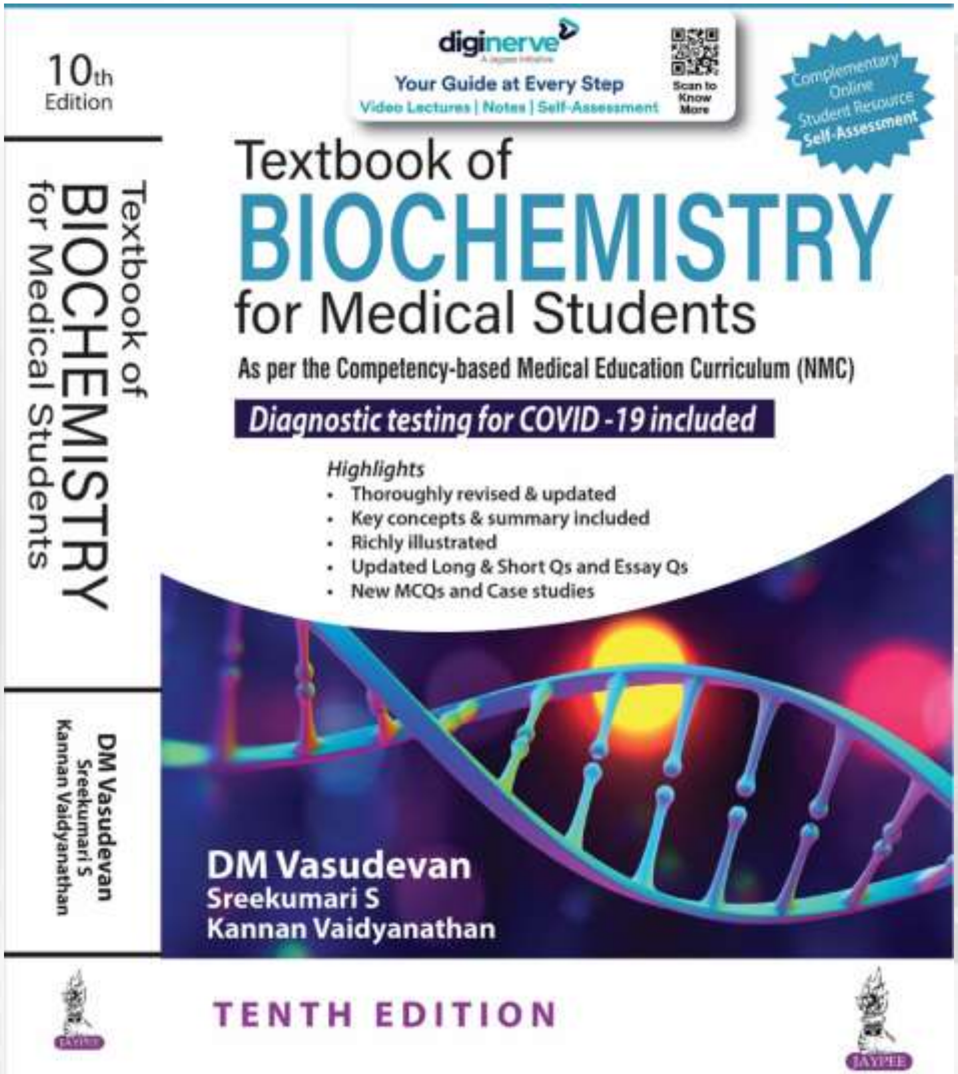


Chapter 8A:

ABSORPTION, GLYCOLYSIS AND GLUCONEOGENEIS

Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

Digestion of Carbohydrates

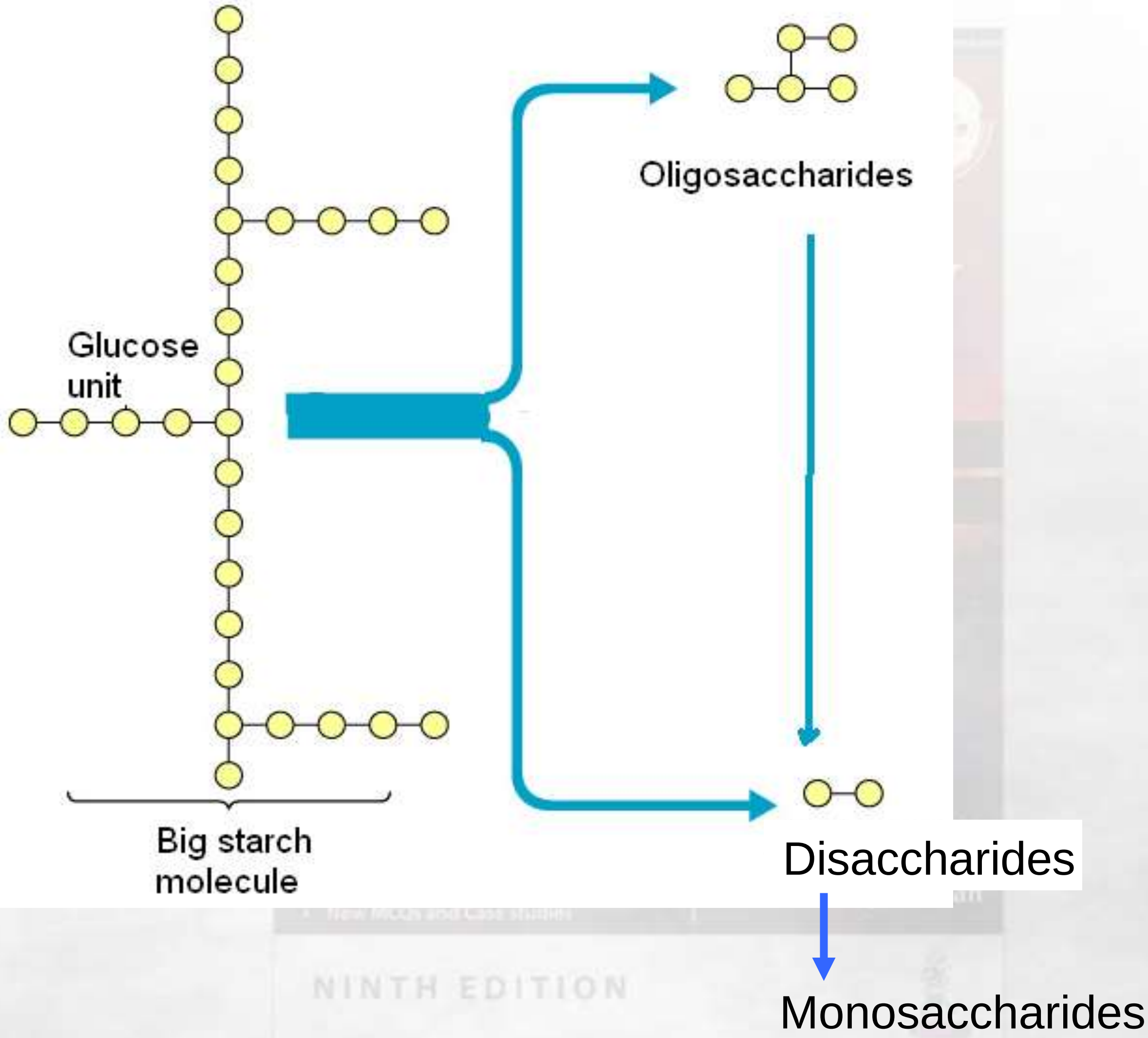
Cooking helps in breaking of glycosidic linkages in polysaccharides and thus makes the digestion process easier

In the diet carbohydrates are available as polysaccharides (starch, glycogen), and as disaccharides (sucrose and lactose). These are hydrolysed to monosaccharide units in gastro intestinal tract.

Digestion in mouth by the salivary alpha-amylase. The gastric HCl inhibits the action of salivary amylase.

In pancreatic juice another alpha-amylase which will hydrolyse alpha-1,4 glycosidic linkages randomly, so as to produce smaller subunits like maltose, isomaltose, dextrins and branched or unbranched oligosaccharides.

The intestinal juice (succus entericus) and brush border of intestinal cells contain sucrase, maltase, isomaltase and lactase, The monosaccharides are then absorbed.


Oligosaccharides
Glucose
unit
Big starch
molecule
Disaccharides
Monosaccharides

Lactose Intolerance

Lactase hydrolyzes lactose to glucose and galactose.
Lactase is present in the brush border of enterocytes.

Deficiency of lactase leads to lactose intolerance. In this condition, lactose accumulates in the gut. Irritant diarrhea and flatulence are seen.

The condition should be recognized and treated immediately in newborns by giving lactose free formula diet instead of milk.

There may be congenital (primary) or acquired (secondary) causes. As age **advances, l**actase enzyme will be lost.

Acquired lactose intolerance sudden change into a milk based diet. Lactase is an **inducible enzyme**. Milk could be withdrawn temporarily, the diarrhoea will be limited.

Curd is an effective treatment, lactobacilli in curd contains the enzyme lactase. Lactase is abundantly seen in **yeast**, which is also used in treatment.

Deficiency of lactase (**alactasia**) is found in Asian population. Adults have low lactase activity than children (**hypolactasia**). So elderly people develop lactose intolerance when more milk is consumed.

Absorption of Carbohydrates

Only monosaccharides are absorbed by the intestine. Minute quantities of disaccharides that may be absorbed, are immediately eliminated through kidneys. Absorption rate

Galactose > glucose > fructose

Absorption of Glucose

Glucose is polar, it cannot diffuse through the lipid bilayer of cell membrane. Hence glucose has transporters, transmembrane proteins spanning the width of the membrane.

Absorption from intestinal lumen into intestinal cell is by co-transport mechanism (secondary active transport)

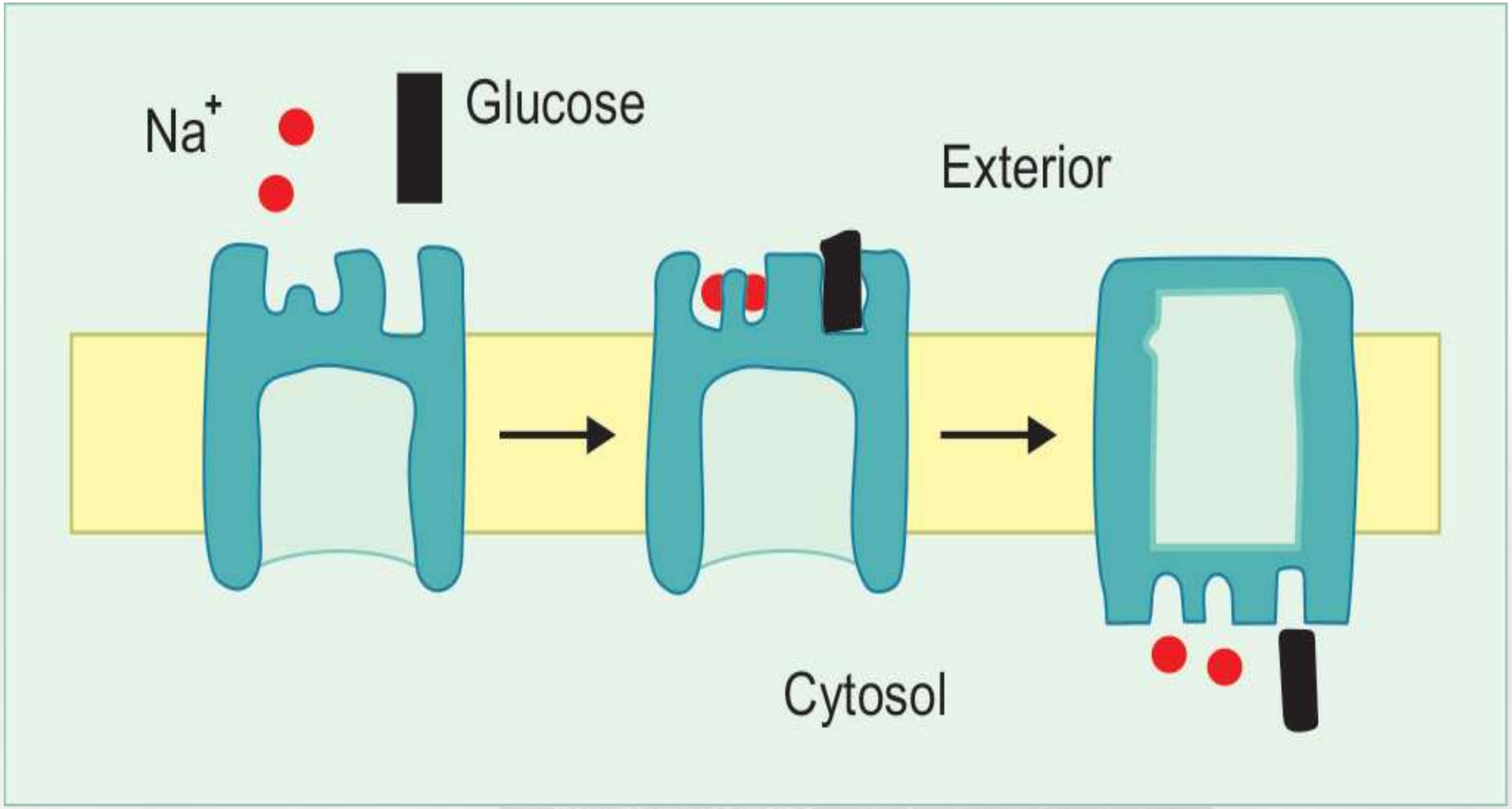
Sodium Dependent Glucose Transporter (SGluT)

Dietary Carbohydrates and their Digestion

Name of CHO	Dietary source	Digestive Enzyme	Location	Products
Starch	Cereals – Rice, Wheat	Alpha amylase	Salivary amylase Pancreatic amylase	Dextrins Maltose Isomaltose
Glycogen	Meat	Alpha amylase	Pancreatic amylase	Maltose and isomaltose
Lactose	Milk sugar	Lactase	Intestinal brush border	Glucose and galactose
Sucrose	Cane sugar	Sucrase	Intestinal brush border	Glucose and fructose

Dietary Carbohydrates and their Digestion, Continued

Name of CHO	Dietary source	Digestive Enzyme	Location	Products
Maltose and iso-maltose	Hydro-lysis of starch	Maltase – isomaltase complex	Intestinal brush border of jejunum.	Glucose
Mono-saccha-rides	Fructose, pentoses Fruits and honey	No digestion		Fructose, pentoses
Fiber Cellulose and hemi-cellulose, pectin etc	Plant polysa-ccharides	No digestion	For bulk of stools and bowel move-ments	Fermented by intestinal bacteria. Can cause flatulence



Sodium dependent glucose transporter (SGluT). Sodium and glucose cotransport system at luminal side; sodium is then pumped out. **Energy is used indirectly**

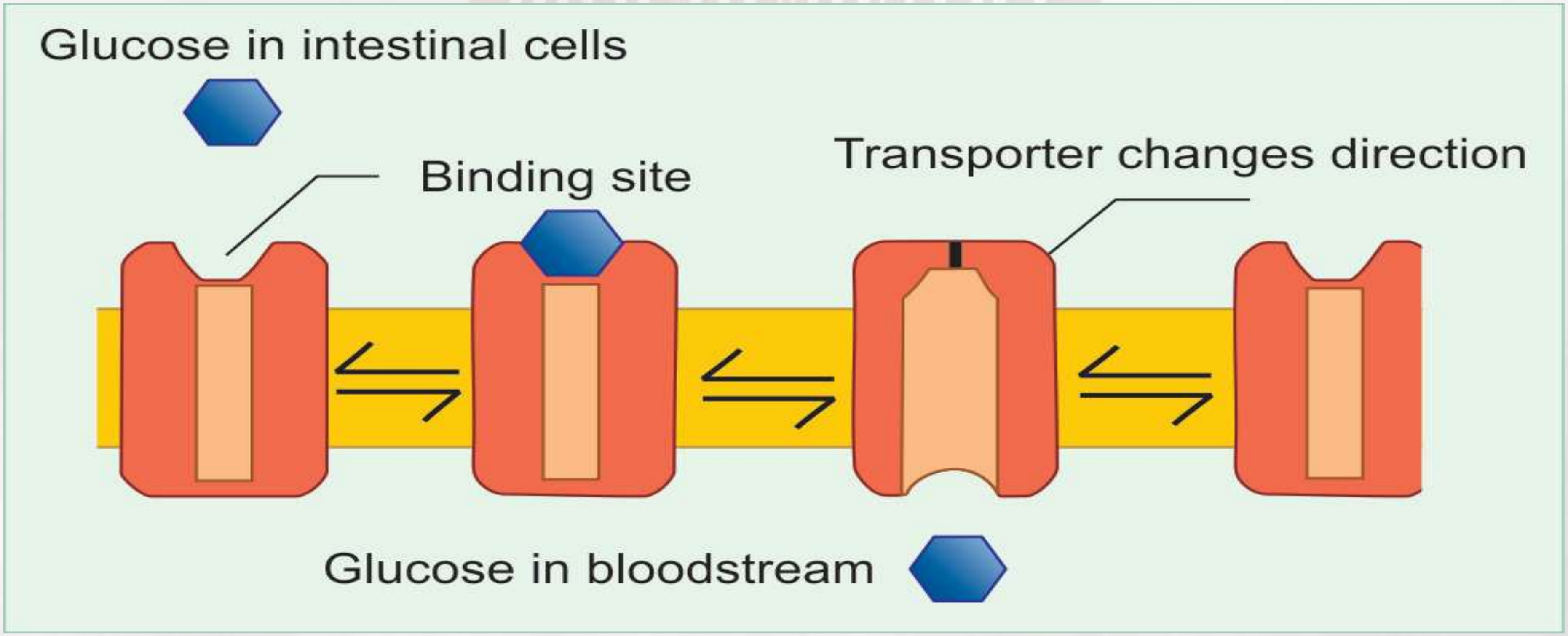
This type of co-transport is also utilised to reabsorb glucose from kidney tubules. Transporter in intestine is SGluT-1 and transporter in the kidney is called SGluT-2.

