Glycolysis

In all tisues , glycolysis which occurs in the cytosol is used for breakdown of glucose to form energy (in the form of ATP) and intermediates that are used in the body for biosynthesis .
Mature RBCs or erythrocytes contain no mitochondria , so they are totally dependent upon glycolysis for ATP production .

Biomedical importance of glycolysis

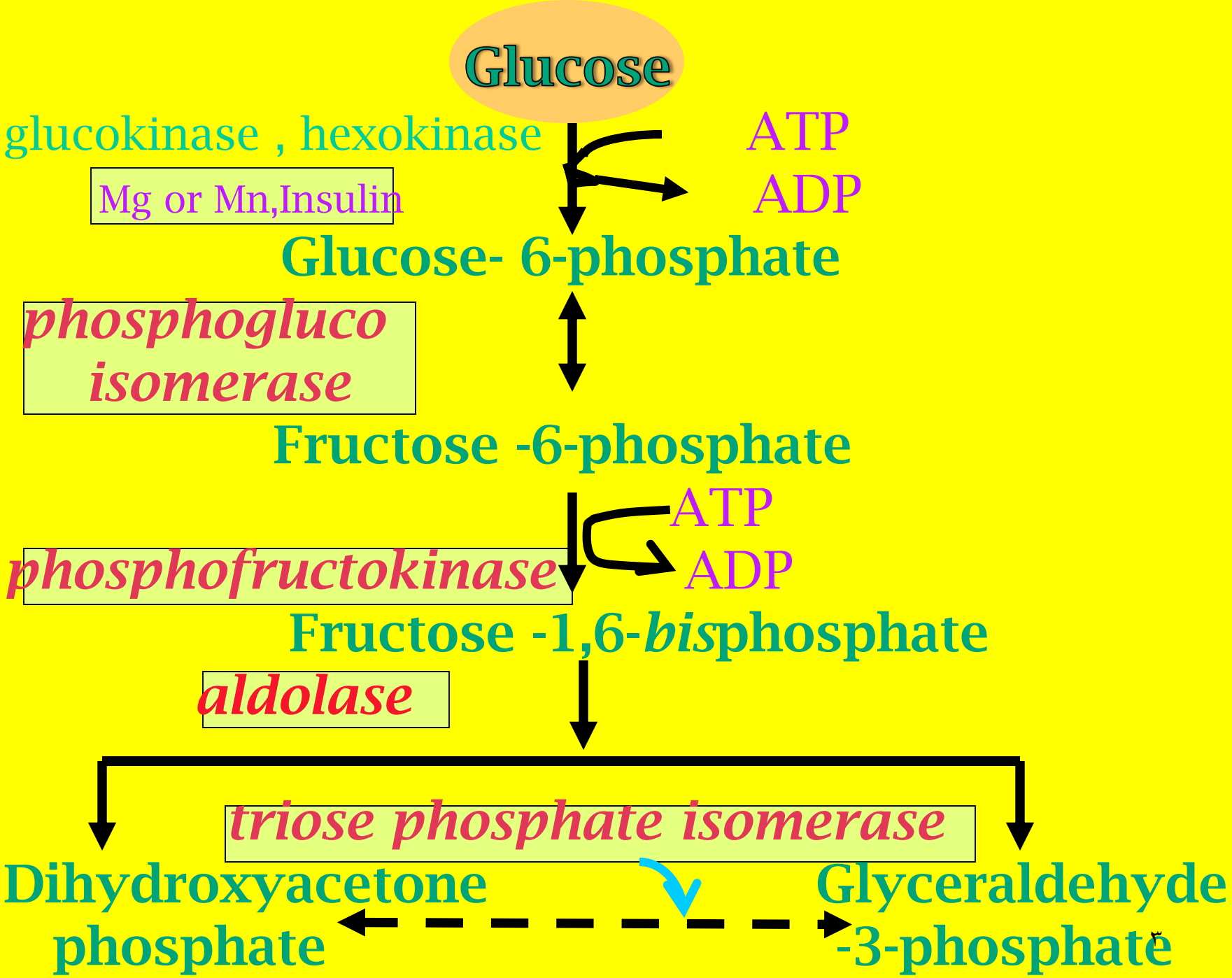
1 . This pathway is meant for provision of energy .
2 . It has importance in skeletal muscle as glycolysis provides ATP even in absence of O2 .
3 . In fast – growing cancer cells , rate of glycolysis is very high , produces more pyruvic acid . Accumulation of pyruvic acid leads to excessive formation of lactic acid producing local lactic acidosis .
4 . A genetic defect of hexokinase and pyruvate kinase lead to low ATP production , decrease RBCs , stability and swelling that result in hemolytic anemia .

