# Metabolism

## UG 5th semester

**BCH522J1**

**BIOCHEMISTRY AND CARBOHYDRATE AND AMINO ACID METABOLISM**

- **CREDITS: THEORY-3; PRACTICAL-1**
- **THEORY (3 CREDITS: 45 HOURS)**

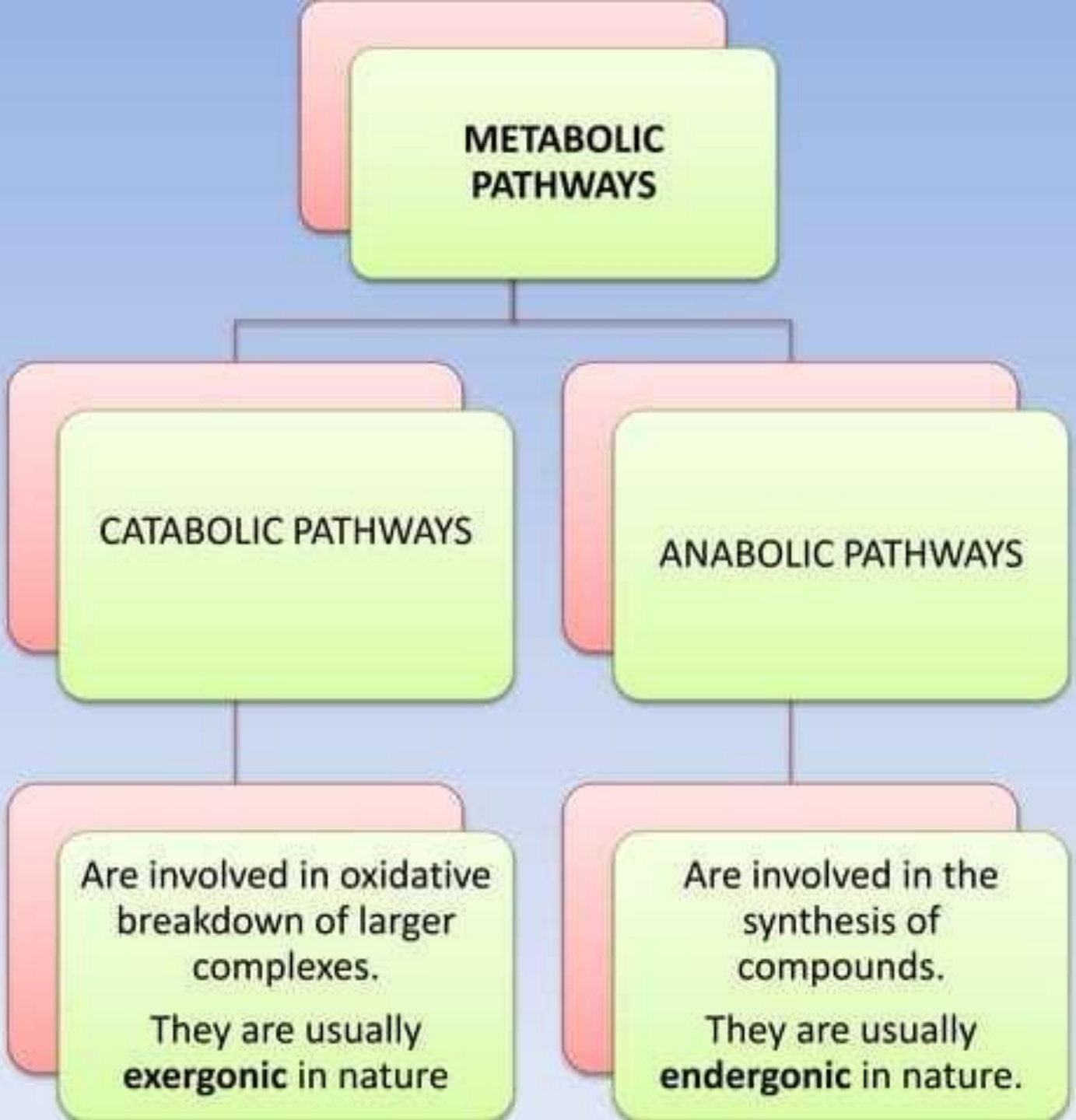

## Department of Biochemistry

## Government Degree College Tral

# General features of metabolic pathways

- **Irreversible: Metabolic pathways are irreversible.**
- **Regulation: All metabolic pathways are regulated.**
- **Subcellular compartments: In eukaryotic cells, metabolic pathways occur in specific subcellular compartments.**
- **Performed by enzymes: Metabolic pathways are occur through enzymes that transform one molecule into another through a series of reactions.**