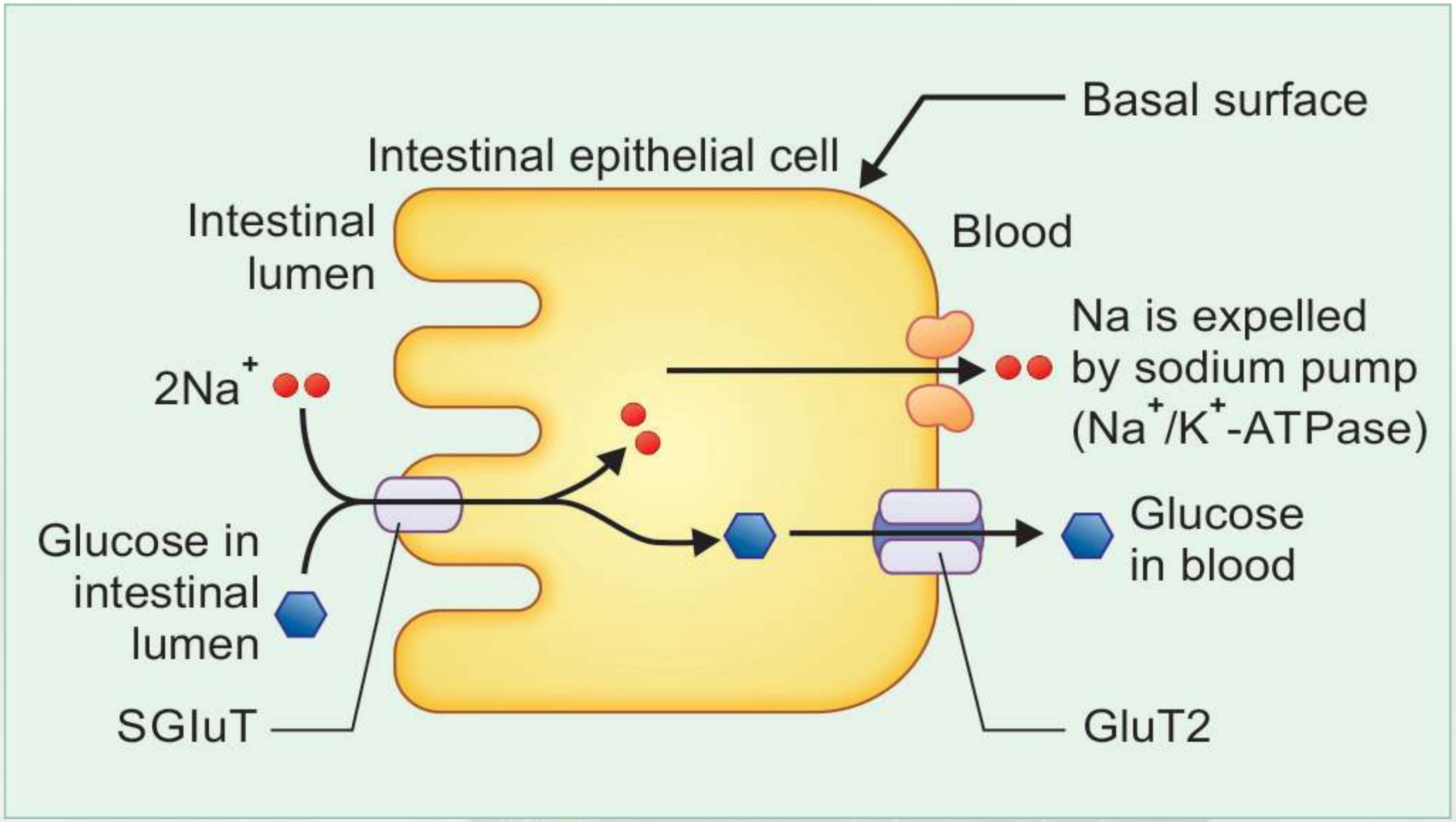
Common treatment for diarrhea is oral rehydration fluid. It contains glucose and sodium. Presence of glucose in oral rehydration fluid allows uptake of sodium to replenish body sodium chloride.

Another Uniport System Releases Glucose into Blood

Glucose Transporter Type 2 (GluT2)

This transporter is not dependent on sodium, but it is a **uniport, facilitated diffusion** system

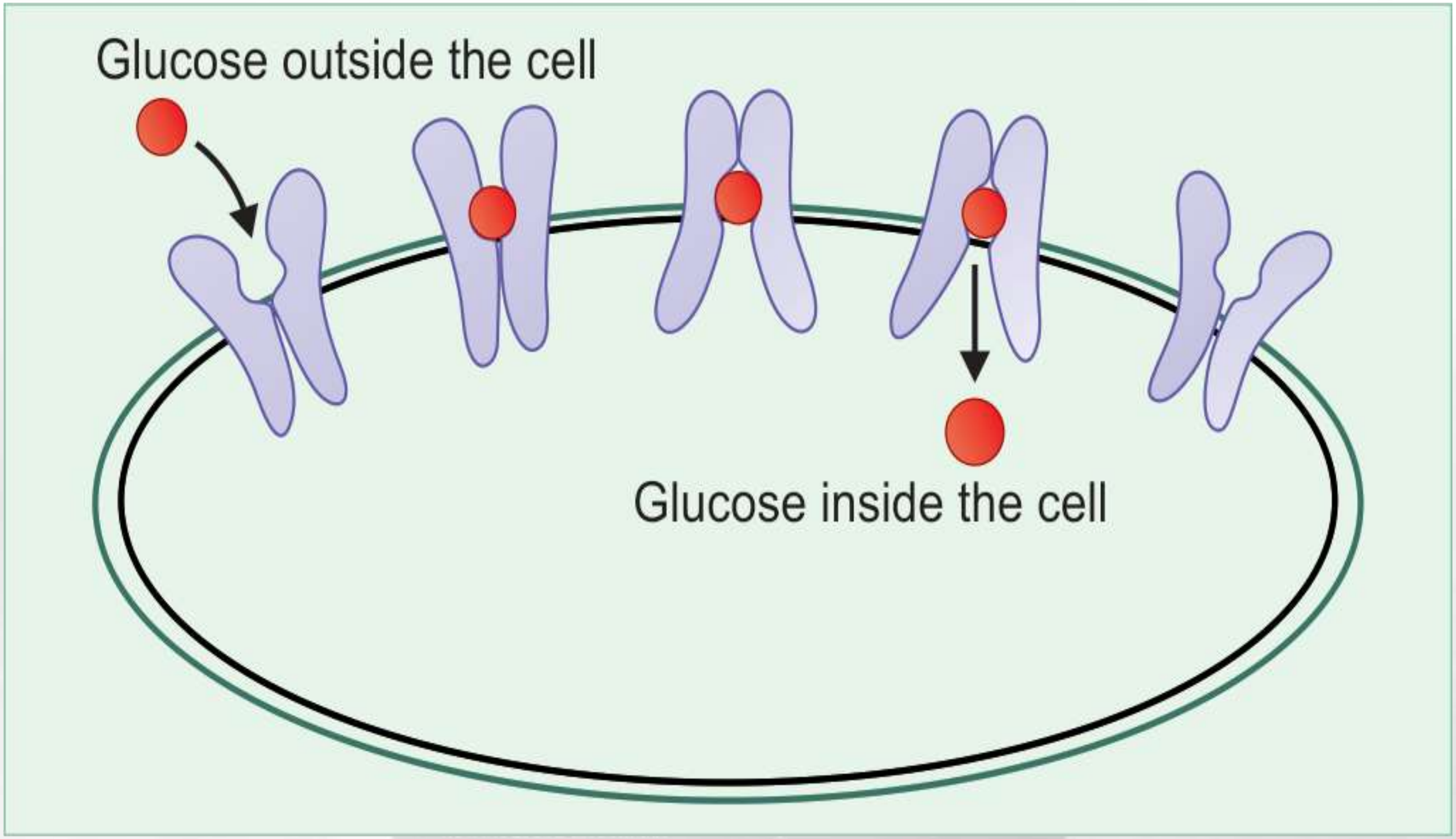




Intestinal absorption of glucose. At the intestinal lumen, absorption is by sodium dependent glucose transporter (SGluT) and at the blood vessel side, absorption is by glucose transporter 2 (GluT2).

GluT2 transports glucose into cells when blood sugar level is high. So in the well-fed state, glucose is taken up by liver and deposited as glycogen.

This mechanism also enables the pancreas to monitor the glucose level and adjust the rate of insulin secretion.



Glucose transporter 4 (GluT4)
Glucose transport in cells

Glucose Transporter 4 in Skeletal Muscle Heart Muscle and Adipose Tissue

During exercise, muscle accounts for 80% of body's glucose utilisation.

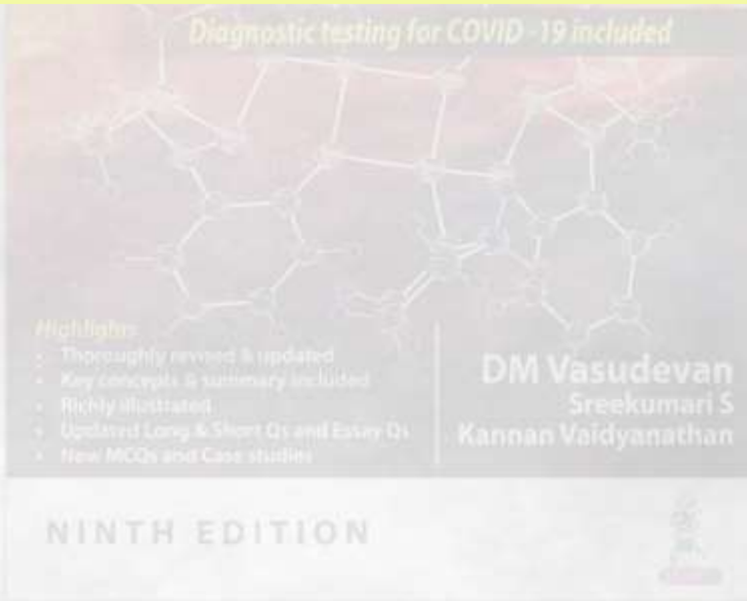
But at basal metabolic state, brain utilises 60% of glucose oxidised in the body.

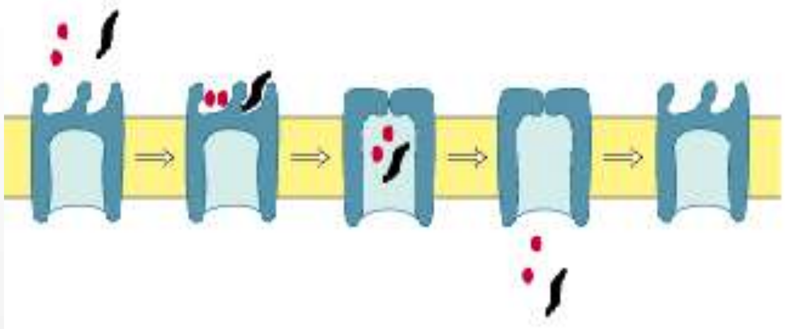
The GluT4 is under control of insulin.
Other glucose transporters are not under the control of insulin.
Insulin induces intracellular GluT4 molecules to move to the cell membrane and thus increases glucose uptake.

In Type 2 diabetes mellitus, insulin resistance is seen in muscle and fat cells.

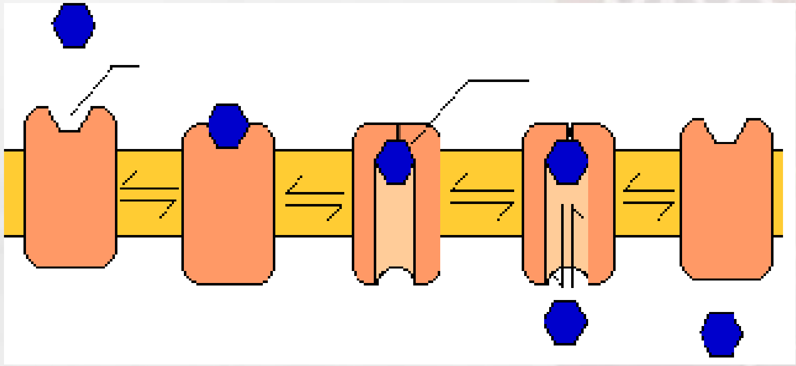
In diabetes, entry of glucose into muscle is only half of normal cells.

Reduced recycling of membrane bound GluT4

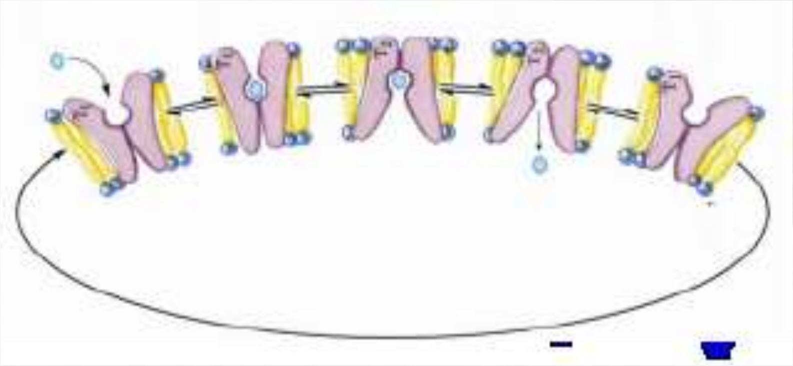




SGluT. Sodium and glucose Co-transport at luminal side; sodium is then pumped out.



Glu2 at vascular site.

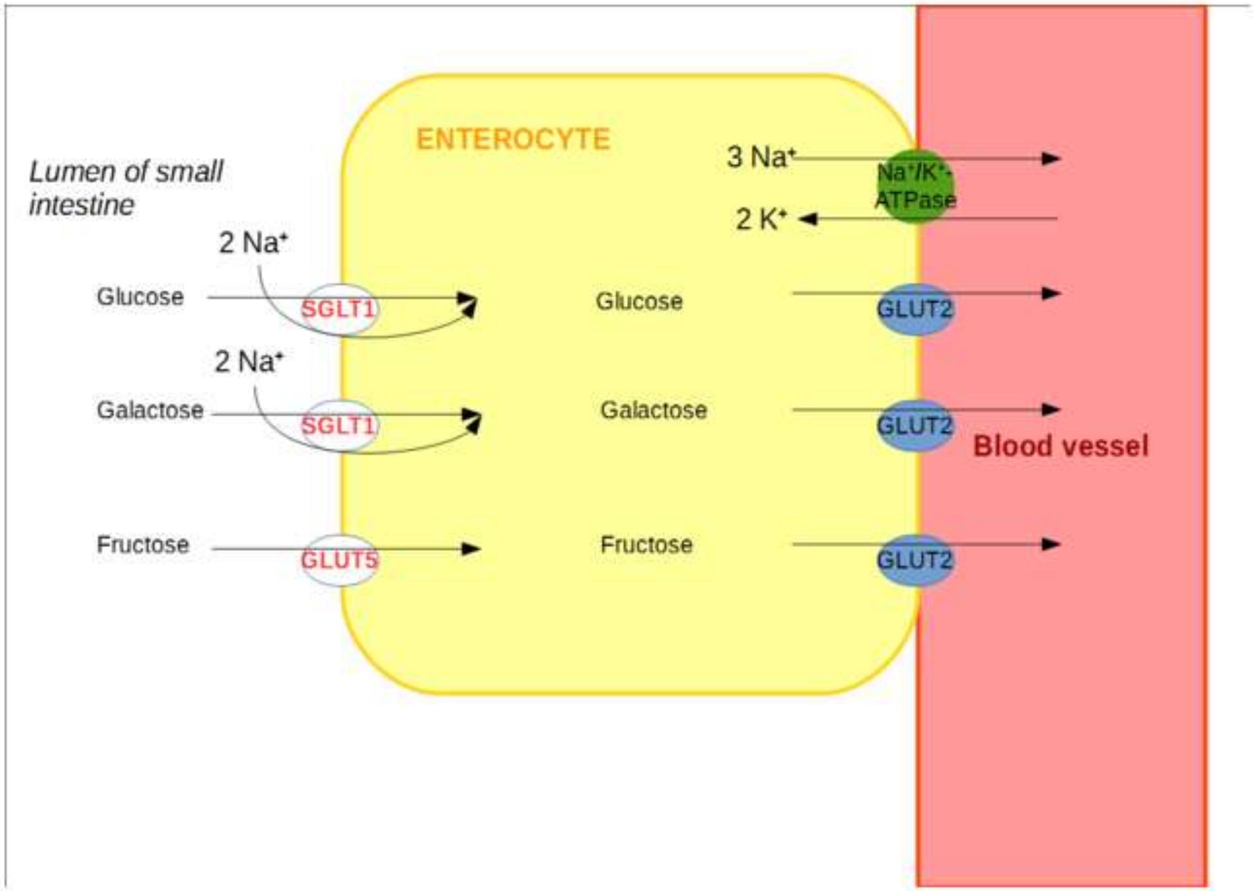


GluT4. Glucose transport in cells

Glucose Transporters

	Present in	Properties
GluT1	RBC, brain, kidney,	Glucose uptake in colon, retina, most of cells placenta
GluT2	Serosal surface of intestinal cells, liver, beta cells of pancreas	Glucose uptake in liver; glucose sensor in beta cells
GluT3	Neurons, brain	Glucose into brain cells
GluT4	Skeletal, heart	Insulin mediated muscle, adipose tissue glucose uptake
GluT5	Small intestine, testis, sperms, kidney	Fructose transporter; poor ability to transport glucose
SGluT	Intestine, kidney	Cotransport; from lumen into cell

Absorption of Monosaccharides



Glycolysis

(Embden-Meyerhof Pathway)

Definition: Glucose is split into two 3-carbon **pyruvate** molecules under aerobic conditions; or **lactate** under anaerobic conditions, along with production of a small quantity of energy.

Site of reactions: All the reaction steps take place in the cytoplasm.

Significance of Glycolysis Pathway

1. It is the only pathway that is taking place in all cells of the body.
2. Glycolysis is the only source of energy in erythrocytes.
3. In strenuous exercise, when muscle tissue lacks enough oxygen, **anaerobic glycolysis forms the major source of energy for muscles**.
4. The glycolytic pathway may be considered as the preliminary step before complete oxidation.
5. The glycolytic pathway provides carbon skeletons for synthesis of non-essential amino acids as well as glycerol part of fat.
6. Most of the reactions of the glycolytic pathway are reversible, which are also used for gluconeogenesis.