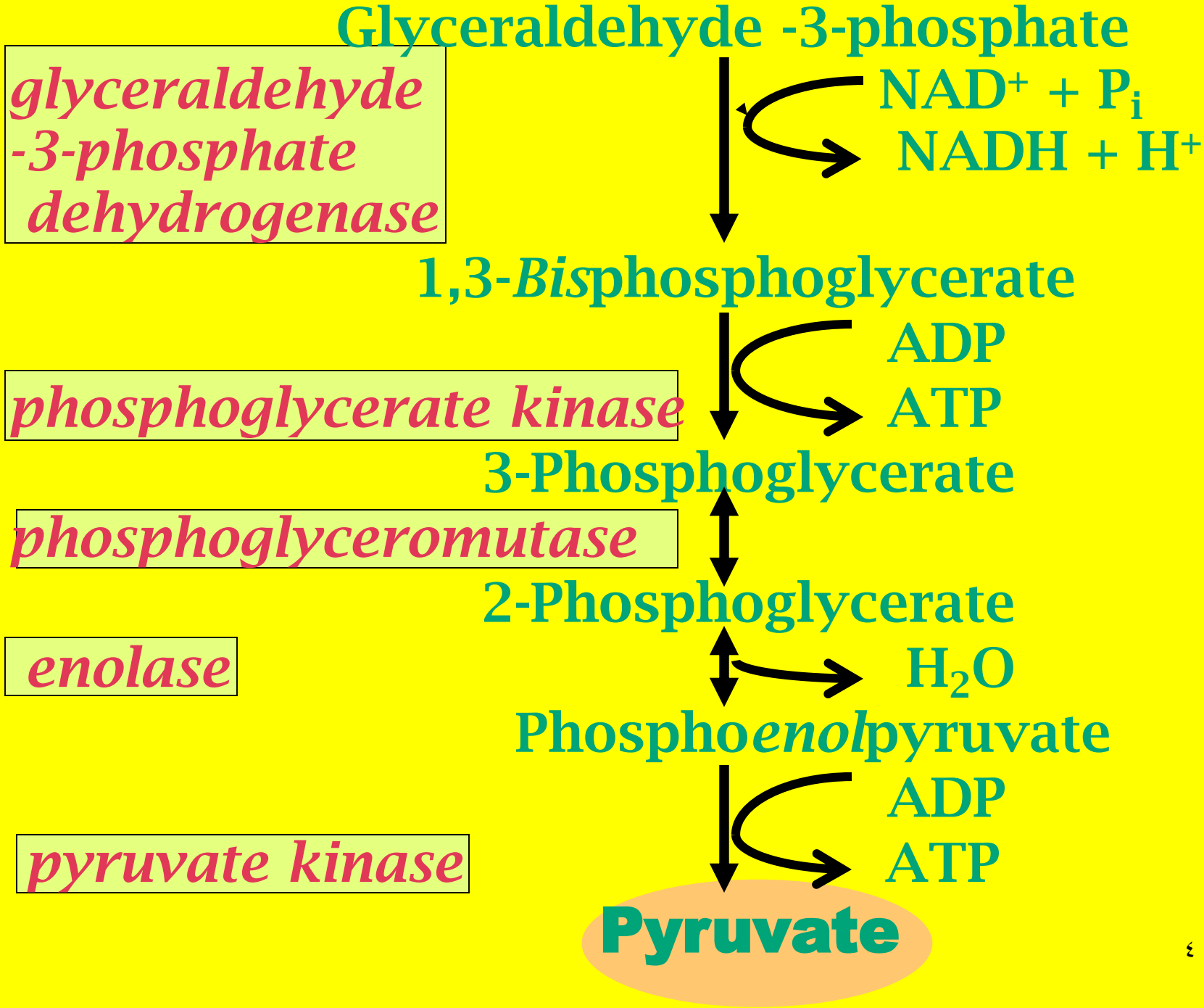
Glycolysis has two stages.