- **Catabolic and anabolic pathways: Catabolic and anabolic pathways must be different.**
- **First committed step: Every metabolic pathway has a first committed step.**
- **May be linear, cyclic or spiral.**
- **Function is to yield energy or intermediates.**


METABOLIC PATHWAYS
CATABOLIC PATHWAYS
ANABOLIC PATHWAYS
Are involved in oxidative breakdown of larger complexes.
They are usually **exergonic** in nature
Are involved in the synthesis of compounds.
They are usually **endergonic** in nature.

# GLYCOLYSIS

Glycolysis comes from a merger of two Greek words:

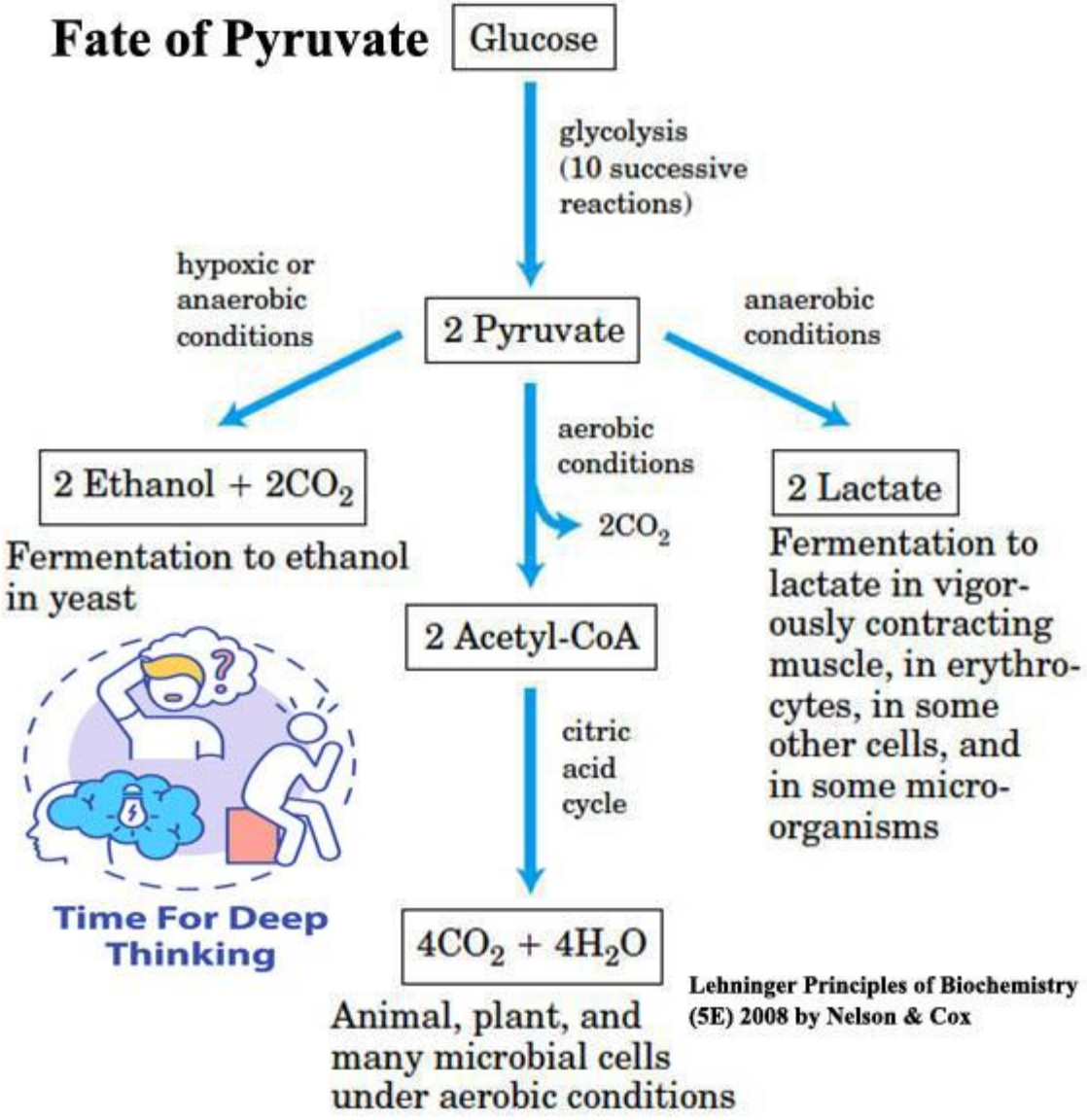
- **Glykys = sweet**
- **Lysis = breakdown/ splitting**