Clinical Importance of Glucose

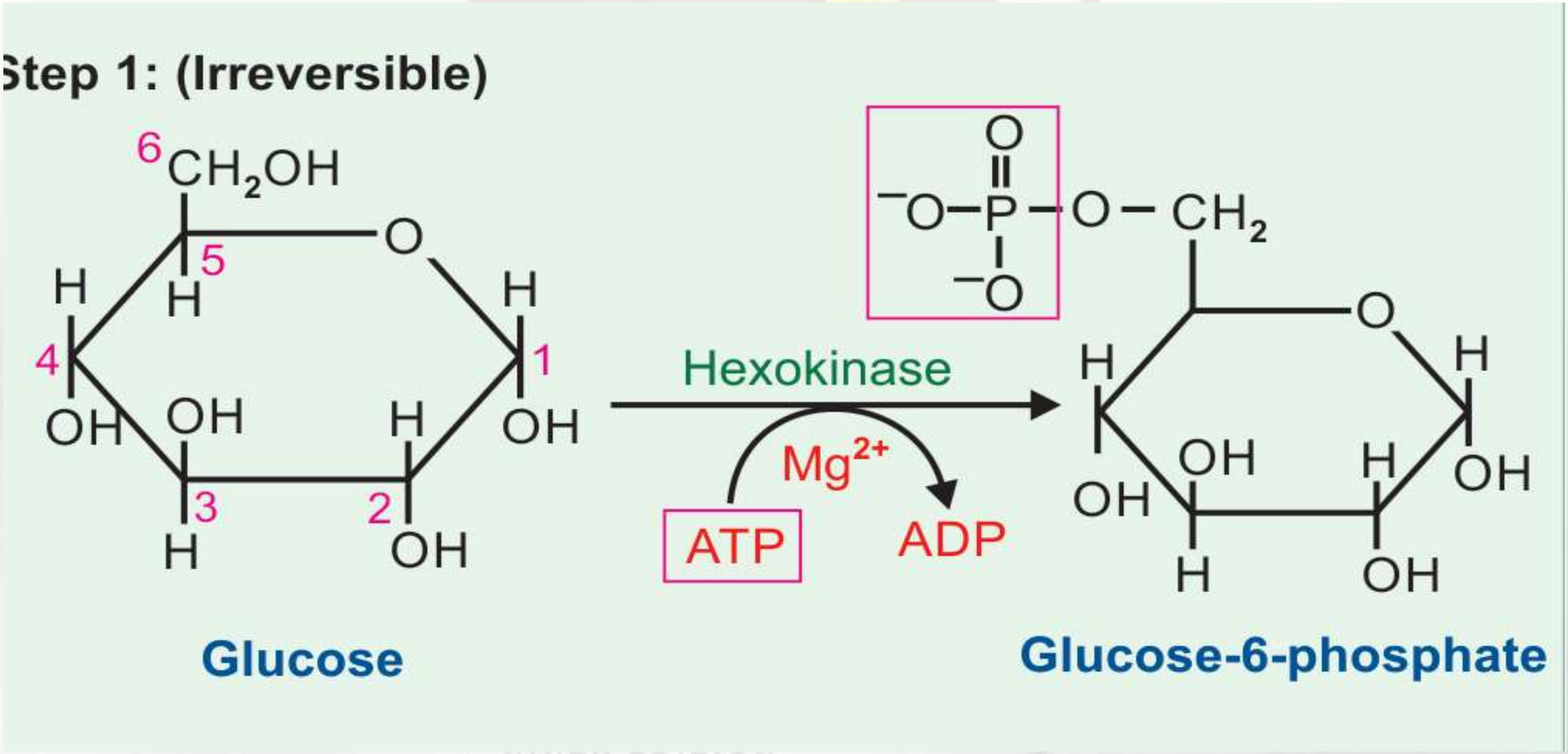
A minimum amount of glucose is always required for normal functioning.

Normal fasting plasma glucose level is 70–100 mg/dL.

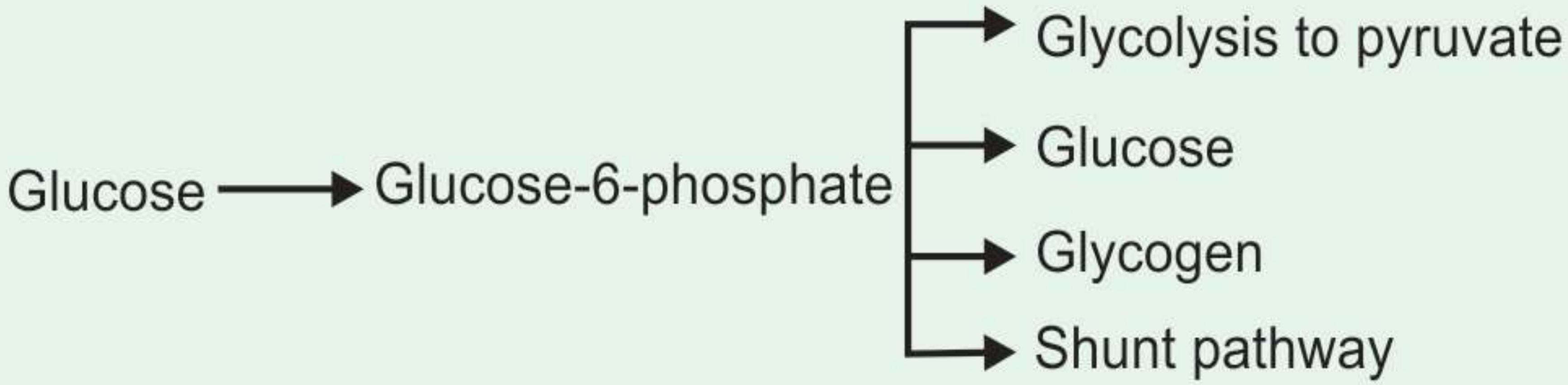
After a heavy carbohydrate meal, it rises; but in a normal person, this level is below 150 mg/dL.

Step 1 of Glycolysis

Activation of glucose by phosphorylation.



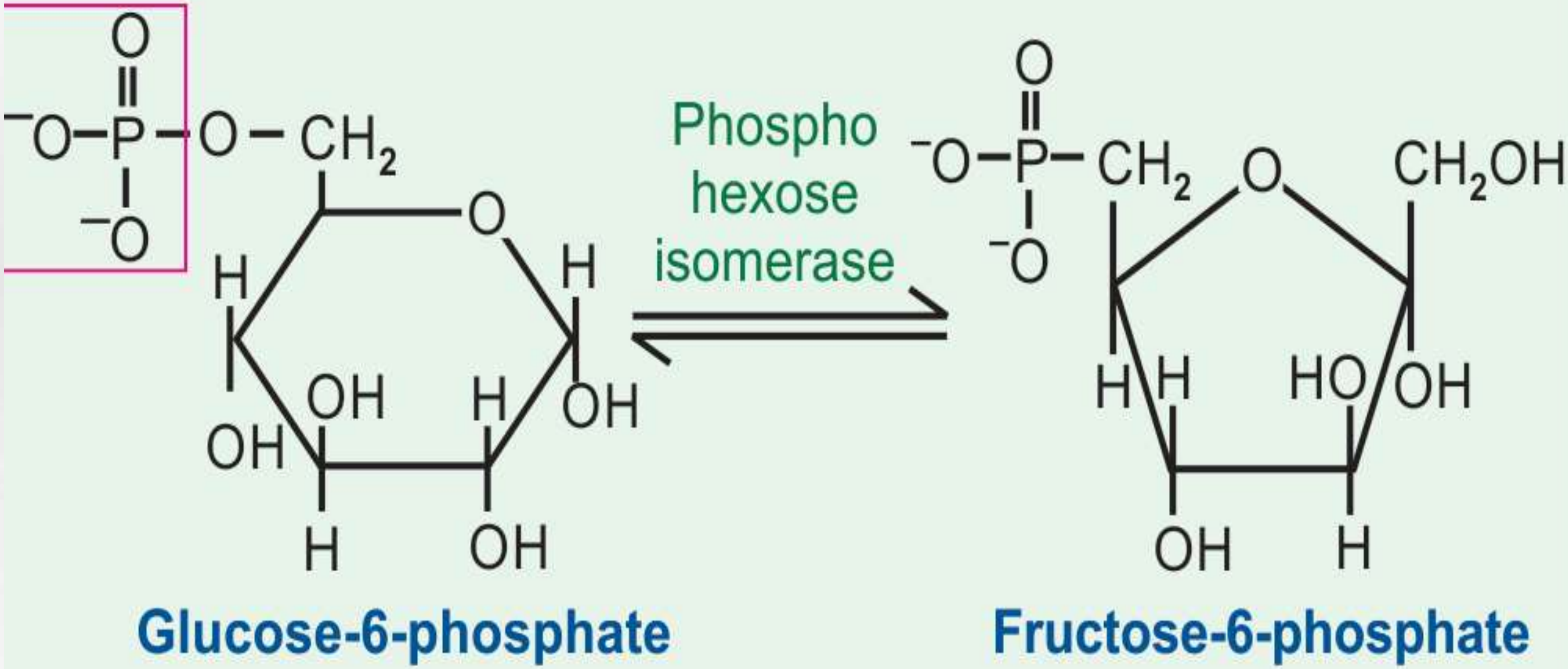
Energy Utilising Step Irreversible



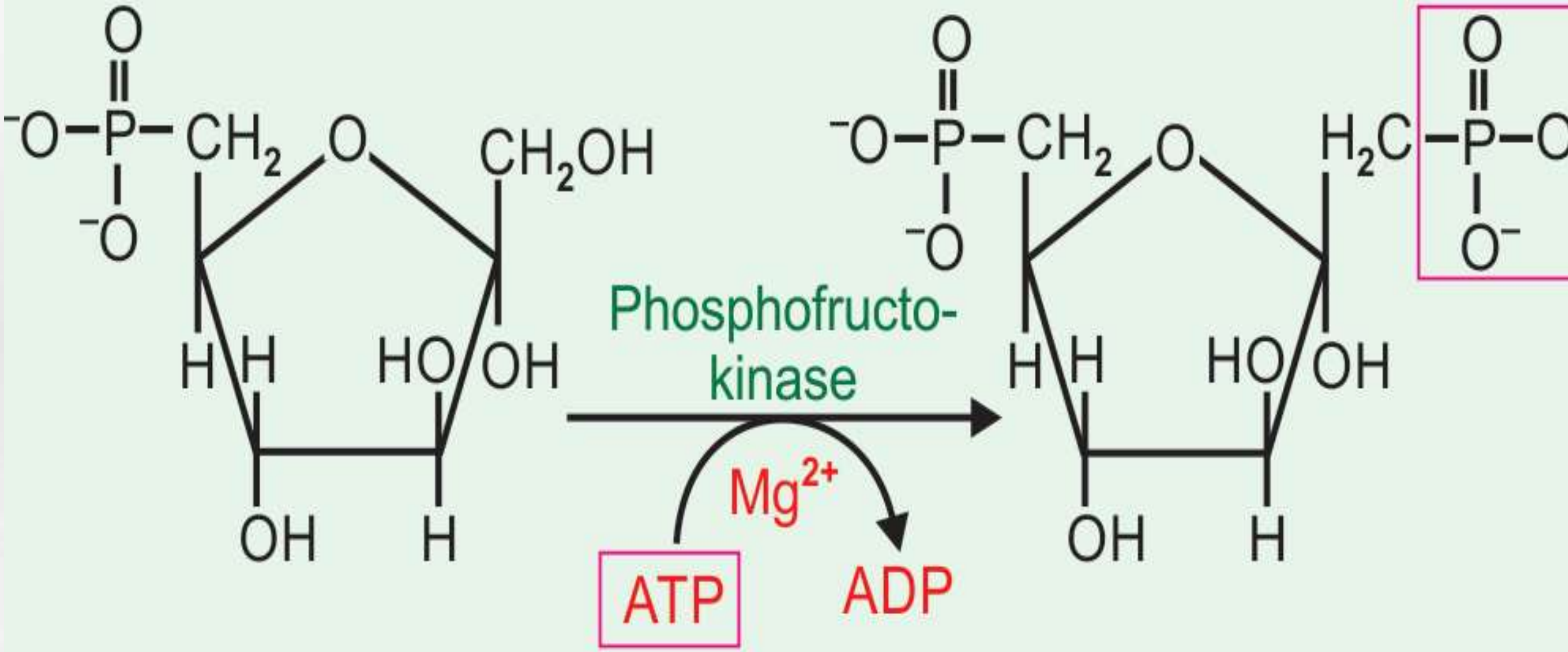
Comparison of hexokinase and glucokinase

	Hexokinase	Glucokinase
Occurrence	In all tissues	Only in liver
Km value	10^{-2} mmol/L	20 mmol/L
Affinity to substrate	High	Low
Specificity	Acts on glucose, fructose and mannose	Acts only on glucose
Induction	Not induced	Induced by insulin and glucose
Function	Even when blood glucose level is low, glucose is utilised by body cells	Acts only when blood glucose level is more than 100 mg/dl; then glucose is taken up by liver cells for glycogen synthesis

Step 2: Phosphohexose isomerase Reaction



Step 3: (Irreversible)



Fructose-6-phosphate

Fructose-1,6-bisphosphate

Step 3 of Glycolysis

i) Fructose-6-phosphate is further phosphorylated to fructose1,6-bisphosphate. The enzyme is **phosphofructo kinase**.

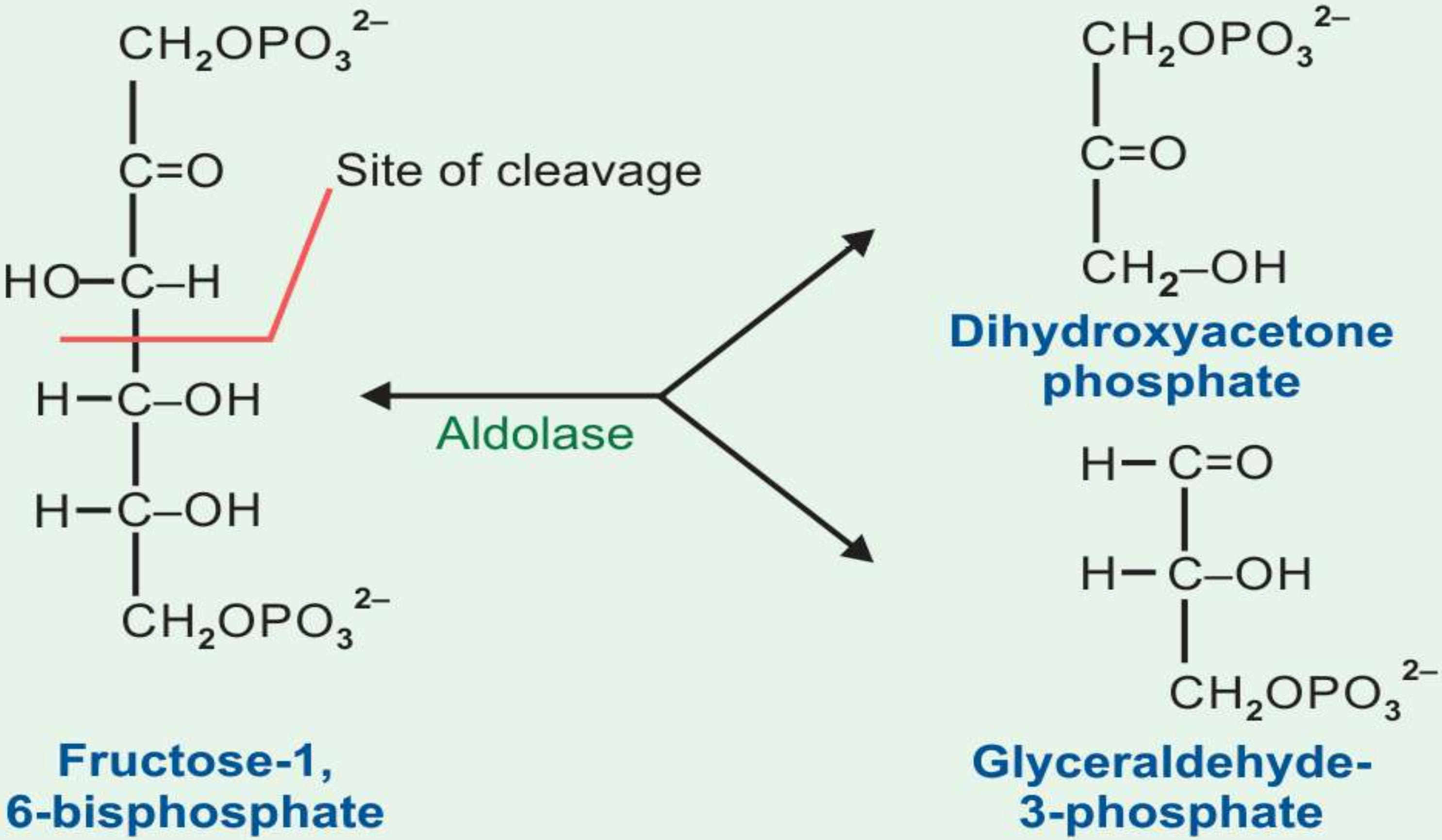
ii) PFK is an allosteric, inducible, regulatory enzyme. It is an important **key enzyme** of this pathway.

iii) This is again an activation process, the energy being derived by hydrolysis of yet another molecule of ATP.

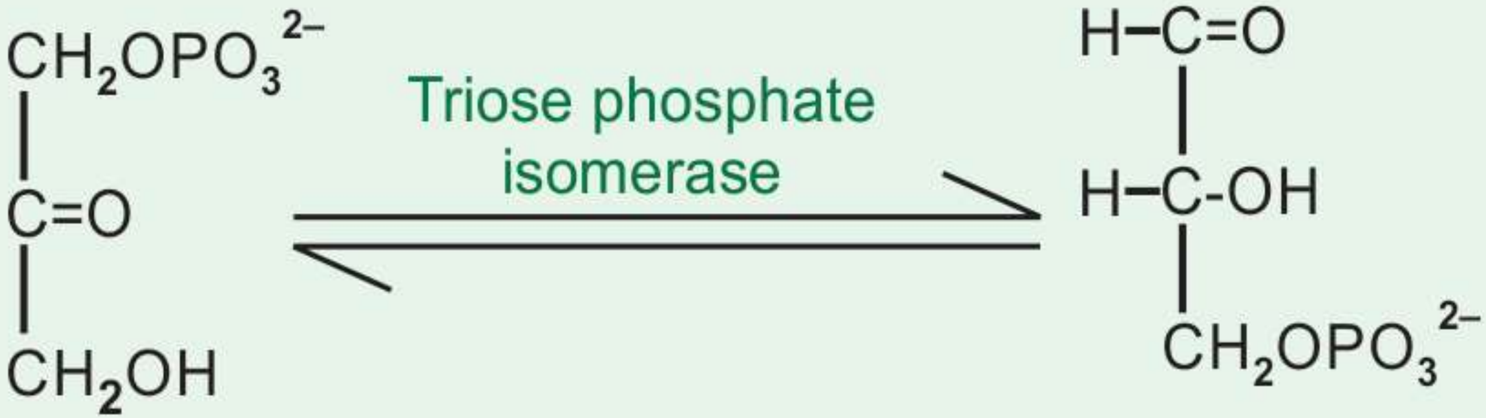
iv) This **irreversible** step is the rate limiting reaction in glycolysis.

v) The steps 1,2 and 3 together are called as the **preparatory phase**.

