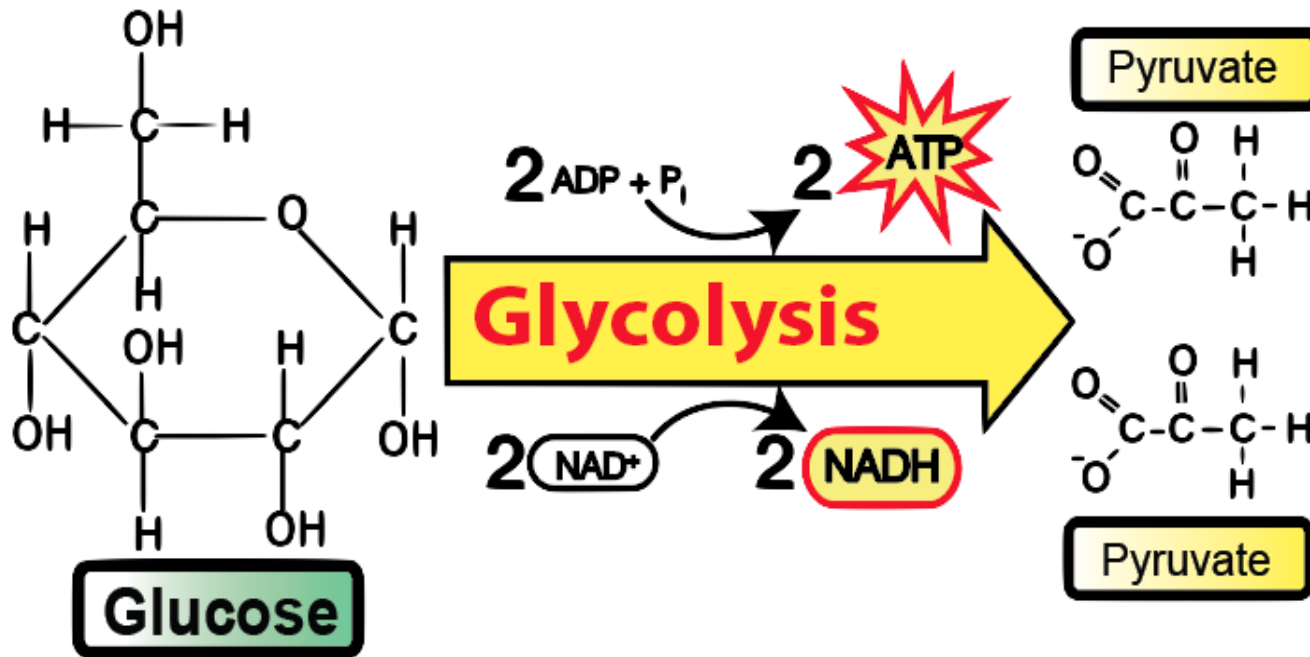




Glycolysis

Reactions and Regulation

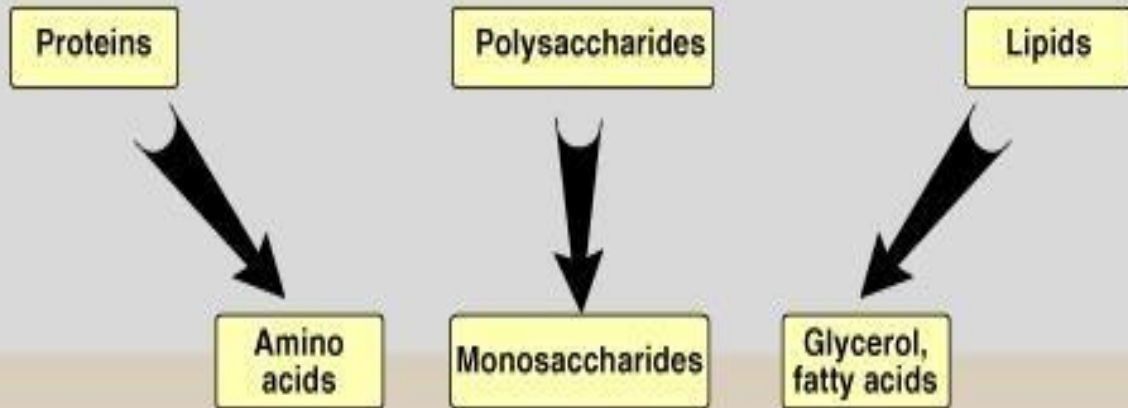


Dr. Diala Abu-Hassan

General Stages of Metabolism

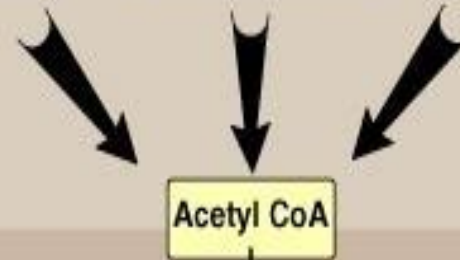
Stage I:

Hydrolysis of complex molecules to their component building blocks



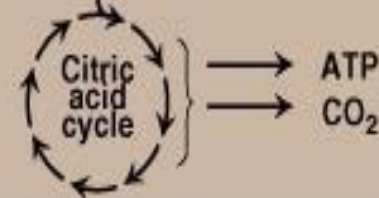
Stage II:

Conversion of building blocks to acetyl CoA (or other simple intermediates)

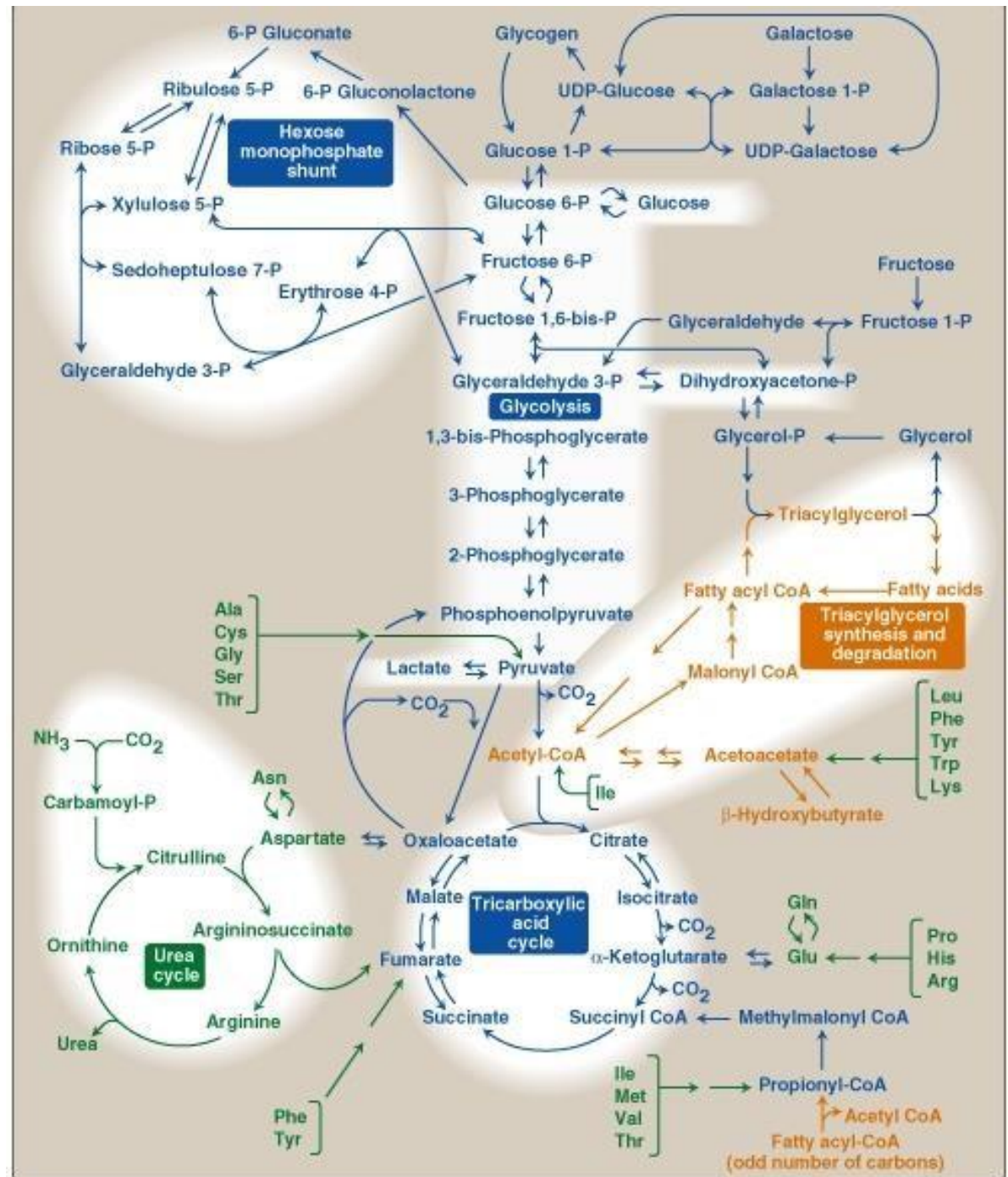


Stage III:

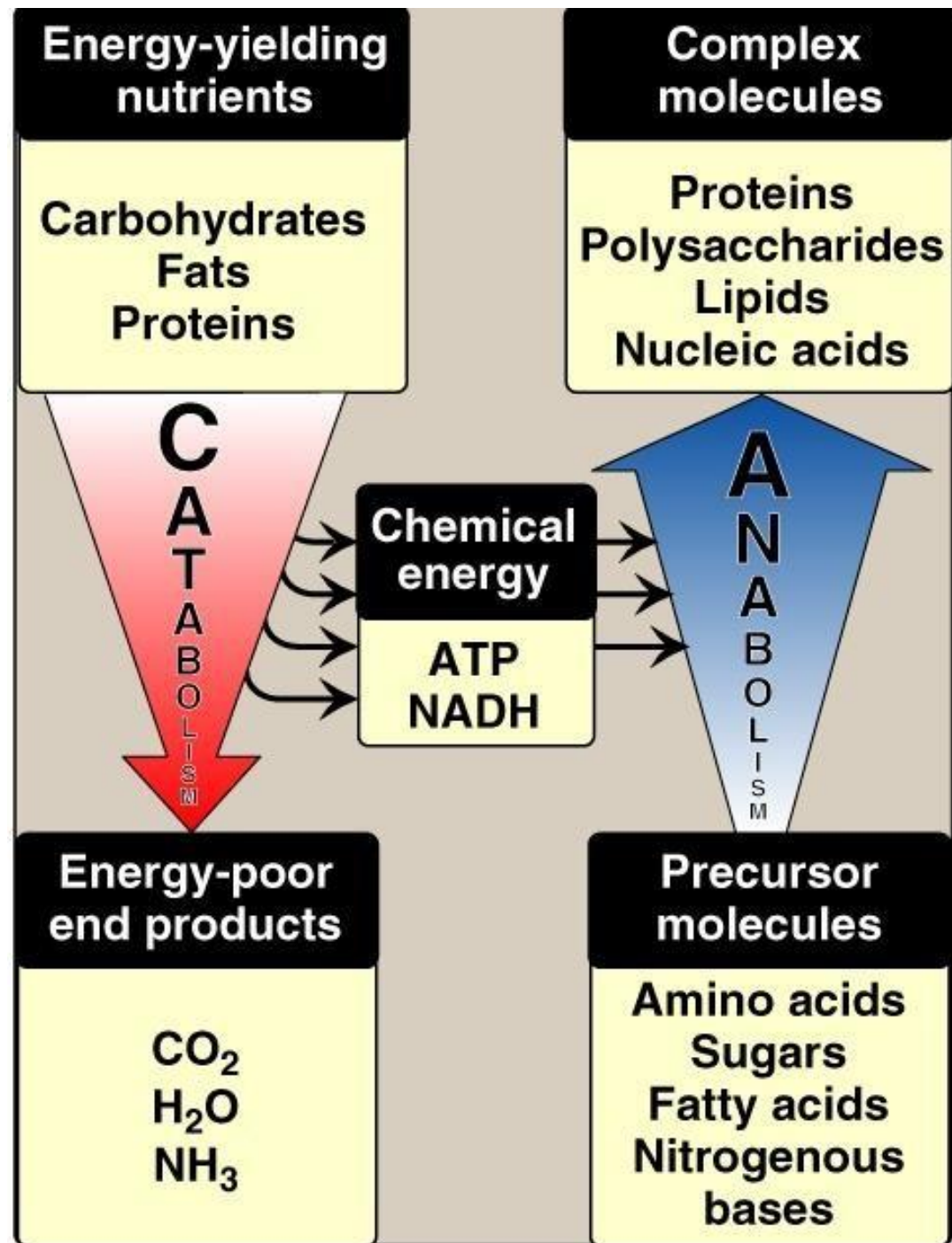
Oxidation of acetyl CoA; oxidative phosphorylation



