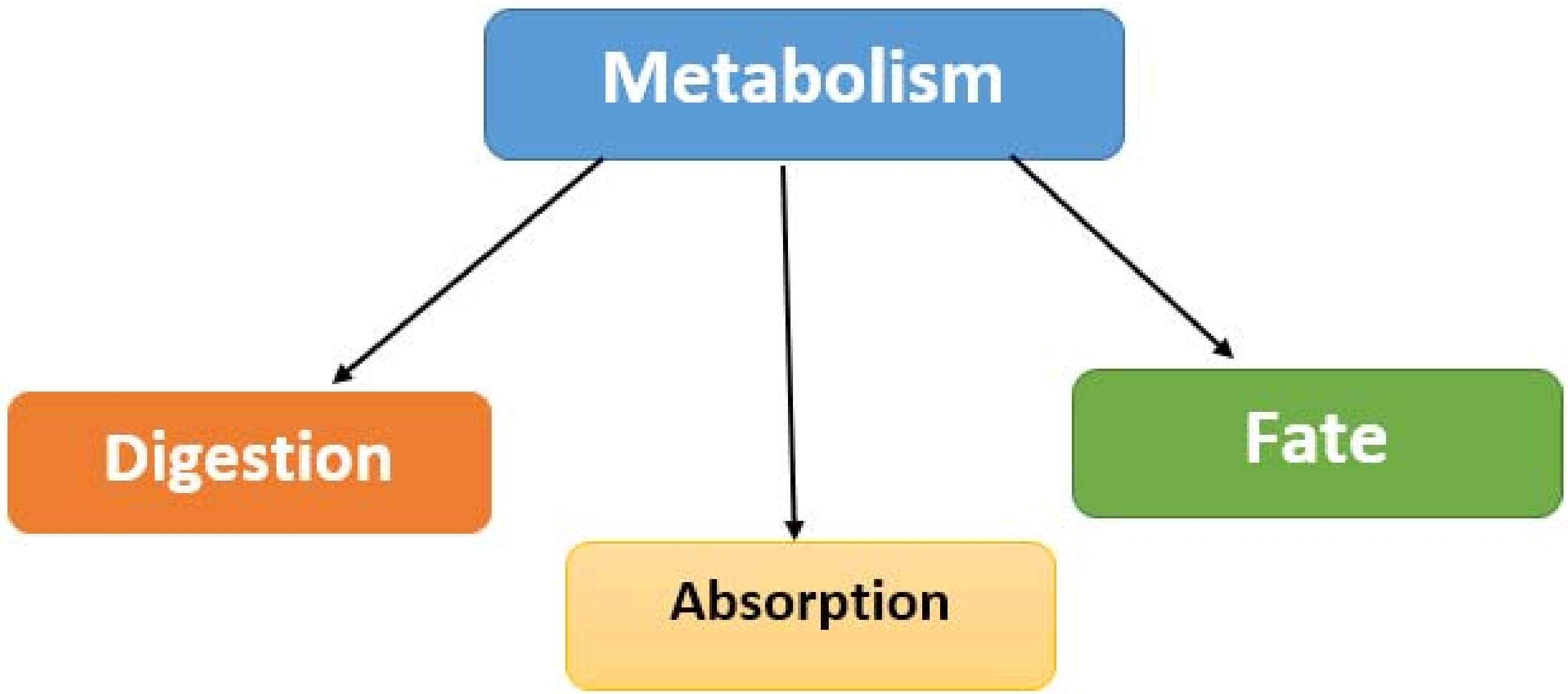
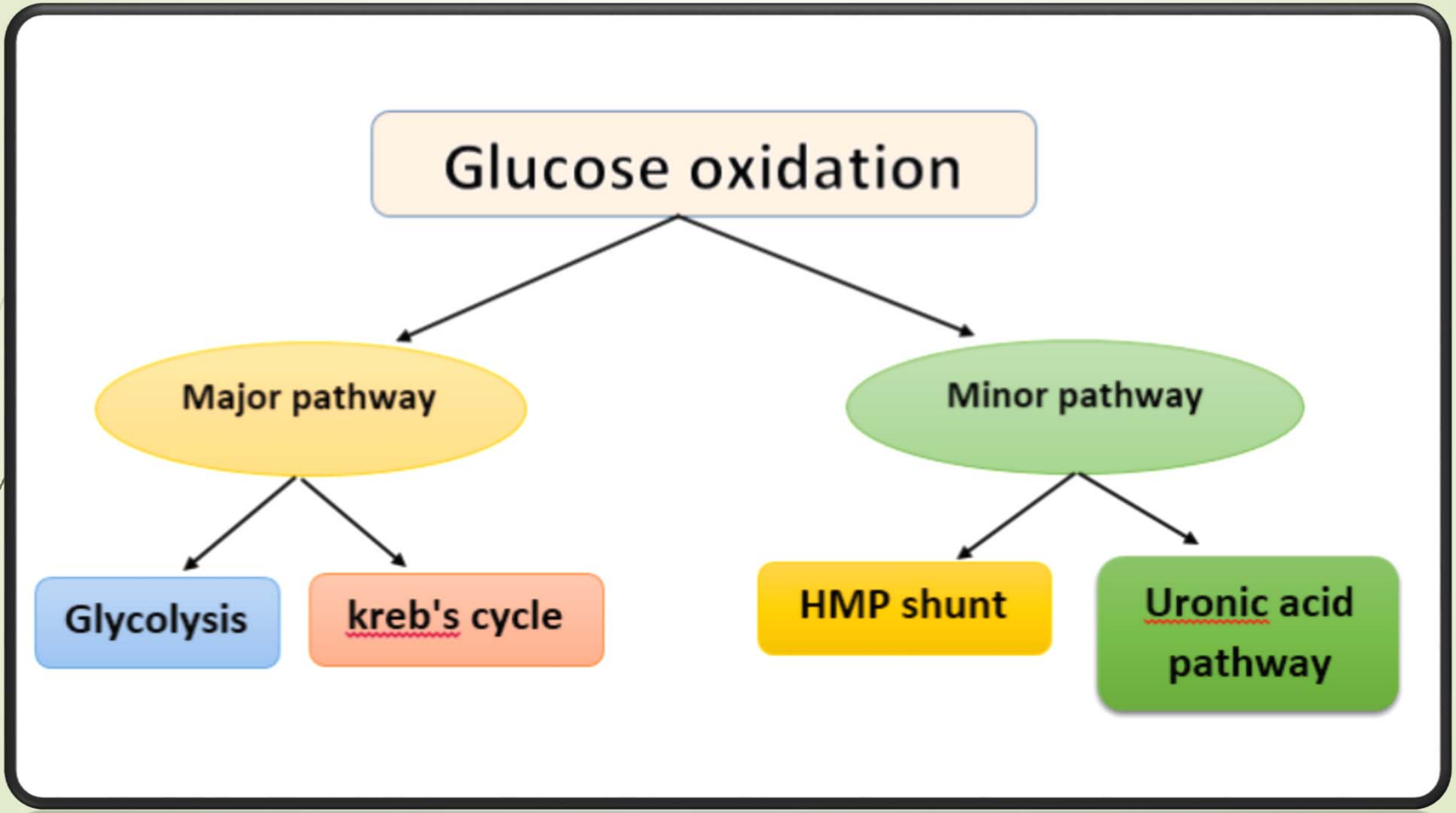
CARBOHYDRATE METABOLISM