Step 4: (Reversible)

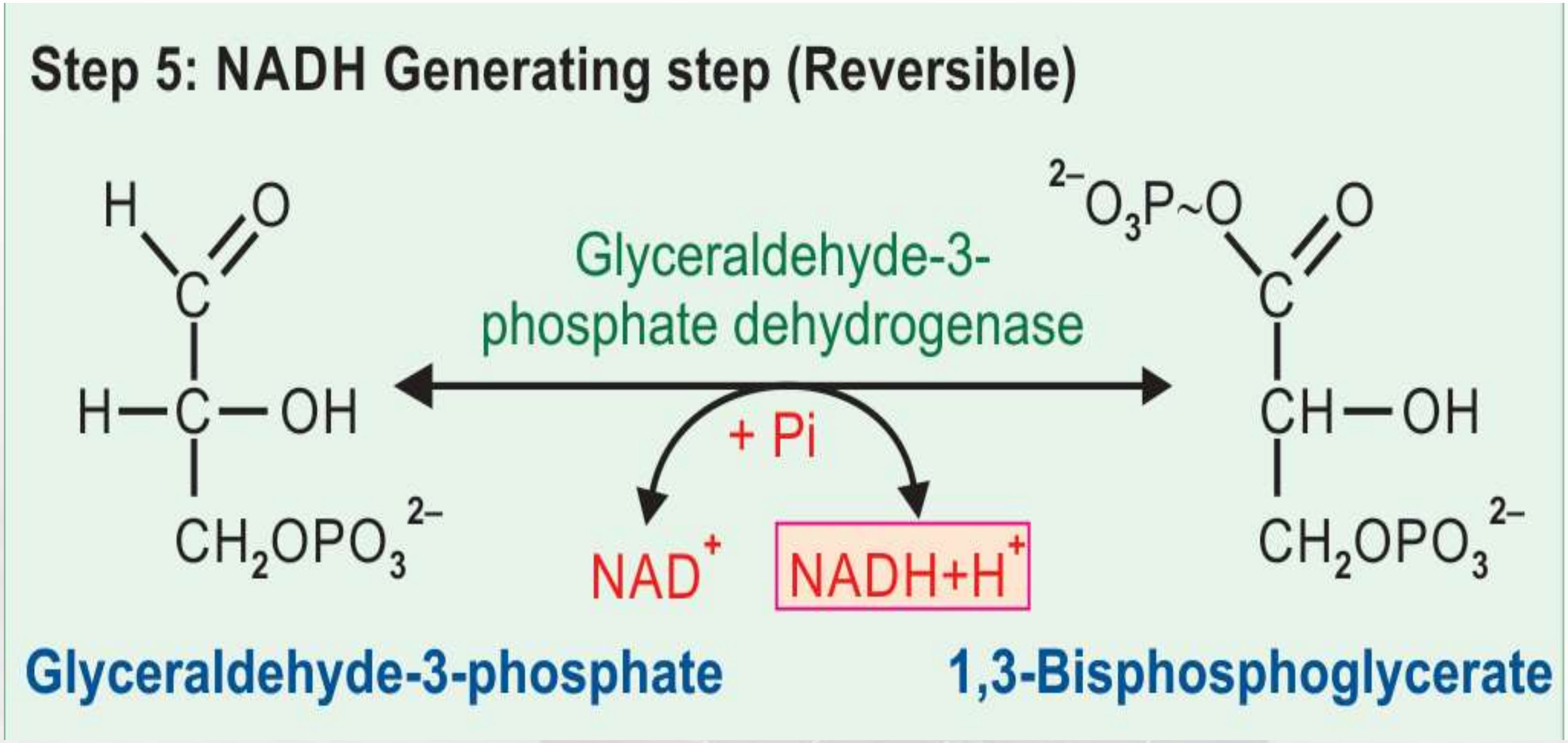


Step 4A: Isomerization (Reversible)



Dihydroxyacetone phosphate **Glyceraldehyde-3-phosphate**

Steps 4 and 4-A are together called the **Splitting Phase**.



Reversible step.

NADH generating step.

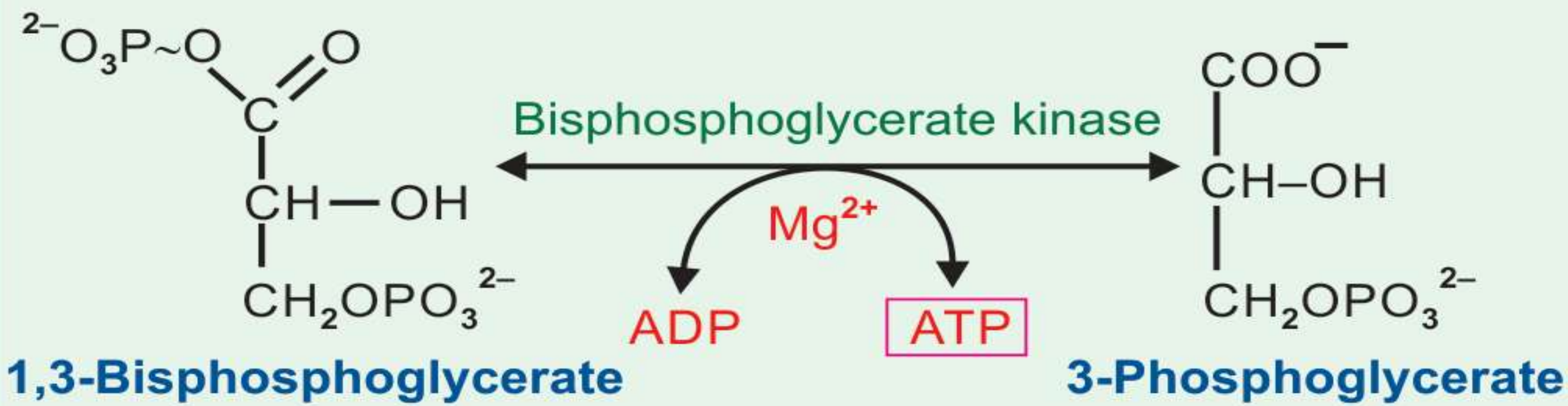
Oxidative phosphorylation

Diphosphate and Bisphosphate are Different

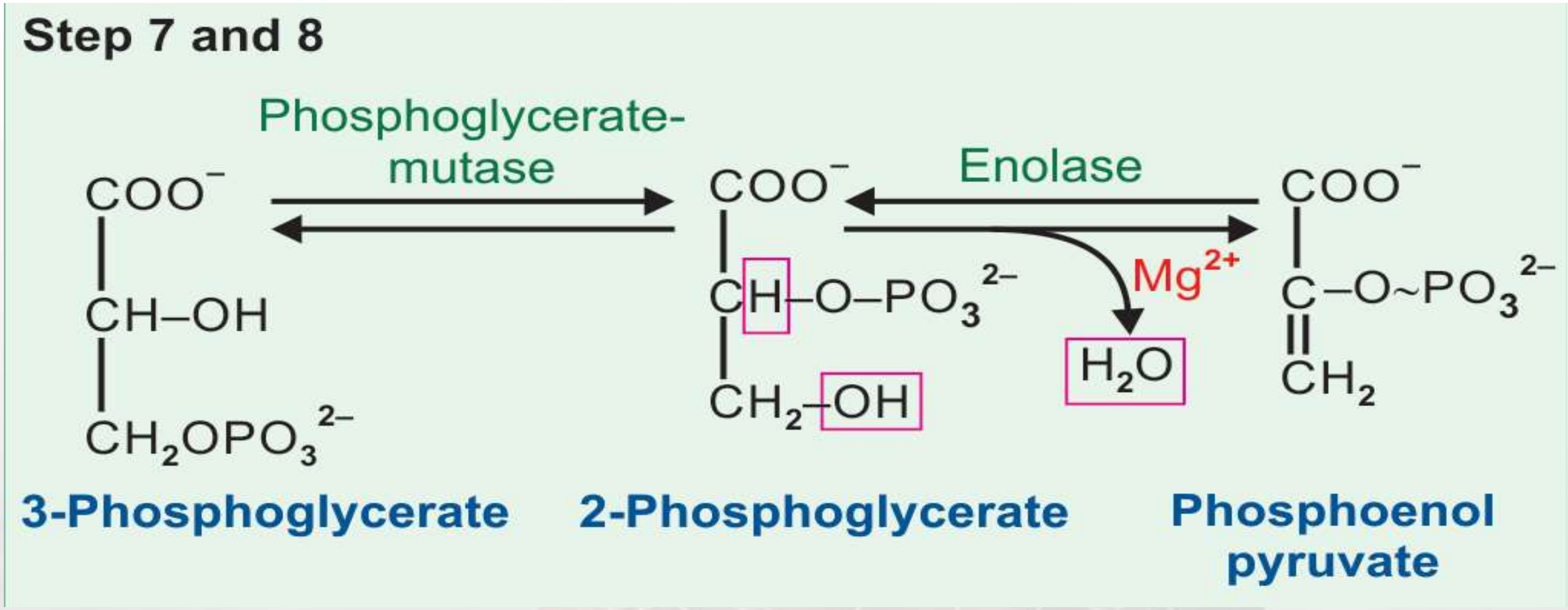
When two phosphate groups are linked together and then attached to a parent compound, it is called diphosphate, e.g. adenosine-diphosphate.

But when phosphoric acid groups are present at two different sites of the compound, it is named as bisphosphate, e.g. fructose-1,6-bisphosphate.

Step 6: ATP Generation (Reversible)



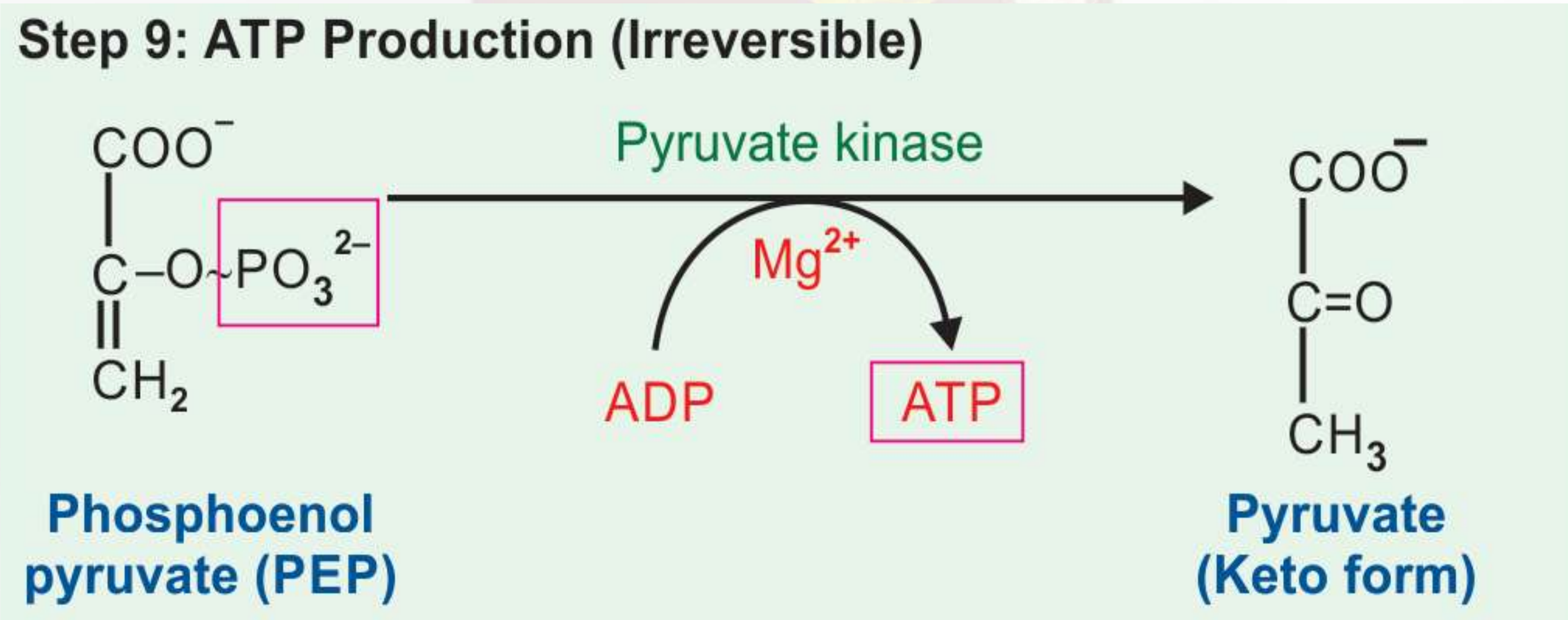
ATP generation step, Example of substrate level phosphorylation



Enolase requires Mg++. Fluoride will remove magnesium ions and inhibit this enzyme.

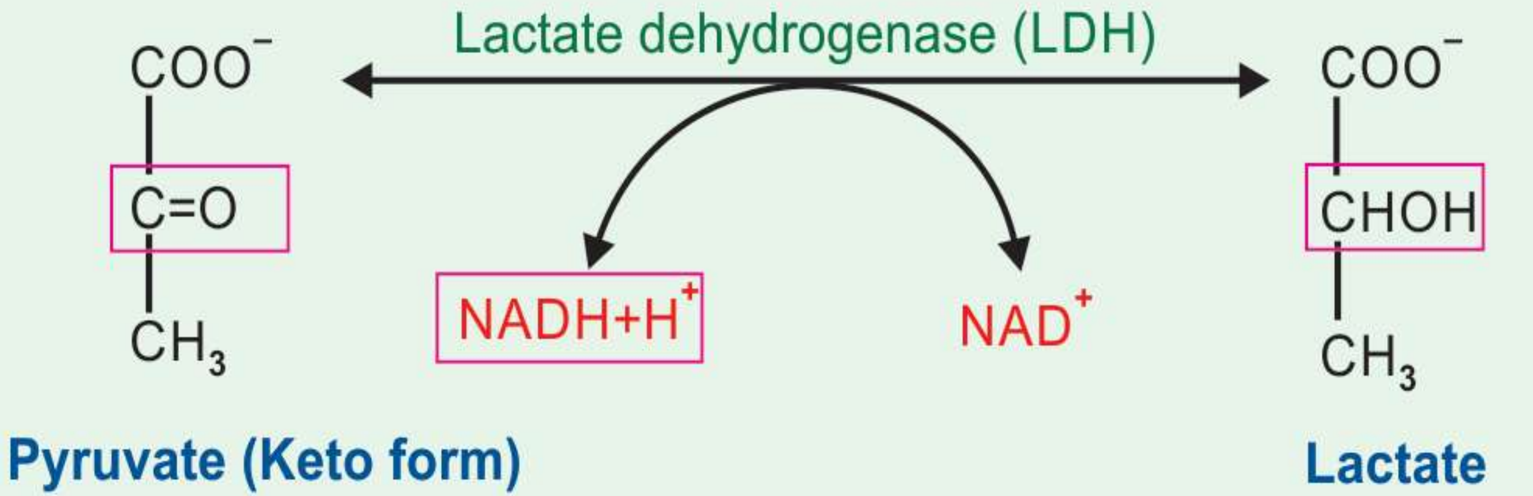
So when taking blood for sugar estimation, fluoride is added to blood.

If not, glucose is metabolised by the blood cells, so that lower blood glucose values are obtained.

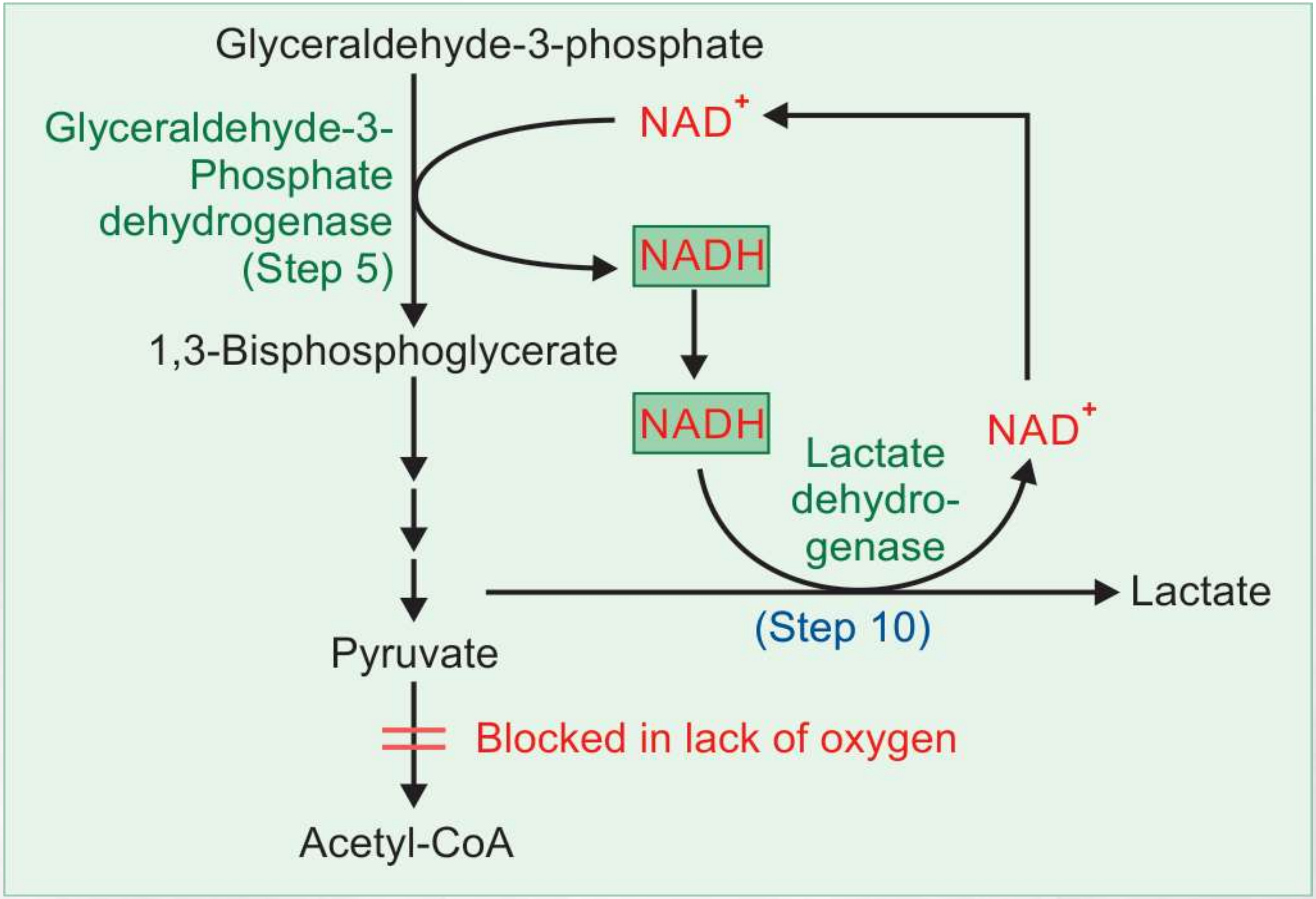


Substrate level phosphorylation

Step 10: Lactate Dehydrogenase Reaction (Reversible)



LDH has 4 subunits and 5 iso-enzymes. The cardiac iso-enzyme of LDH (H4) will Increase in myocardial infarction


Glyceraldehyde-3-phosphate
Glyceraldehyde-3-Phosphate dehydrogenase (Step 5)
NAD+
NADH
1,3-Bisphosphoglycerate
NADH
NAD+
Lactate dehydro-genase
Lactate
(Step 10)
Pyruvate
Blocked in lack of oxygen
Acetyl-CoA