Metabolic pathways intersect to form network of chemical reactions

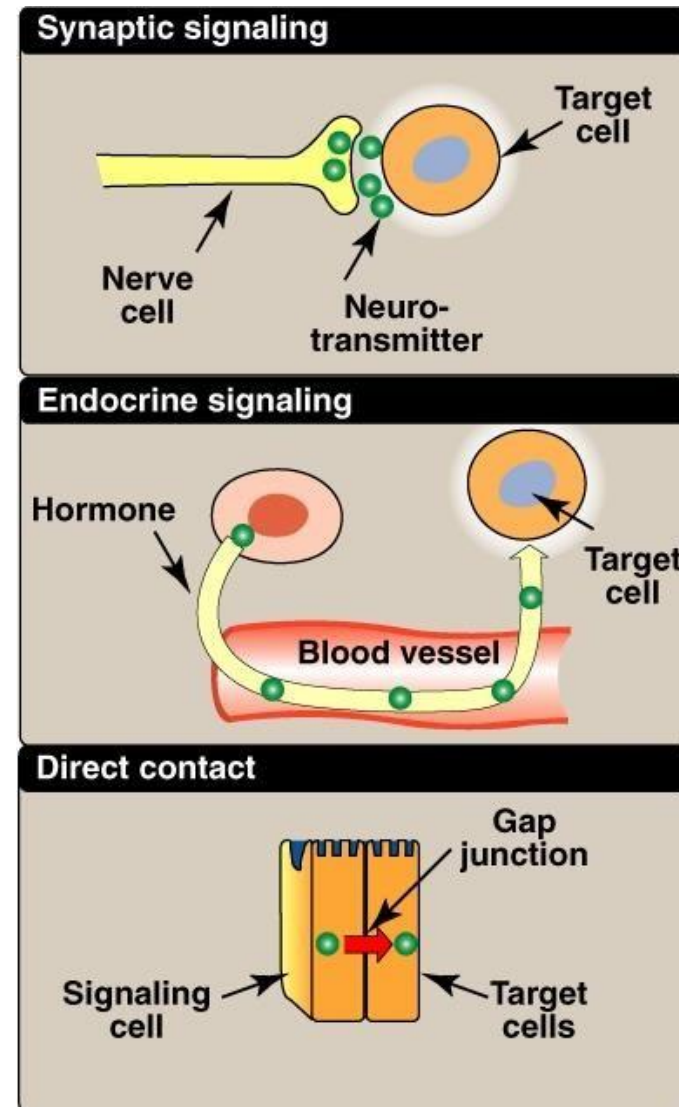


Types of Metabolic Pathways



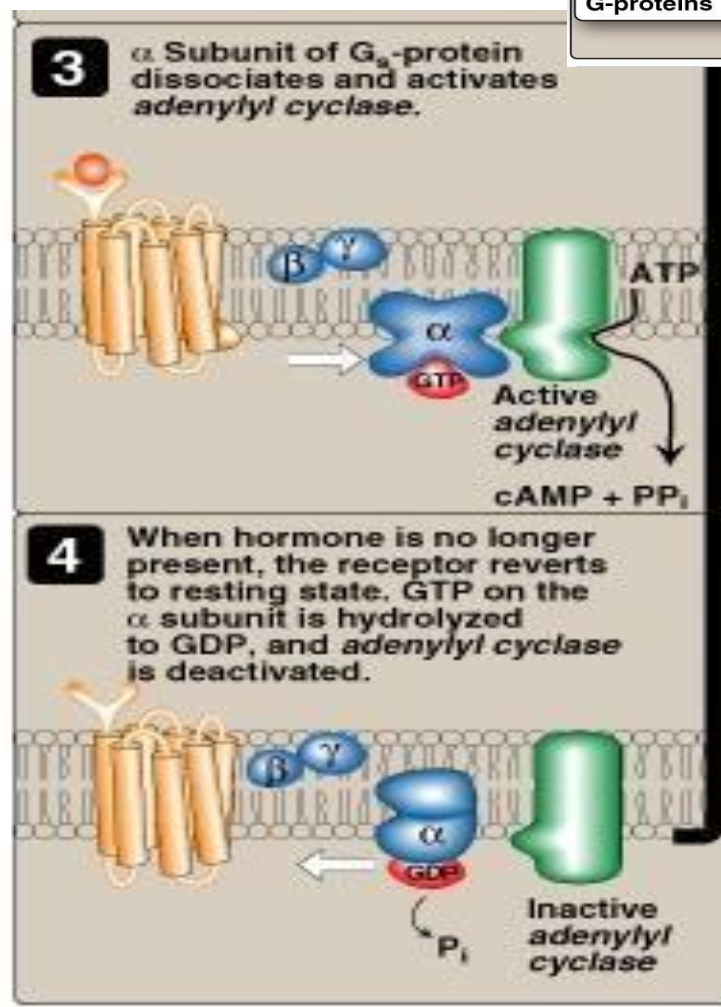
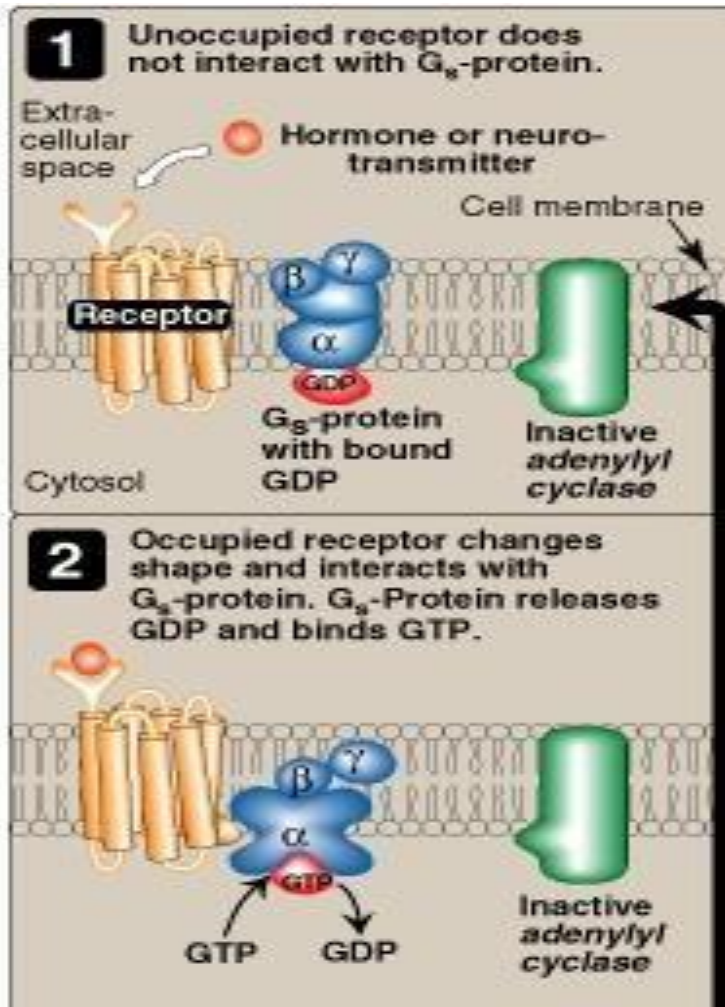
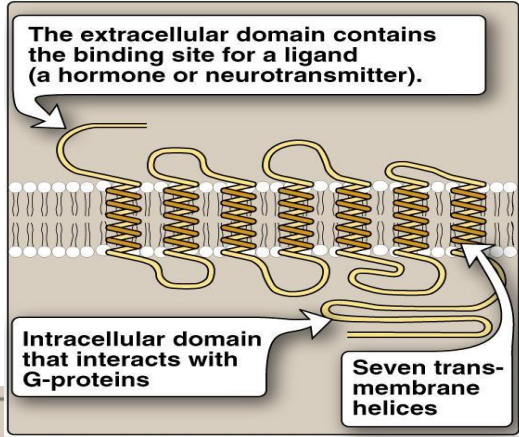
Regulation of Metabolism

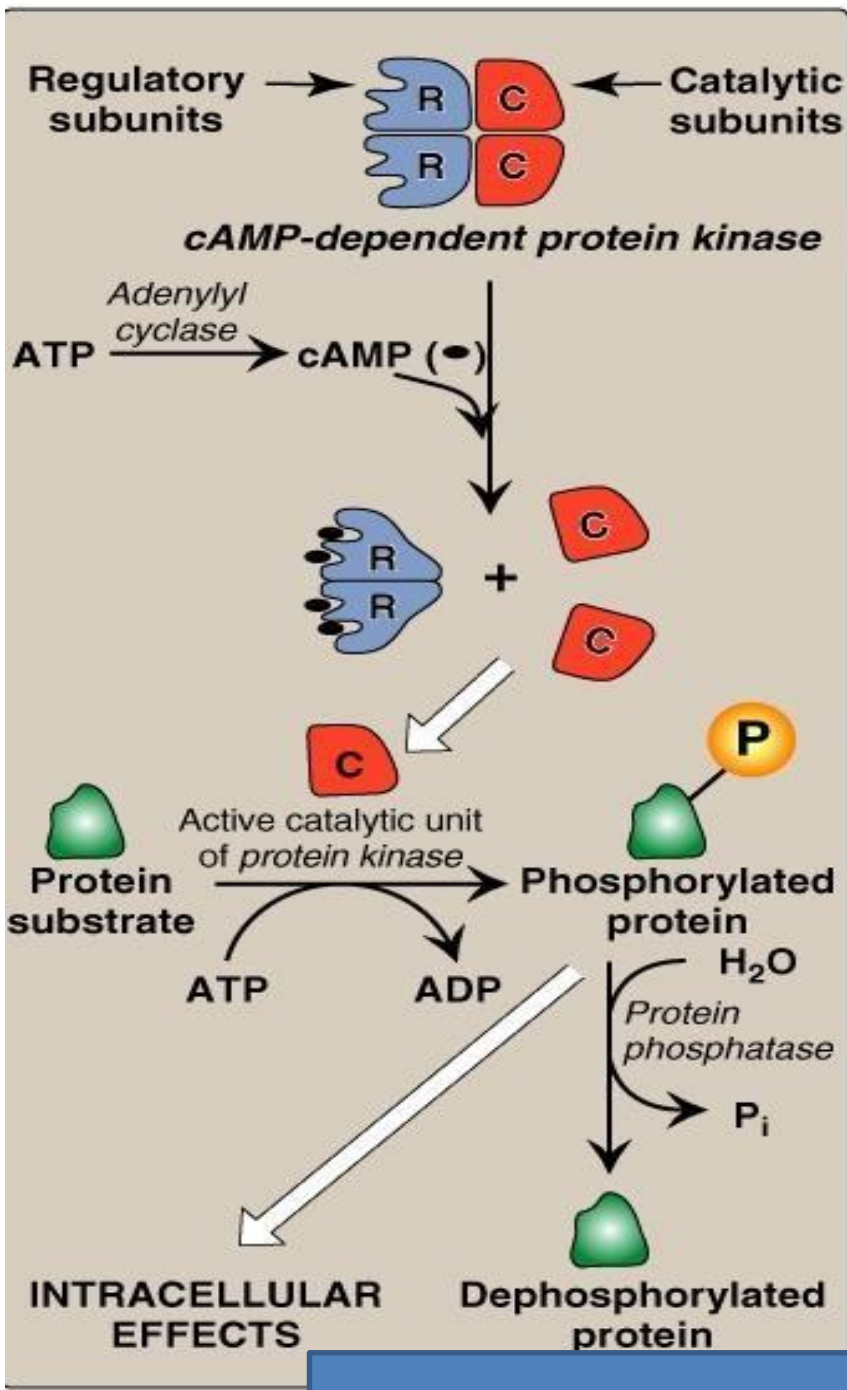
- Signals from within the cell
 - Substrate availability, product inhibition, allosteric
 - Rapid response, moment to moment
- Communication between cells (intercellular)
 - Slower response, longer range integration
- Second messenger
 - Ca^{2+} / phosphatidylinositol system
 - Adenylcyclase system



