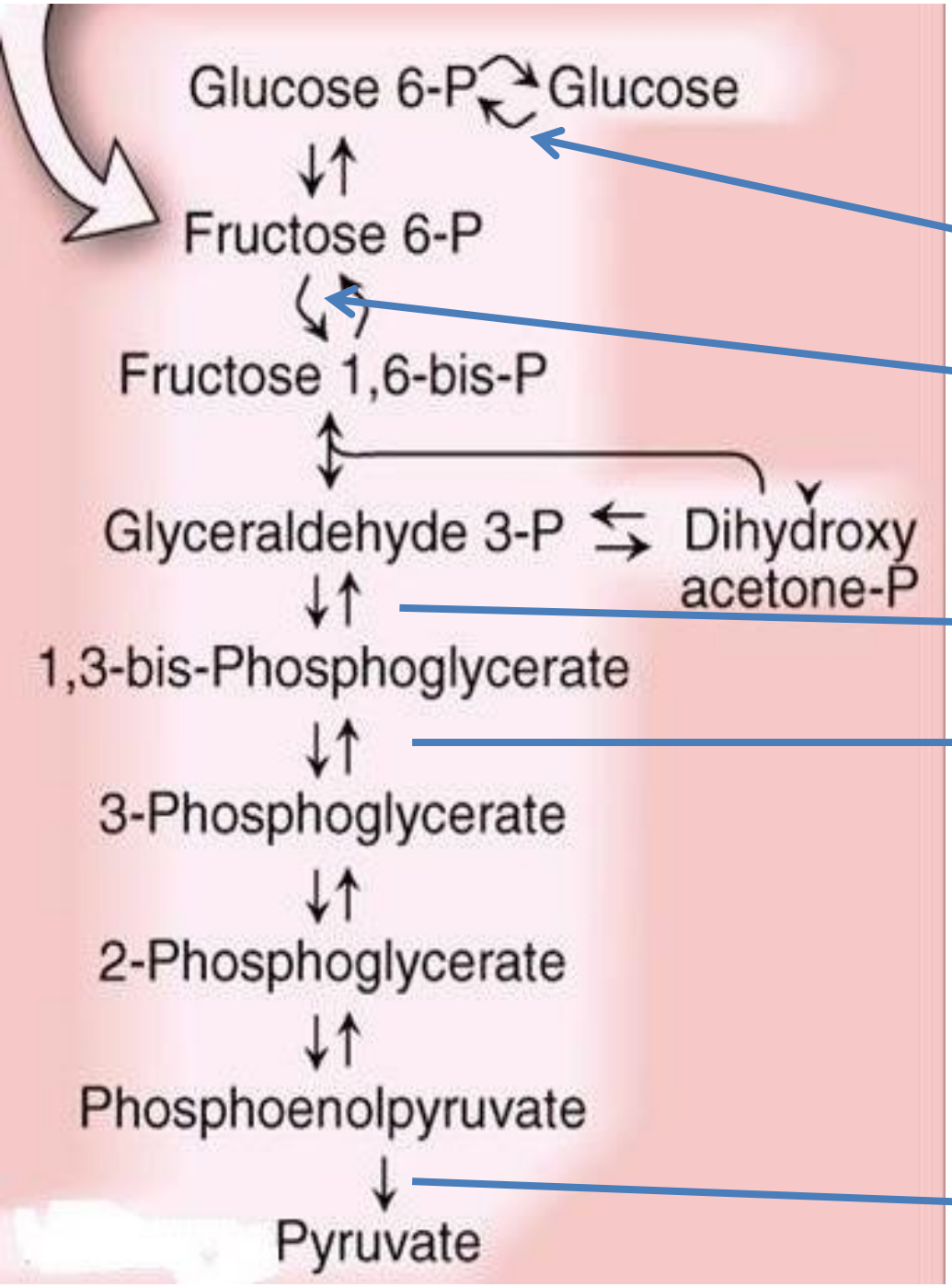

Phosphoglycerate mutase
Enolase
H_2O
ADP + H^+
ATP
Pyruvate kinase
3-Phosphoglycerate
2-Phosphoglycerate
Phosphenolpyruvate
Pyruvate