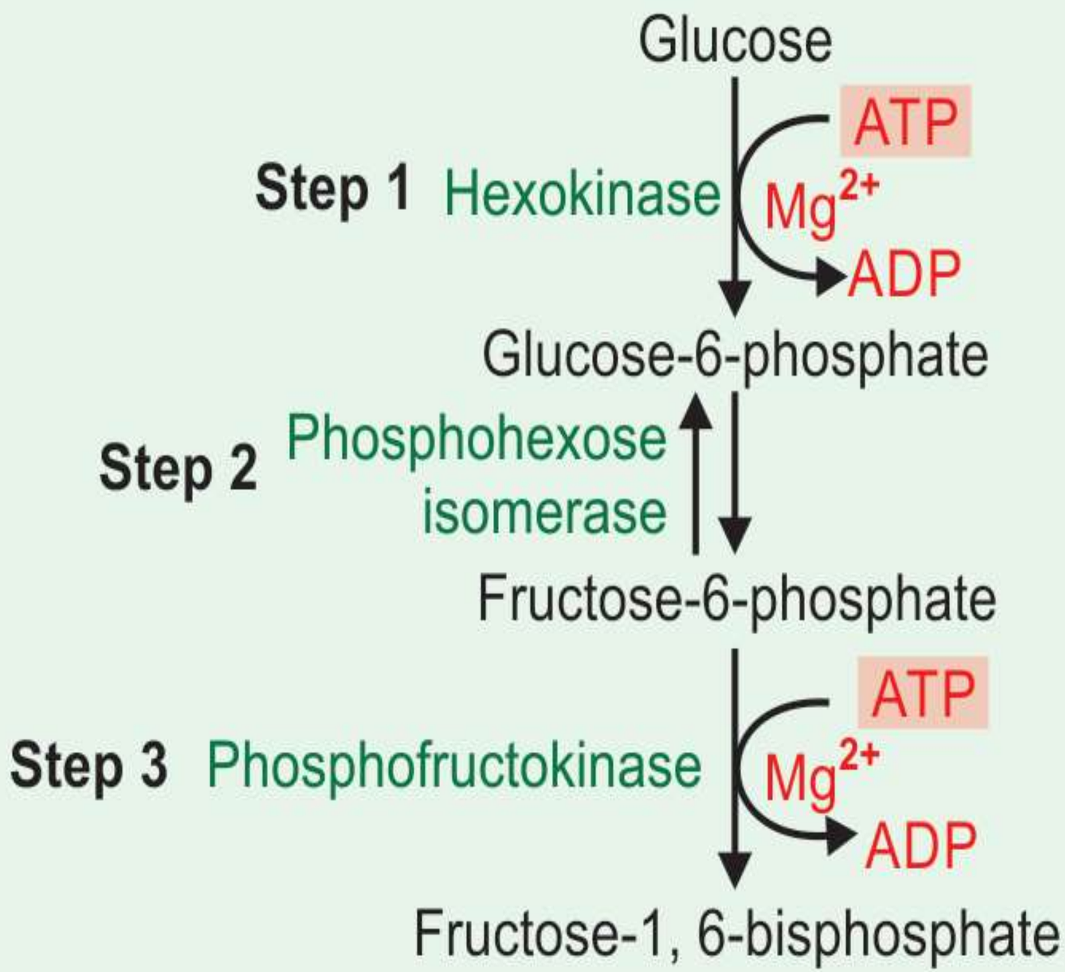
Steps 5 and 10 are Coupled

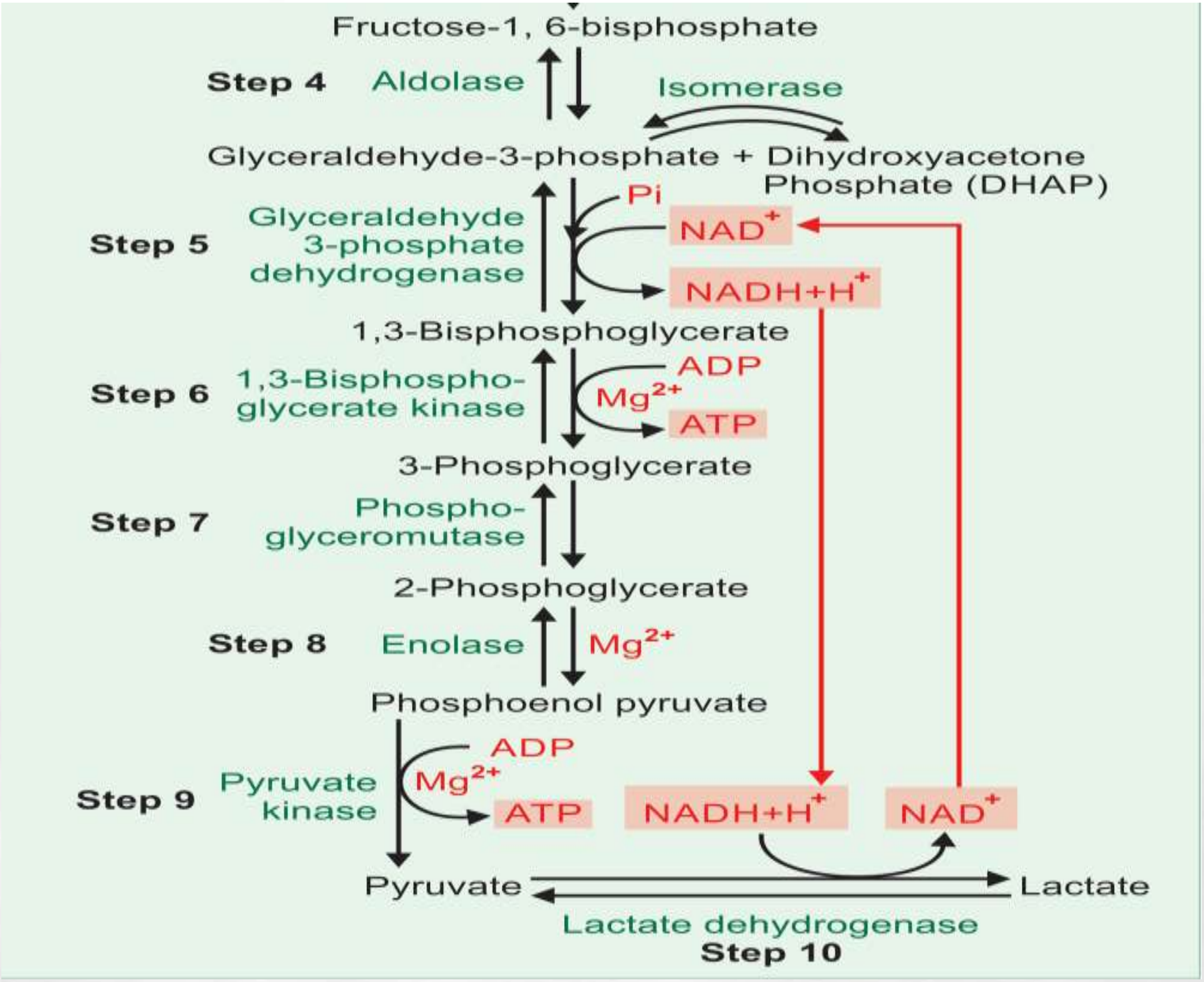
Significance of lactate production

In the actively contracting muscles, there is comparative lack of oxygen.

In anaerobiosis the major pathway of Utilisation of pyruvate is thus blocked.

Lactate formation is necessary for re-conversion of NADH to NAD+ in anaerobic conditions


Glucose
Step 1
Hexokinase
ATP
Mg2+
ADP
Glucose-6-phosphate
Step 2
Phosphohexose
isomerase
Fructose-6-phosphate
Step 3
Phosphofructokinase
ATP
Mg2+
ADP
Fructose-1, 6-bisphosphate



Fructose-1, 6-bisphosphate
Step 4
Aldolase
Isomerase
Glyceraldehyde-3-phosphate + Dihydroxyacetone Phosphate (DHAP)
Step 5
Glyceraldehyde 3-phosphate dehydrogenase
Pi
NAD+
NADH+H+
1,3-Bisphosphoglycerate
Step 6
1,3-Bisphospho-glycerate kinase
ADP
Mg2+
ATP
3-Phosphoglycerate
Step 7
Phospho-glyceromutase
2-Phosphoglycerate
Step 8
Enolase
Mg2+
Phosphoenol pyruvate
Step 9
Pyruvate kinase
ADP
Mg2+
ATP
NADH+H+
NAD+
Pyruvate
Lactate
Lactate dehydrogenase
Step 10

Insulin favours glycolysis

Insulin activates key glycolytic enzymes (glucokinase, phosphofructokinase and pyruvate kinase)

Glucocorticoids inhibit glycolysis and favours gluconeogenesis

Phospho fructo kinase (PFK) (step 3) rate-limiting enzyme for glycolysis pathway

PFK is an allosterically regulated enzyme

ATP is allosteric inhibitor

Citrate is another inhibitor

AMP acts as an allosteric activator

Fructose-6-phosphate increases activity

Regulatory enzymes of glycolysis

Enzyme	Activation	Inhibition
HK		G-6-P
GK	Insulin	Glucagon
PFK	Insulin, AMP F-6-P, PFK-2 F-2,6-BP	Glucagon, ATP Citrate, Low pH Cyclic AMP
PK	Insulin, F-1,6-BP	Glucagon, ATP Cyclic AMP
PDH	CoA , NAD	Acetyl CoA, NADH

Hormonal Regulation of Glycolysis

Glucose

↓ **Key glycolytic enzymes**
Glucokinase

Glu-6-P

F-6-P

↓ **Phospho fructo kinase**

F-1,6-bisP

glceal3P

BPG

3PG

2PG

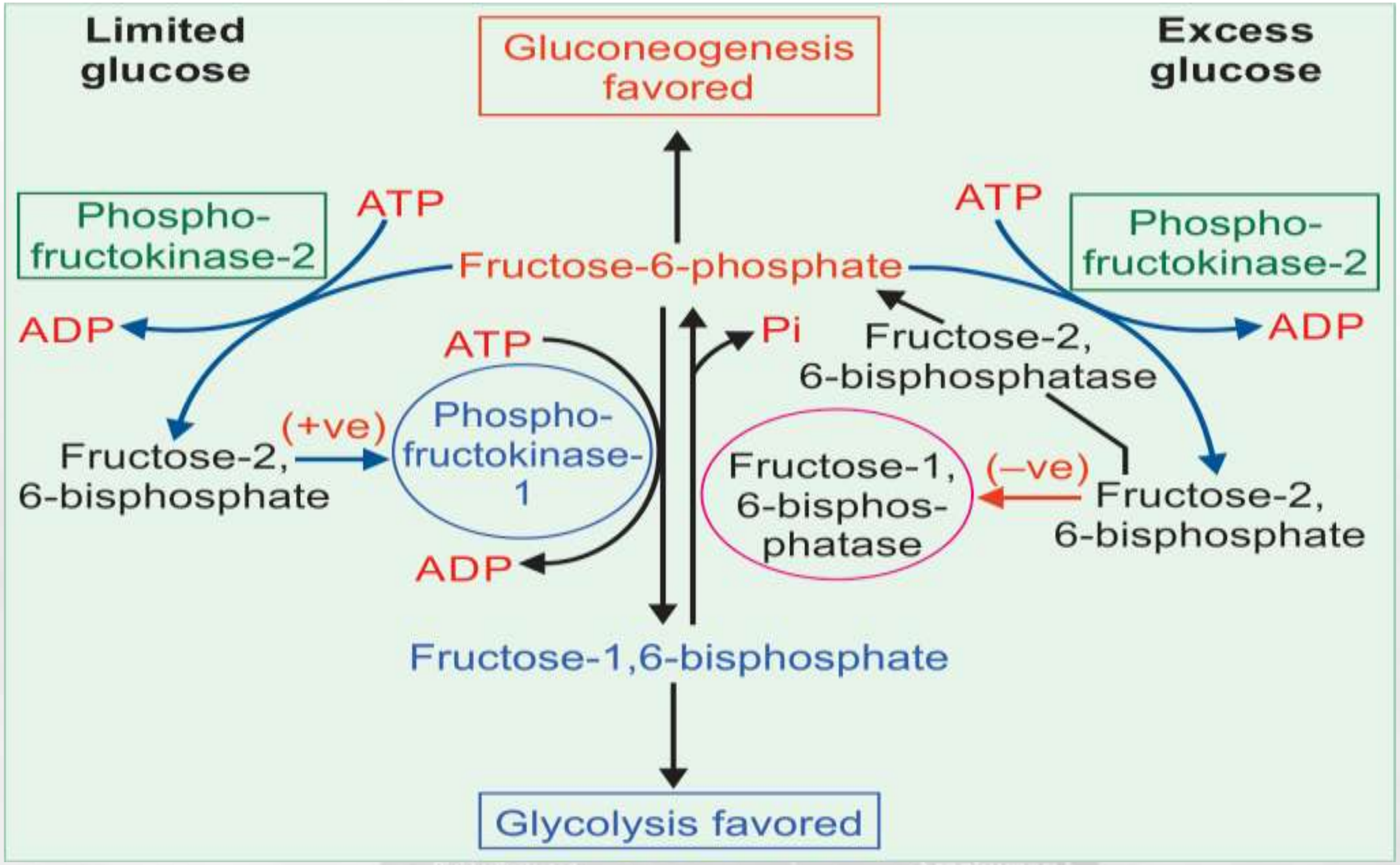
PEP

↓ **Pyruvate kinase**

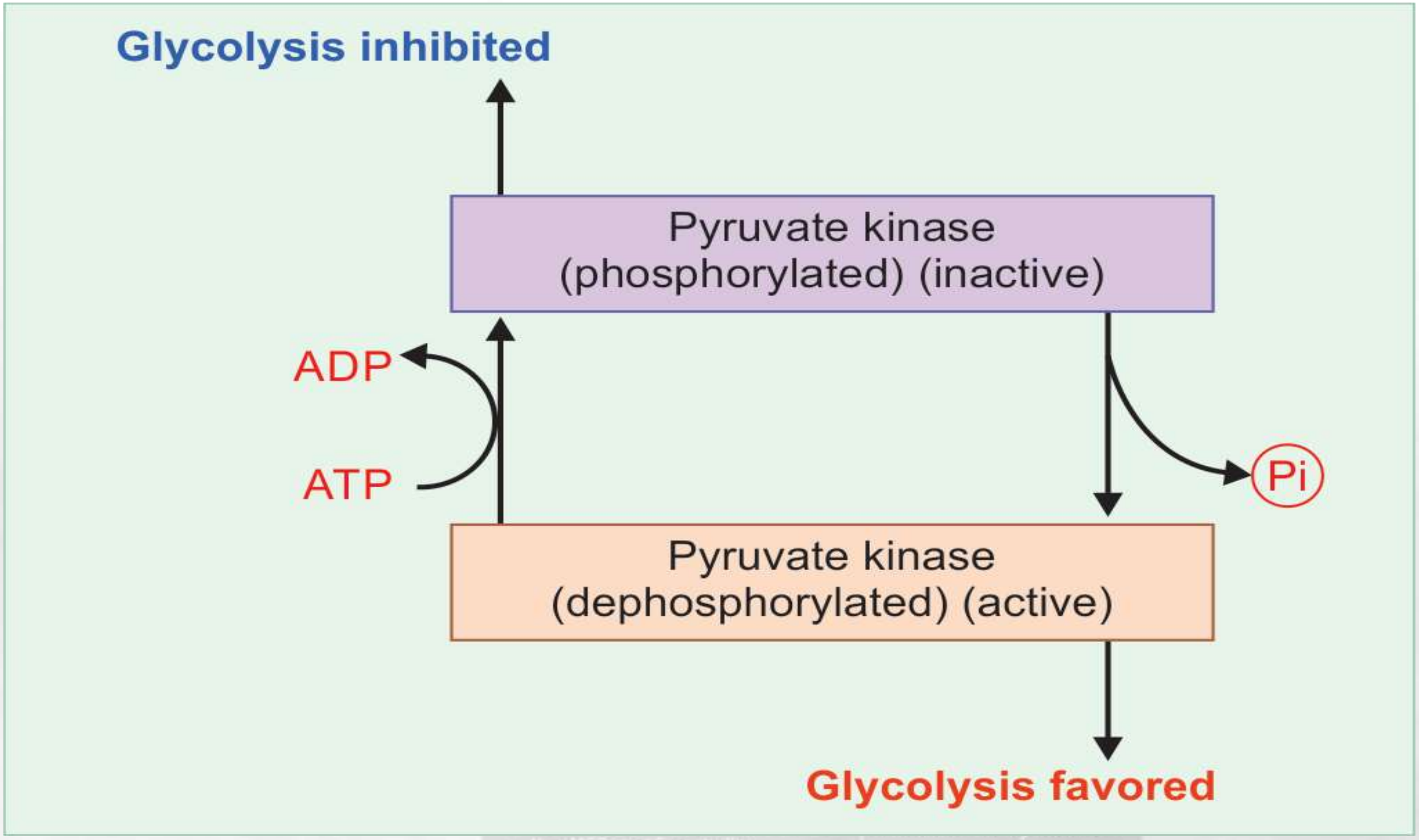
Pyruvate

Insulin stimulates
Key glycolytic enzymes

Glucagon
Inhibits
Key glycolytic enzymes

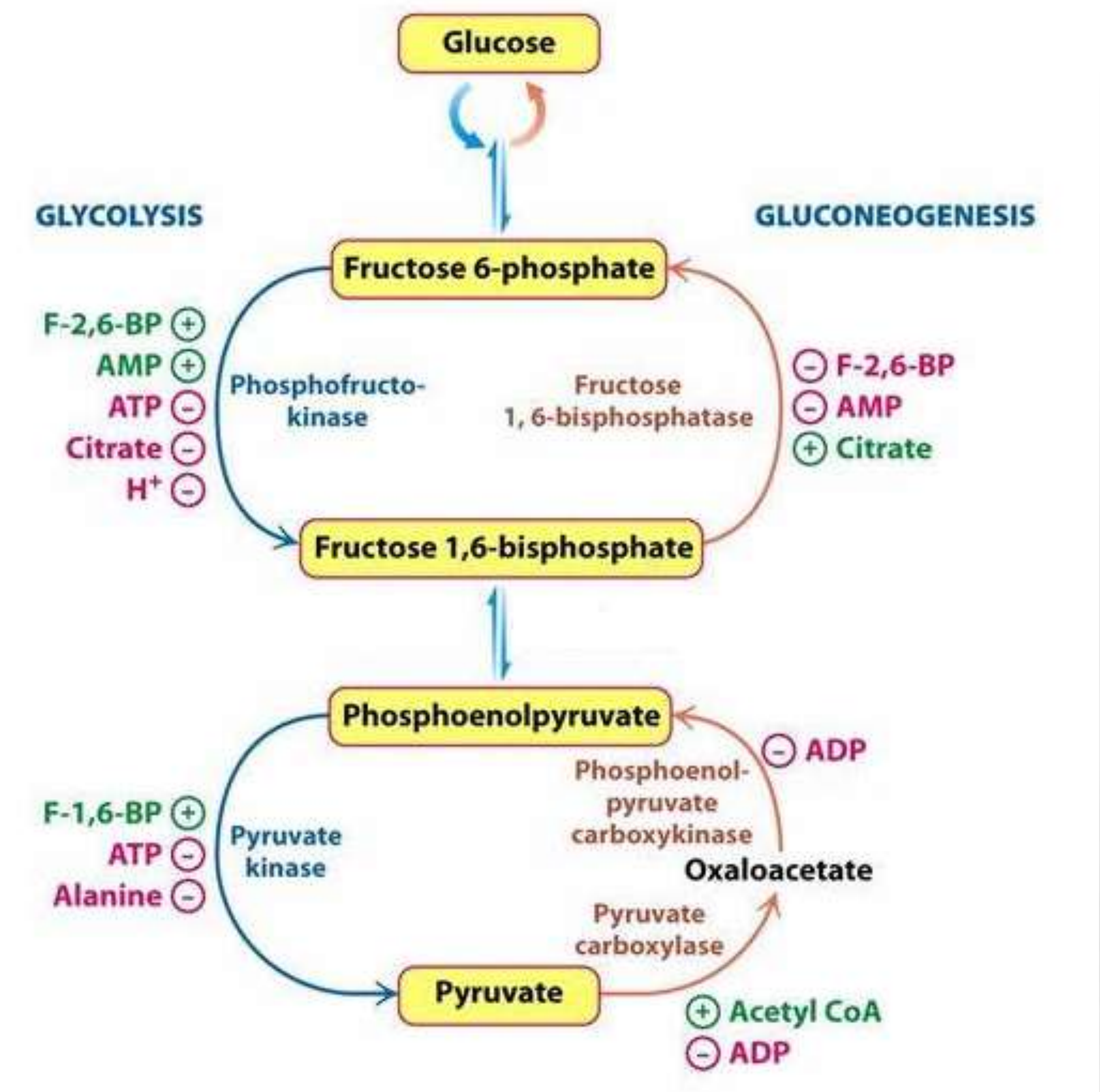


Reciprocal regulation of PFK-2 and fructose-2,6-bisphosphatase by phosphorylation.