It is also known as Embden-Meyerhof-Parnas pathway or EMP pathway.

# INTRODUCTION

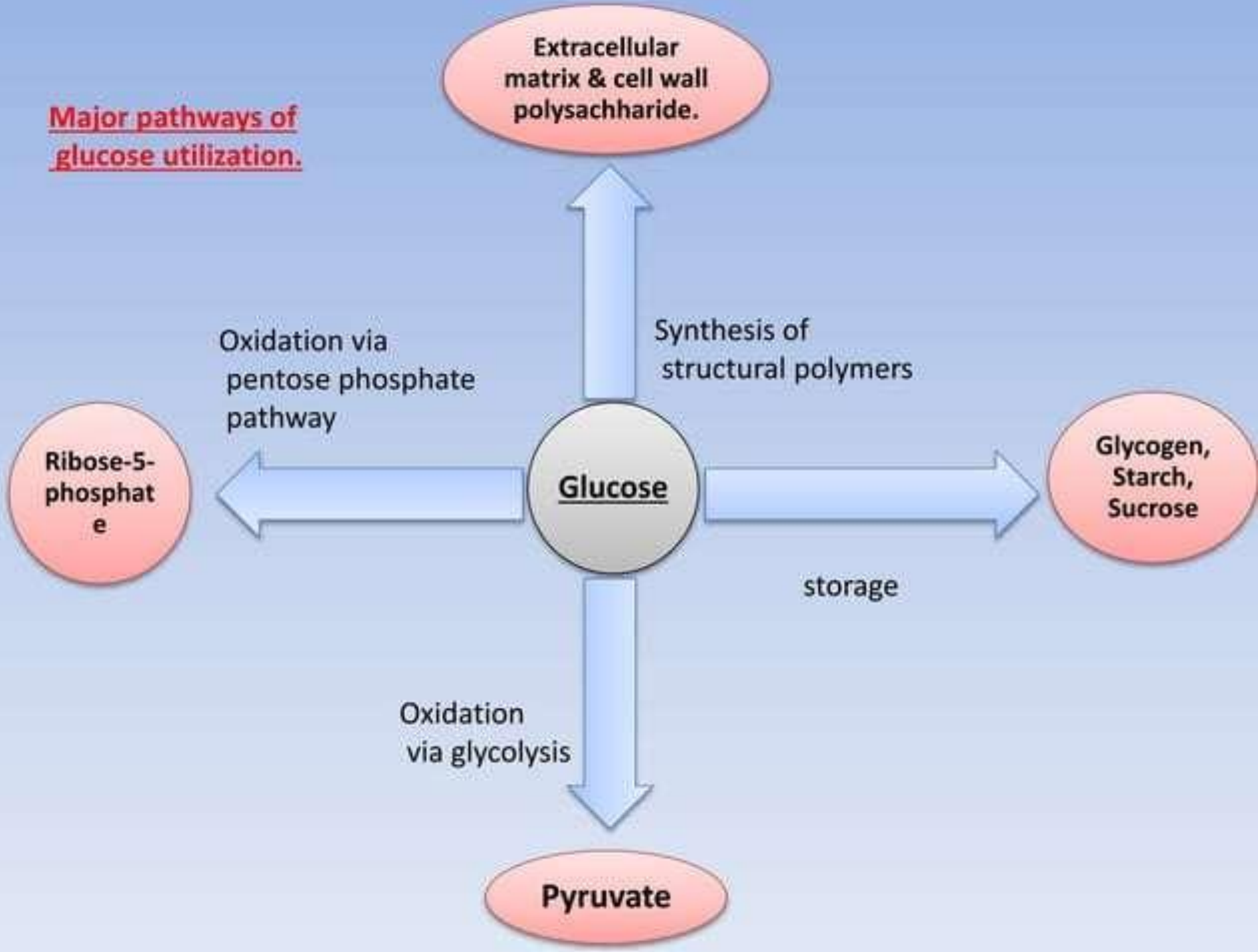
- GLYCOLYSIS is the sequence of 10 enzyme-catalyzed reactions that converts glucose into pyruvate with simultaneous production on of ATP.
- In this oxidative process, 1mol of glucose is partially oxidised to 2 moles of pyruvate.
- This major pathway of glucose metabolism occurs in the cytosol of all cell.
- This unique pathway occurs **aerobically** as well as **anaerobically & doesn't involve molecular oxygen.**