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

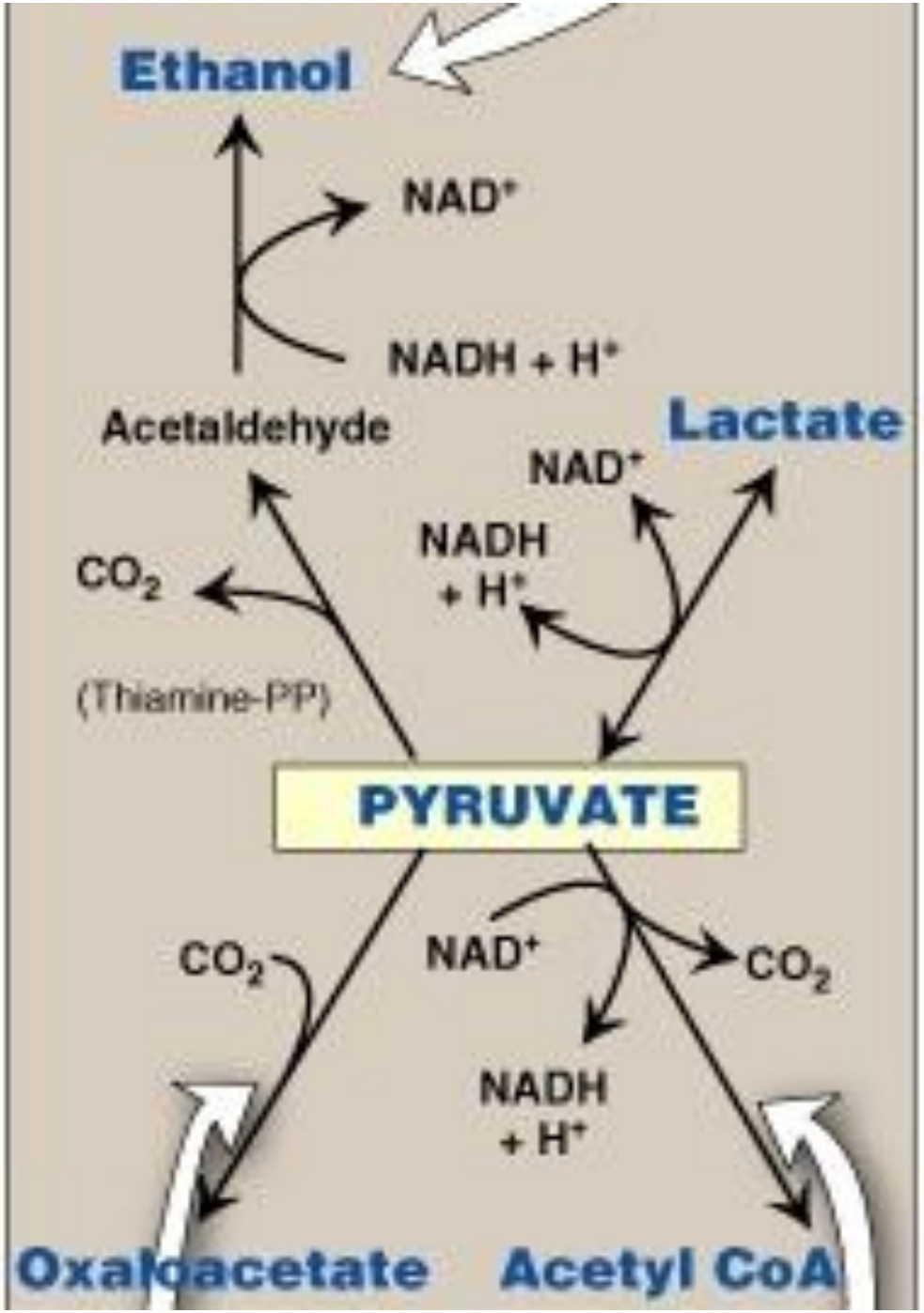
-ATP

2 NADH

2 ATP

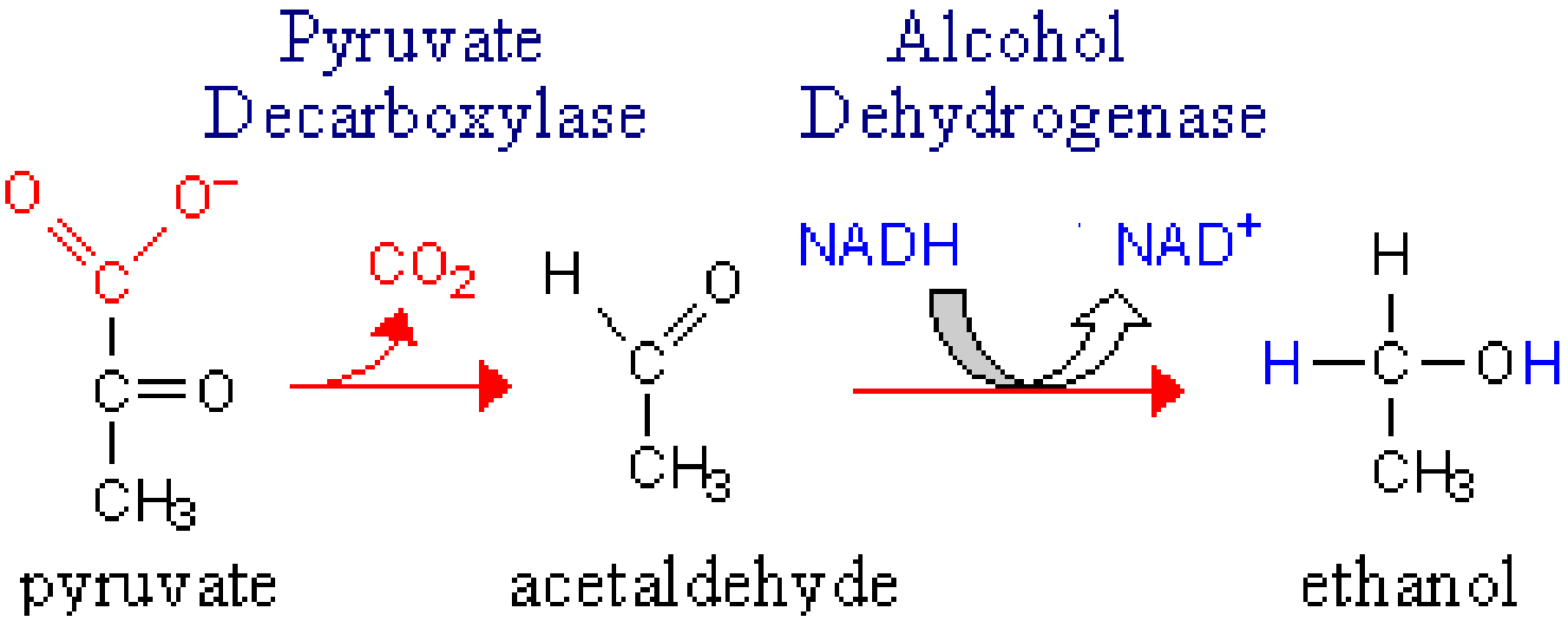
Is Oxygen needed?