A. An ***energy investment*** phase. Reactions, 1-5. Glucose to two glyceraldehyde-3-phosphate molecules.

B. An ***energy payoff*** phase. Reactions 6-10 . Two glyceraldehyde -3-phosphate molecules to two pyruvate plus four ATP molecules.

-- A **net of two ATP** molecules overall plus **two NADH** .


Glucose
glucokinase , hexokinase
Mg or Mn,Insulin
ATP
ADP
Glucose- 6-phosphate
phosphogluco isomerase
Fructose -6-phosphate
ATP
ADP
phosphofructokinase
Fructose -1,6-bisphosphate
aldolase
triose phosphate isomerase
Dihydroxyacetone phosphate
Glyceraldehyde -3-phosphate


Glyceraldehyde -3-phosphate
glyceraldehyde -3-phosphate dehydrogenase
NAD+ + Pi
NADH + H+
1,3-Bisphosphoglycerate
ADP
ATP
phosphoglycerate kinase
3-Phosphoglycerate
phosphoglyceromutase
2-Phosphoglycerate
enolase
H2O
Phosphoenolpyruvate
ADP
ATP
pyruvate kinase
Pyruvate

Hexokinase

-Non – specific , can phosphorylate any of the hexoses .

- found in *all tissues* .

-Km is low = 0.1 mM , hence high affinity for glucose .

-Allosteric inhibition by G6P .

- No change with glucose feeding .

-Main function to make available glucose to tissues for oxidation at lower blood glucose level .

Glucokinase

-Specific , can phosphorylate glucose only .

-Found in liver .

- Km is high = 10mM , low affinity for glucose .

-Not inhibited by G6P .

- Increased by feeding glucose after fasting .

-Main function to clear glucose from blood after meals and at blood level greater than 100 mg / dl .

Summary of energy relationships for glycolysis (aerobic phase)

Input **= 2 ATP**

1. glucose + ATP → glucose-6-P
2. fructose-6-P + ATP → fructose-1,6 - *bis*phosphate

Output **= 4 ATP + 2 NADH**

1. 2 – glyceraldehyde- 3-P + 2 P_i + 2 NAD^+ → 2 (1,3- *bis*phosphoglycerate) + 2 NADH
2. 2 (1,3 -*bis*phosphoglycerate) + 2 ADP → 2 (3-P-glycerate) + 2 ATP
3. 2 PEP + 2 ADP → 2 pyruvate + 2 ATP

Net **= 2 ATP and 2 NADH**

Two phases of glycolysis

1 . Aerobic phase

Aerobic phase includes the conversion of glucose to pyruvate . Oxidation is carried out by dehydrogenation and reducing equivalent is transferred to NAD .

NADH + H in the presence of O2 is oxidized in electron transport chain (ETC) producing ATP . In this phase , 8 ATP will be produced per molecule of glucose oxidation .

2 . Anaerobic phase

This phase includes the conversion of glucose to lactate. NADH cannot be oxidized ,so no ATP is produced in ETC . But the NADH is oxidized to NAD by conversion of pyruvate to lactate , without producing ATP . In this phase , 2 ATP will be produced per molecule of glucose oxidation .

Fate of p*yruvic acid depends on the redox state of the tissues :*

a)In the presence of O2:pyruvic acid is oxidatively decarboxylated to acetyl CoA .

b)In the absence of O2 : pyruvic acid is converted to lactic acid .

Other fates of pyruvic acid can be summed up as follows :

-Pyruvic acid can be aminated to form the amino acid alanine .