# Fate of Pyruvate

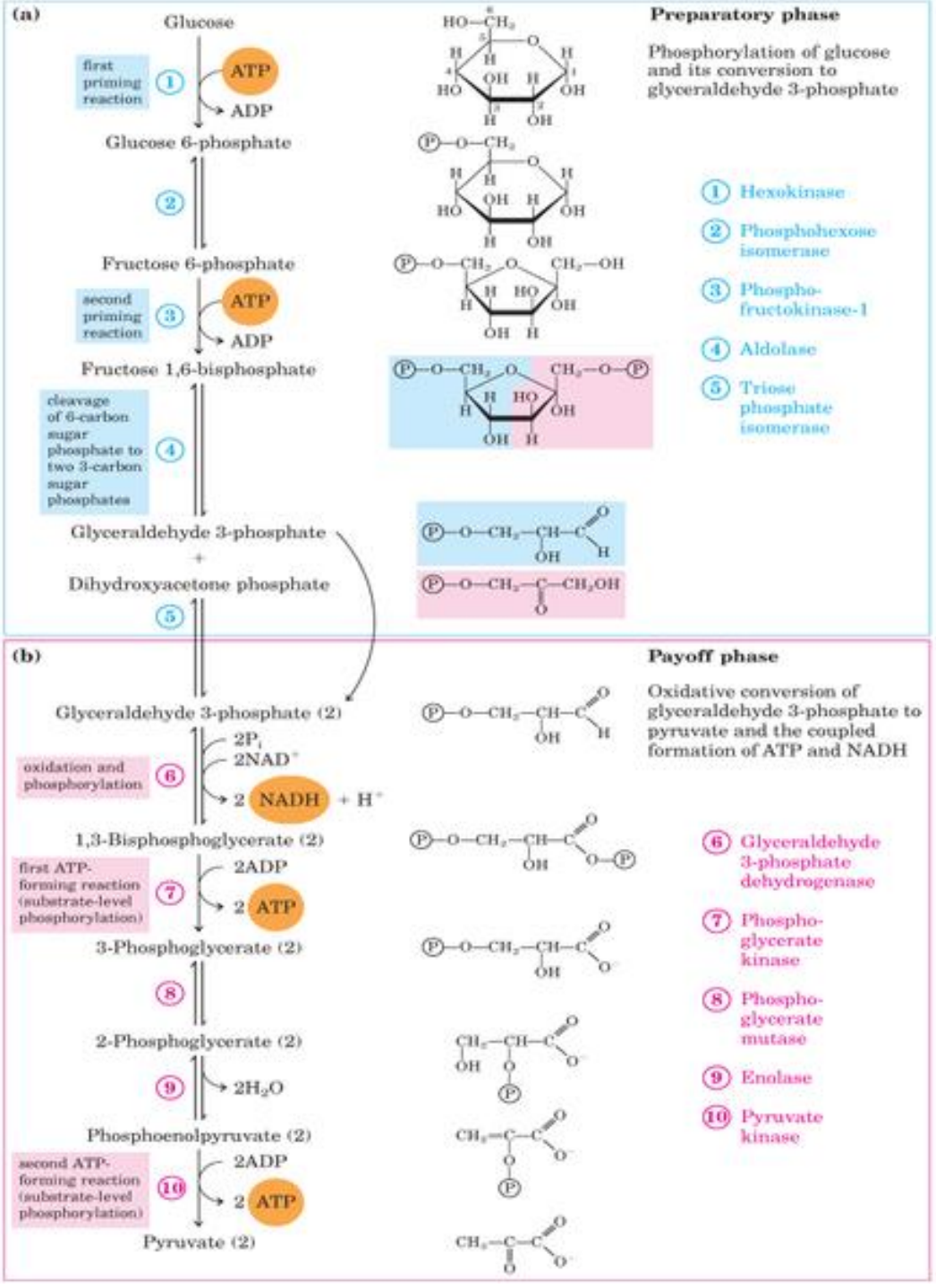



Lehninger Principles of Biochemistry (5E) 2008 by Nelson & Cox

## Major pathways of glucose utilization.



# Glycolysis


(a)
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to two 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase
(b)
Glyceraldehyde 3-phosphate (2)
oxidation and phosphorylation
6
2Pi
2NAD+
2 NADH + H+
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
7
2ADP
2 ATP
3-Phosphoglycerate (2)
8
2-Phosphoglycerate (2)
9
2H2O
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
10
2ADP
2 ATP
Pyruvate (2)
Payoff phase
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
6 Glyceraldehyde 3-phosphate dehydrogenase
7 Phospho-glycerate kinase
8 Phospho-glycerate mutase
9 Enolase
10 Pyruvate kinase

# TWO PHASES OF GLYCOLYSIS

- Glycolysis leads to breakdown of 6-C glucose into two molecules of 3-C pyruvate with the enzyme catalyzed reactions being bifurcated or categorized into 2 phases:

1. **Phase 1- preparatory phase**
2. **Phase 2- payoff phase.**

# PREPARATORY PHASE

- It consists of the 1st 5 steps of glycolysis in which the glucose is enzymatically phosphorylated by ATP to yield Fructose-1,6-biphosphate.
- This fructuse-1,6-biphosphate is then split in half to yield 2 molecules of 3-carbon containing Glyceraldehyde-3-phosphate/ dihyroxyacteone phosphate.

- Thus the first phase **results in cleavage of the hexose chain.**

- This cleavage requires an investment of 2 ATP molecules to activate the glucose mole and prepare it for its cleavage into 3-carbon compound.

# PAYOFF PHASE

- This phase constitutes the last 5 reactions of Glycolysis.
- This phase marks the release of ATP molecules during conversion of Glyceraldehyde-3-phosphtae to 2 moles of Pyruvate.
- Here 4 moles of ADP are phosphorylated to ATP. Although 4 moles of ATP are formed, the net result is only 2 moles of ATP per mole of Glucose oxidized, since 2 moles of ATP are utilized in Phase 1.