Commonly used mechanisms of communication between cells

Communication between cells through **G-Protein Coupled Receptors (GPCRs)**

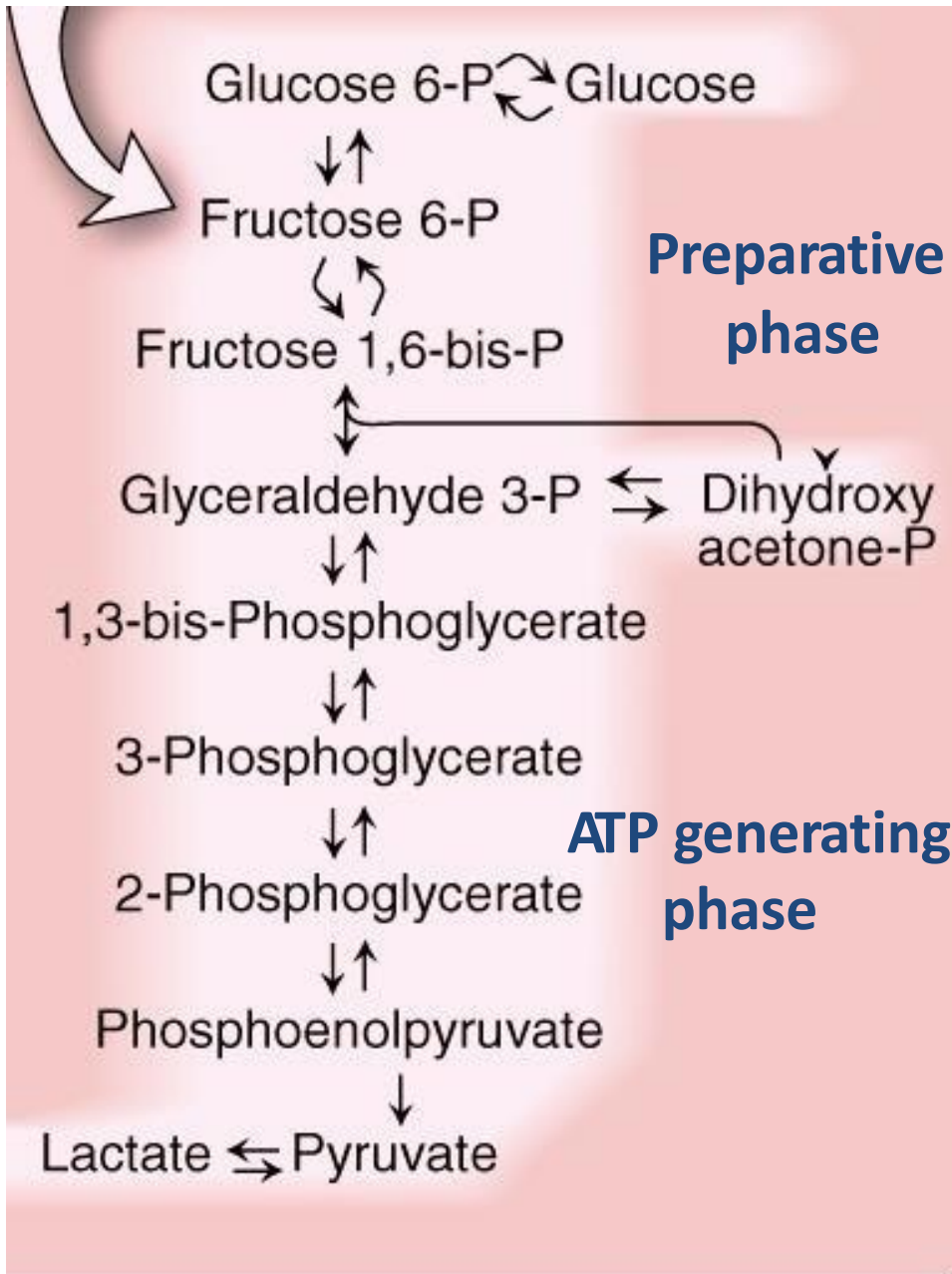




INTRACELLULAR EFFECTS

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

GLYCOLYSIS

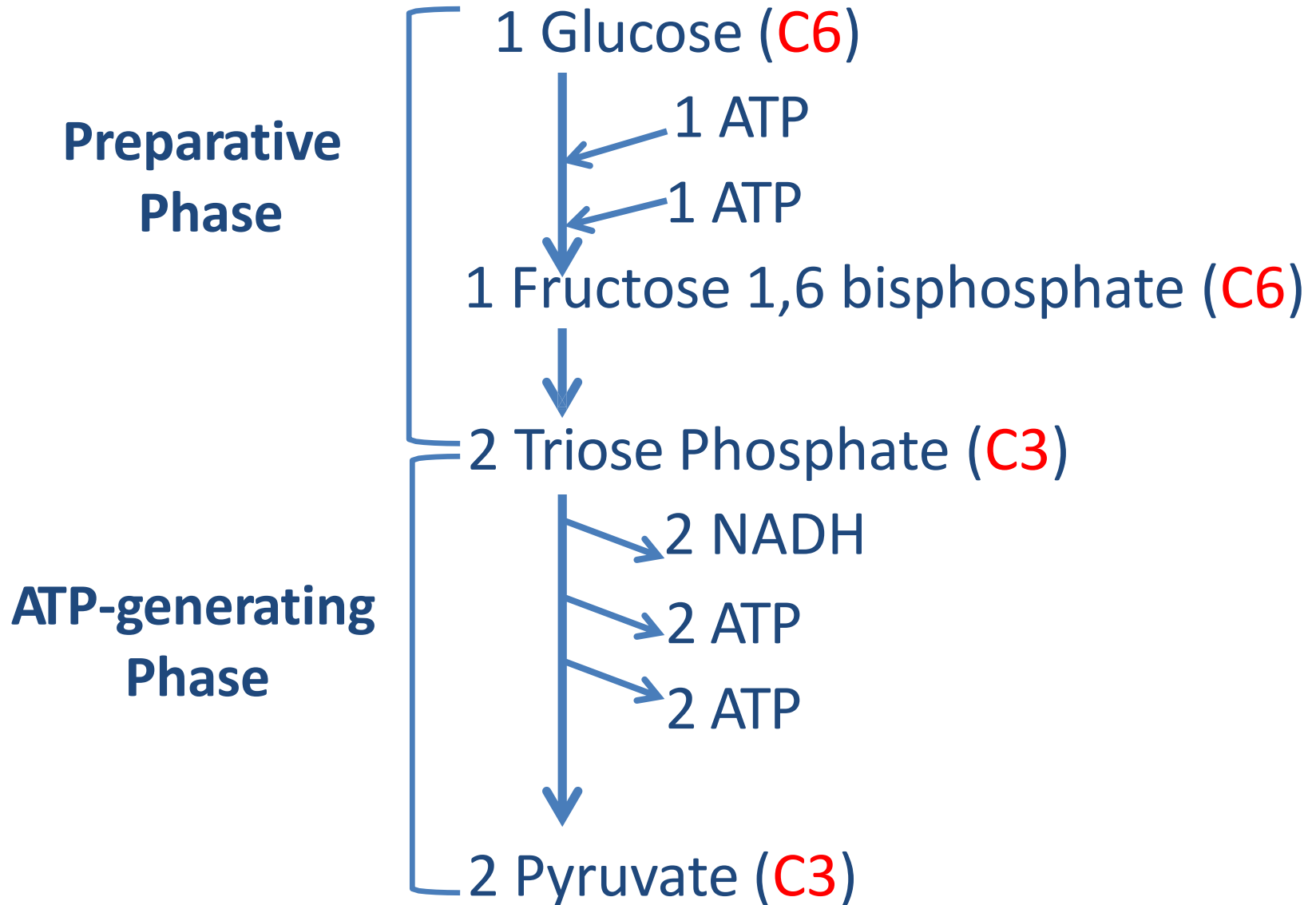


✓ Breakdown of glucose to pyruvate Pathway characteristics

- Universal Pathway: In all cell types
- Generation of ATP
- With or without O₂

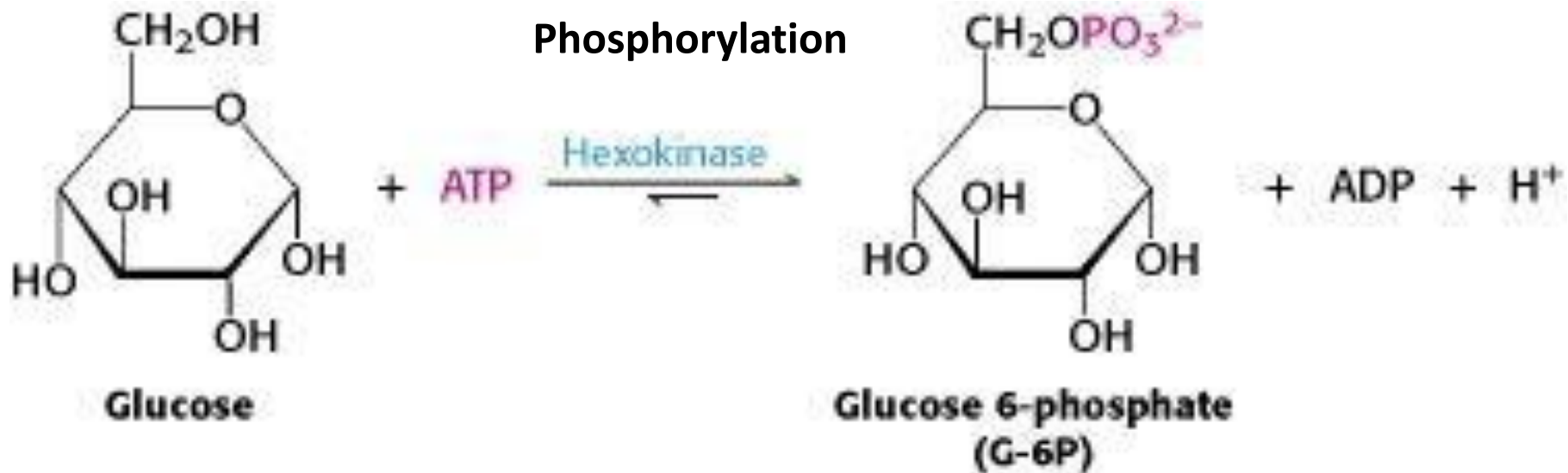
The product of one reaction is the substrate of the next reaction