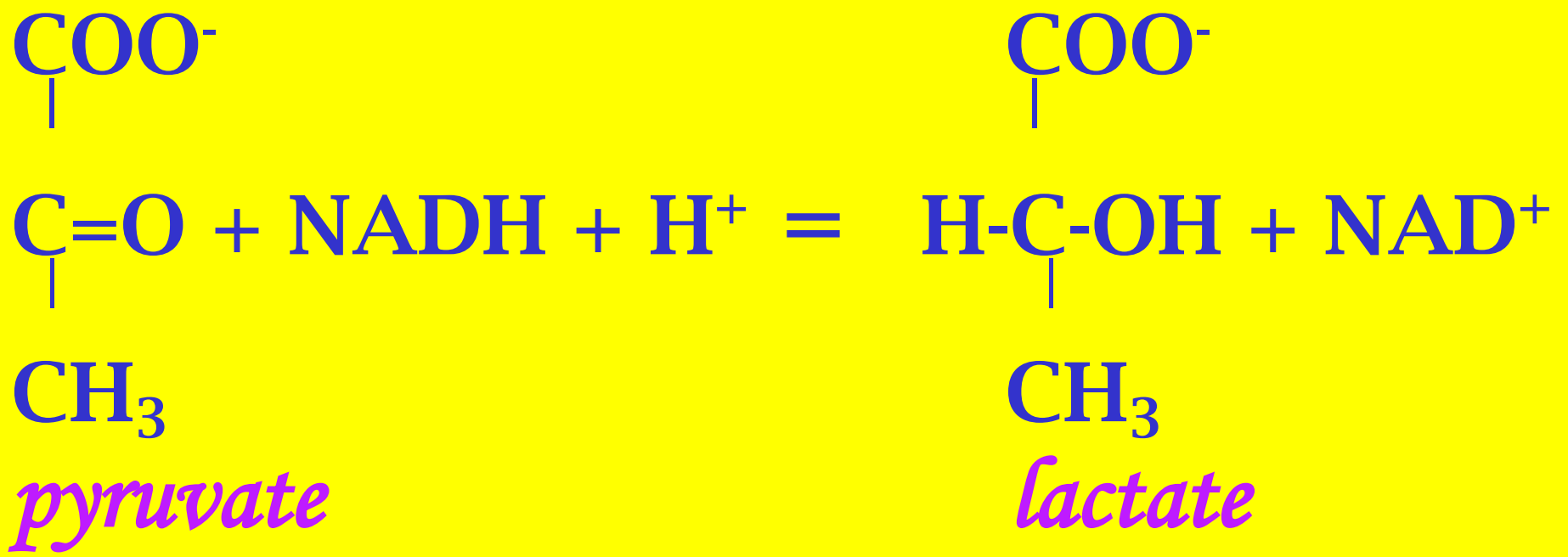
-Pyruvic acid can be converted to form glucose in the body .

-Pyruvic acid can be converted to malic acid , which is turn can form oxalo acetic acid (OAA) .

-Pyruvic acid can be converted directly to OAA in the body by CO_2 fixation reaction .

(Lactate Fermentation)

Enzyme = *Lactate Dehydrogenase*



- Note : Uses up all the NADH (reducing equivalents) produced in glycolysis.

-- ***Lactate Dehydrogenase (LDH)***

It is an isozyme .Two polypeptides M and H come together to form LDH .

It is a tetramer so a mixture is formed : M4 , M3H , M2H2 , MH3 and H4 .

Skeletal muscle and liver contain predominantly the M form ; heart the H form . During and after myocardial infraction (heart attack) , heart cells die releasing LDH into the circulation.

-- Diagnostic

The function of LDH in muscle is mainly conversion of pyruvic acid to lactic acid , so it is activated by high level of pyruvic acid and inhibited by high level of lactic acid .
In the heart , the reverse occurs , it act for conversion of lactic acid to pyruvic acid in order to supply high energy , so it is inhibited by high level of pyruvic acid and stimulated by high level of lactic acid .

Notes :

1 .The lactate which is formed is transported by blood to liver and become glucose and transport by blood to the tissues .

2 . Phosphofructokinase inhibited in high conc. of ATP (when ATP is high , the cell dose not need ATP and glycolysis inhibited) and citrate (high level of citrate indicate the adequate amount of substrate are entering CAC , therefor , glycolysis slow down) .

3.Serum aldolase level are elevated in poly myocytosis , multiple seclerosis and poly neuritis .