2ATP

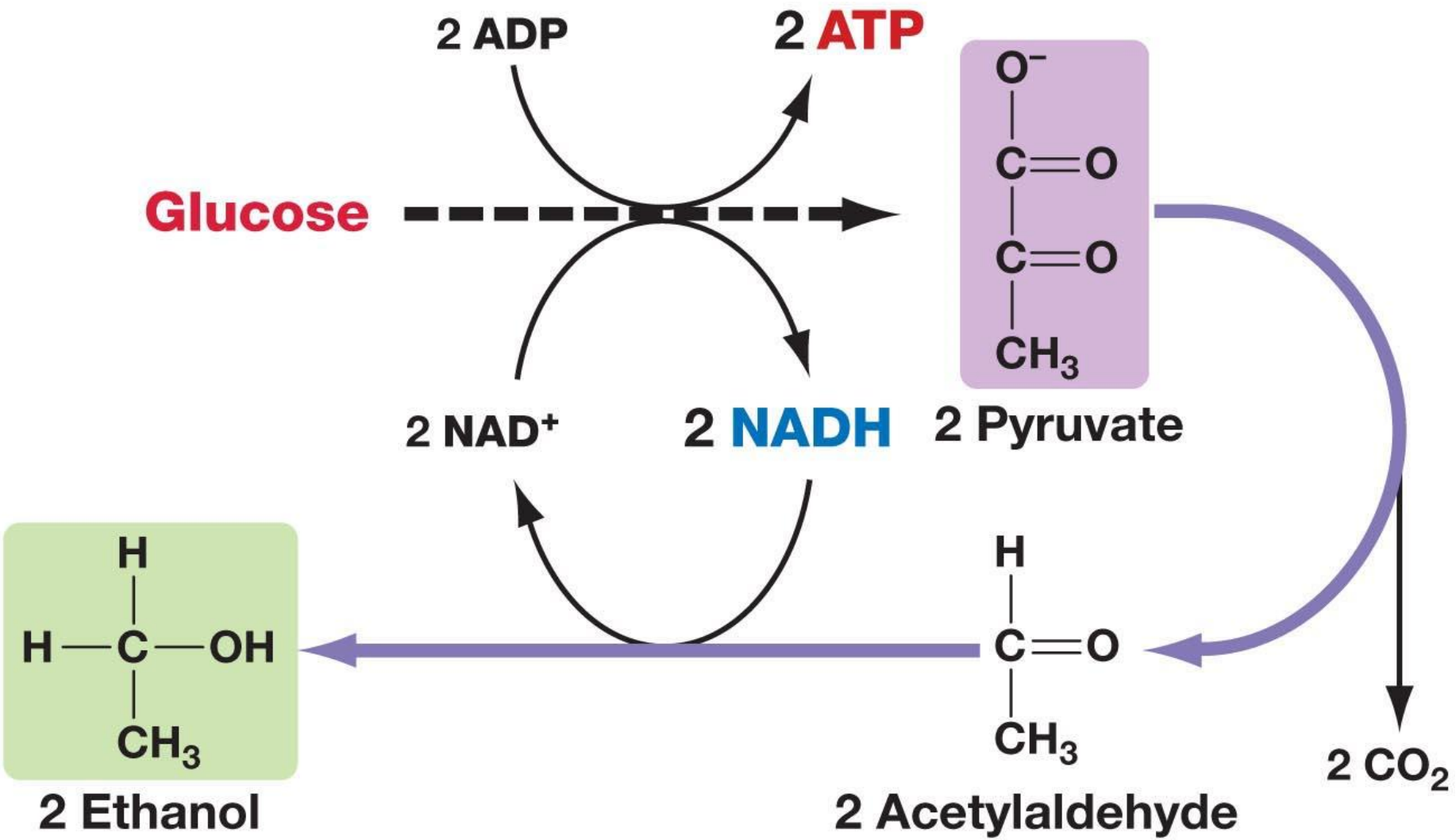


Pyruvate Fates

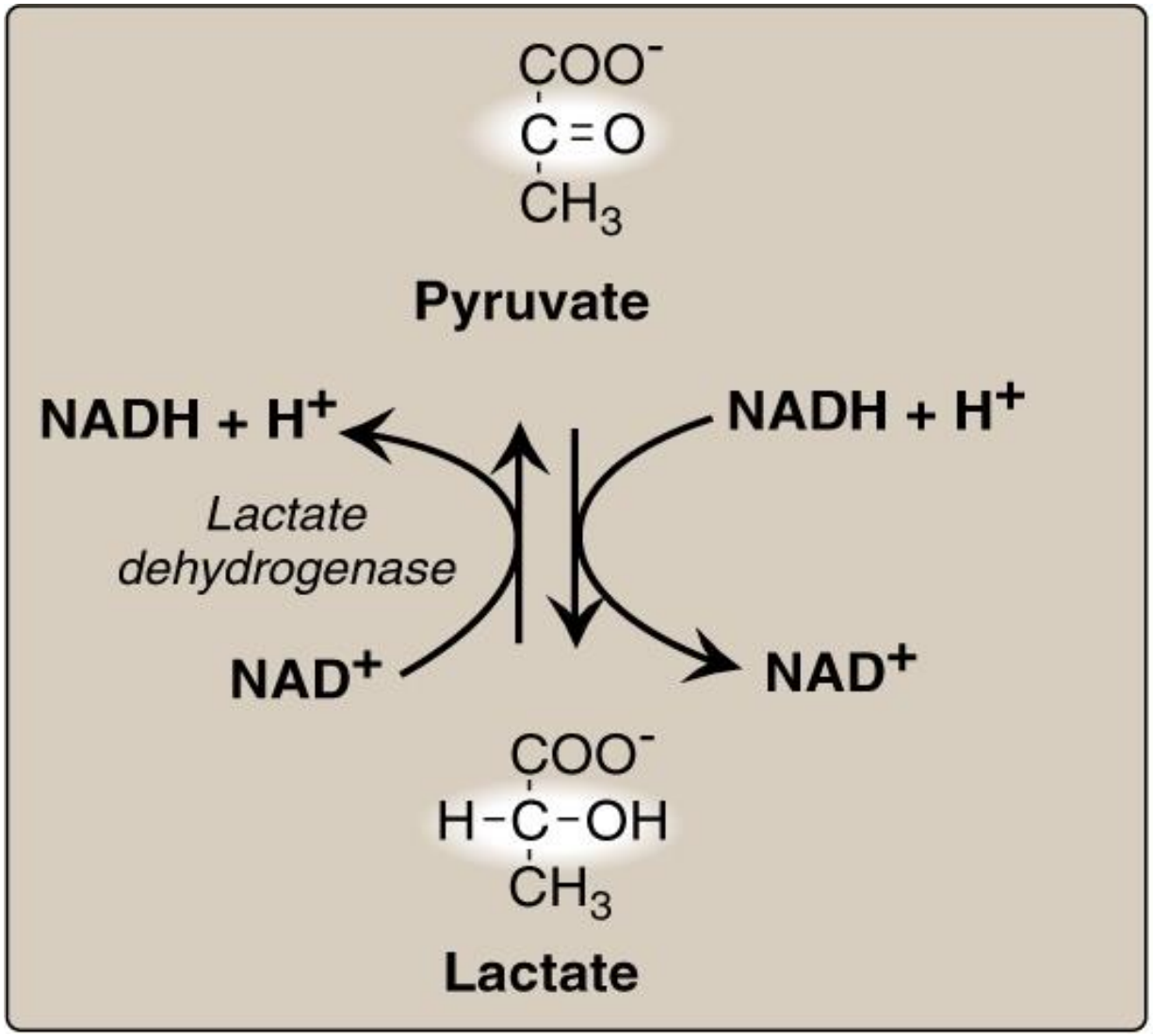
From Pyruvate to Ethanol



(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

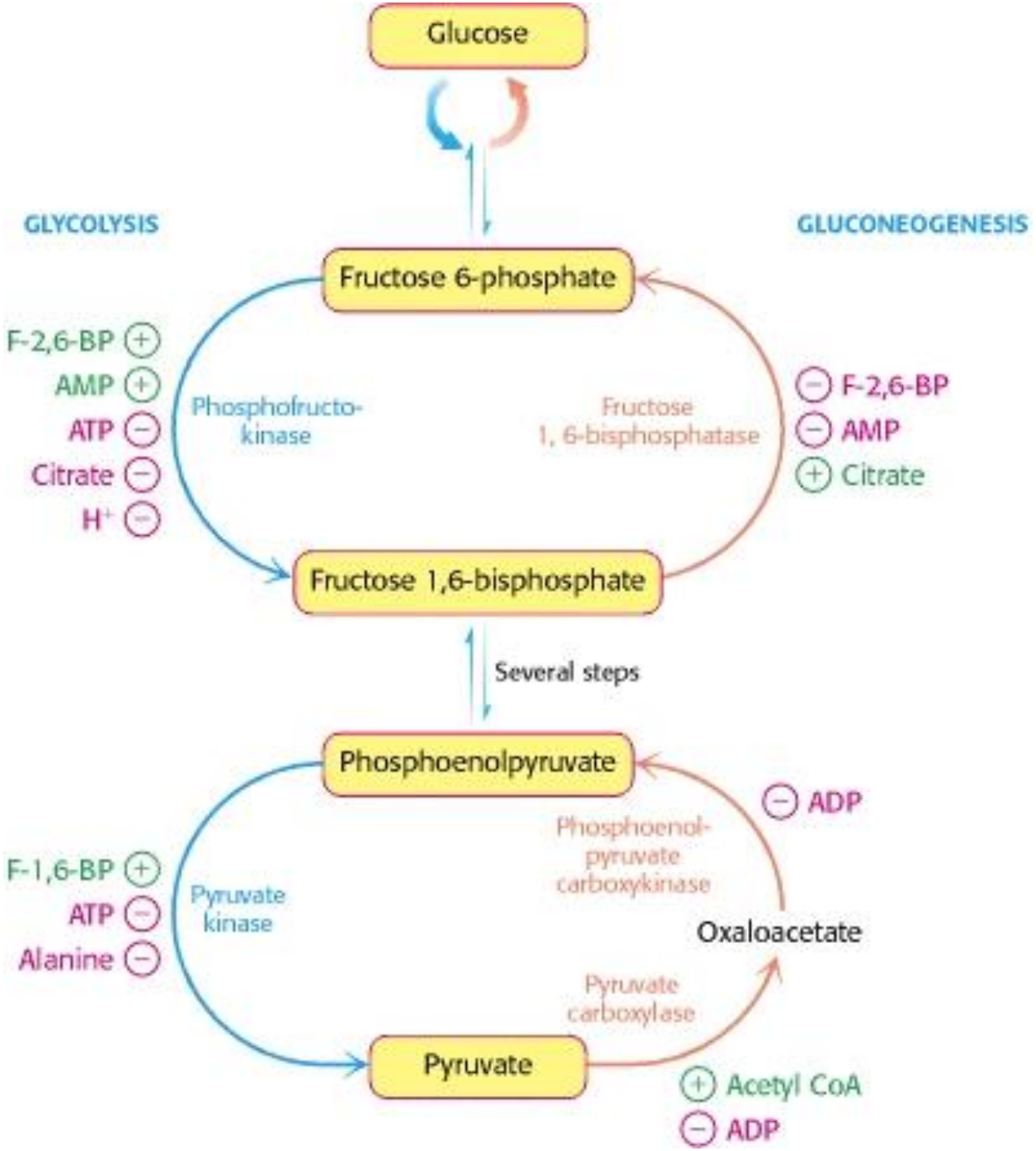
- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired O_2 transport
  - Respiratory failure
  - Uncontrolled hemorrhage