The Two Phases of the glycolytic Pathway



Steps of Glycolysis

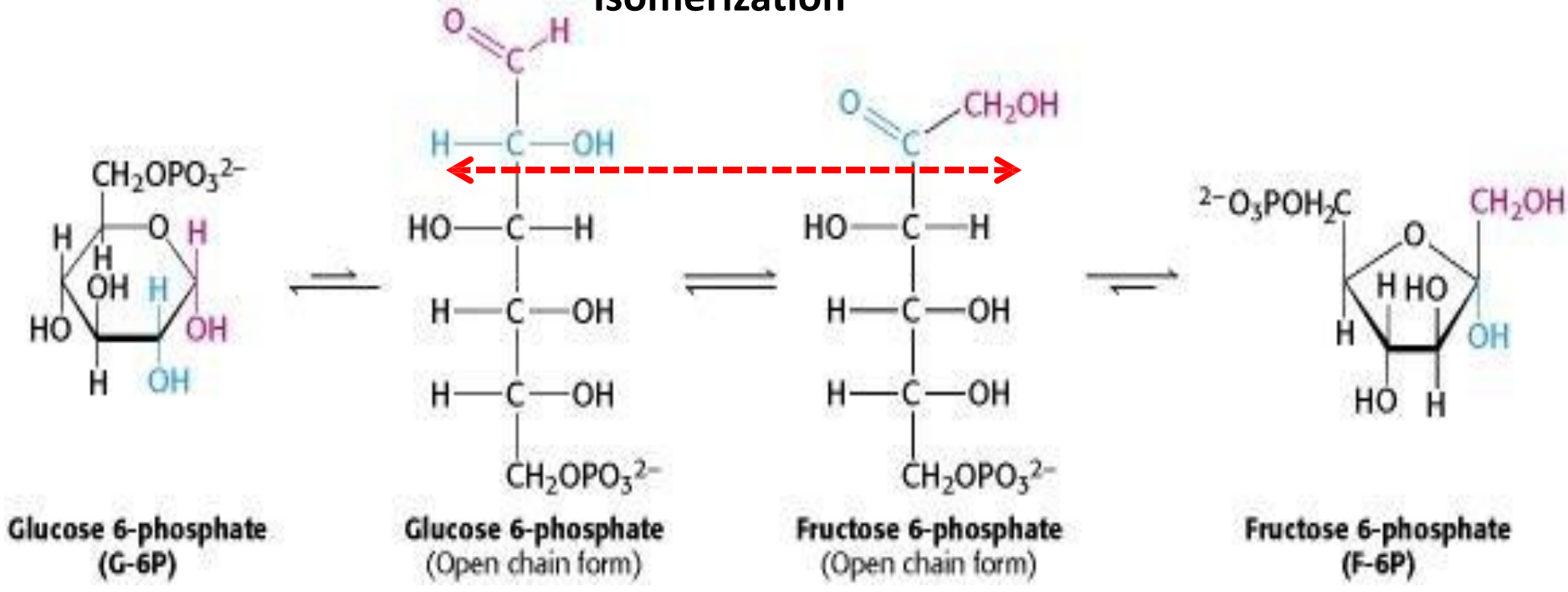
Step 1



	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

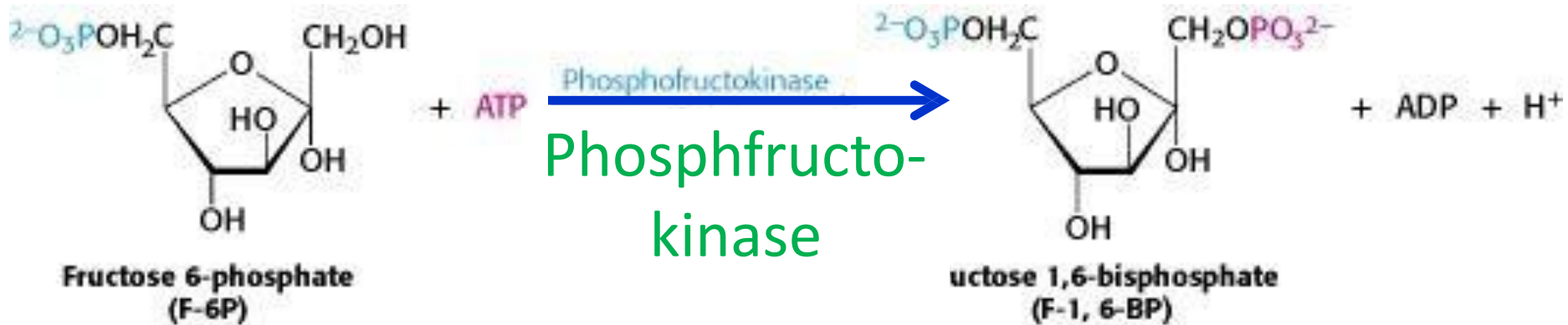
Isomerization



Phosphoglucose
Isomerase

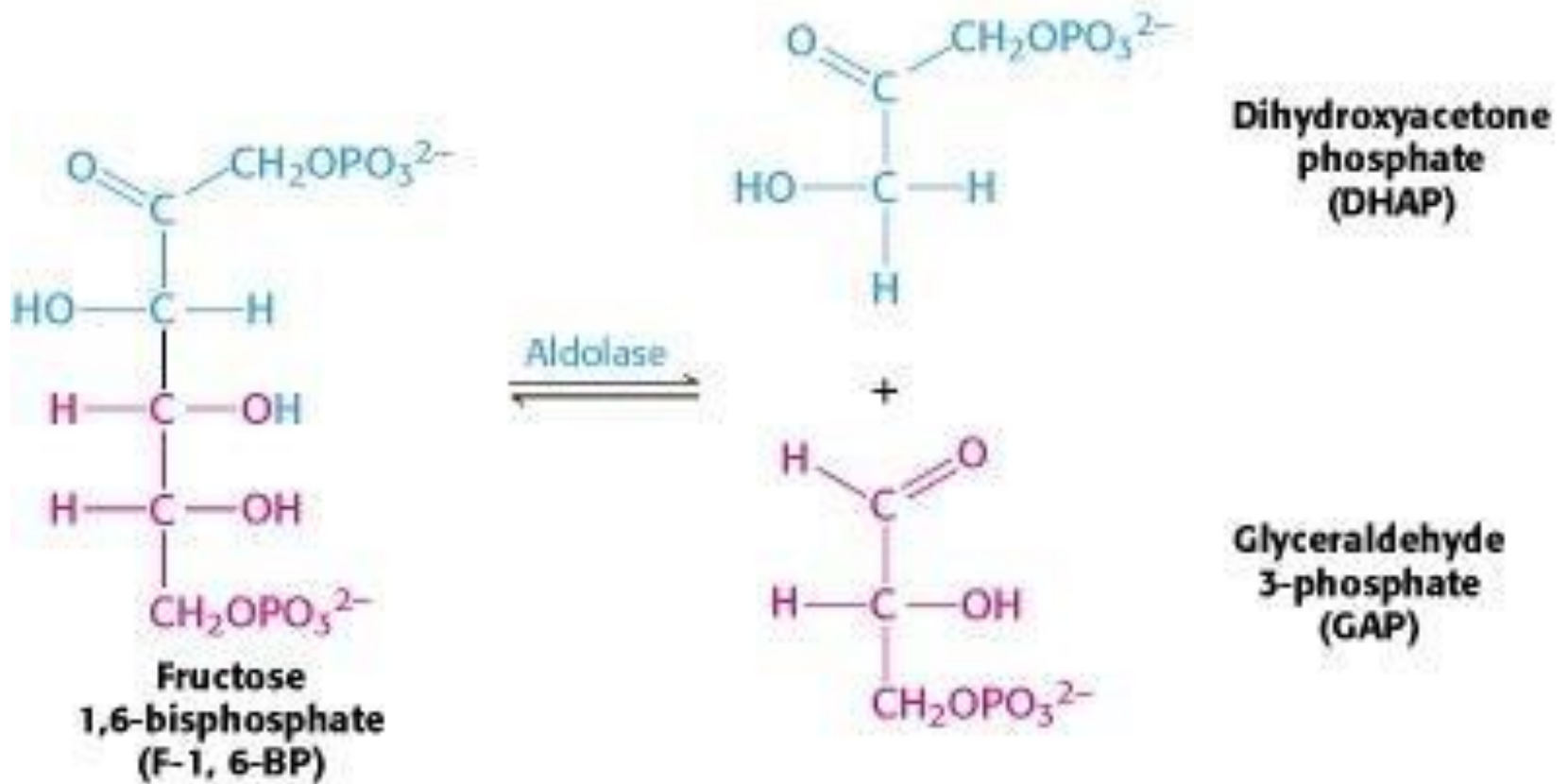
Step 3

Phosphorylation

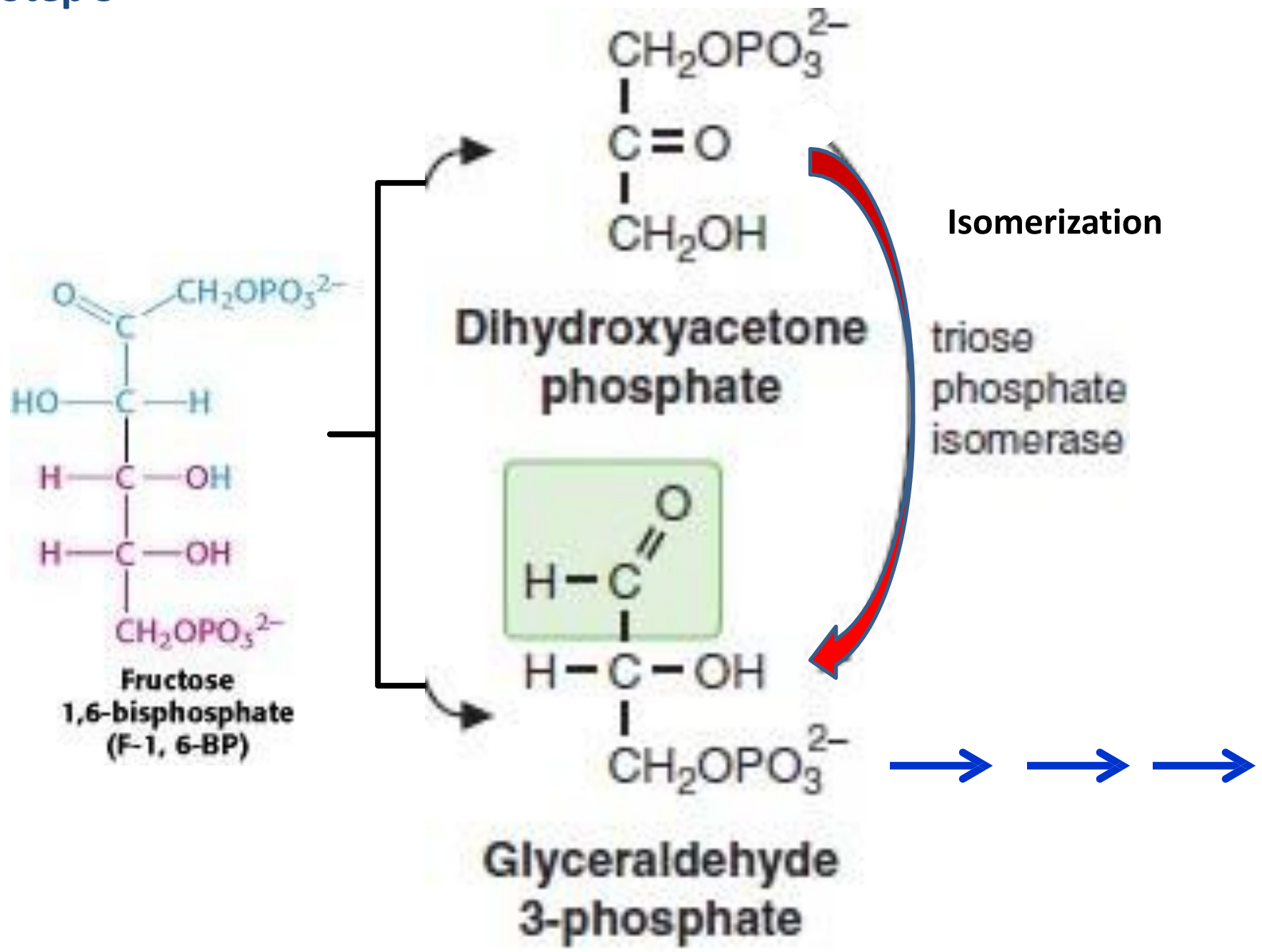


Step 4

Cleavage

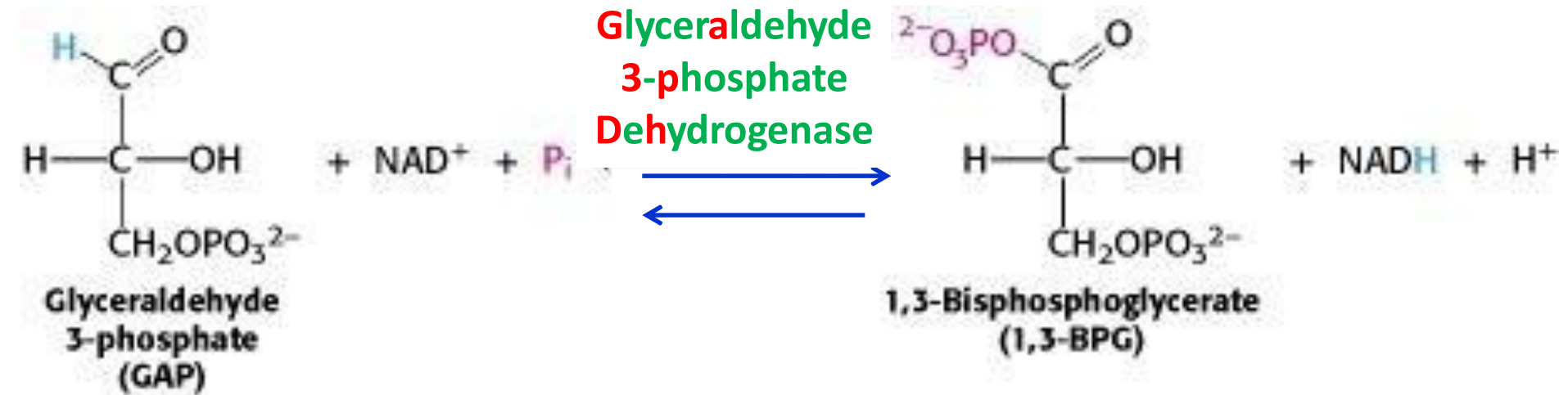


Step 5



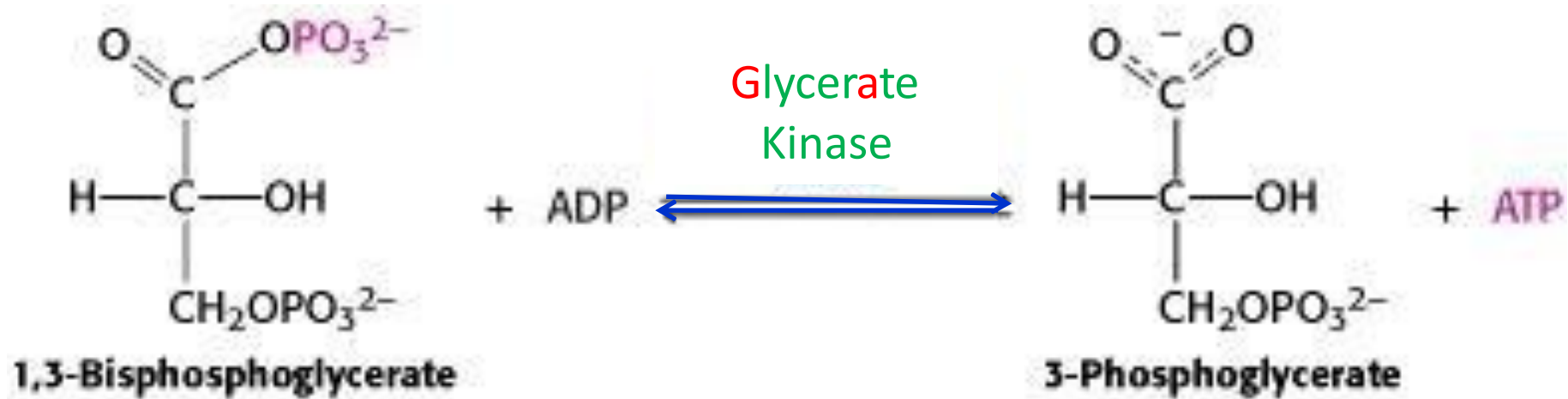
Step 6

Oxidation-reduction



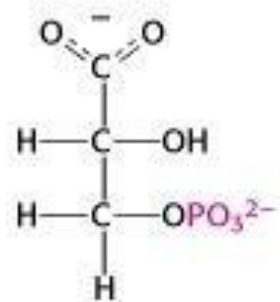
Step 7

Phosphorylation



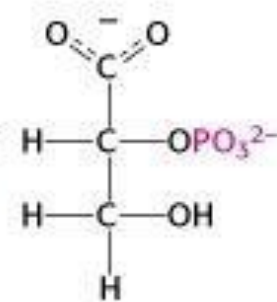
Step 8-10

Phosphoryl-shift isomerization



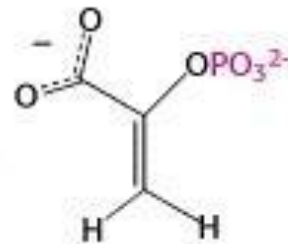
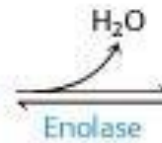
3-Phosphoglycerate

Phosphoglycerate mutase



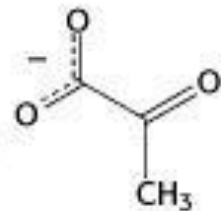
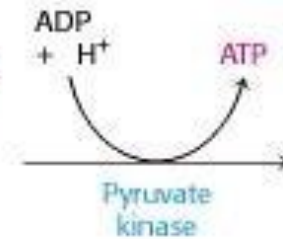
2-Phosphoglycerate

Dehydration



Phosphoenolpyruvate

Phosphorylation



Pyruvate

Energy Need and Production

Glucose 6-P ↔ Glucose

↓↑
Fructose 6-P

-ATP

↔
Fructose 1,6-bis-P

-ATP

↔
Glyceraldehyde 3-P ↔ Dihydroxy acetone-P

2 NADH

↓↑
1,3-bis-Phosphoglycerate

2 ATP

↓↑
3-Phosphoglycerate

↓↑
2-Phosphoglycerate

Is Oxygen needed?