Covalent modification of pyruvate kinase reaction; this is similar to phosphofructokinase-2 (PFK-2).

Summary of Regulation of Glycolysis



Energy yield (number of ATP generated) per molecule of glucose in the glycolytic pathway, under anaerobic conditions (Oxygen deficiency)			
Step	Enzyme	Source	**gained per glucose mol**
1	Hexokinase	-	**Minus 1**
3	Phosphofructokinase	-	**Minus 1**
6	1,3-bisphosphoglycerate kinase	ATP	**1 x 2 = 2**
9	Pyruvate kinase	ATP	**1 x 2 = 2**
		Total = 4 minus 2 = 2	

Energy yield (number of ATP generated) per molecule of glucose in the glycolytic pathway, under aerobic conditions (oxygen is available)

Step	Enzyme	Source	**No of ATP gained per glucose mol**
1	Hexokinase	-	**Minus 1**
3	Phosphofructokinase	-	**Minus 1**
5	Glyceraldehyde-3-phosphate dehydrogenase	NADH	**2.5 × 2 = 5**
6	l,3-bisphosphoglycerate kinase	ATP	**1 × 2 = 2**
9	Pyruvate kinase	ATP	**1 × 2 = 2**
		Total = 9 minus 2 = 7	

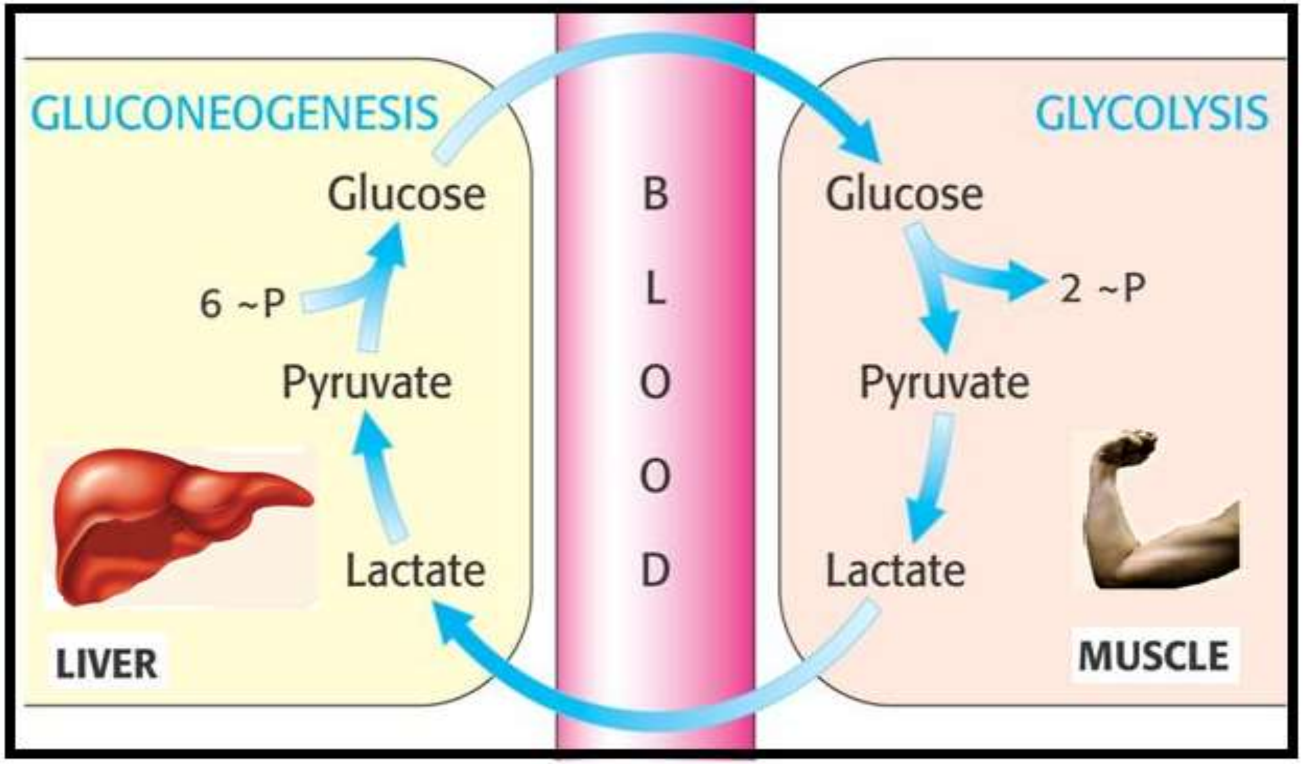
Energy yield (number of ATP generated) per molecule of glucose when it is completely oxidised through glycolysis plus citric acid cycle, under *aerobic conditions*.

Net generation in glycolytic pathway 9 minus 2 = 7

Generation in pyruvate dehydrogenase (pyruvate to acetyl CoA) = 5

Generation in citric acid cycle = 20

Net generation of ATP from one glucose mol = 32

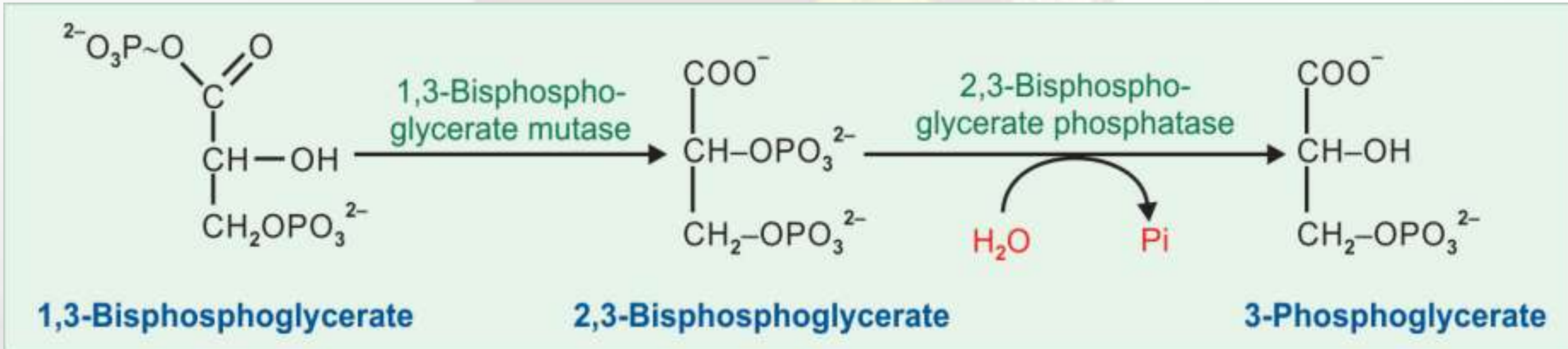


Cori's cycle.

Contracting muscle has lack of oxygen. So pyruvate is reduced to lactate. This can be reconverted to glucose in liver by gluconeogenesis.

Efficient Utilisation of Lactate.

Rapaport Leubering Cycle (BPG Shunt) in RBCs



Erythrocytes

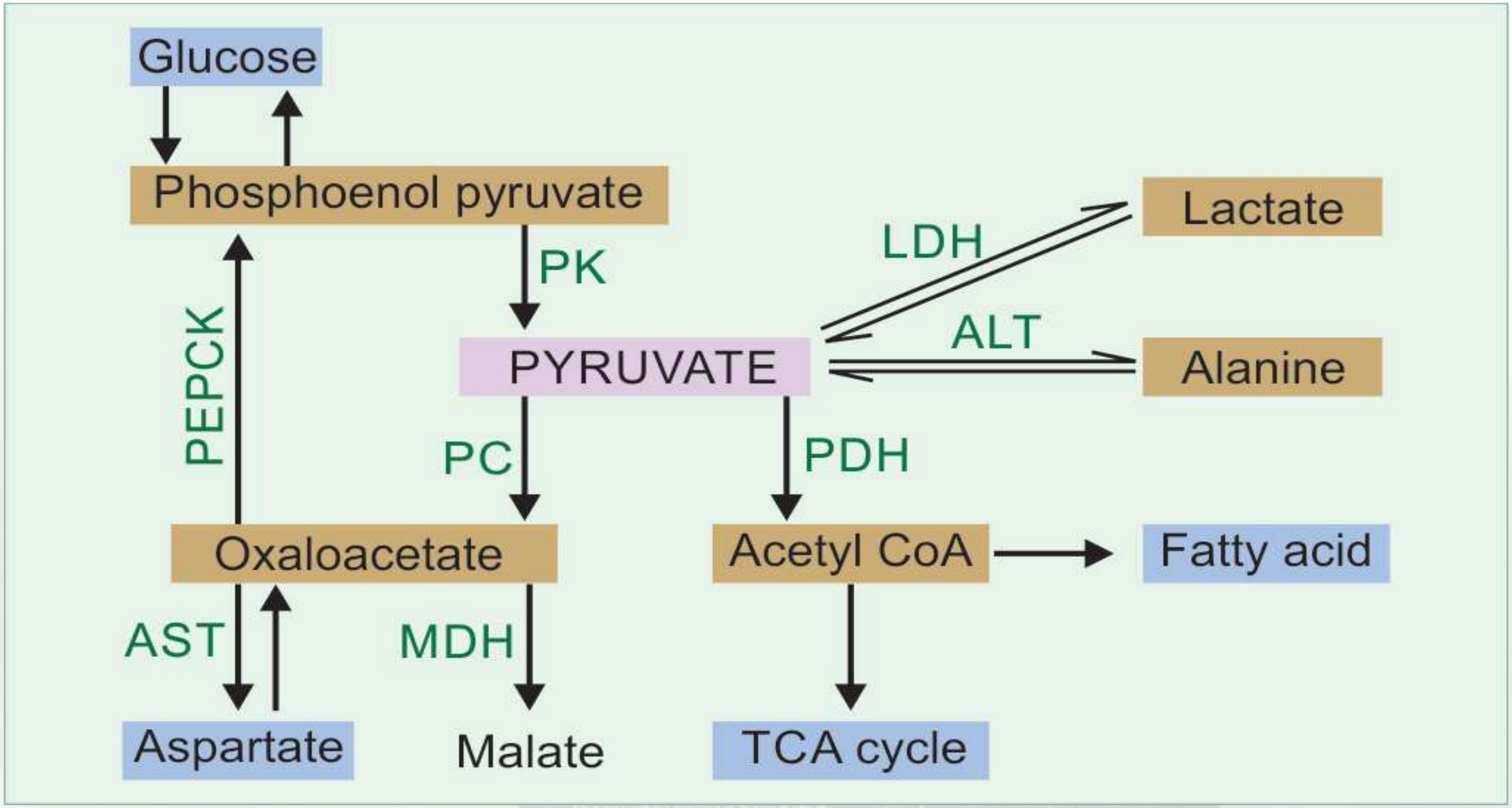
In this pathway, no ATP is generated.

Significance of Bisphosphoglycerate

- The 2,3-BPG combines with hemoglobin, and **reduces the affinity towards oxygen**. So, in presence of 2,3-BPG,oxyhemoglobin will unload oxygen more easily in tissues.
- Under **hypoxic conditions the 2,3-BPG concentration in the RBC increases**, thus favoring the release of oxygen to the tissues even when pO2 is low.
- The compensatory increase in 2,3-BPG in high altitudes favors oxygen dissociation. BPG is increased in fetal circulation.
- In this shunt pathway, **no ATP is generated**

Metabolic Fate of Pyruvate

Under aerobic conditions, pyruvate is converted to acetyl CoA which enters the TCA cycle to be oxidised to CO2. ATP is generated. Glycolysis is taking place in cytoplasm. So pyruvate is generated in cytoplasm. This is transported into mitochondria by a **pyruvate transporter**.



Pyruvate as a metabolic junction point

Glucose

Glucose to fatty acid is possible

Fat to glucose IS NOT possible

Glucose → **Pyruvate**

Completely irreversible

Pyruvate → (Pyruvate Dehydrogenase) → **Acetyl CoA**

Fatty acid synthesis ← Acetyl CoA

Pyruvate Dehydrogenase

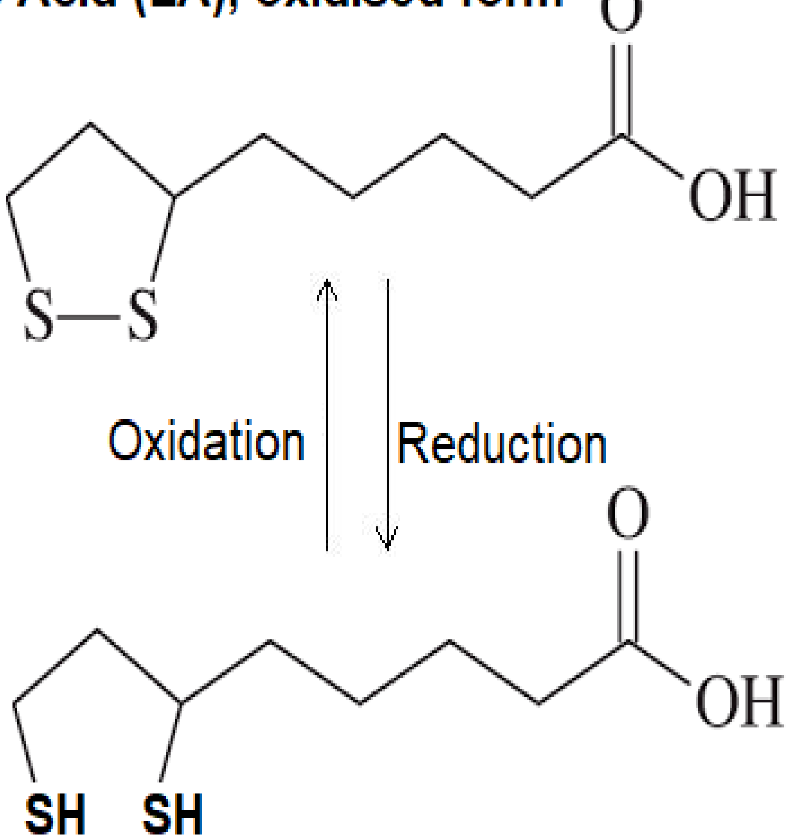
3 COMPONENTS :

- ✓Pyruvate decarboxylase / dehydrogenase
- ✓Dihydrolipoyl transacetylase
- ✓Dihydro lipoyl dehydrogenase

Co-factors / co-enzymes:

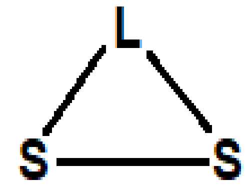
- ✓Thiamine pyrophosphate
- ✓lipoamide
- ✓CoA
- ✓FAD
- ✓NAD

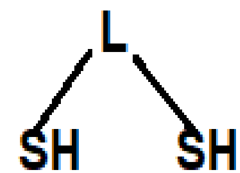
Lipoic Acid (LA), oxidised form



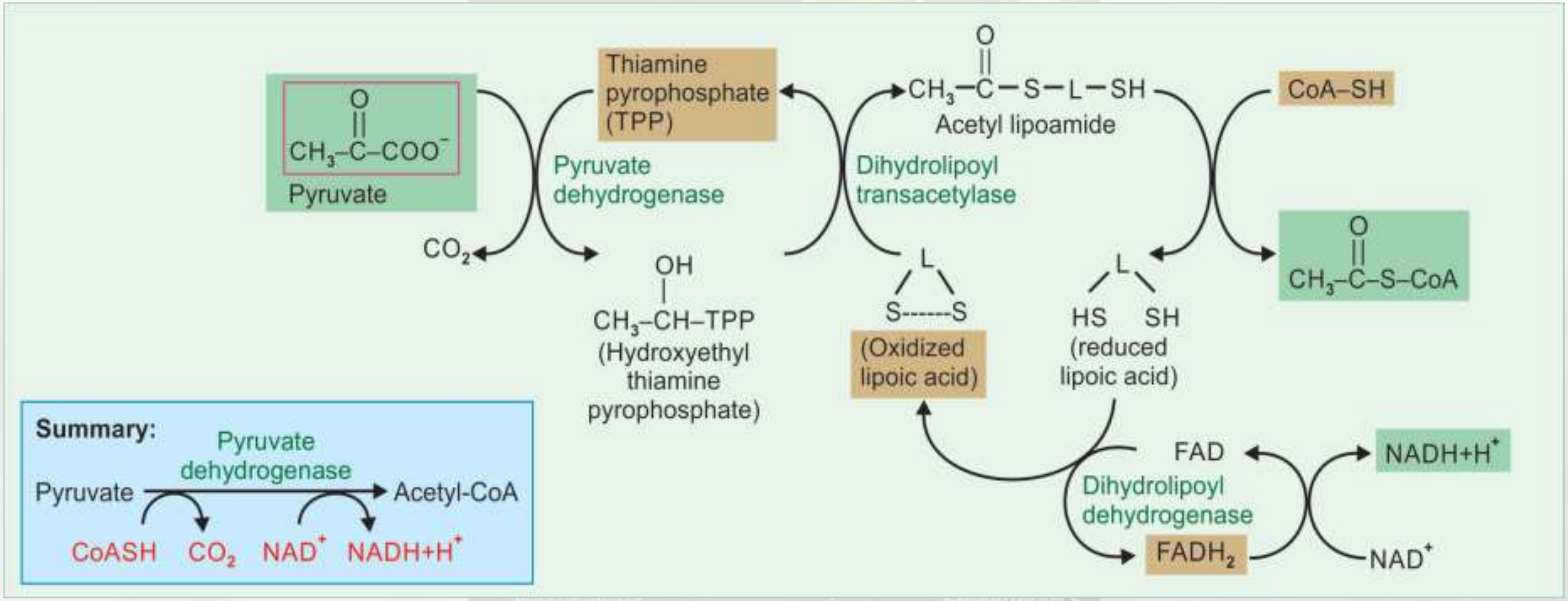
Dihydrolipoic Acid (DHLA), reduced form

Lipoic acid, short form





DHLA, short form



Pyruvate dehydrogenase

Pyruvate

Pyruvate Dehydrogenase

COMMITTED STEP

Completely irreversible

→ CO_2

THIAMINE PYRO PHOSPHATE
LIPOIC ACID
FAD
NAD^+
CoA-SH

→ NADH → 2 .5 ATPs

Acetyl CoA

CH_3—CO--SCoA

Regulation of PDH

✓End product inhibition by

- acetyl CoA
- NADH

✓Co-valent modification of PDH enzyme

CLINICAL ASPECTS

1. Thiamine deficiency:
   - PDH activity decreased
   - pyruvate is converted to lactate
   - lactic acidosis
2. Inherited deficiency of glycolytic enzymes
   - Pyruvate kinase
   - aldolase

Clinical Applications of Glycolytic Enzymes

1. **Lactic acidosis** may be seen in hypoxia, shock, pulmonary failure, alcohol abuse, diabetes mellitus and mitochondrial cytopathies.
2. **Deficiency of glycolytic enzymes**: These conditions are rare, out of which **pyruvate kinase** deficiency and **hexokinase** deficiency are comparatively common. They lead to hemolytic anemia, because energy depleted RBCs are destroyed.
3. **Pyruvate dehydrogenase (PDH):** PDH requires thiamine pyrophosphate (TPP); this explains the serious afflictions in **beriberi** due to thiamine deficiency. TPP deficiency in alcoholism causes pyruvate accumulation in tissues and resultant lactic acidosis. Inherited PDH deficiency may also lead to lactic acidosis.