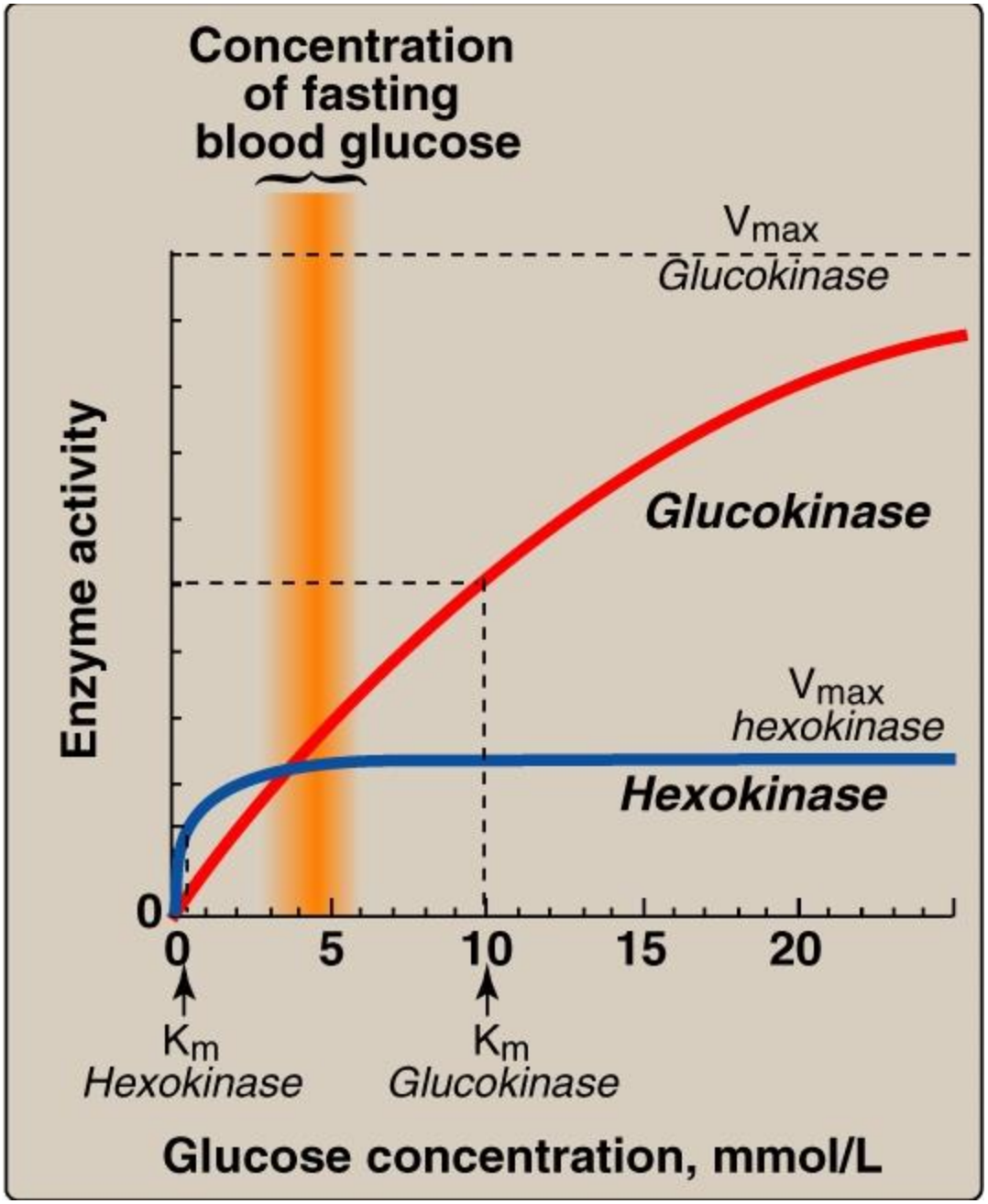
Clinical Hint: Lactic Acidosis

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

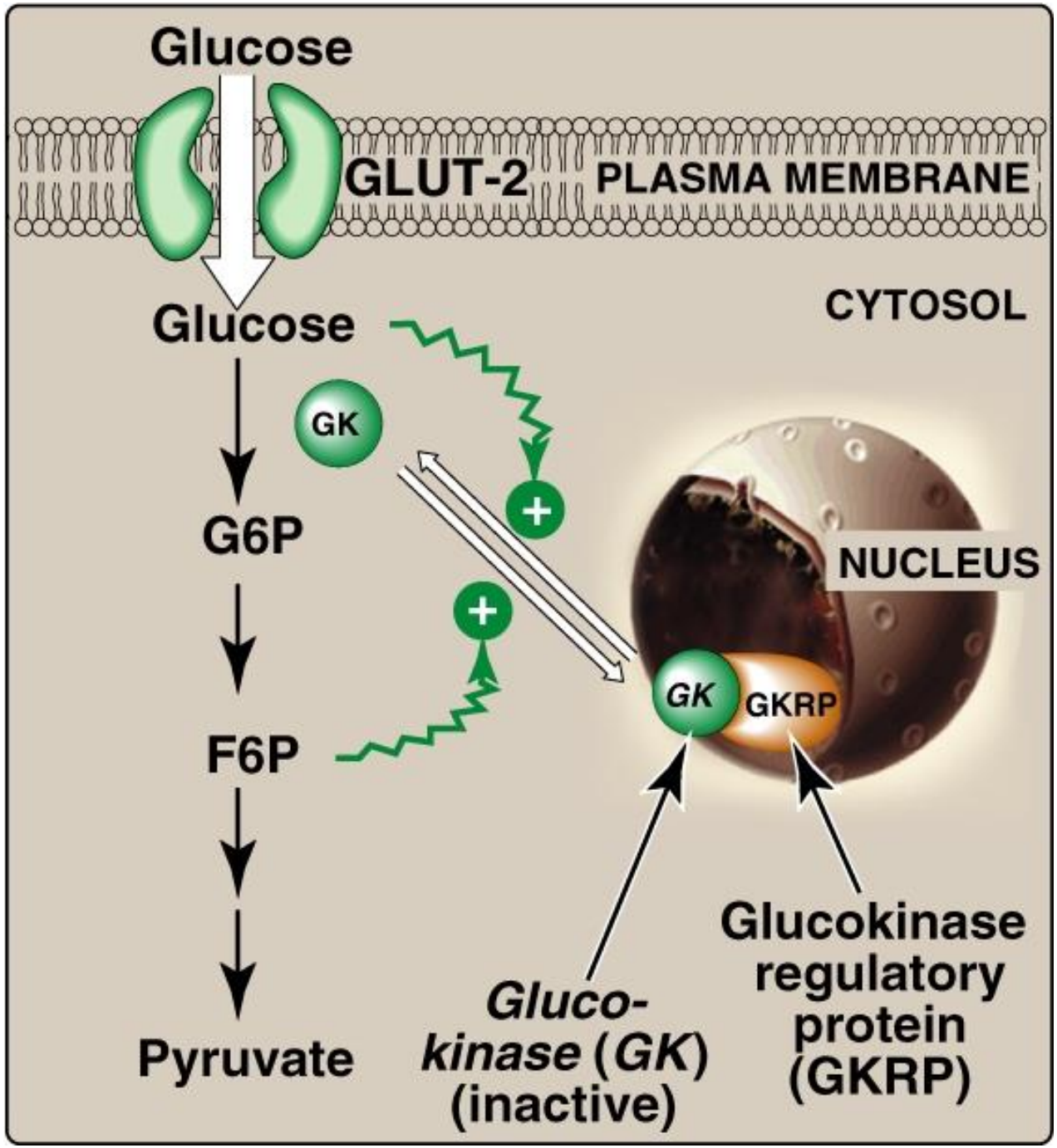
Regulation of Glycolysis

Regulators of PFK and PK