Metabolism
Digestion
Absorption
Fate

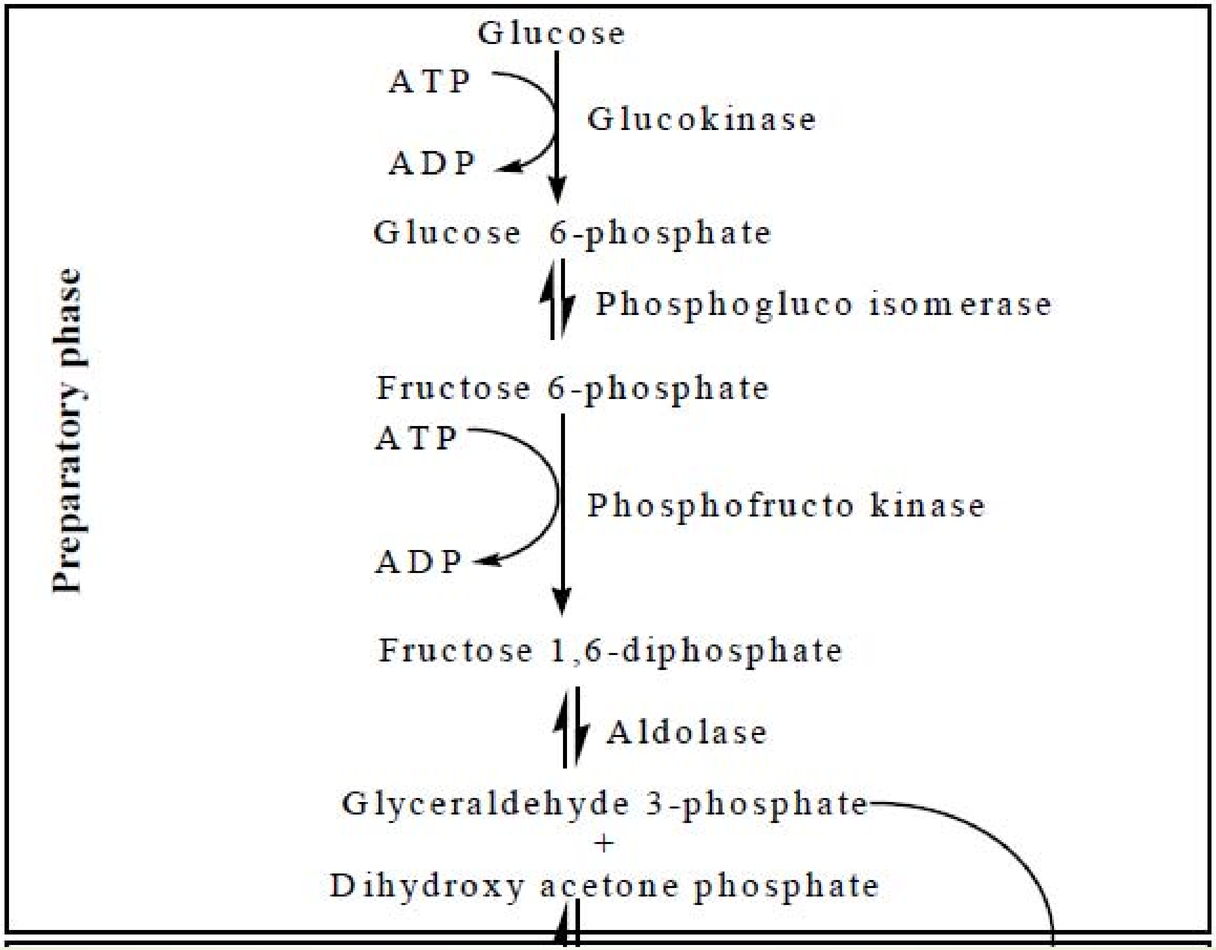
Carbohydrate metabolism

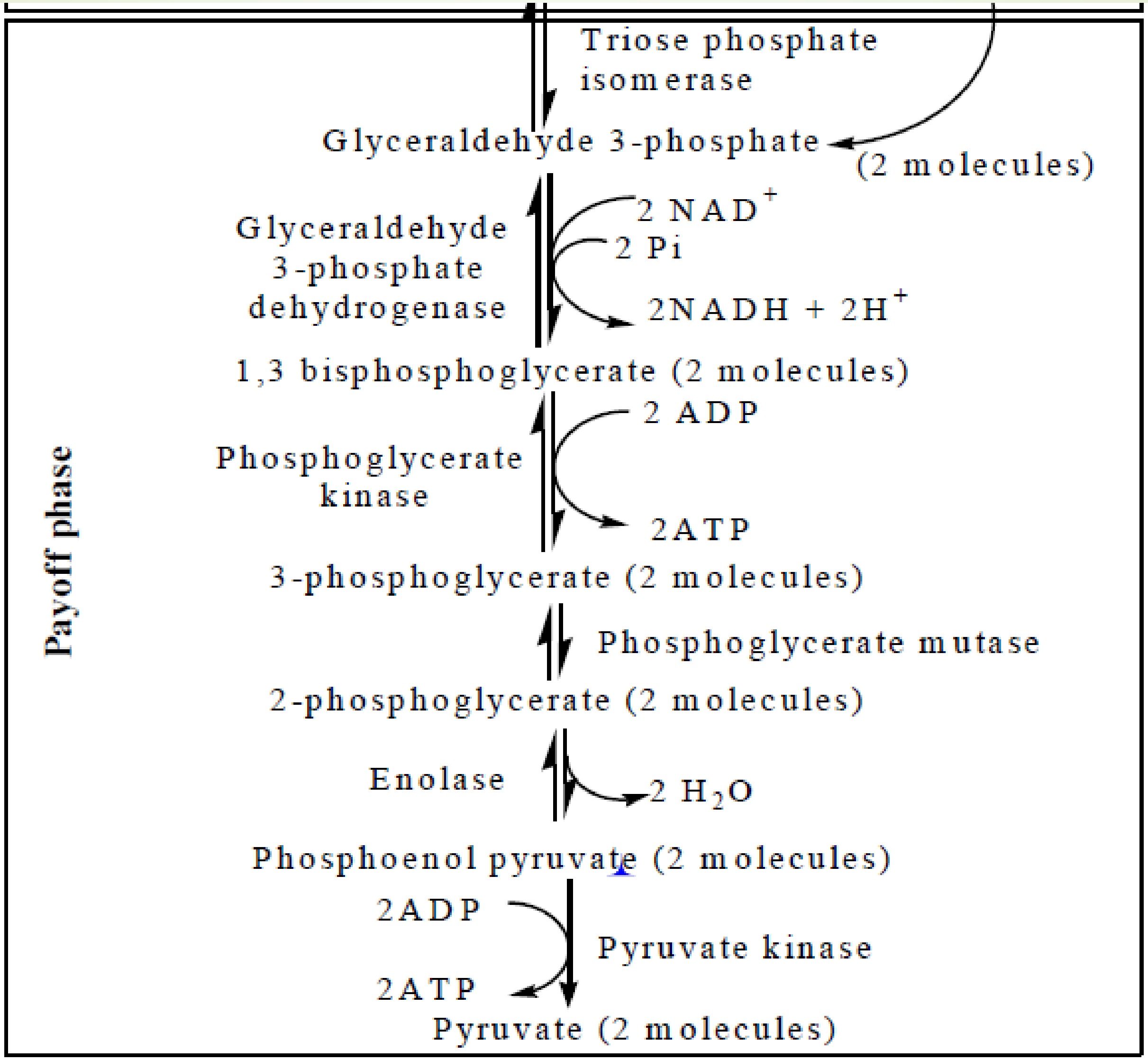
- **Fate of absorbed carbohydrate includes**
- **1- Uptake by tissues.**
- All tissues take glucose by active process under insulin control except brain, liver, RBCs and gut.
- **2- Utilization.**
- Oxidation for production of energy + CO_2 +H_2O
- Conversion to useful substance.
- **3- Storage.**
- Glucose is stored in the form of glycogen by glycogenesis or lipid by lipogenesis.
- **4- Excretion.**
- Excreted by kidney