Gluconeogenesis

Definition

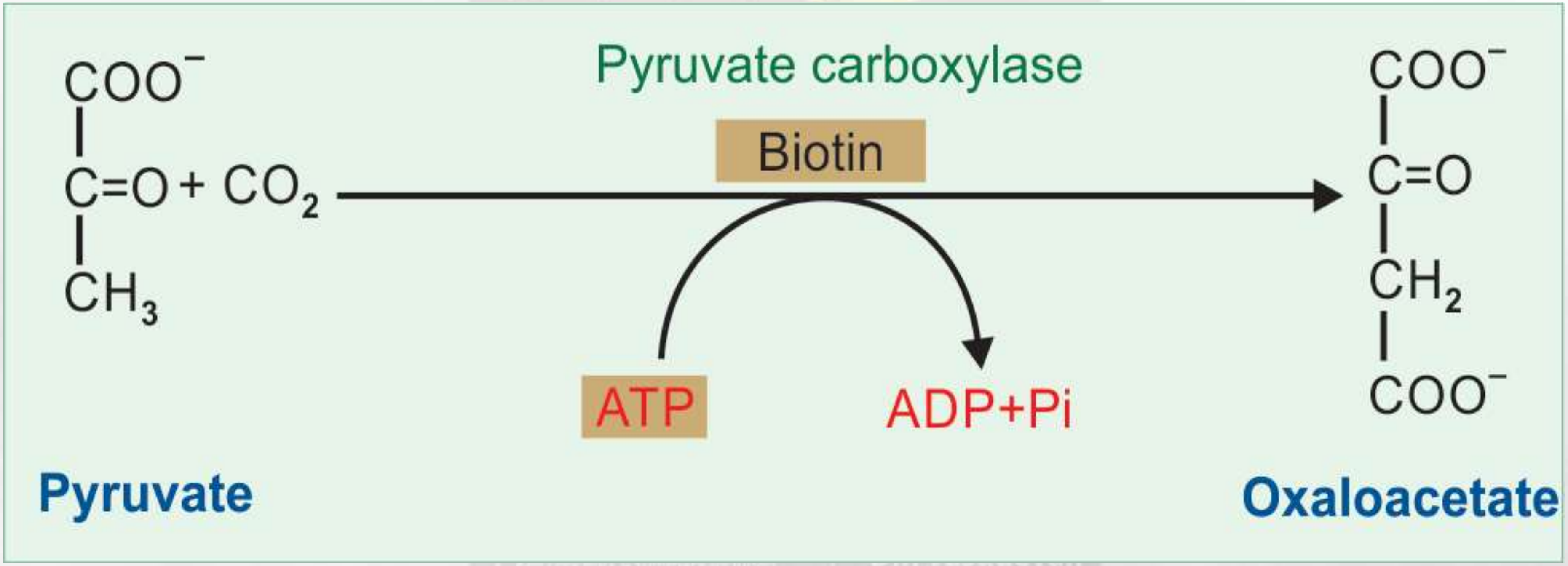
It is the process by which glucose is produced from non-carbohydrate precursors.

Site

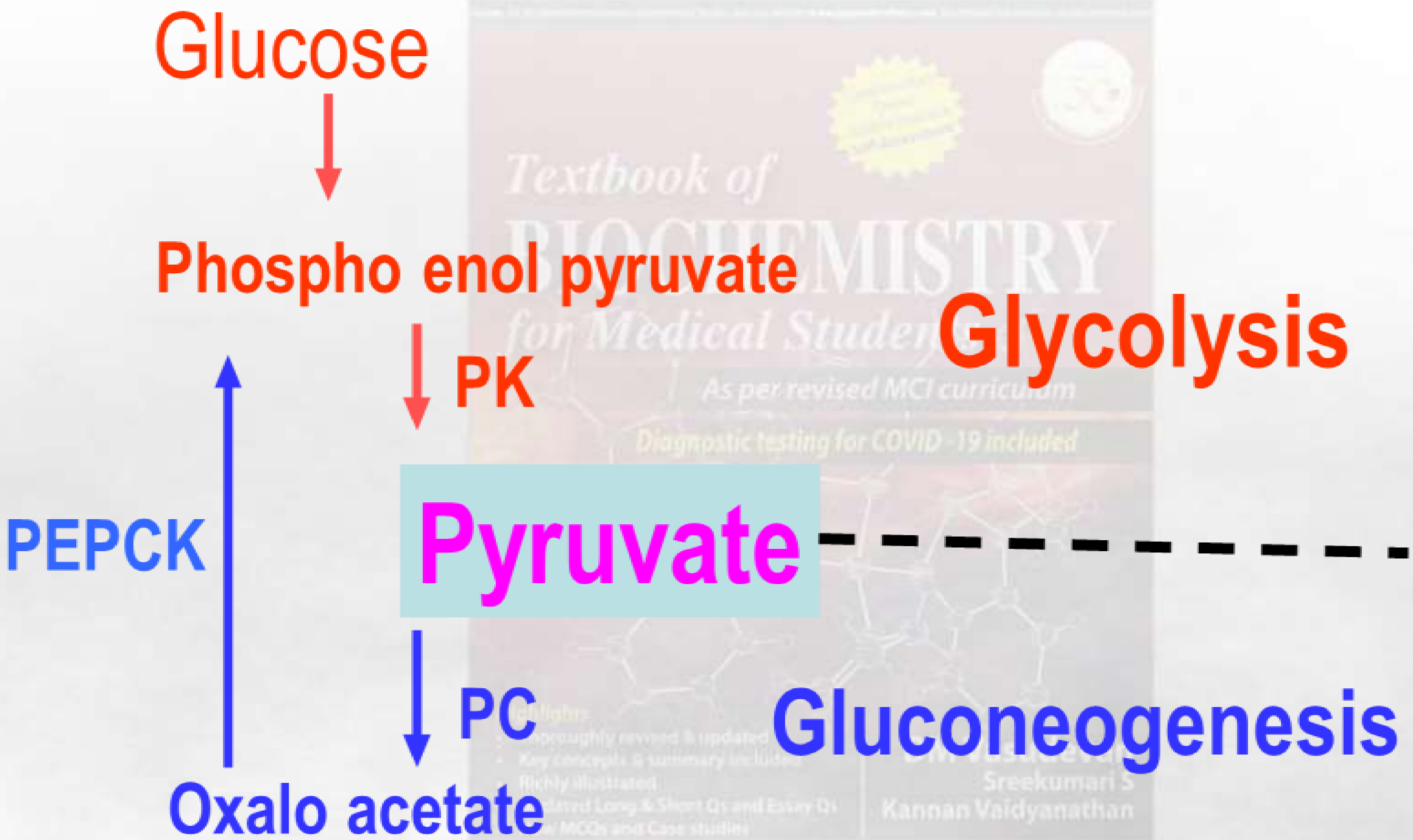
Gluconeogenesis occurs mainly in the liver, and to a lesser extent in the renal cortex. The pathway is partly mitochondrial and partly cytoplasmic.

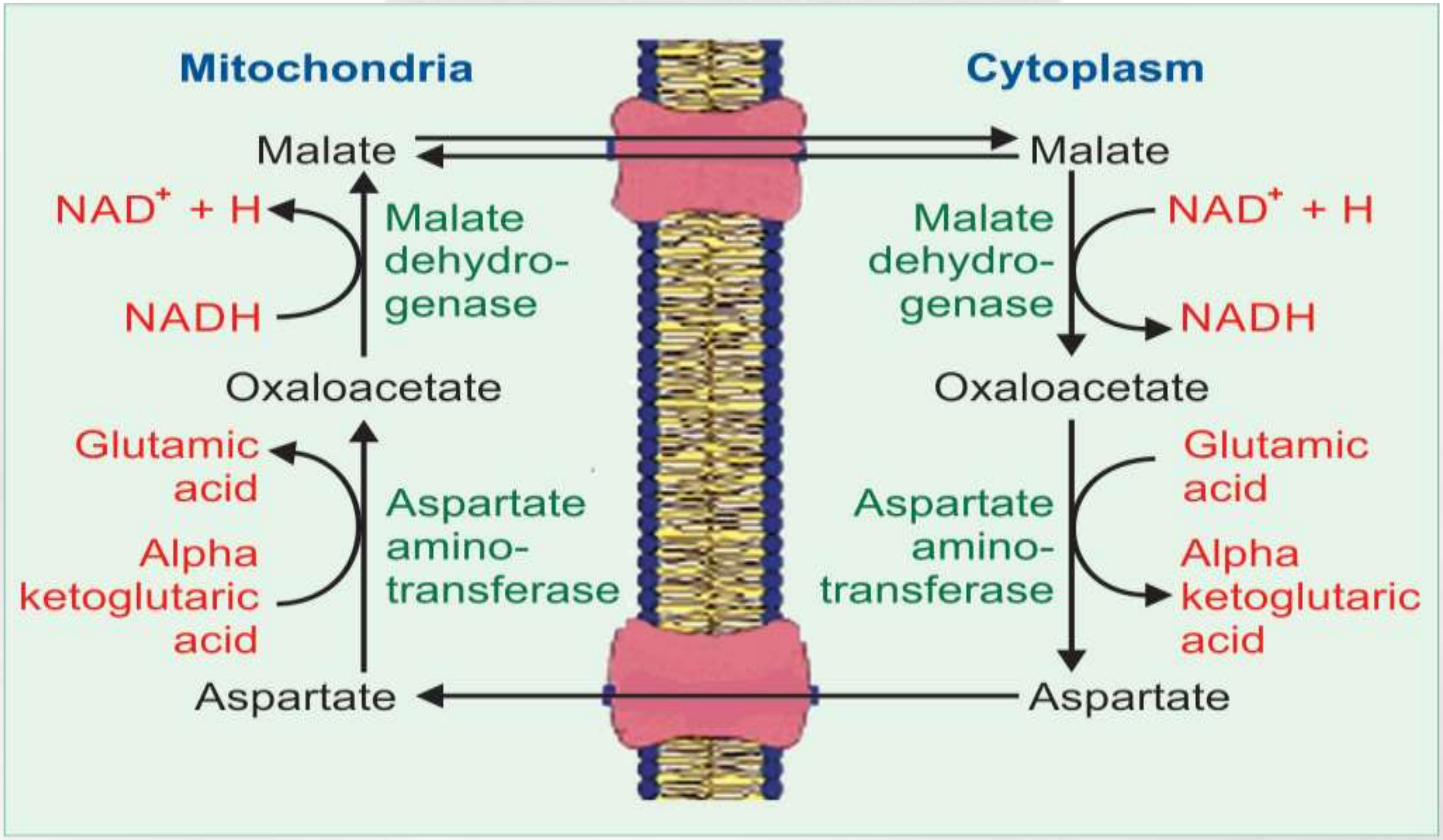
Key Gluconeogenic Enzymes

1. Pyruvate carboxylase
2. Phosphoenol pyruvate carboxykinase
3. Fructose-1-6-bisphosphatase
4. Glucose-6-phosphatase

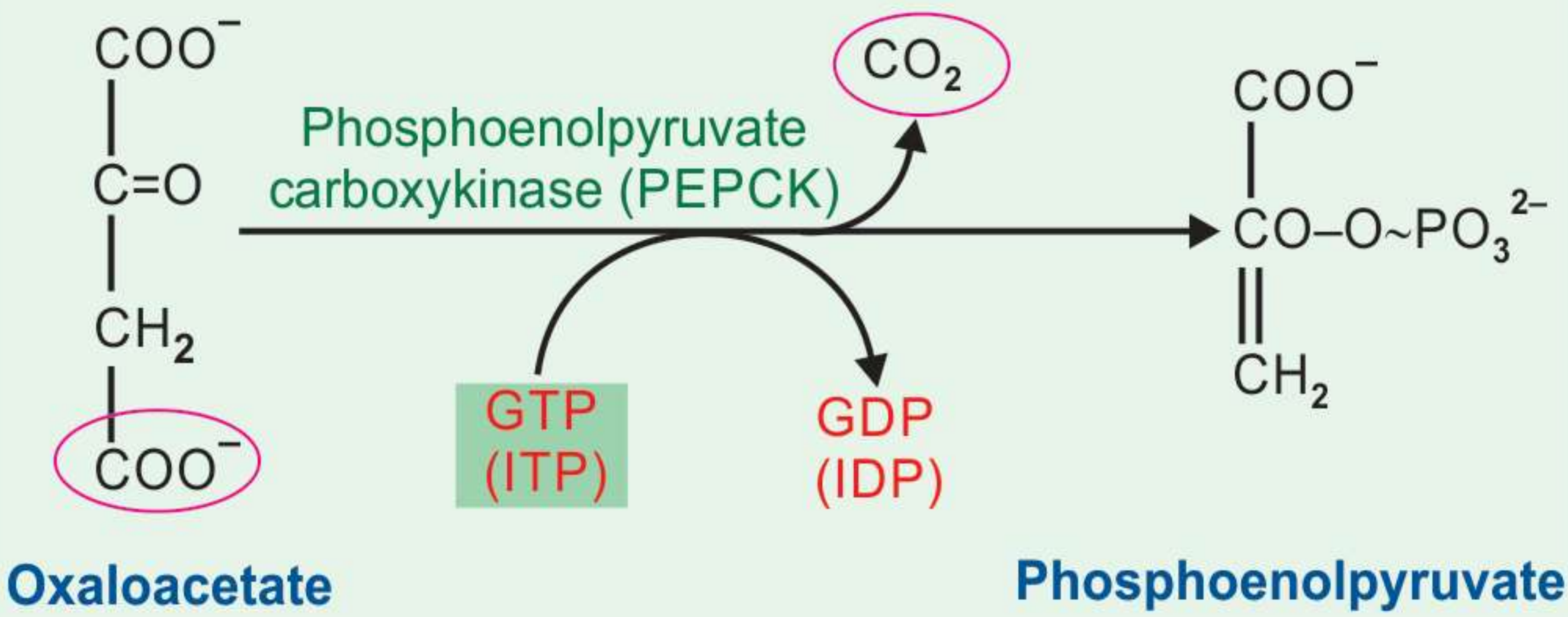


First step of gluconeogenesis

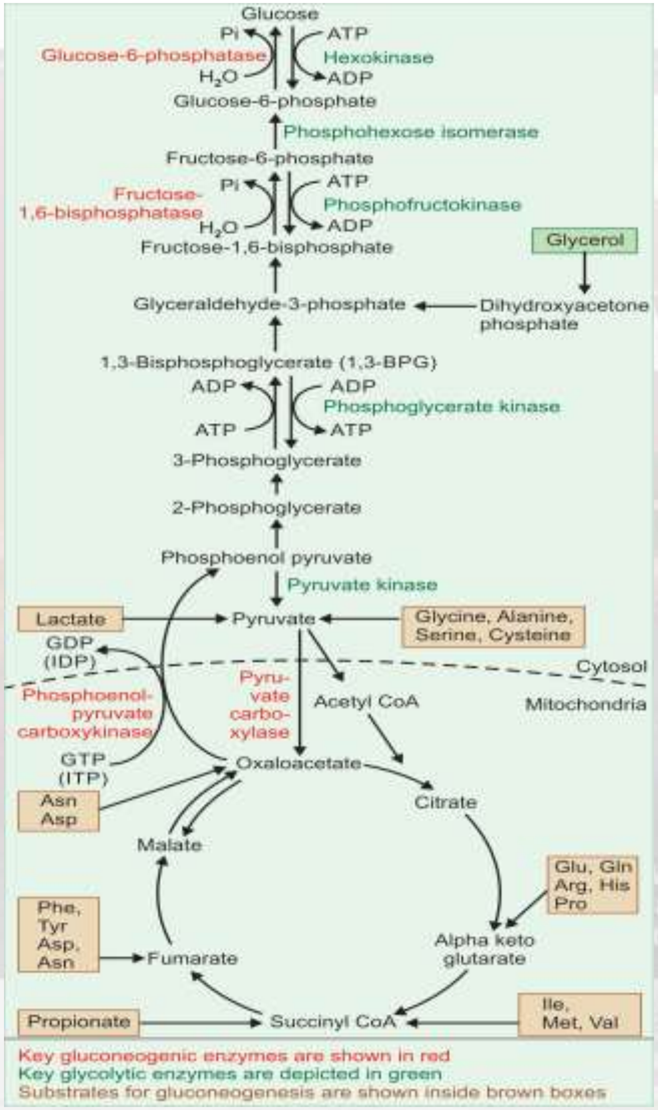

Glucose
Phospho enol pyruvate
PK
Glycolysis
PEPCK
Pyruvate
PC
Gluconeogenesis
Oxalo acetate



Malate-Aspartate shuttle.