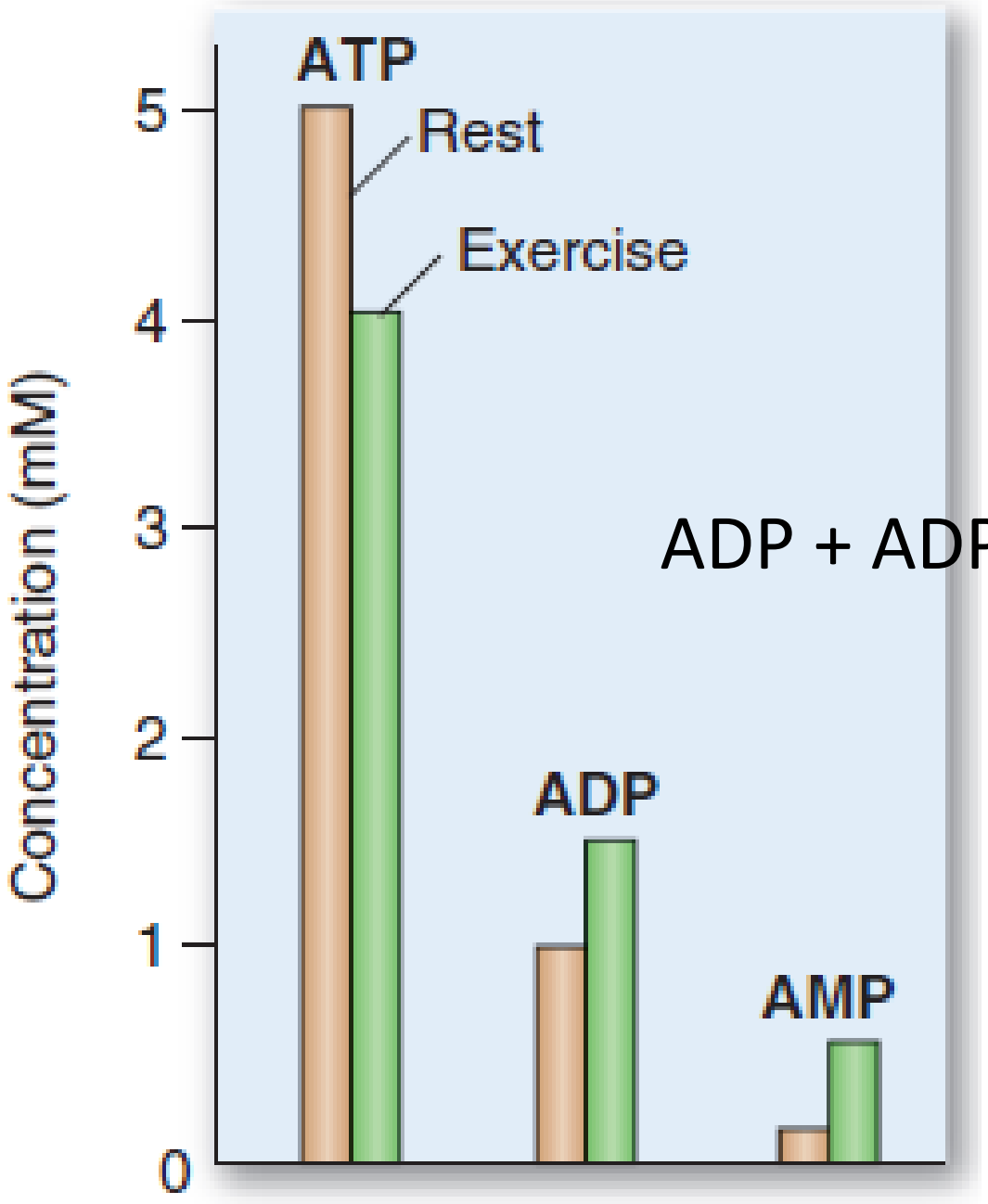




Glucokinase and Hexokinase Activity

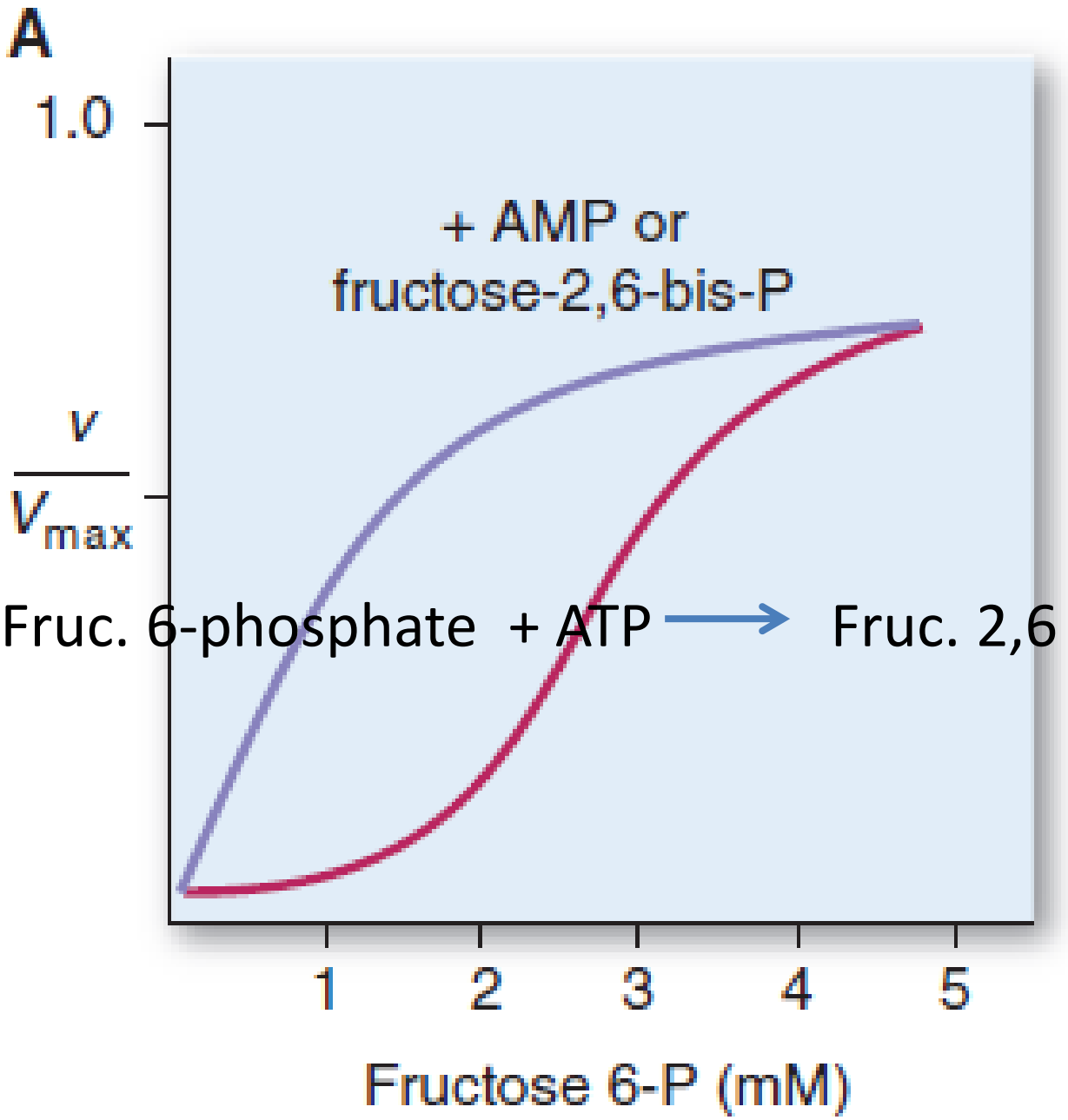


Glucokinase Regulation



Regulation by ATP and AMP

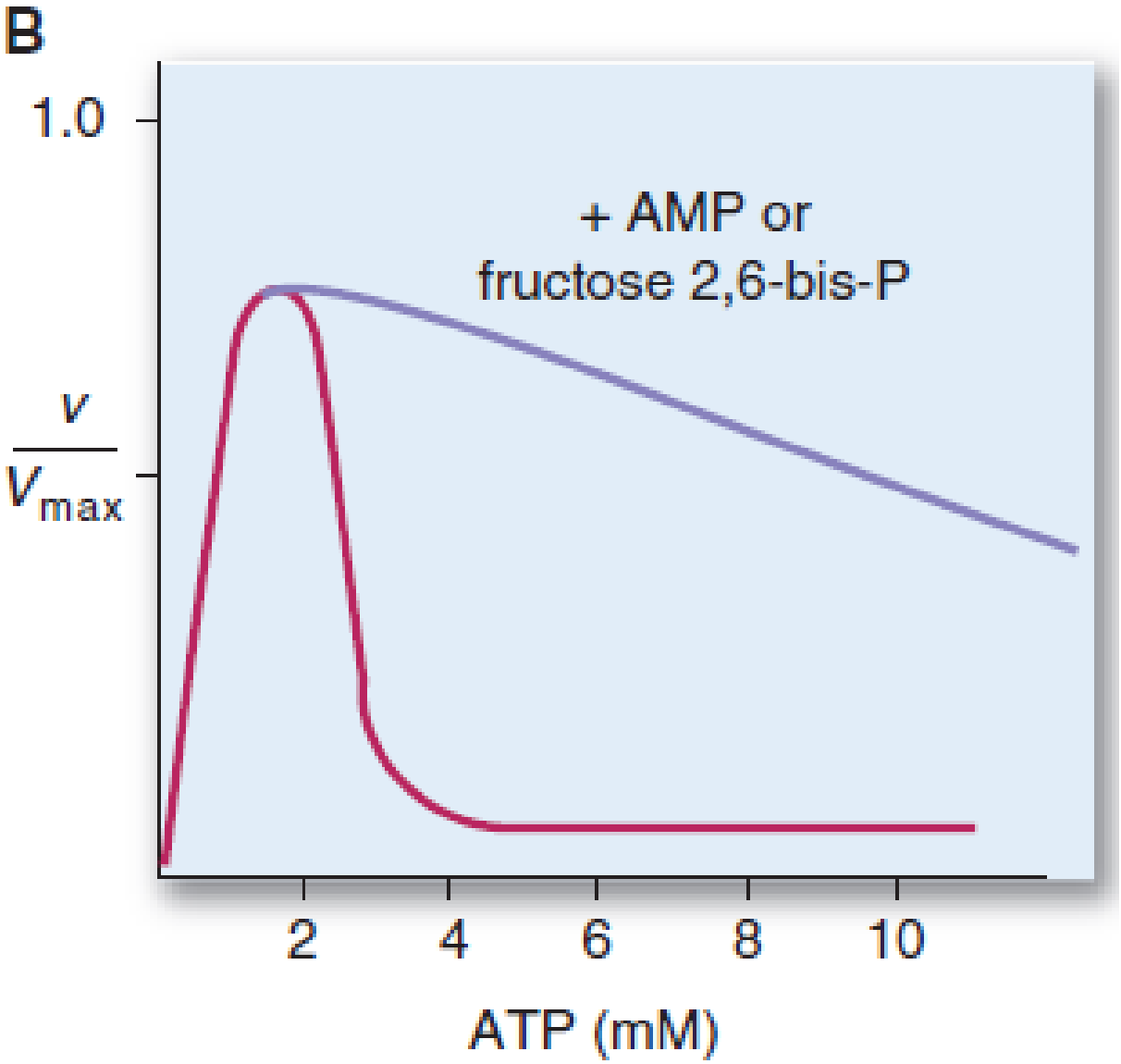