# OVERALL BALANCE SHEET OF GLYCOLYSIS

- Each molecule of glucose gives 2 molecules of Glyceraldehyde-3-phosphate. Therefore , the total input of all 10 reactions can be summarized as:

$$\text{Glucose} + 2\text{ATP} + 2\text{Pi} + 2\text{NAD}^+ + 2\text{H}^+ + 4\text{ADP}$$

$$\downarrow$$

$$2\text{Pyruvate} + 2\text{H}^+ + 4\text{ATP} + 2\text{H}_2\text{O} + 2\text{NADH} + 2\text{ADP}$$

On cancelling the common terms from the above equation, we get the net equation for Glycolysis:

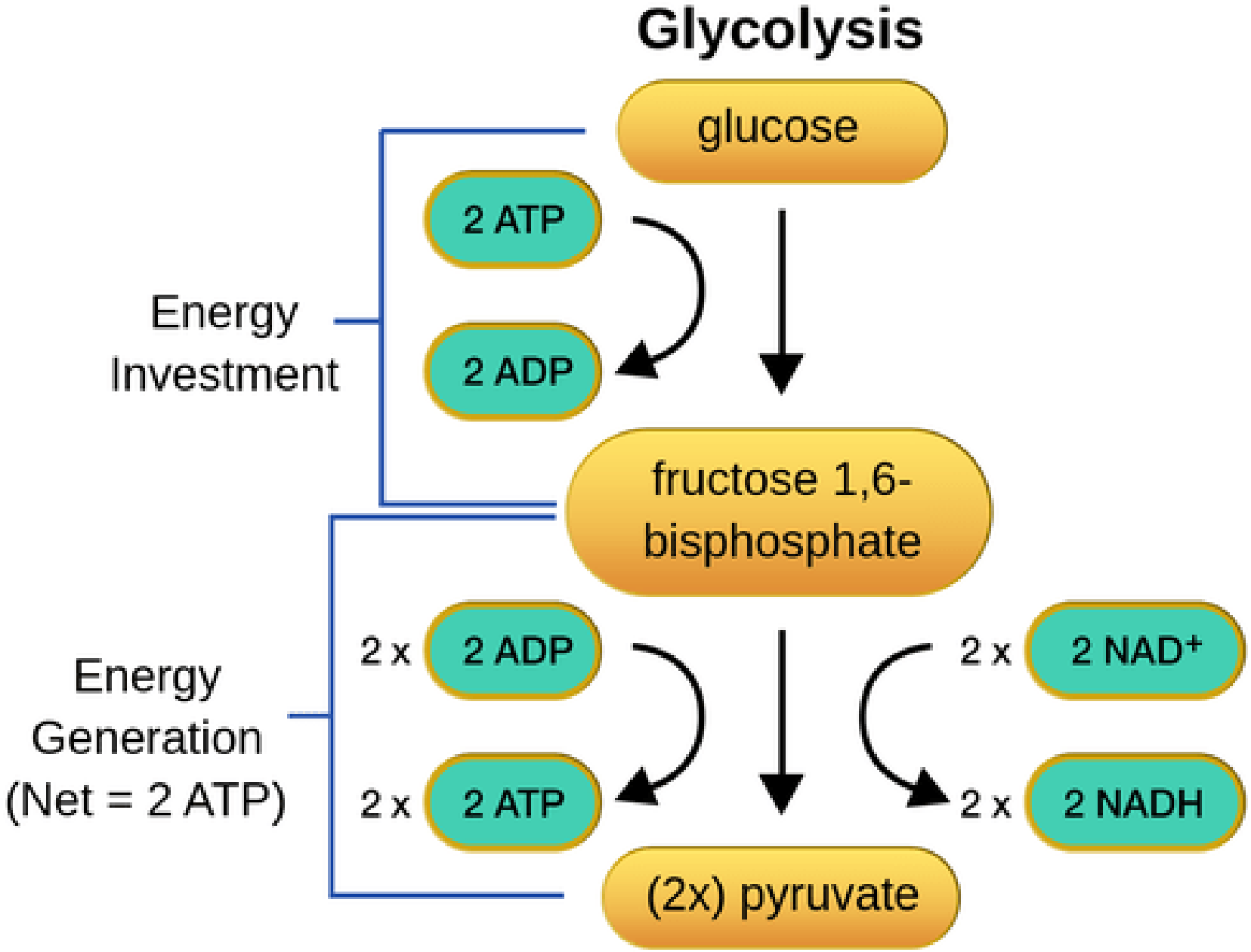
Glucose+ 2Pi+ 2ADP+ 2$NAD^+$

↓

2Pyruvate+ 2NADH+ 2ATP+ $2H^+$ + $2H_2O$

**THUS THE SIMULTANEOUS REACTIONS INVOLVED IN GLYCOLYSIS ARE:**

- ***Glucose is oxidized to Pyruvate***
- ***$NAD^+$ is reduced to NADH***
- ***ADP is phosphorylated to ATP***


Glycolysis
glucose
2 ATP
2 ADP
Energy Investment
fructose 1,6-bisphosphate
2 x
2 ADP
2 x
2 NAD+
Energy Generation (Net = 2 ATP)
2 x
2 ATP
2 x
2 NADH
(2x) pyruvate

## Table 1: Energetics of Glycolysis under aerobic and anaerobic conditions

| | Aerobic conditions | Anaerobic conditions |
|---|---|---|
| Step-1 | -1 ATP | -1 ATP |
| Step-3 | -1 ATP | -1 ATP |
| Step-5 | 2 x NADH = 5 ATP | 2 x NADH = 5 ATP |
| Step-6 | 2 x ATP | 2 x ATP |
| Step-9 | 2 x ATP | 2 x ATP |
| Regeneration of $NAD^+$ | | – 2 NADH = 5 ATP |
| NET ATP | 9-2=7 | 4-2=2 |

# Regulation of Glycolysis

## REGULATED STEPS IN GLYCOLYSIS

*Hexokinase: first step in glycolysis*

- Phosphorylates glucose
- Consumes ATP
- Traps glucose within cell
- Muscle: inhibited by glucose 6-P
- Liver: glucokinase isozyme

*Phosphofructokinase: committed step*

- Most important control element
- First reaction unique to glycolysis
- Phosphorylates fructose 6-P to form fructose 1,6-BP
- Consumes ATP