↓↑
Phosphoenolpyruvate

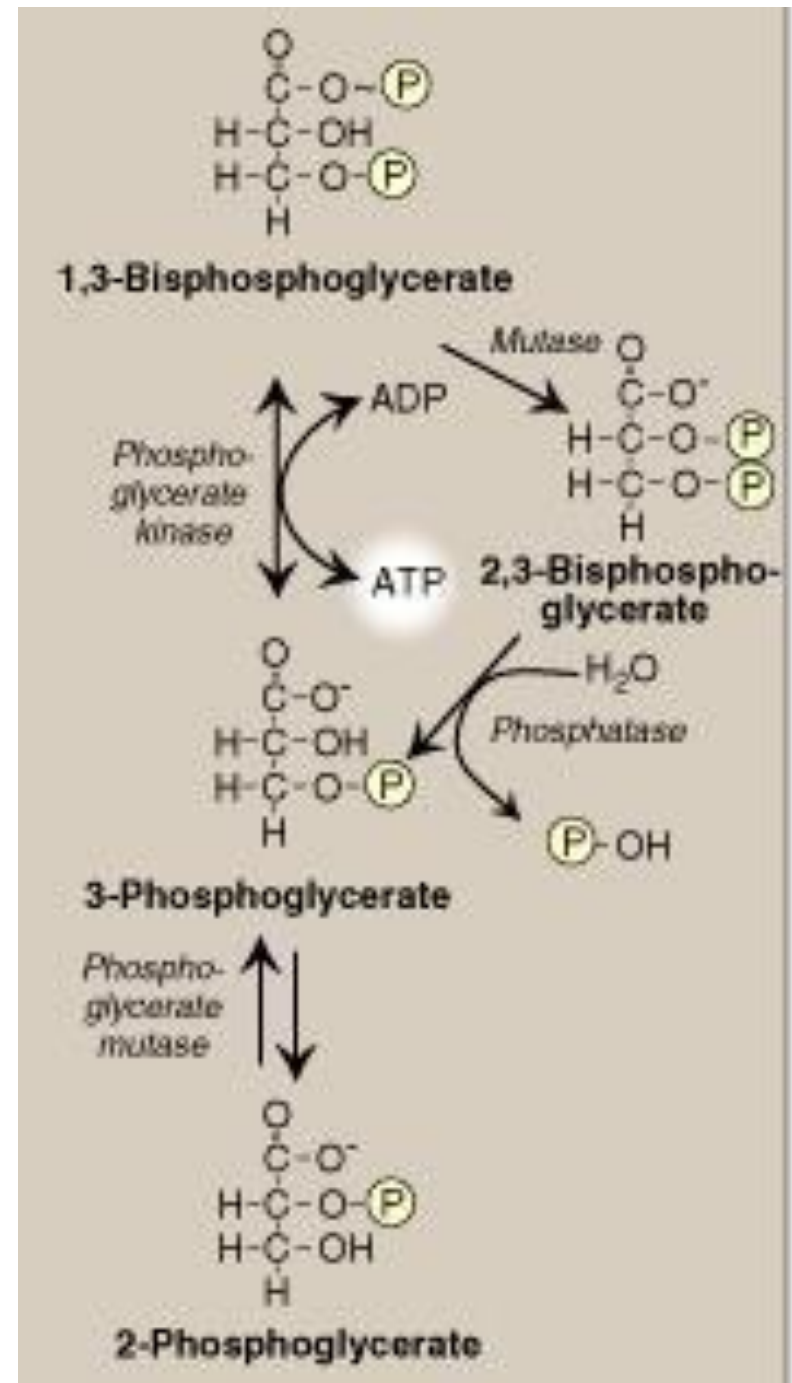
↓
Pyruvate

2ATP

Synthesis of 2,3 bisphosphoglycerate in RBC

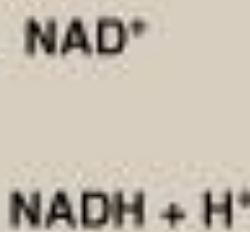
↑↑ Oxygen delivery to
tissues

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



4

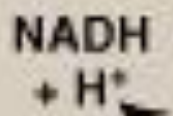
Ethanol



Acetaldehyde

Lactate

CO_2

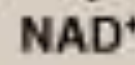


2

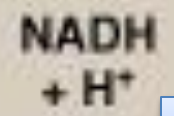
(Thiamine-PP)