ADP + ADP $\rightleftharpoons$ ATP + AMP



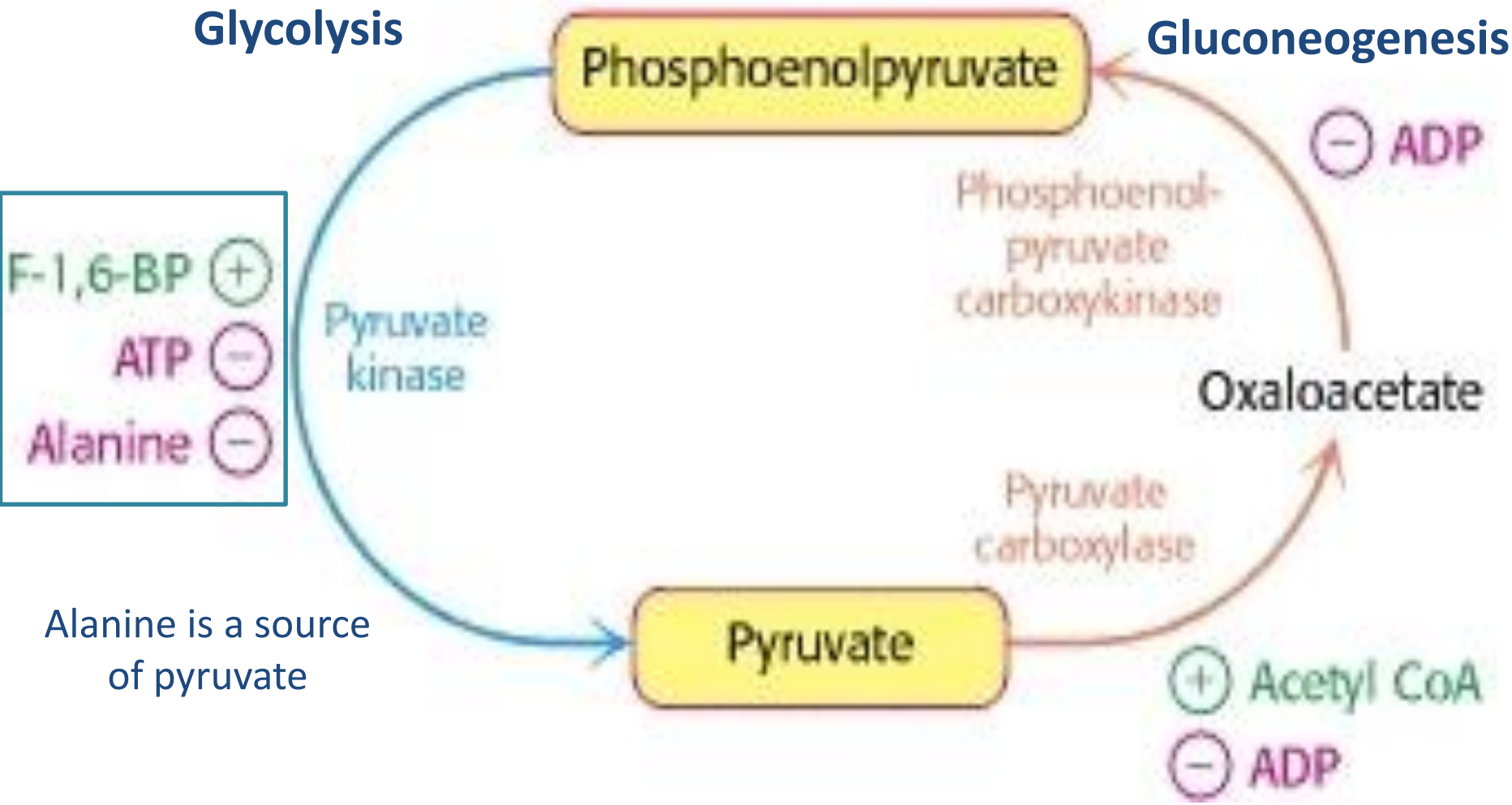
Regulation of PFK by Fructose 2,6-bisphosphate

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

How about the other substrate?