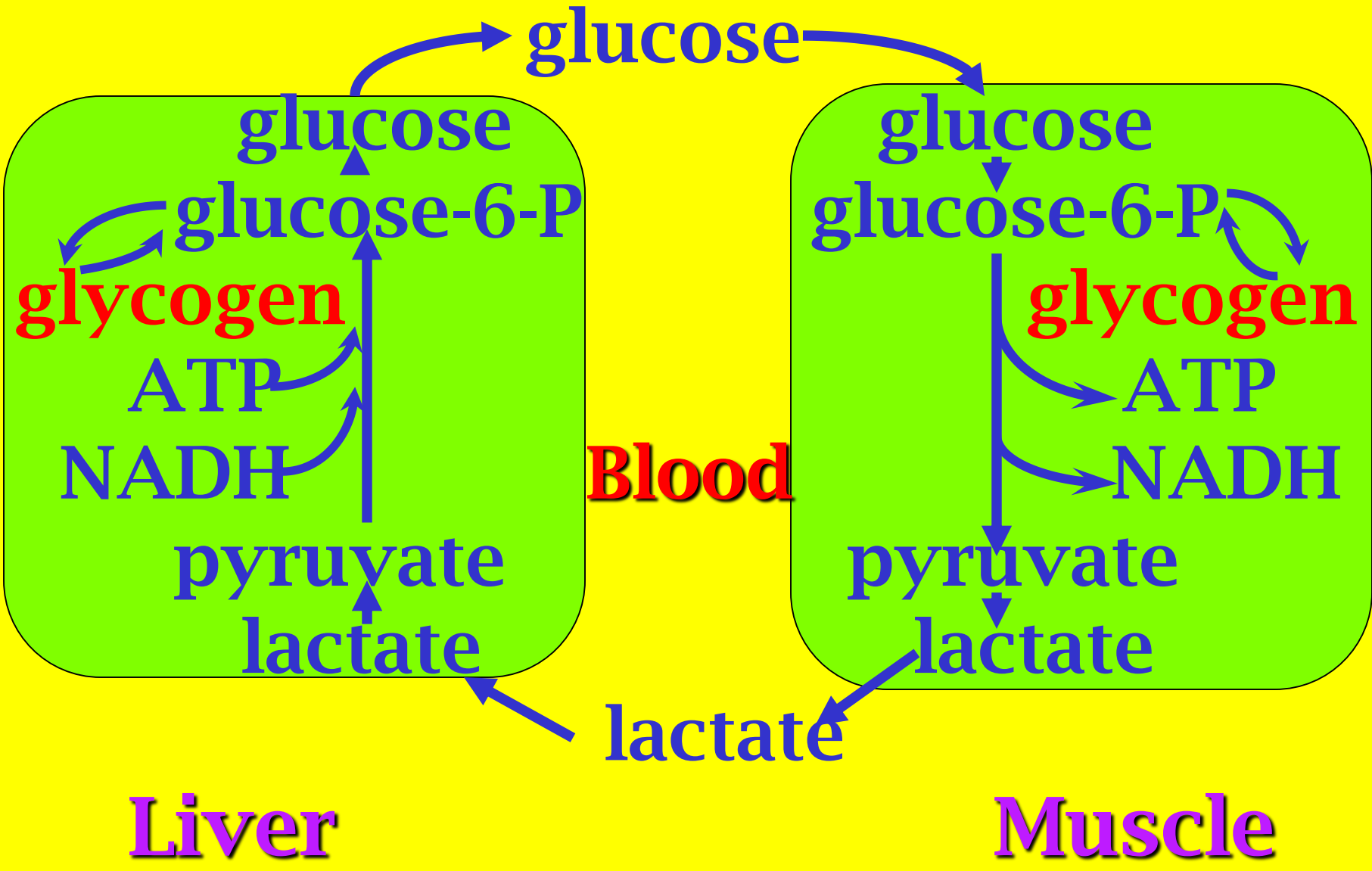
4 .A side reaction of the glycolytic pathway occur in which 1,3-Bisphosphoglycerate is converted to 2,3-Bisphosphoglycerate. This is carried by bisphosphoglycerate mutase and this found in RBCs and its functions :

a.Regulate the oxygen binding and release of O_2 with Hb .

b. In human ,2,3-BPG is a major component of the organic acid-soluble phosphates .

c. Facilate transport of O_2 from RBCs to the tissues .

LACTIC ACID (CORI) CYCLE



-- REGULATION OF GLYCOLYSIS --

Three irreversible kinase reactions primarily drive glycolysis forward.

1 . Hexokinase (HK) .
2 . Phosphofructokinase (PFK) .
3 . Pyruvate kinase (PK) .