PYRUVATE

CO_2



CO_2



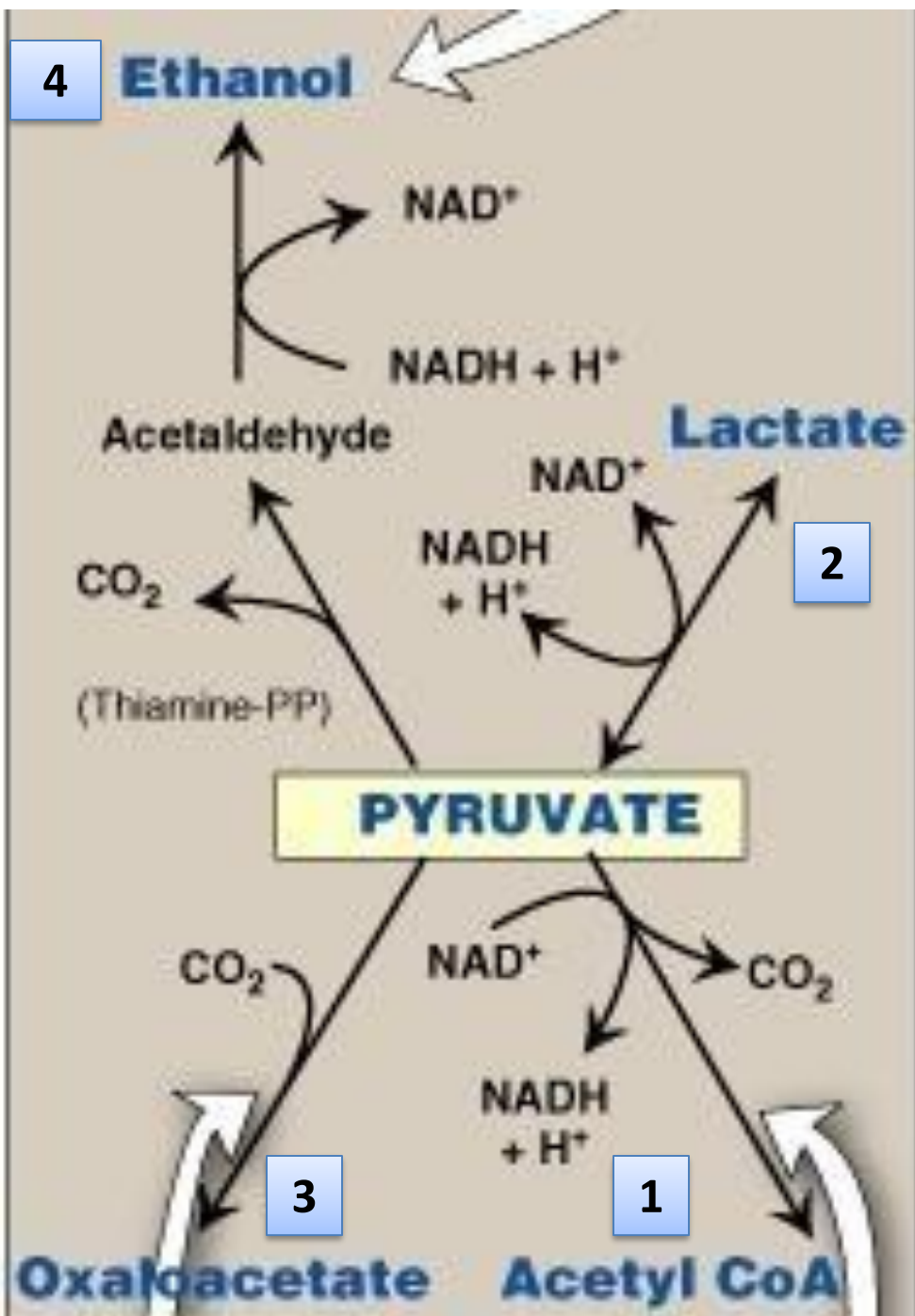
3

1

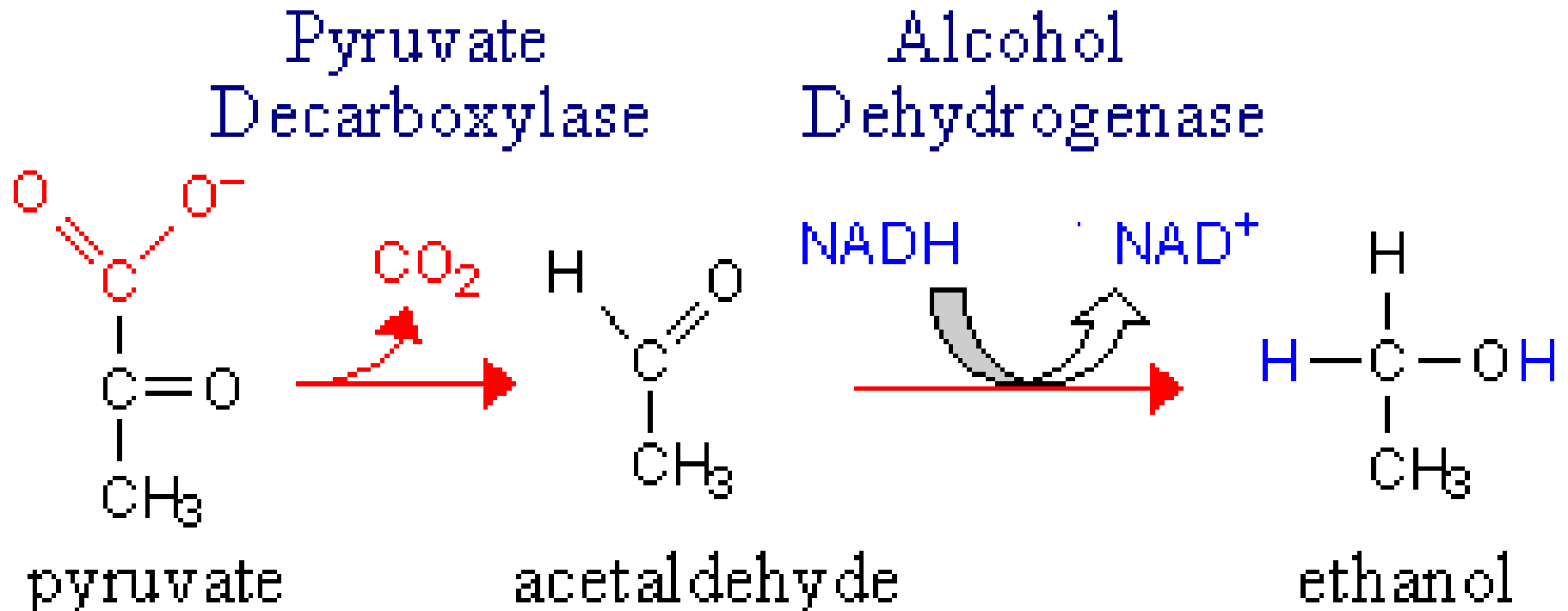
Oxaloacetate

Acetyl CoA

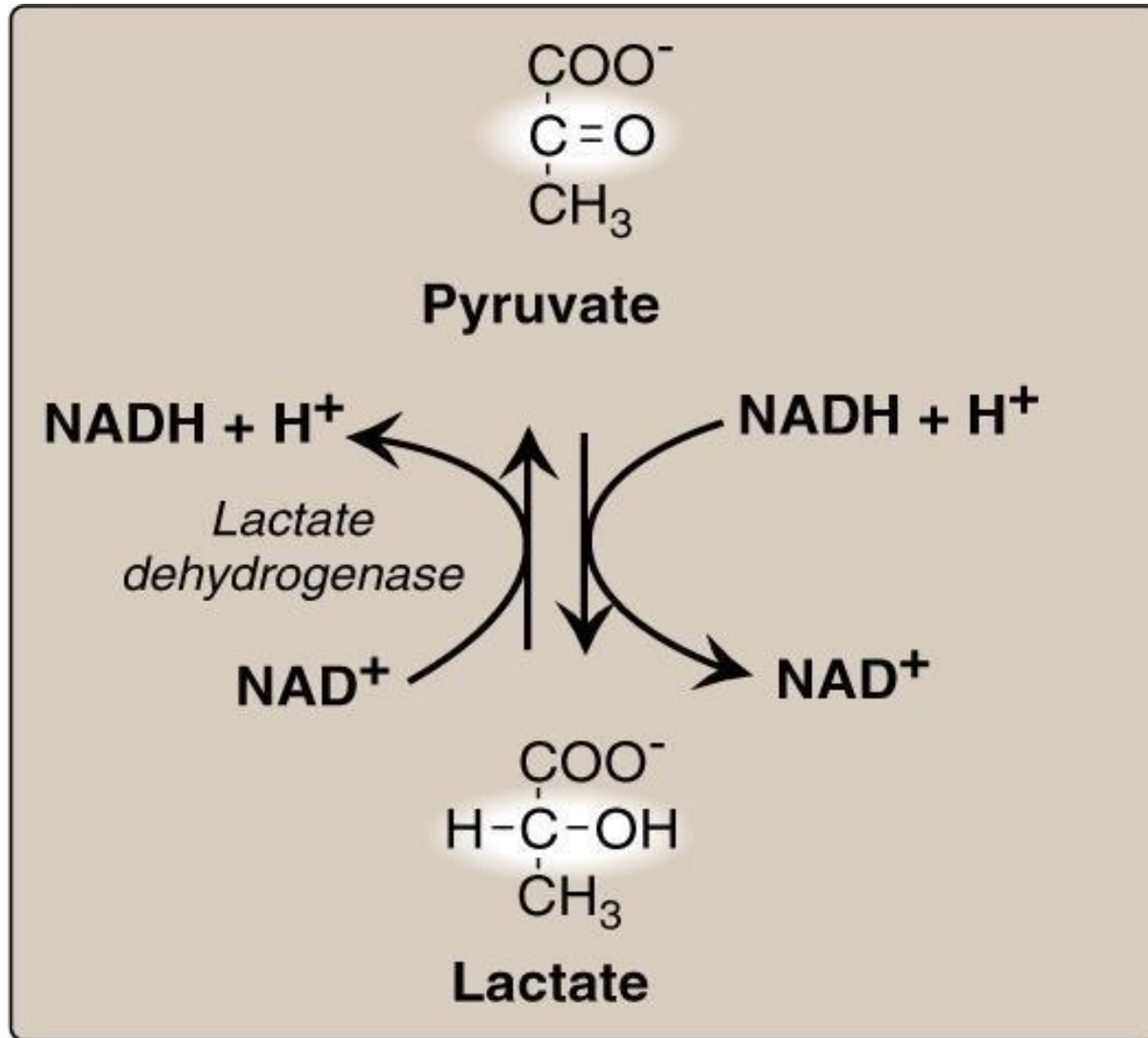
Pyruvate Fates



1. From Pyruvate to Ethanol



2. From Pyruvate to Lactate



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



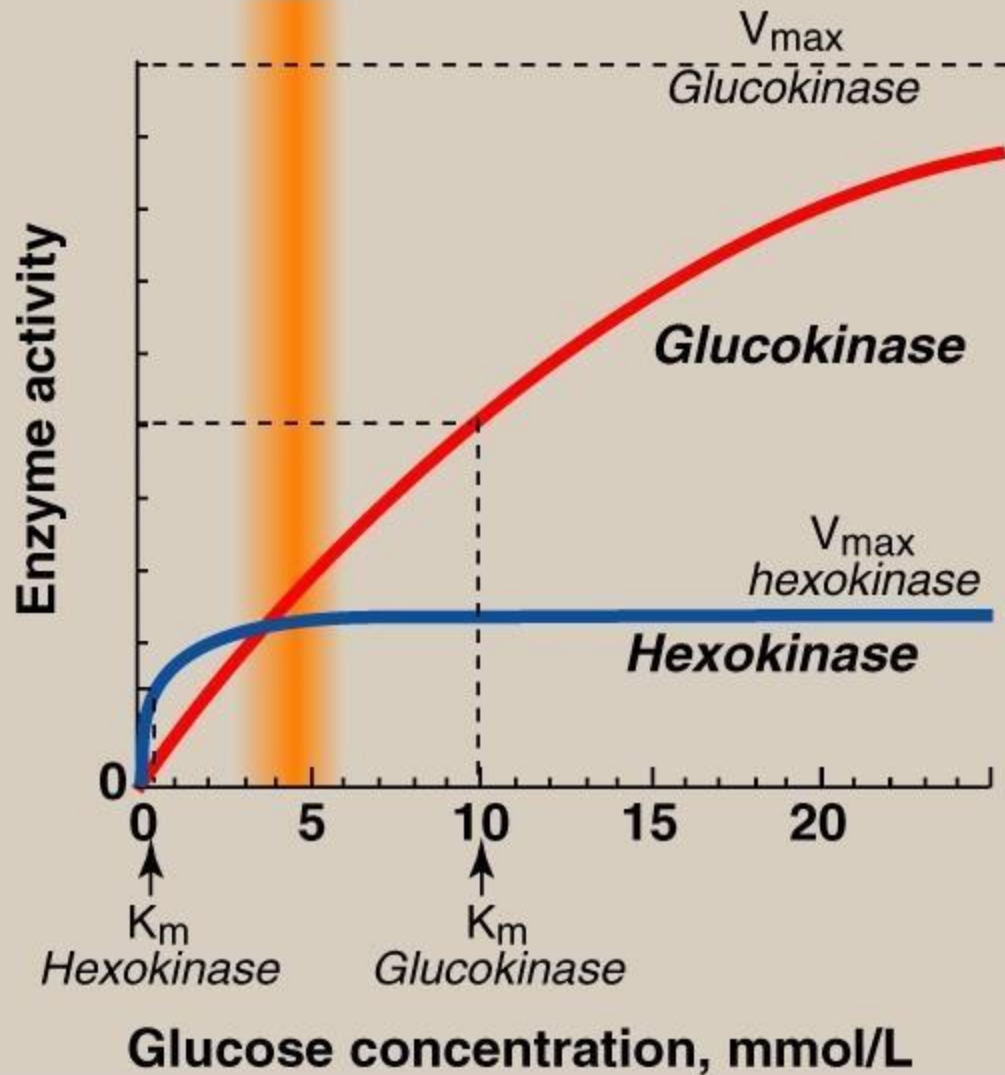
- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
 - Impaired O₂ transport
 - Respiratory failure
 - Uncontrolled hemorrhage

Clinical Hint: Lactic Acidosis

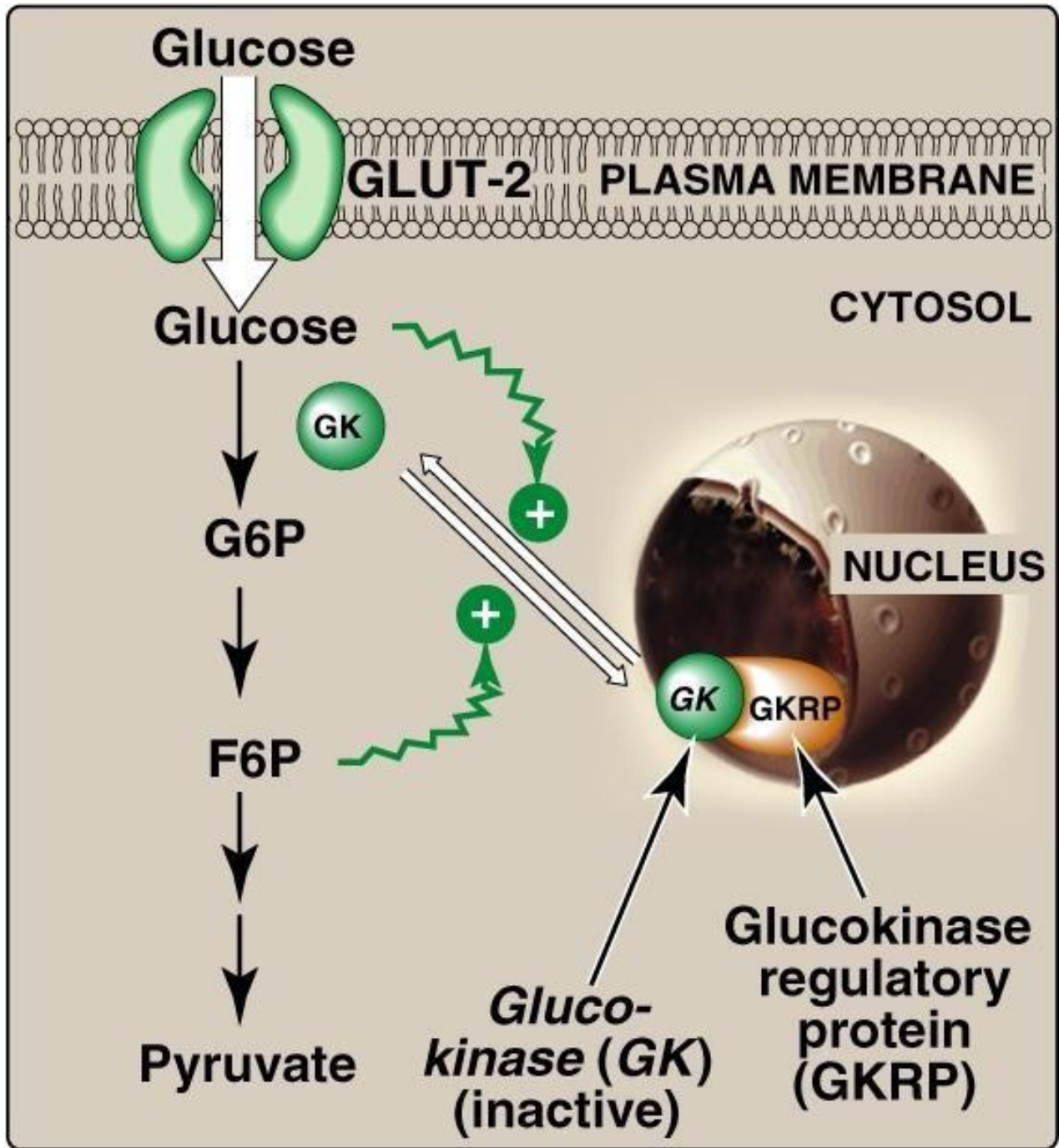
- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissue
- Alcohol intoxication (high NADH/ NAD⁺)
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydrogenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase

Regulation of Glycolysis

Concentration
of fasting
blood glucose

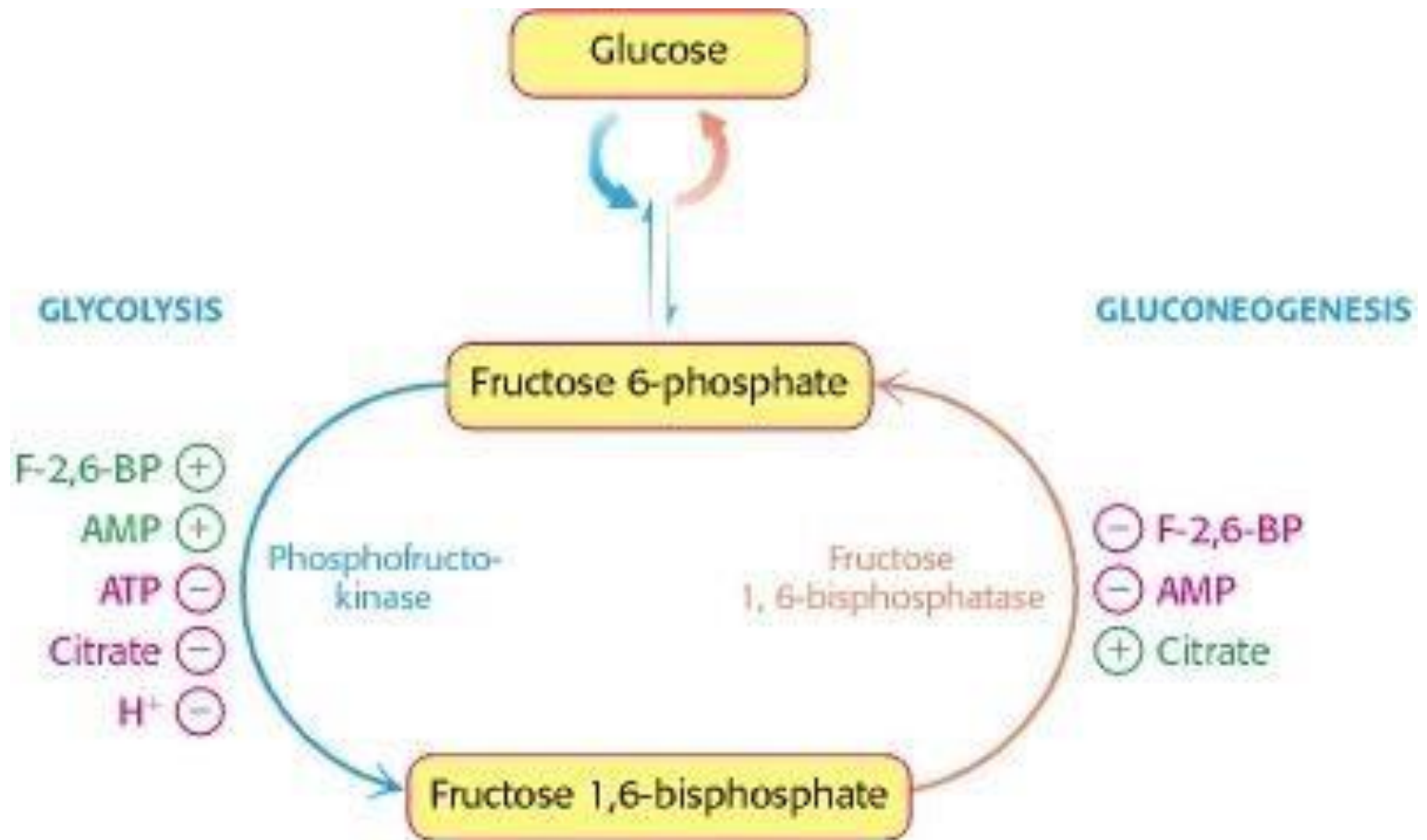


Glucokinase and Hexokinase Activity

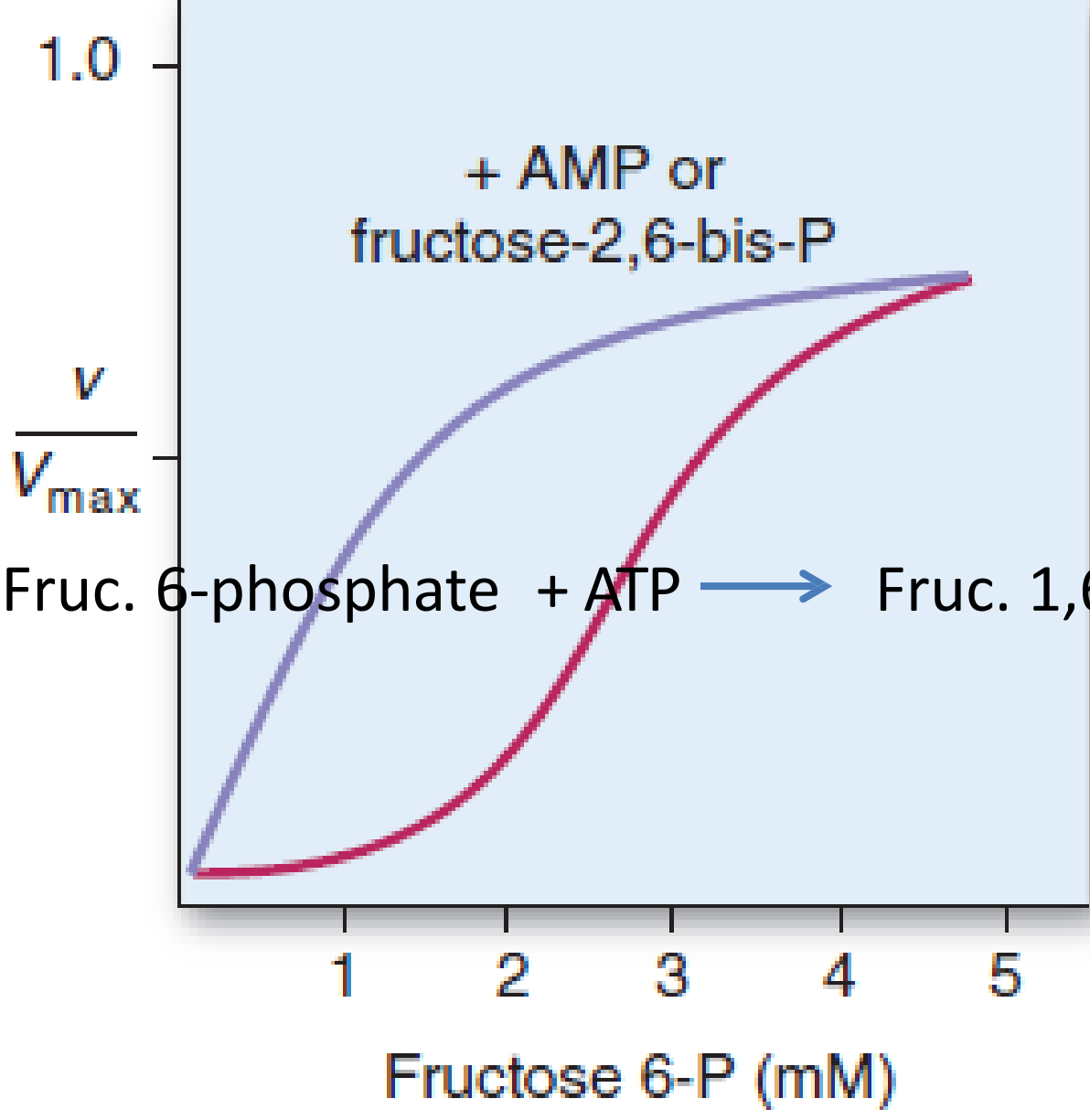


Glucokinase Regulation

Allosteric Regulators of PFK1



A

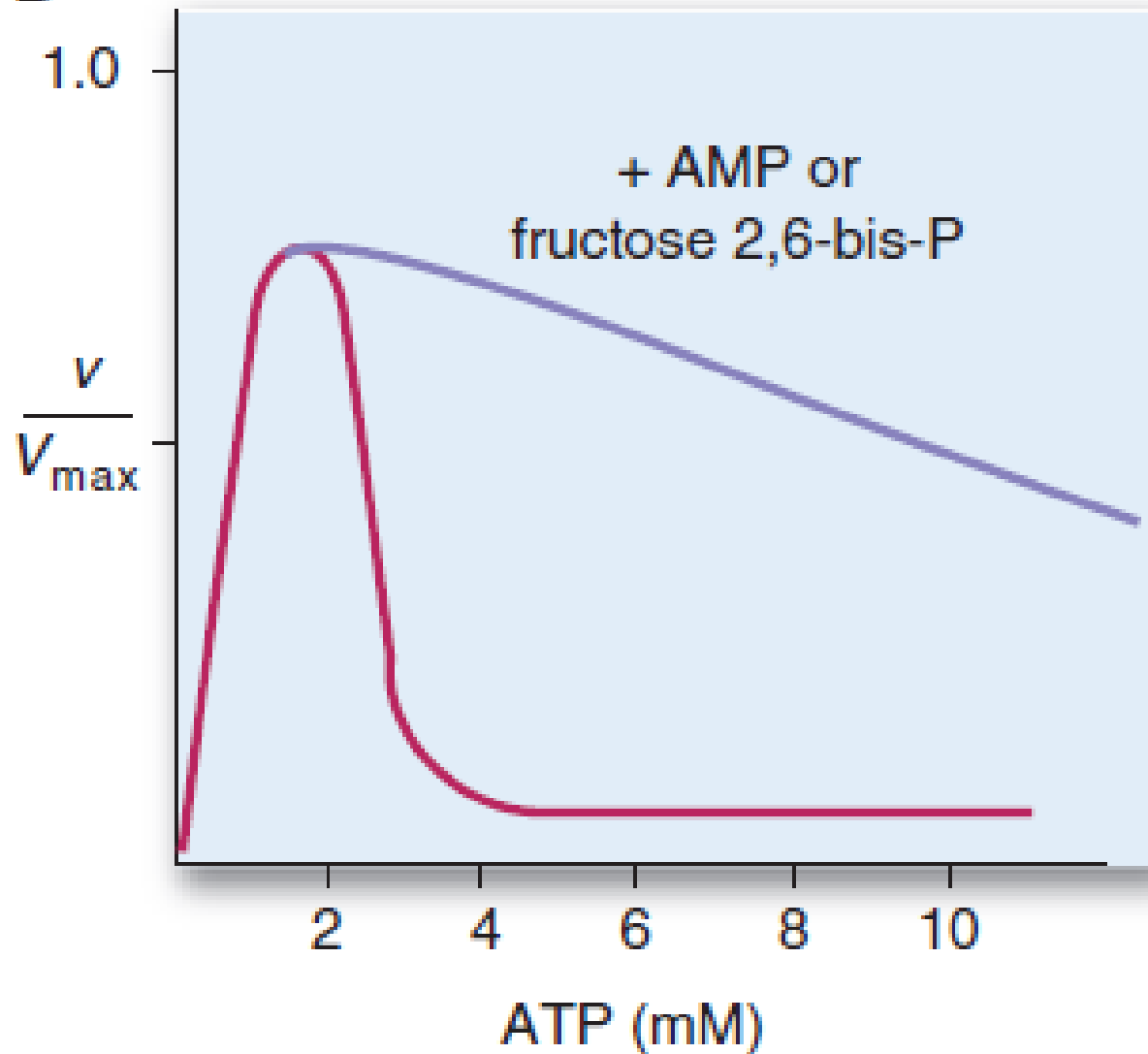


Regulation of PFK1 by Fructose 2,6-bisphosphate

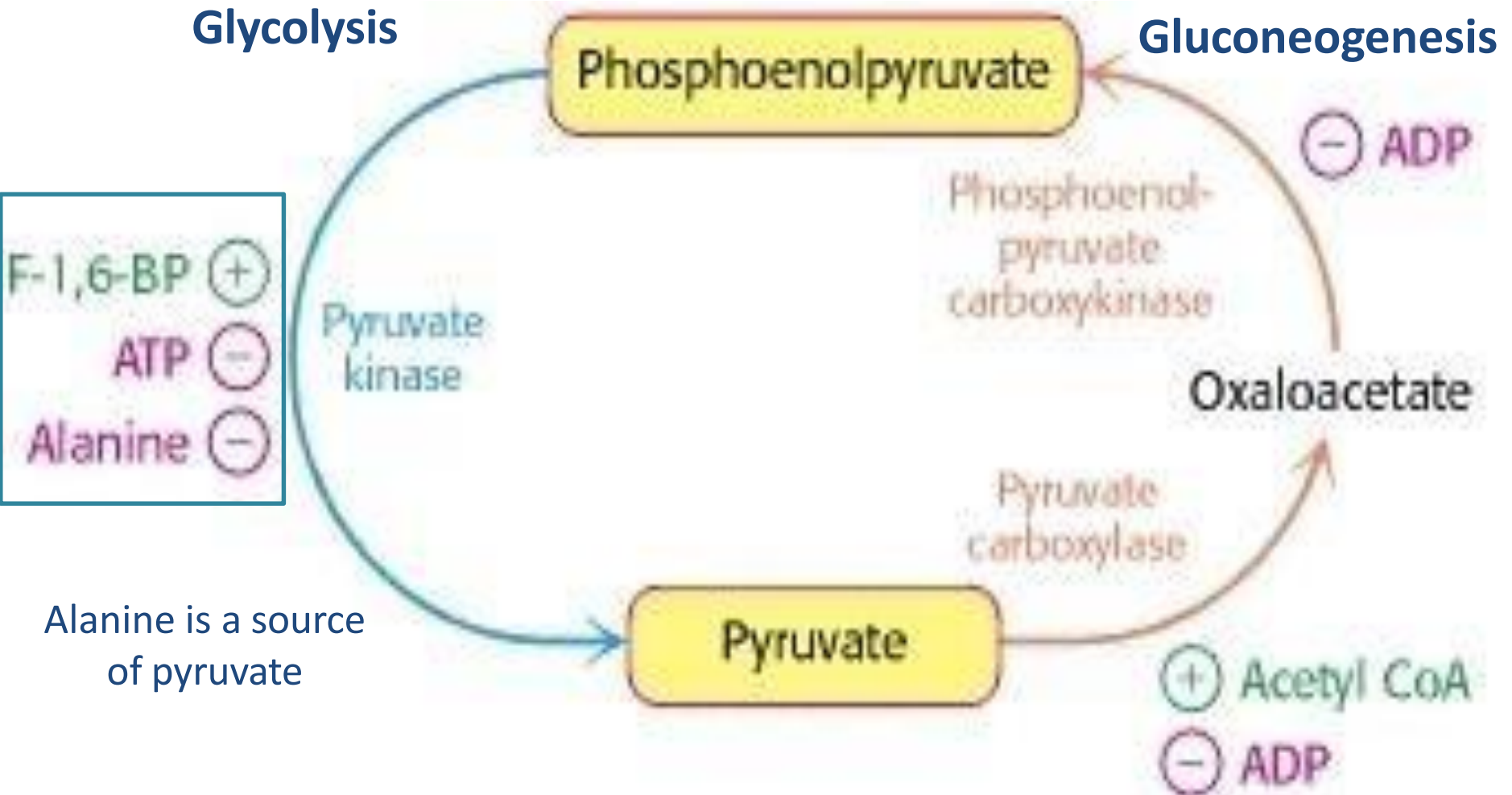


How about the other substrate?