Glucose oxidation
Major pathway
Minor pathway
Glycolysis
kreb's cycle
HMP shunt
Uronic acid pathway

Glycolysis

- Oxidation of glucose to pyruvate is called glycolysis.
- Glycolysis occurs virtually in all tissues. Erythrocytes and nervous tissues derive the energy mainly from glycolysis.
- This pathway is unique in the sense that it can proceed in both aerobic (presence of O2) and anaerobic (absence of O2) conditions.
- All the enzymes of glycolysis are found in the extra mitochondrial soluble fraction of the cell, the cytosol.


Glucose
ATP
Glucokinase
ADP
Glucose 6-phosphate
Phosphogluco isomerase
Fructose 6-phosphate
ATP
Phosphofructo kinase
ADP
Fructose 1,6-diphosphate
Aldolase
Glyceraldehyde 3-phosphate
+
Dihydroxy acetone phosphate
Preparatory phase

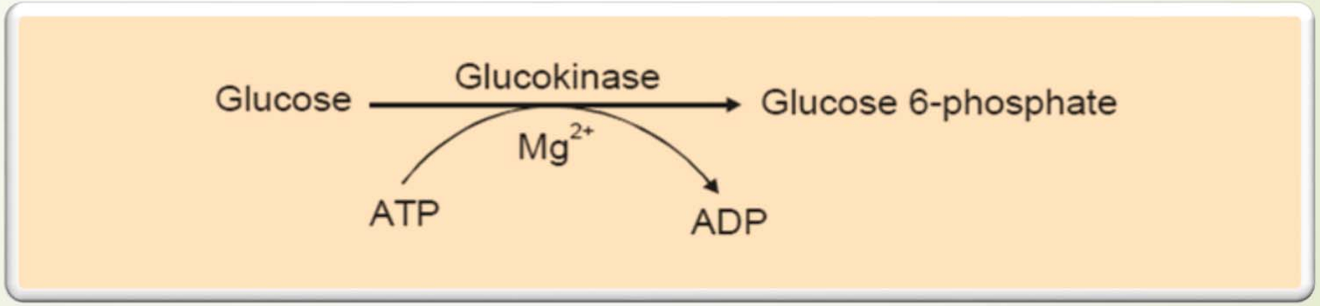


Triose phosphate isomerase
Glyceraldehyde 3-phosphate
(2 molecules)
Glyceraldehyde 3-phosphate dehydrogenase
2 NAD+
2 Pi
2NADH + 2H+
1,3 bisphosphoglycerate (2 molecules)
Phosphoglycerate kinase
2 ADP
2ATP
Payoff phase
3-phosphoglycerate (2 molecules)
Phosphoglycerate mutase
2-phosphoglycerate (2 molecules)
Enolase
2 H2O
Phosphoenol pyruvate (2 molecules)
2ADP
2ATP
Pyruvate kinase
Pyruvate (2 molecules)

Reactions of glycolytic pathway

- Series of reactions of glycolytic pathway which degrades glucose
- to pyruvate .
- in glycolysis may be considered under **four stages.**
- ***Stage I***
- **This is a *preparatory phase***. Before the glucose molecule can be
- split, the rather asymmetric glucose molecule is converted to almost
- symmetrical form, fructose 1,6-diphosphate by donation of two phosphate groups from ATP.