- Activated by AMP and fructose 2,6-BP (more important in liver)
- Inhibited by ATP, citrate and low pH (muscle)

*Pyruvate kinase: last step in glycolysis*

- Dephosphorylates phosphenol pyruvate to form pyruvate
- Generates ATP
- Activated by fructose 1,6-bisphosphate and AMP
- Inhibited by: ATP, alanine & Acetyl CoA

## MAJOR REGULATION SITES IN GLYCOLYSIS

*Muscle*

- Requires energy for contraction
- ATP: AMP ratio determines whether glycolysis should move forward
- When ratio is low: glycolysis activated
- 2 ADP combine to form 1 ATP and 1 AMP (free ADP does not persist)

*Liver*

- Uses molecules from glycolysis to start biosynthetic/metabolic reactions
- High glucose levels: liver stores glucose as glycogen
- Low glucose levels: liver releases glucose
- Liver isozymes allow glucose to be prioritized for brain & muscles

# Glycolysis is regulated by a number of mechanisms, including:

- Allosteric regulation

  Cells use allosteric effectors to rapidly respond to changes in energy demand by adjusting the activity of glycolytic enzymes.
- Hormonal signals

  Hormones like insulin and glucagon help coordinate glycolytic activity in response to changes in nutrient availability and metabolic state.
- Enzyme activity

  The activity of key regulatory enzymes, such as hexokinase, phosphofructokinase, and pyruvate kinase, is regulated.
- Metabolite concentrations

  Transient changes in key metabolite concentrations can balance ATP production and consumption within the cell.
- Cytoskeleton architecture

  The actin cytoskeleton is sensitive to environmental mechanical changes, which can regulate glycolysis.
- Acetylation

  Acetylation of metabolic enzymes regulates their activity and targets them for degradation.