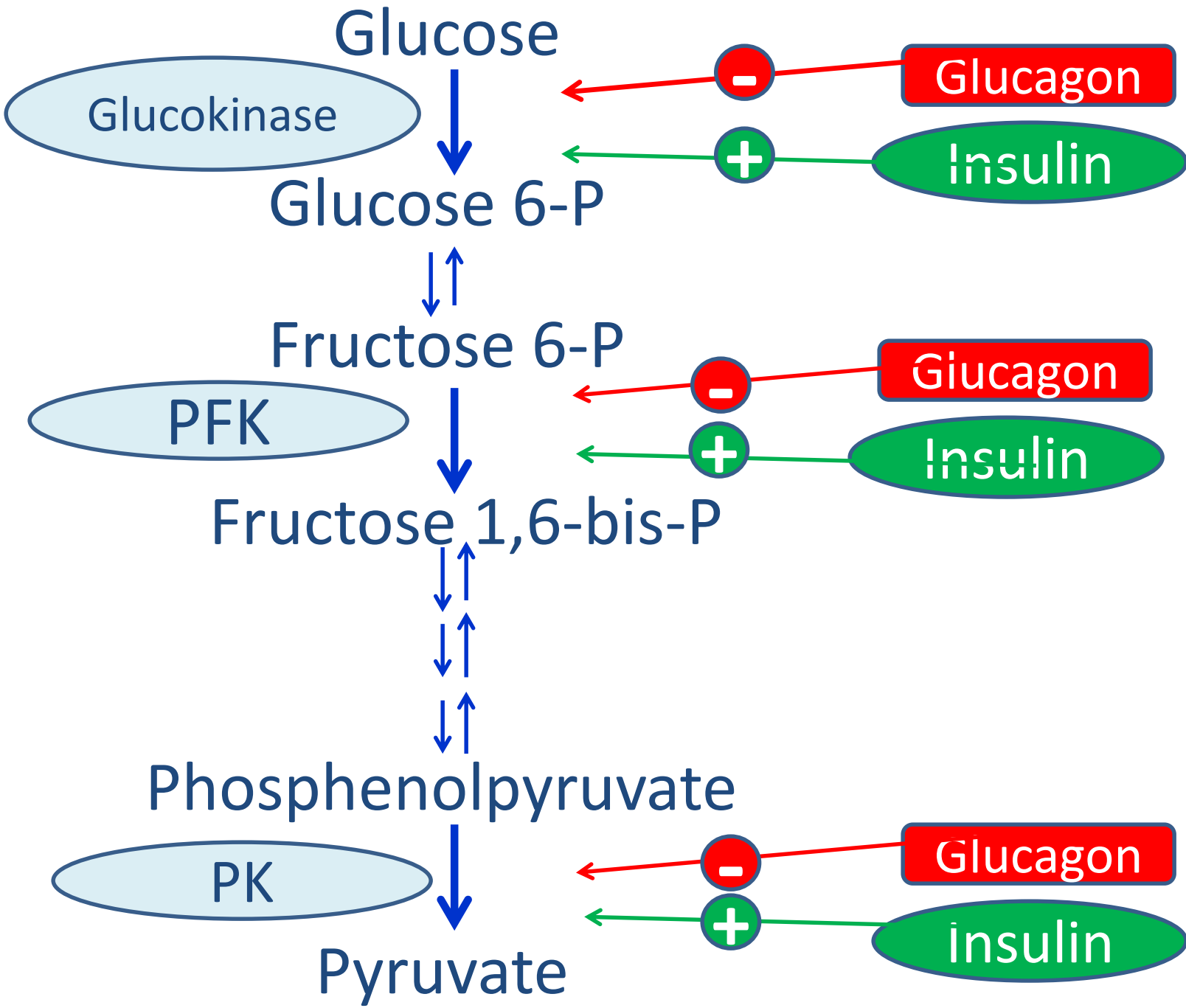


Regulation of Pyruvate Kinase

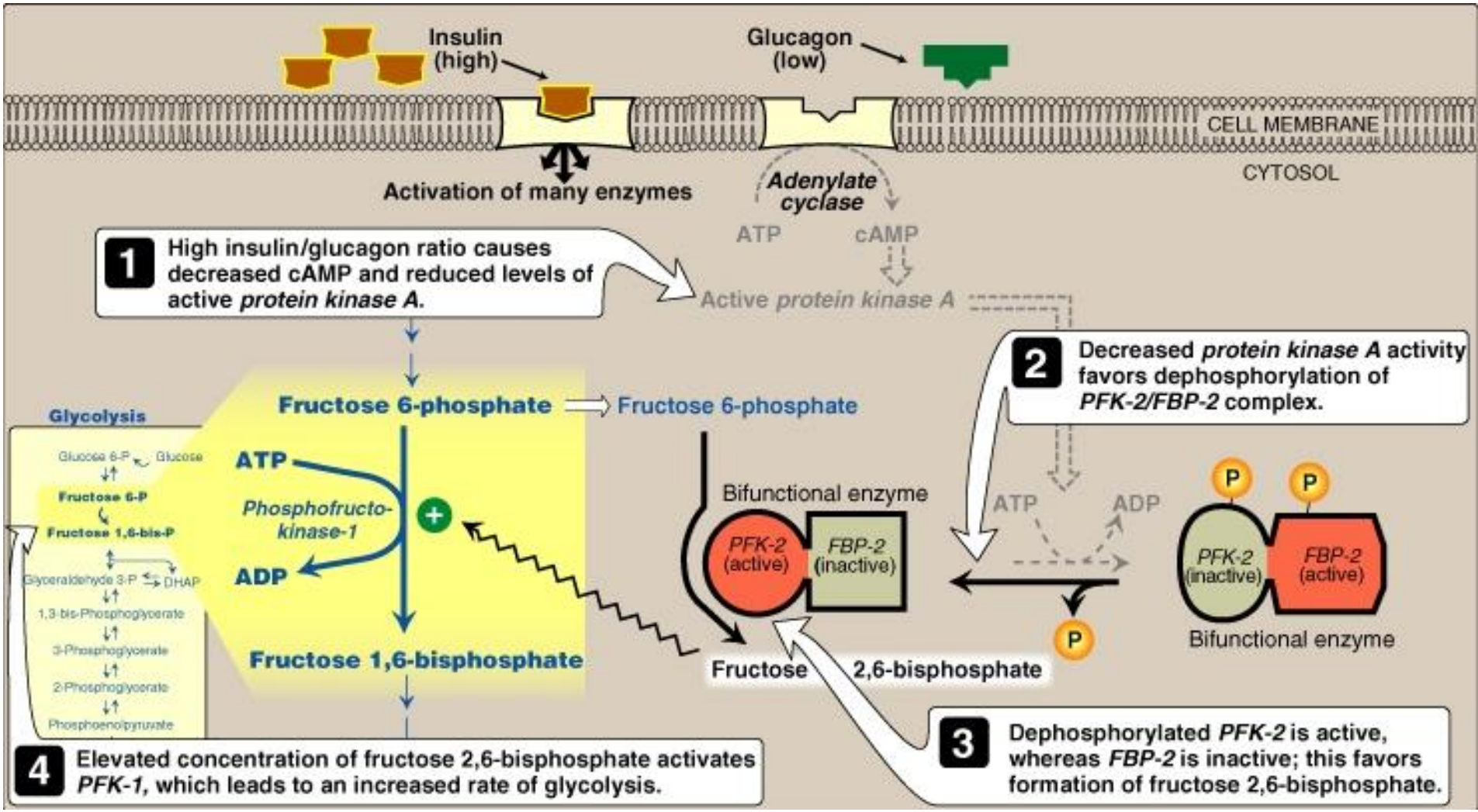


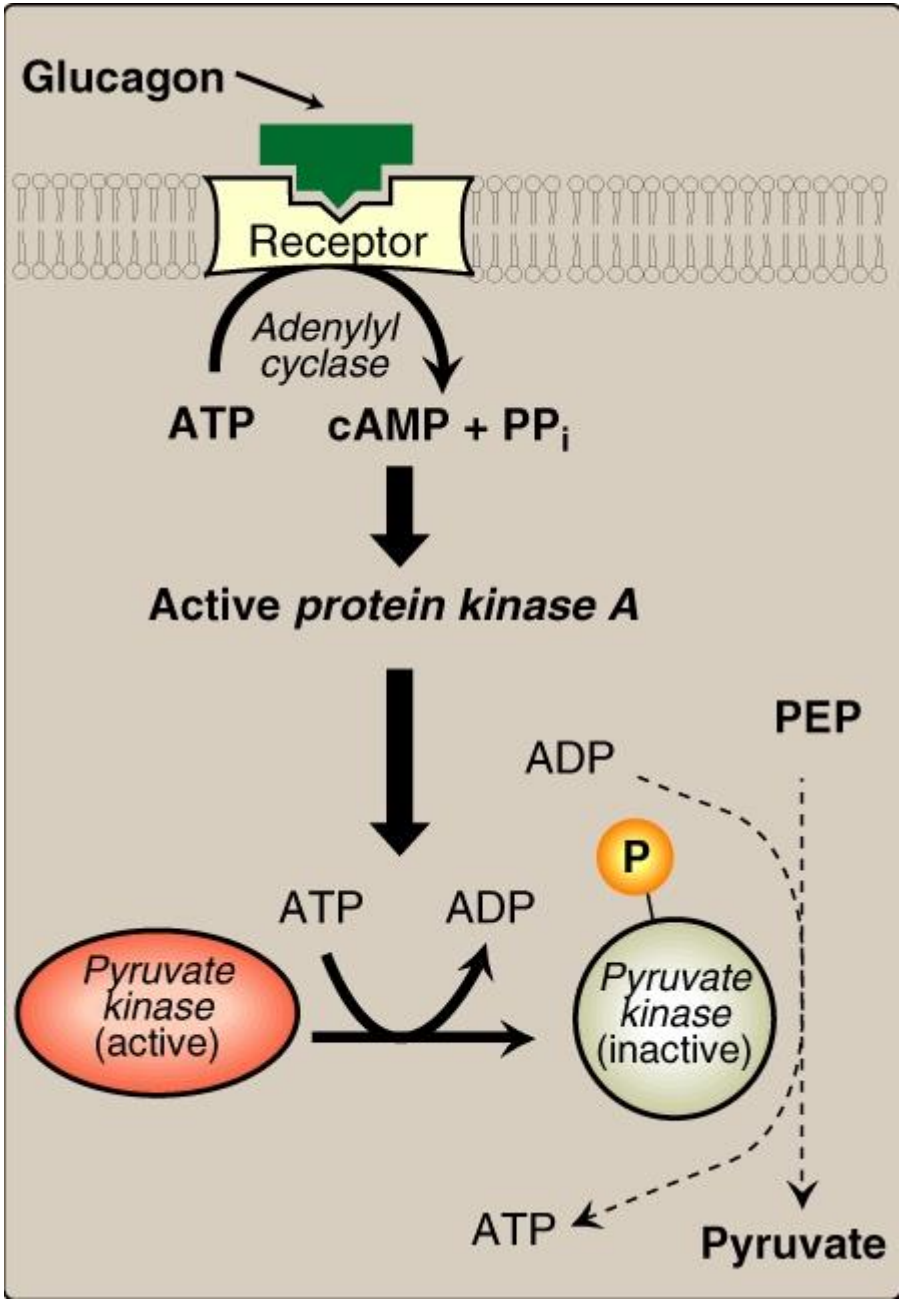
Alanine is a source of pyruvate

Hormonal Regulation



Hormonal Regulation of Phosphofructokinase

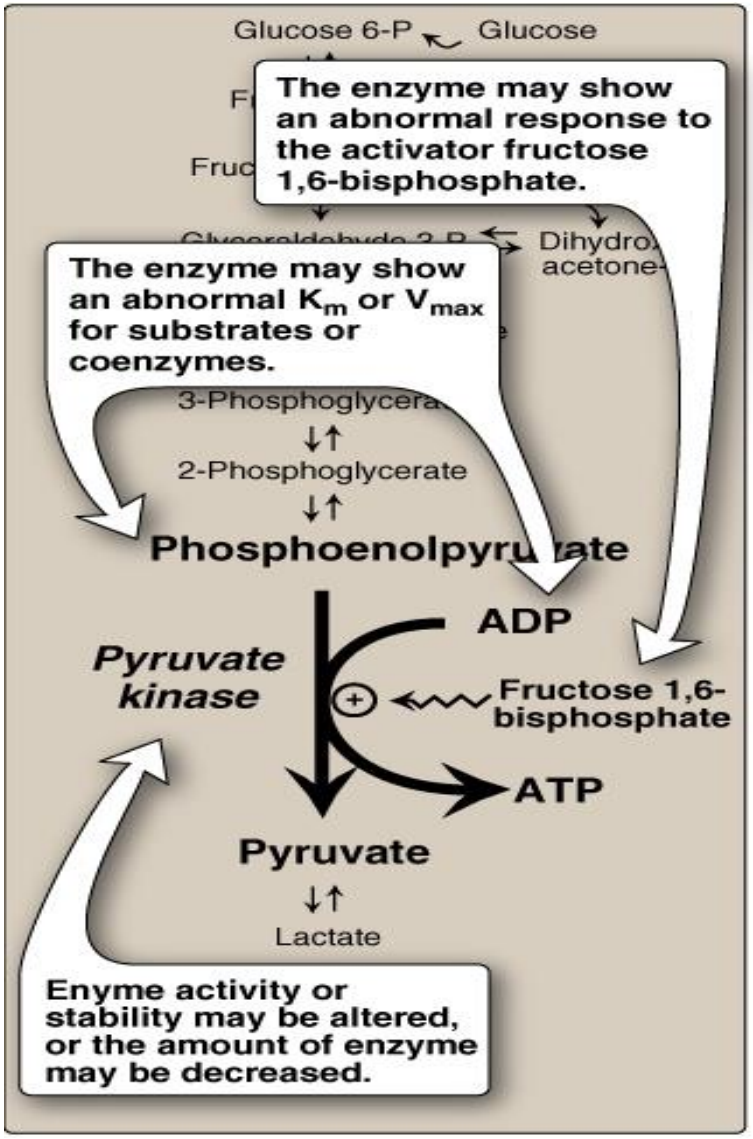