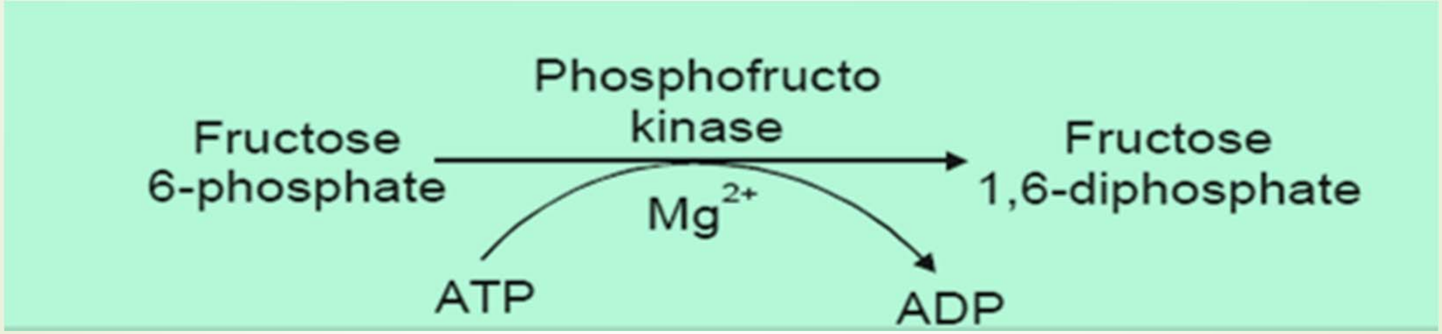
- **Uptake of glucose by cells and its phosphorylation**
- Glucose is freely permeable to liver cells, intestinal mucosa and
- kidney tubules where glucose is taken up by 'active' transport. In other
- tissues insulin facilitates the uptake of glucose. Glucose is phosphorylated
- to form glucose 6-phosphate. The enzyme involved in this reaction is
- glucokinase. This reaction is irreversible.



- **Conversion of glucose 6-phosphate to fructose 6-phosphate**
- Glucose 6-phosphate is converted to fructose 6-phosphate by the enzyme phosphogluco isomerase.

$$\text{Glucose 6-phosphate} \xrightleftharpoons{\text{Phosphogluco isomerase}} \text{Fructose 6-phosphate}$$

- **Conversion of fructose 6-phosphate to fructose 1,6 diphosphate**
- Fructose 6-phosphate is phosphorylated irreversibly at 1 position
- catalyzed by the enzyme phosphofructokinase to produce fructose 1,6-diphosphate.



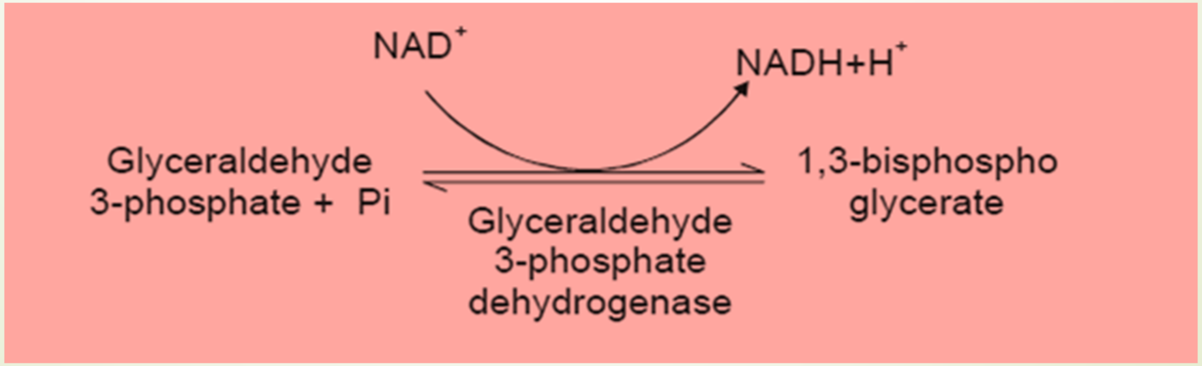
- ***Stage II***
- **Actual splitting of fructose 1,6 diphosphate**
- Fructose 1,6 diphosphate is split by the enzyme aldolase into two molecules of triose phosphates, an aldotriose-glyceraldehyde 3-phosphate and one ketotriose - dihydroxy acetone phosphate. The reaction is reversible. There is neither expenditure of energy nor formation of ATP.

$$\text{Fructose 1,6-diphosphate} \xrightleftharpoons{\text{Aldolase}} \begin{array}{c}\text{Glyceraldehyde}\\ \text{3-phosphate}\\ +\\ \text{Dihydroxy acetone}\\ \text{phosphate}\end{array}$$

- **Interconvertion of triose phosphates**
- Both triose phosphates are interconvertible

$$\text{Dihydroxy acetone phosphate} \xrightleftharpoons{\text{Triose phosphate isomerase}} \text{Glyceraldehyde 3-phosphate}$$

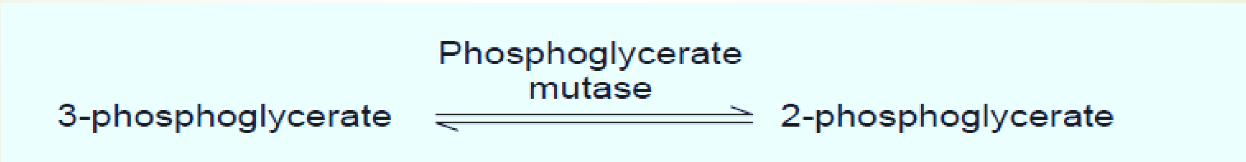
- ***Stage III***
- It is the energy yielding stage. Reactions of this type in which an aldehyde group is oxidised to an acid are accompanied by liberation of large amounts of potentially useful energy.
- **1. Oxidation of glyceraldehyde 3-phosphate to**
- **1,3-bisphosphoglycerate**
- Glycolysis proceeds by the oxidation of glyceraldehyde 3-phosphate to form 1,3-bisphosphoglycerate. The reaction is catalyzed by the enzyme glyceraldehyde 3-phosphate dehydrogenase