# Regulation

- Glycolysis is also regulated by the hormones **Glucagon, Epinephrin**, and **Insulin** and by the changes in gene expression of several glycolytic enzymes.

- Allosteric regulation of several glycolytic enzyme:-

**1. Hexokinase**:

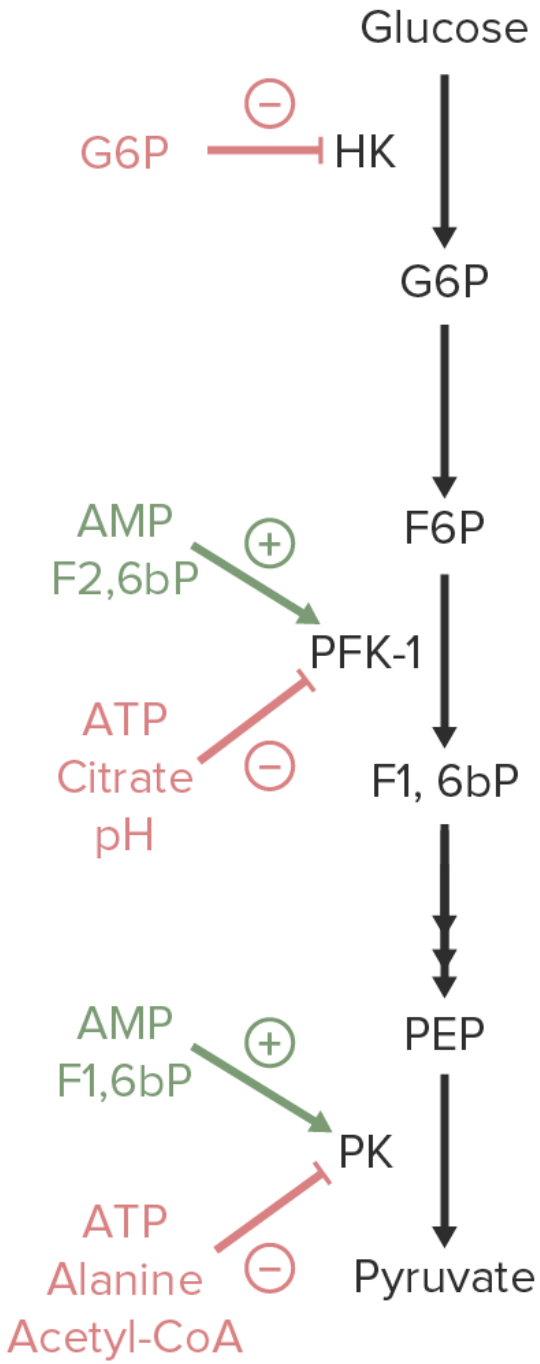
Inhibited by glucose-6- phosphate.

**2. Phosphofructokinase-1**:

- **Inhibitor**-ATP, Citrate and $h^+$ ion in low pH.
- **Activater**- fructose-2,6-bisphosphate, AMP, Fructose-6 Phosphate

**3. Pyruvate kinase**:

- **Inhibitor**- ATP and Acetyl-CoA
- **Activater** -fructose 1,6 bisphosphate and AMP


Glucose
G6P
HK
G6P
F6P
AMP
F2,6bP
PFK-1
ATP
Citrate
pH
F1, 6bP
PEP
AMP
F1,6bP
PK
ATP
Alanine
Acetyl-CoA
Pyruvate