Hormonal Regulation of Pyruvate Kinase

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

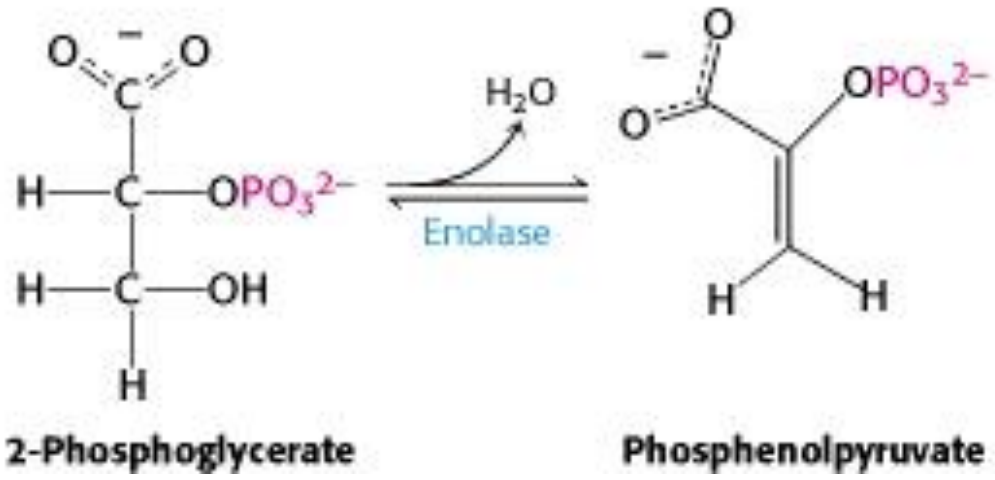


Alterations observed with various mutant forms of pyruvate kinase

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**