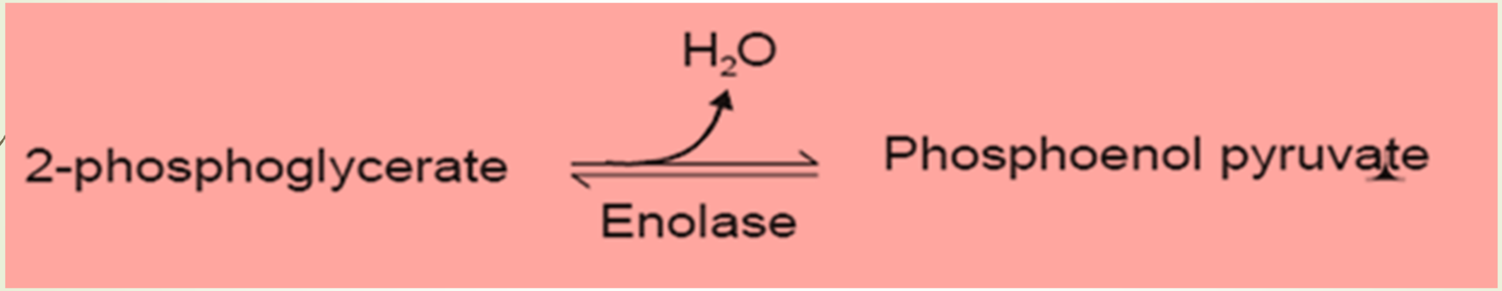
- **Conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate**
- The reaction is catalyzed by the enzyme phosphoglycerate kinase.
- The high energy phosphate bond at position - 1 is transferred to ADP to form ATP molecule.

$$\text{1,3-bisphosphoglycerate} + \text{ADP} \xrightleftharpoons[\text{Phosphoglycerate kinase}]{Mg^{2+}} \text{3-phosphoglycerate} + \text{ATP}$$

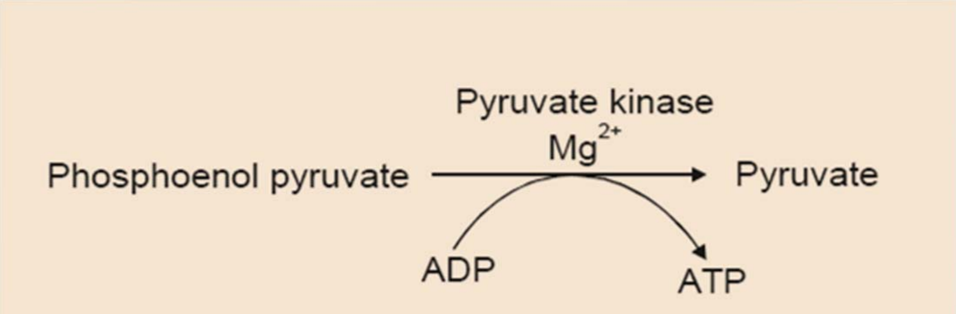
- ***Stage IV***
- It is the recovery of the phosphate group from 3-phosphoglycerate.
- The two molecules of 3-phosphoglycerate, the end-product of the previous stage, still retains the phosphate group, originally derived from ATP in Stage I.
- **Conversion of 3-phosphoglycerate to 2-phosphoglycerate.**
- 3-phosphoglycerate formed by the above reaction is converted to 2-phosphoglycerate, catalyzed by the enzyme phosphoglycerate mutase.



- **Conversion of 2-phosphoglycerate to phosphoenol pyruvate**
- The reaction is catalyzed by the enzyme enolase, the enzyme requires the presence of either Mg2+ or Mn2+ ions for activity.



- **Conversion of phosphoenol pyruvate to pyruvate**
- Phosphoenol pyruvate is converted to pyruvate, the reaction is catalysed by the enzyme pyruvate kinase. The high energy phosphate group of phosphoenol pyruvate is directly transferred to ADP, producing ATP.
- The reaction is irreversible.



Energy yield per glucose molecule oxidation

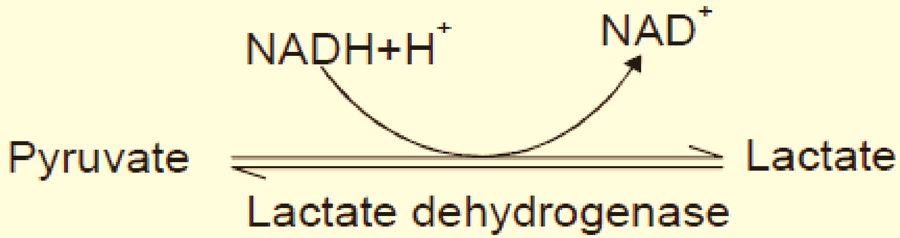
- During glycolysis ATP molecules are used and formed in the following reactions (aerobic phase).