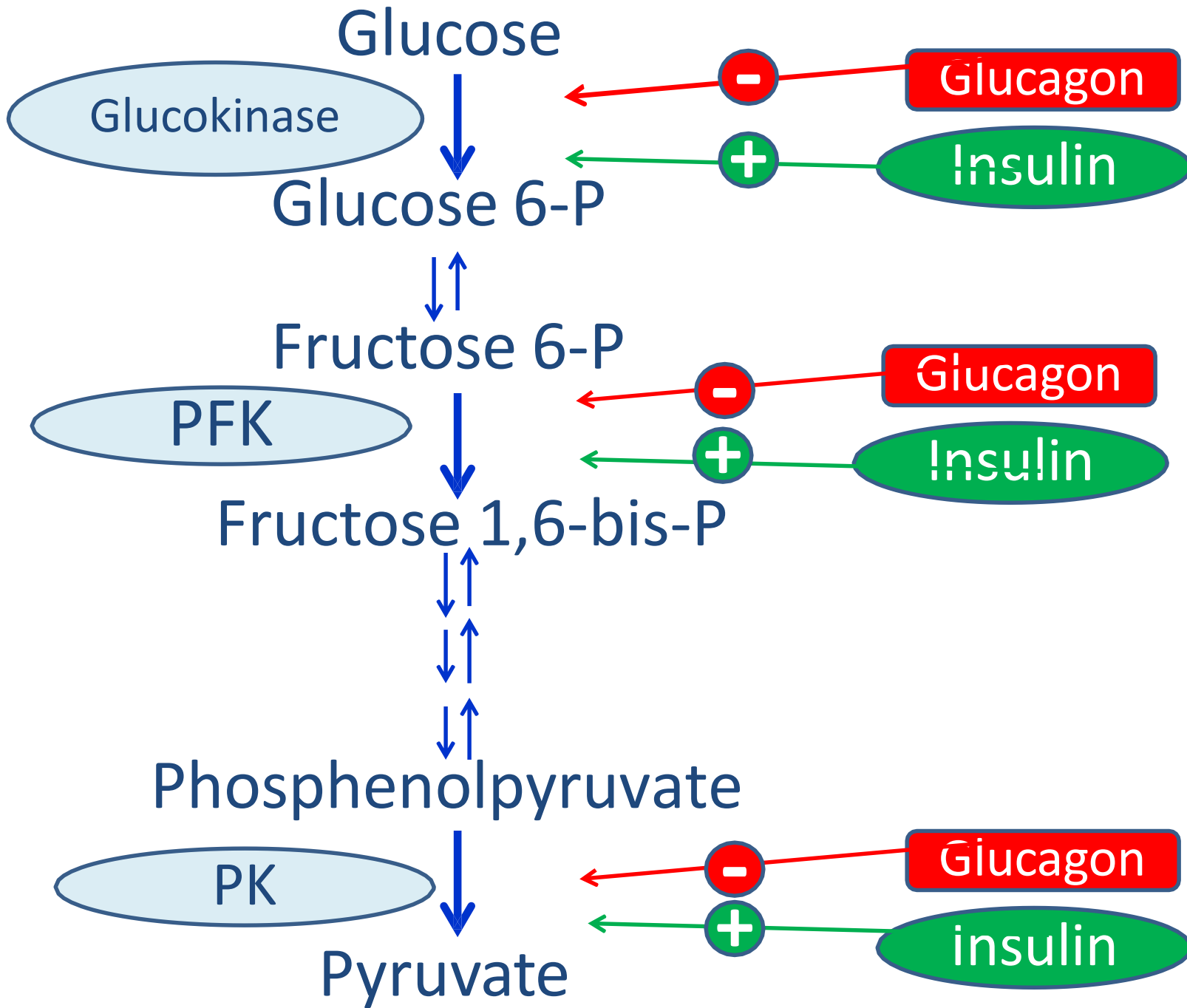
B



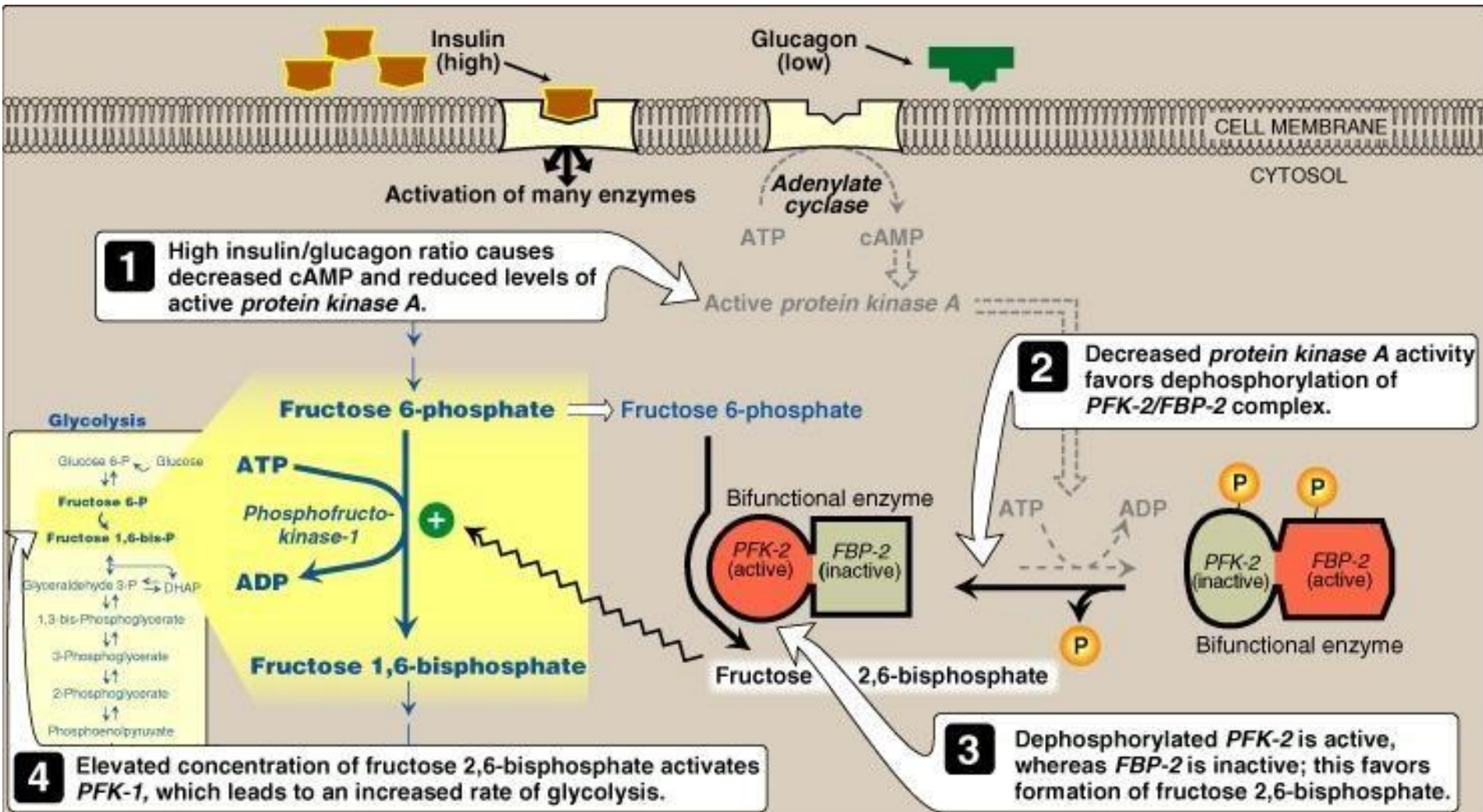
Regulation of Pyruvate Kinase

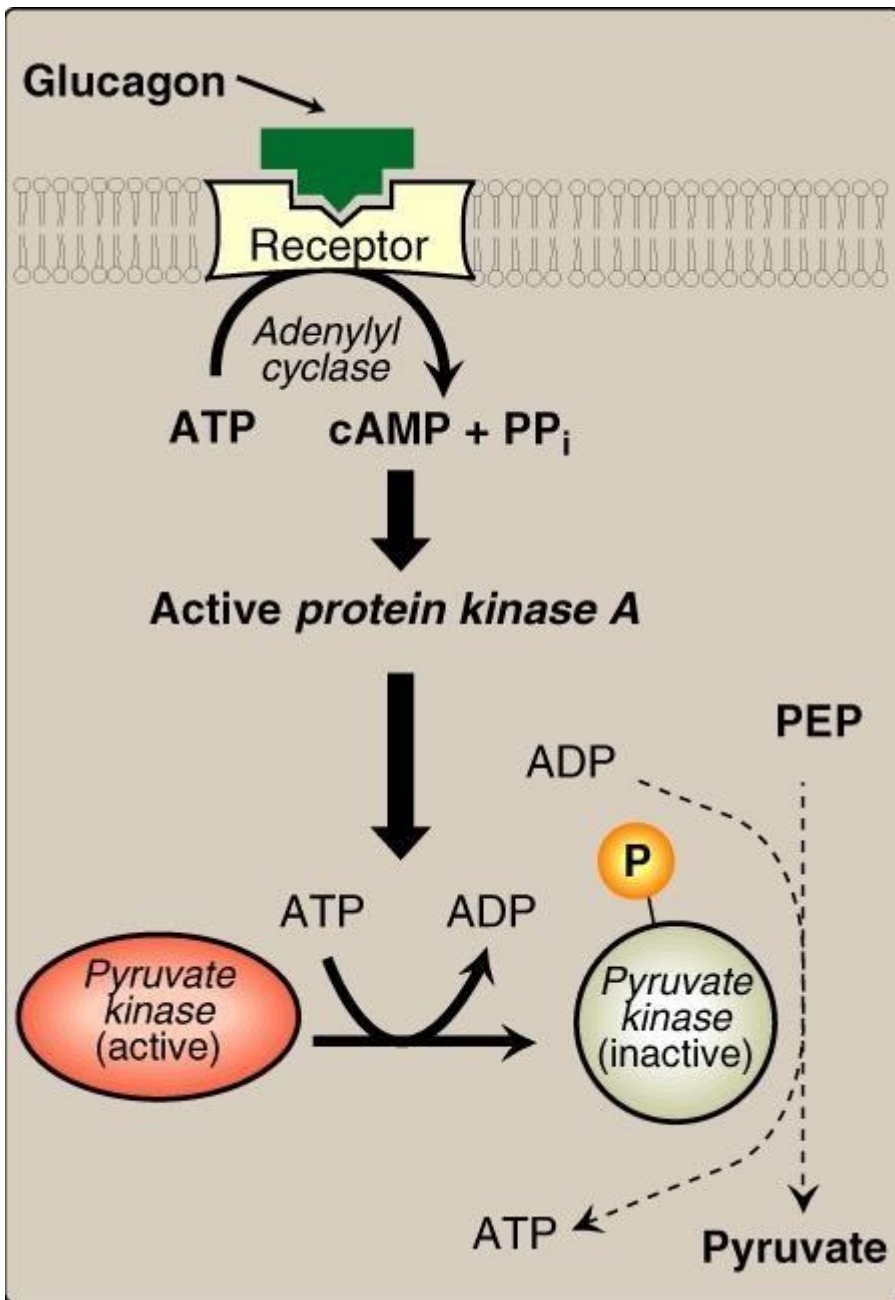


Hormonal Regulation



Hormonal Regulation of Phosphofructokinase

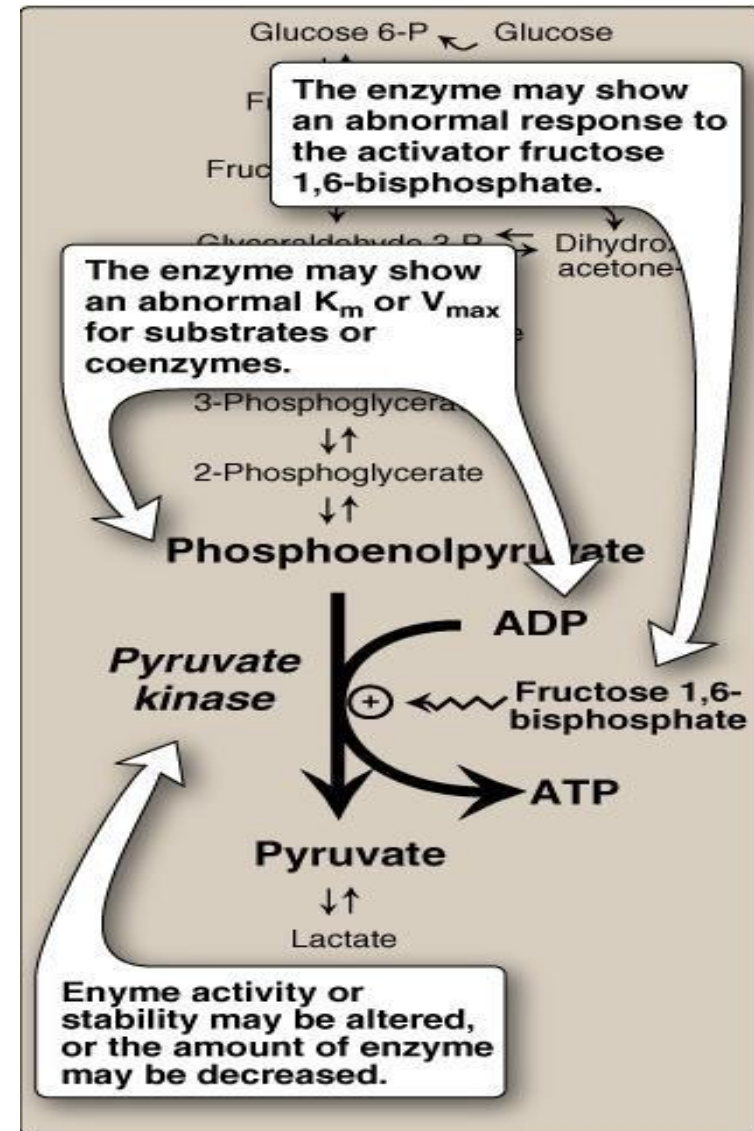




Hormonal Regulation of Pyruvate Kinase

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



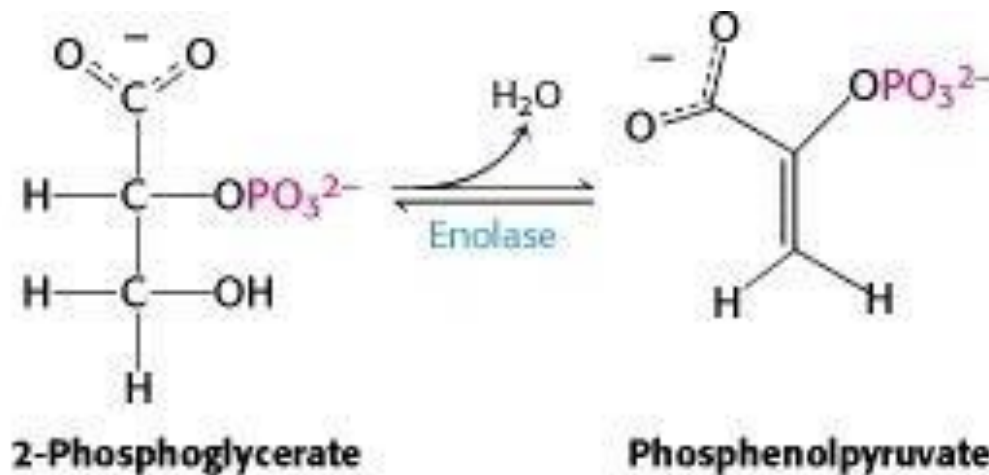
Alterations observed with various mutant forms of pyruvate kinase

External (non-physiological) Inhibitors of Glycolysis

Inorganic Inhibitors of Glycolysis, non-physiologic

Fluoride

- Fluoride inhibits Enolase



Fluoridated water → ↓ bacterial enolase →
Prevention of Dental Carries

Inorganic Inhibitors of Glycolysis, non-physiologic

➤ 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**