Reactions Catalyzed	ATP used	ATP formed
Stage I 1. Glucokinase (for phosphorylation)	1	
2. Phosphofructokinase I (for phosphorylation)	1	
Stage II 3. Glyceraldehyde 3-phosphate dehydrogenase (oxidation of 2 NADH in respiratory chain)		6
4. Phosphoglycerate kinase (substrate level phosphorylation)		2
Stage IV 5. Pyruvate kinase (substrate level phosphorylation)		2
Total	2	10

Net gain = 8 ATP

Anaerobic phase

In the absence of O_2, reoxidation of NADH at glyceraldehyde 3-phosphate dehydrogenase stage cannot take place in respiratory chain. But the cells have limited coenzyme. Hence to continue the glycolysis NADH must be reoxidized to NAD^+. This is achieved by reoxidation of NADH by conversionof pyruvate to lactate (without producing ATP).



It is to be noted that in the reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase, therefore, no ATP is produced.

In the anaerobic phase oxidation of one glucose molecule produces $4 - 2 = 2$ ATP.

GLYCOLYSIS FUNCTION

Aerobic: To convert *glucose* to pyruvate and ATP. Pyruvate can be burned for energy (TCA) or converted to fat (fatty acid synthesis).

Anaerobic: ATP production. Recycle NADH by making lactate.

GLYCOLYSIS LOCATION

Cytosol of all cells.

GLYCOLYSIS CONNECTIONS

Glucose *in*, pyruvate or lactate *out*.
Glucose 6-phosphate to glycogen (reversible).
Glucose 6-phosphate to pentose phosphates (*not* reversible).
Pyruvate to TCA via acetyl-CoA (*not* reversible).
Pyruvate to *fat* via acetyl-CoA (*not* reversible).

GLYCOLYSIS REGULATION

Primary signals:	*Insulin* turns *on*.
	Glucagon turns *off*.
	Epinephrine turns *on* in *muscle*, *off* in *liver*.
	Phosphorylation turns *off* in *liver*, *on* in *muscle*.
Secondary signals:	Glucose signals activate (fructose 2,6-bis-phosphate activates phosphofructokinase).
	Low-glucose signals inhibit.
	High-energy signals inhibit.
	Low-energy signals activate.

GLYCOLYSIS ATP YIELDS

Aerobic:	1 glucose $\longrightarrow$ 2ATP + 2NADH + 2 pyruvate
Anaerobic:	1 glucose $\longrightarrow$ 2ATP + 2 lactate
Complete:	1 glucose $\longrightarrow$ $6CO_2$ + 38ATP (using malate/aspartate shuttle to oxidize NADH)
From glycogen:	$(\text{Glycogen})_n$ $\longrightarrow$ 3ATP + 2NADH + 2 pyruvate

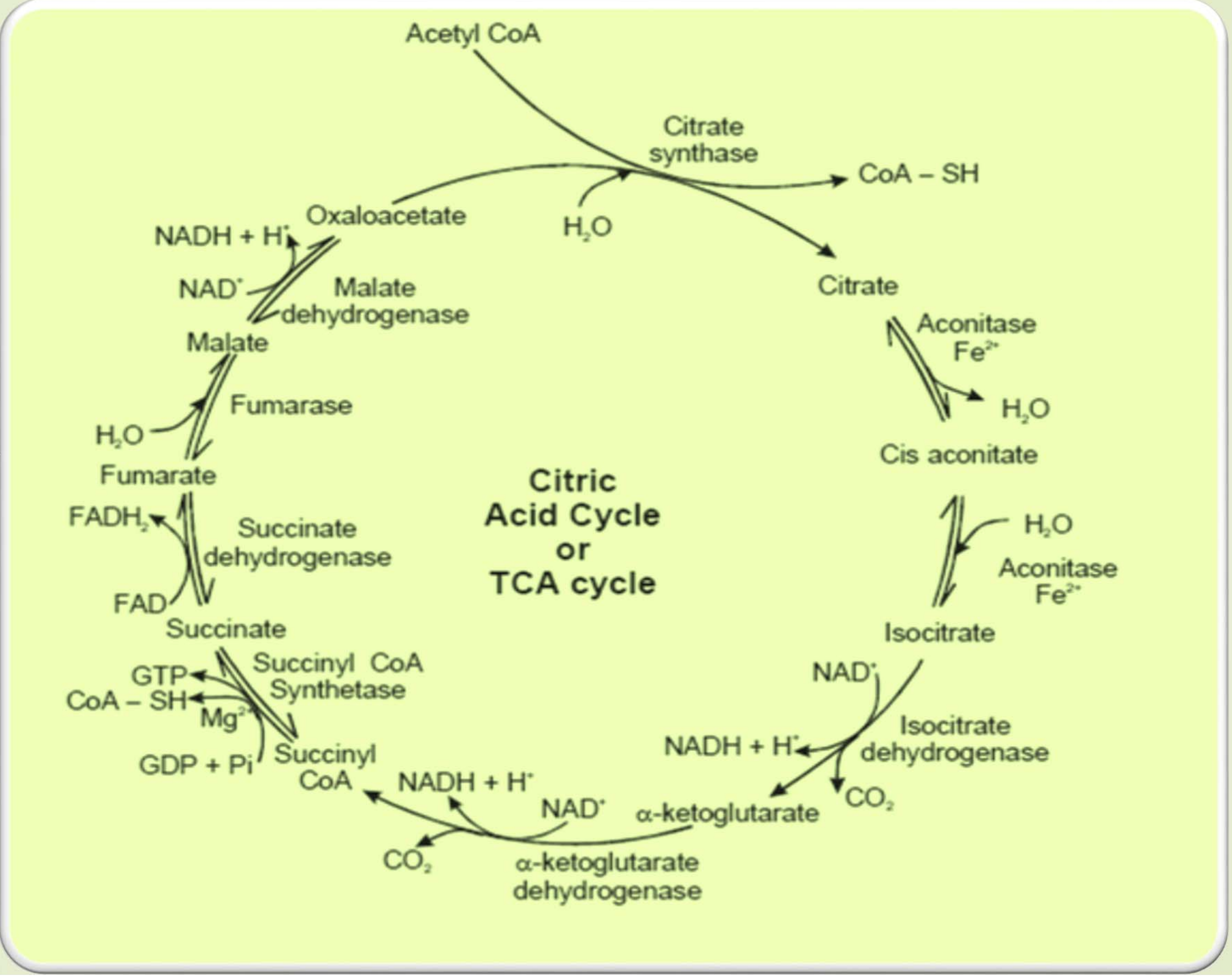
GLYCOLYSIS EQUATIONS

Aerobic: $\text{Glucose} + 2\text{ADP} + 2\text{P}_i + 2\text{NAD}^+ \longrightarrow 2\text{ pyruvate} + 2\text{ATP} + 2\text{NADH} + 2\text{H}^+$

Anaerobic: $\text{Glucose} + 2\text{ADP} + 2\text{P}_i \longrightarrow 2\text{ lactate} + 2\text{ATP}$

Tricarboxylic acid cycle (TCA cycle)

- This cycle is the aerobic phase of carbohydrate metabolism and follows the anaerobic pathway from the stage of pyruvate and is called as citric acid cycle or TCA cycle. The name citric acid cycle stems from citric acid which is formed in the first step of this cycle. This cycle is also named "Kerbs cycle" after H.A. Krebs, an English biochemist who worked on it.
- Under aerobic conditions, pyruvate is oxidatively decarboxylated to acetyl coenzyme A (active acetate) before entering the citric acid cycle.
- This occurs in the mitochondrial matrix and forms a link between glycolysis and TCA cycle.



Acetyl CoA
Citrate synthase
CoA – SH
H_2O
Oxaloacetate
NADH + H^+
NAD^+
Malate dehydrogenase
Malate
Fumarase
H_2O
Fumarate
$FADH_2$
Succinate dehydrogenase
FAD
Succinate
Succinyl CoA Synthetase
GTP
CoA – SH
Mg^{2+}
GDP + Pi
Succinyl CoA
NADH + H^+
NAD^+
CO_2
α-ketoglutarate dehydrogenase
α-ketoglutarate
CO_2
NADH + H^+
NAD^+
Isocitrate dehydrogenase
Isocitrate
H_2O
Aconitase Fe^{2+}
Cis aconitate
H_2O
Aconitase Fe^{2+}
Citrate
Citric Acid Cycle or TCA cycle

Reactions	No.of ATP formed
1. 2 isocitrate $\rightarrow$ 2 α-ketoglutarate (2 NADH + 2H$^+$) (2 $\times$ 3)	6
2. 2 α-ketoglutarate $\rightarrow$ 2 succinyl CoA (2 NADH + 2H$^+$) (2 $\times$ 3)	6
3. 2 succinyl CoA $\rightarrow$ 2 succinate (2 GTP = 2ATP)	2
4. 2 succinate $\rightarrow$ 2 Fumarate (2 $FADH_2$) (2 $\times$ 2)	4
5. 2 malate $\rightarrow$ 2 oxaloacetate (2 NADH + 2H$^+$) (2 $\times$ 3)	6
Total No.of ATP formed	24

Calculation of energy

- One molecule of glucose gives 36-38 ATP.
- Glycolysis gives 2 ATP in absence of oxygen.
- Glycolysis gives 6 ATP or 8 ATP in the presences of oxygen.
- Glucose oxidation gives 2 molecule of pyruvic acid
- The conversion of pyruvic acid to active acetate gives 3ATP.
- In kreb's cycle gives 12 ATP
- (2 X (12+3) ATP) $\longrightarrow$ 30 ATP.
- 30 ATP+ 6 or 8 ATP $\longrightarrow$ 36 ATP OR 38 ATP