COO⁻
C=O
CH2
COO⁻
Oxaloacetate
Phosphoenolpyruvate carboxykinase (PEPCK)
CO2
GTP (ITP)
GDP (IDP)
COO⁻
CO–O~PO3 2–
CH2
Phosphoenolpyruvate

Irreversible steps in glycolysis	Corresponding key gluconeogenic enzymes
Pyruvate kinase (Step 9)	Pyruvate carboxylase; Phosphoenol pyruvate carboxy kinase
Phosphofructokinase (Step 3)	Fructose-1,6-bisphosphatase
Hexokinase (Step 1)	Glucose-6-phosphatase


Glucose
Pi
ATP
Glucose-6-phosphatase
Hexokinase
H_2O
ADP
Glucose-6-phosphate
Phosphohexose isomerase
Fructose-6-phosphate
Pi
ATP
Fructose-
1,6-bisphosphatase
Phosphofructokinase
H_2O
ADP
Fructose-1,6-bisphosphate
Glycerol
Glyceraldehyde-3-phosphate
Dihydroxyacetone phosphate
1,3-Bisphosphoglycerate (1,3-BPG)
ADP
ADP
Phosphoglycerate kinase
ATP
ATP
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenol pyruvate
Pyruvate kinase
Lactate
Pyruvate
Glycine, Alanine, Serine, Cysteine
GDP (IDP)
Cytosol
Mitochondria
Phosphoenol-pyruvate carboxykinase
Pyru-vate carbo-xylase
Acetyl CoA
GTP (ITP)
Oxaloacetate
Asn Asp
Citrate
Malate
Glu, Gln Arg, His Pro
Phe, Tyr Asp, Asn
Alpha keto glutarate
Fumarate
Propionate
Succinyl CoA
Ile, Met, Val
Key gluconeogenic enzymes are shown in red
Key glycolytic enzymes are depicted in green
Substrates for gluconeogenesis are shown inside brown boxes

Gluco Neogenesis - Energy Requirement

1) Pyruvate $\xrightarrow{PC}$ Oxaloacetate — I ATP

2) Oxaloacetate $\xrightarrow{PEPCK}$ Phsphoemol pyruvate — I ATP

3) Phosphoglycerate $\longrightarrow$ 1,3 – Bisphospho glycerate — I ATP

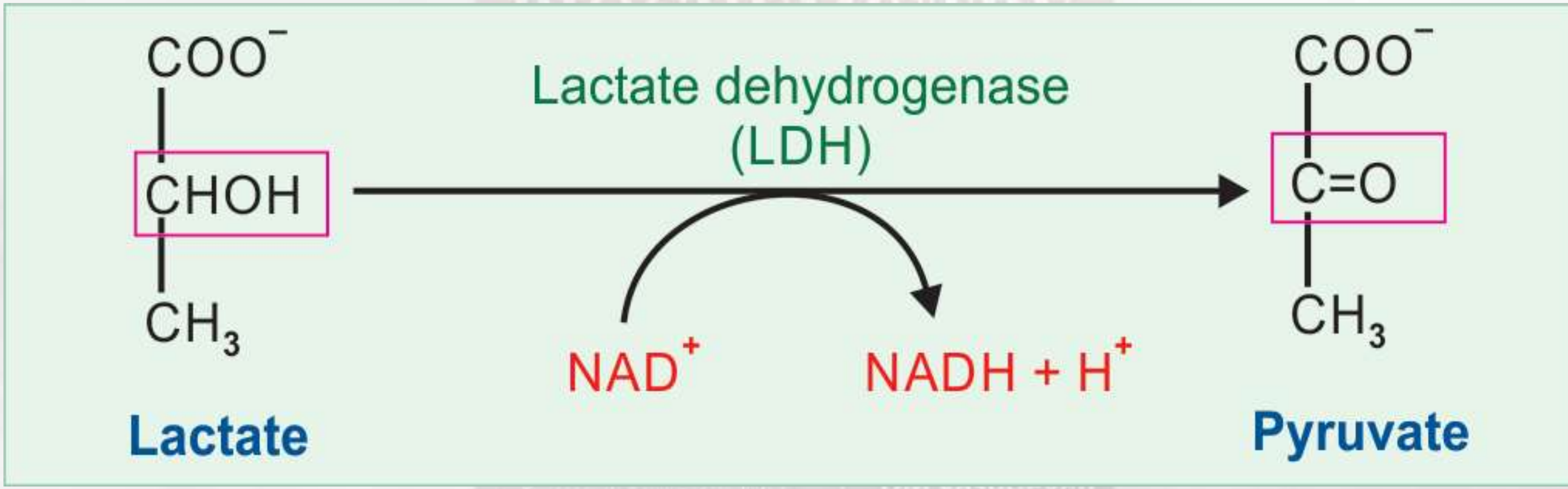
3 x 2 = 6 ATP moleacules for 1 moleacule of glucose

NON-CARBOHYDRATE PRECURSORS

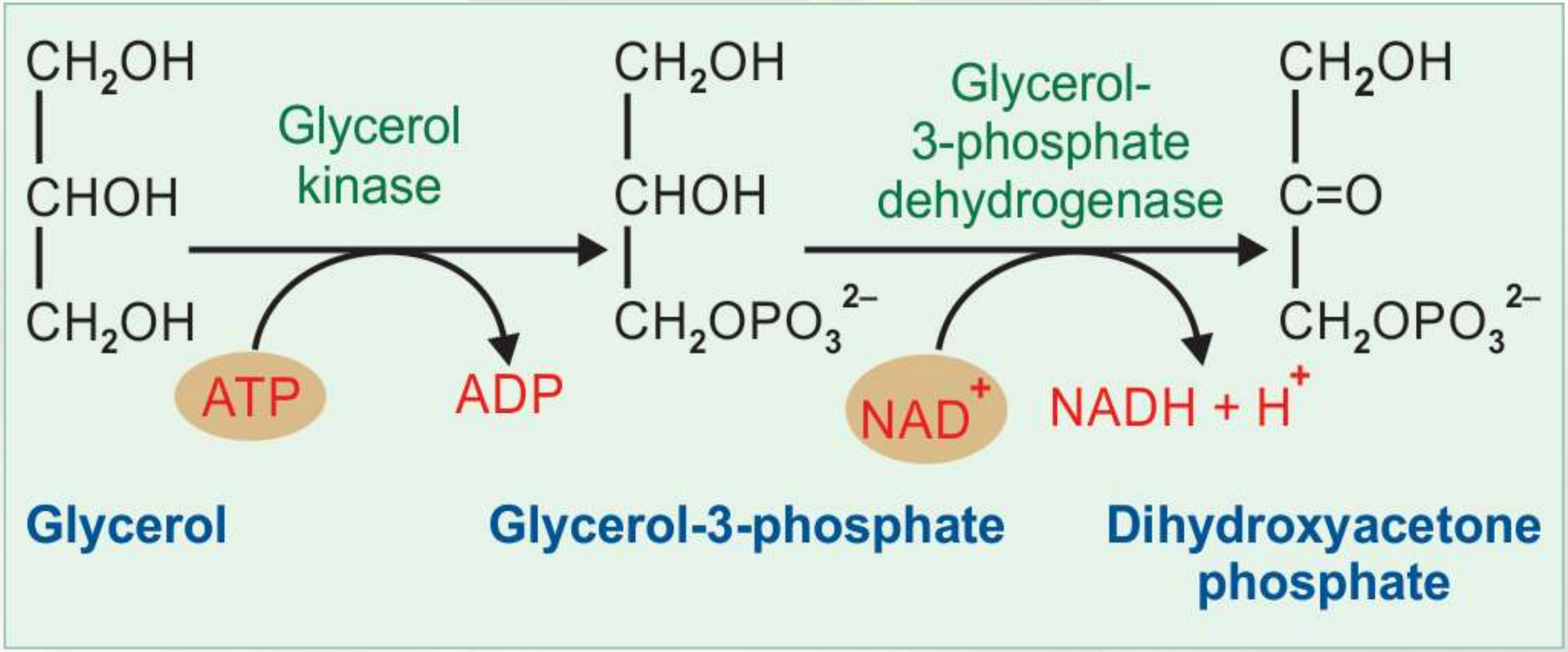
- **LACTATE**
- **GLUCOGENIC AMINO ACIDS**
- **GLYCEROL**
- **PROPIONIC ACID**

FATTY ~~ACID~~ cannot gives rise to glucose

Gluconeogenesis Substrate Lactate

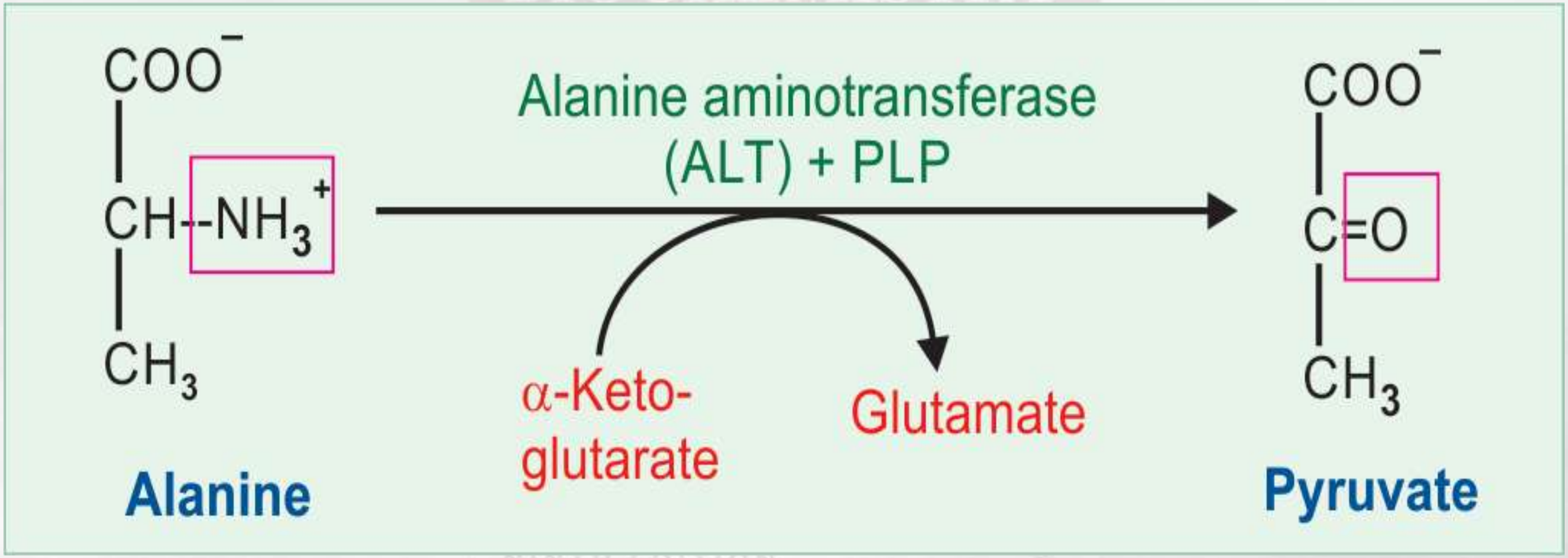


Gluconeogenesis from Glycerol

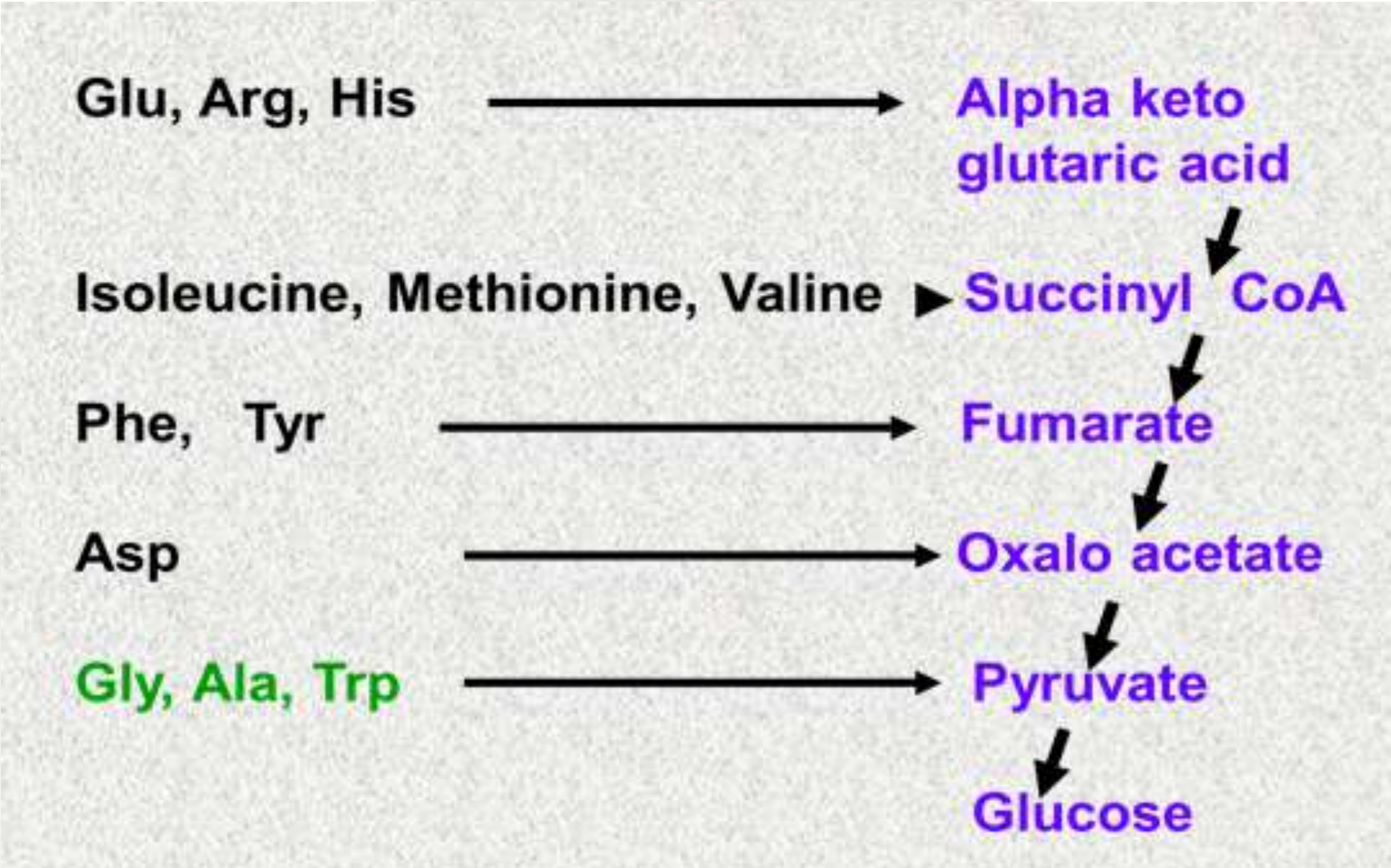


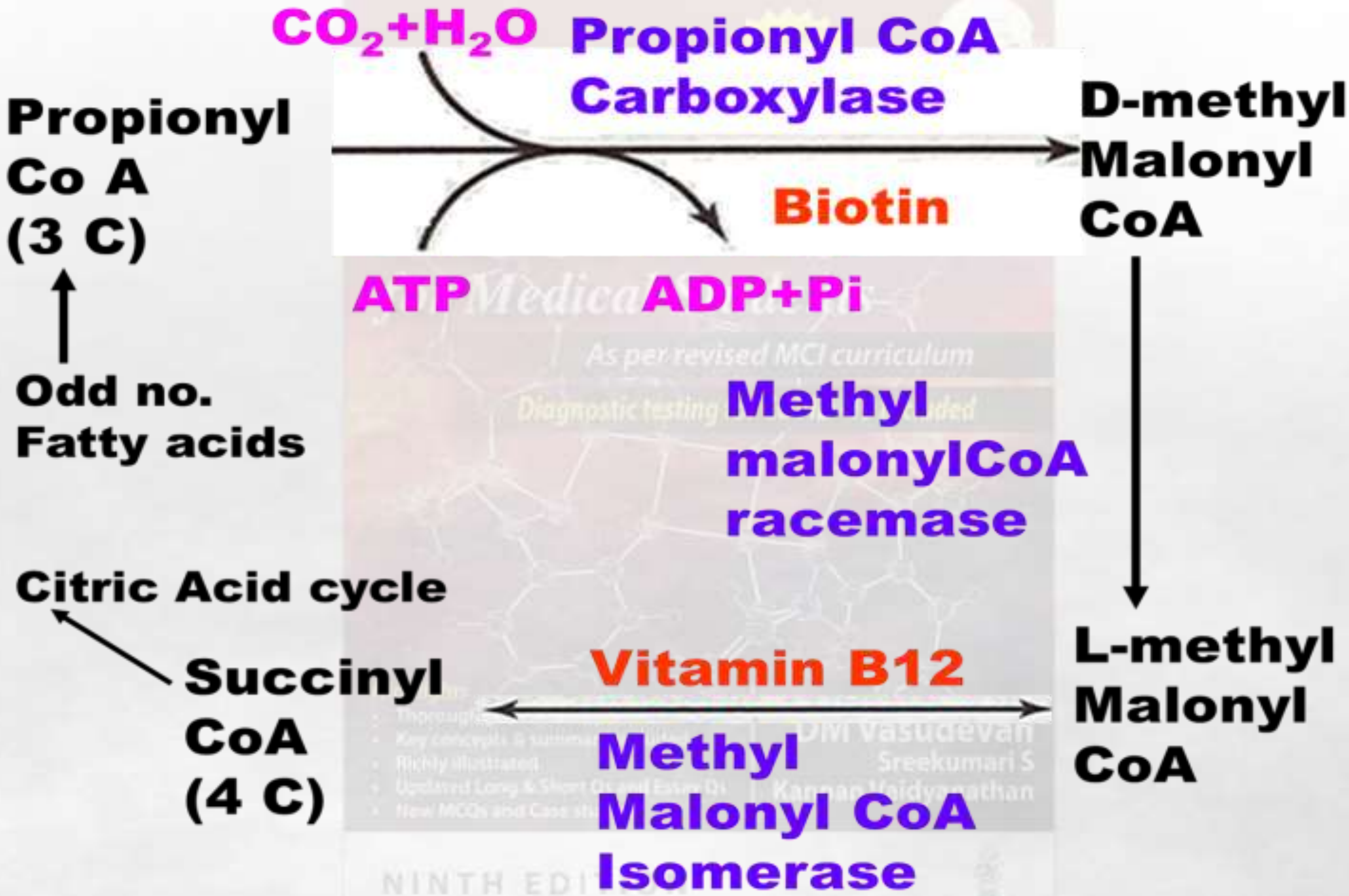
Transamination Reaction

Alanine ⇌ **Pyruvate**



Gluconeogenesis from Glucogenic Amino Acids




Propionyl
Co A
(3 C)
CO_2+H_2O
Propionyl CoA
Carboxylase
D-methyl
Malonyl
CoA
Biotin
ATP
ADP+Pi
Odd no.
Fatty acids
Methyl
malonylCoA
racemase
Citric Acid cycle
Succinyl
CoA
(4 C)
Vitamin B12
L-methyl
Malonyl
CoA
Methyl
Malonyl CoA
Isomerase

Hormonal Regulation of Gluconeogenesis

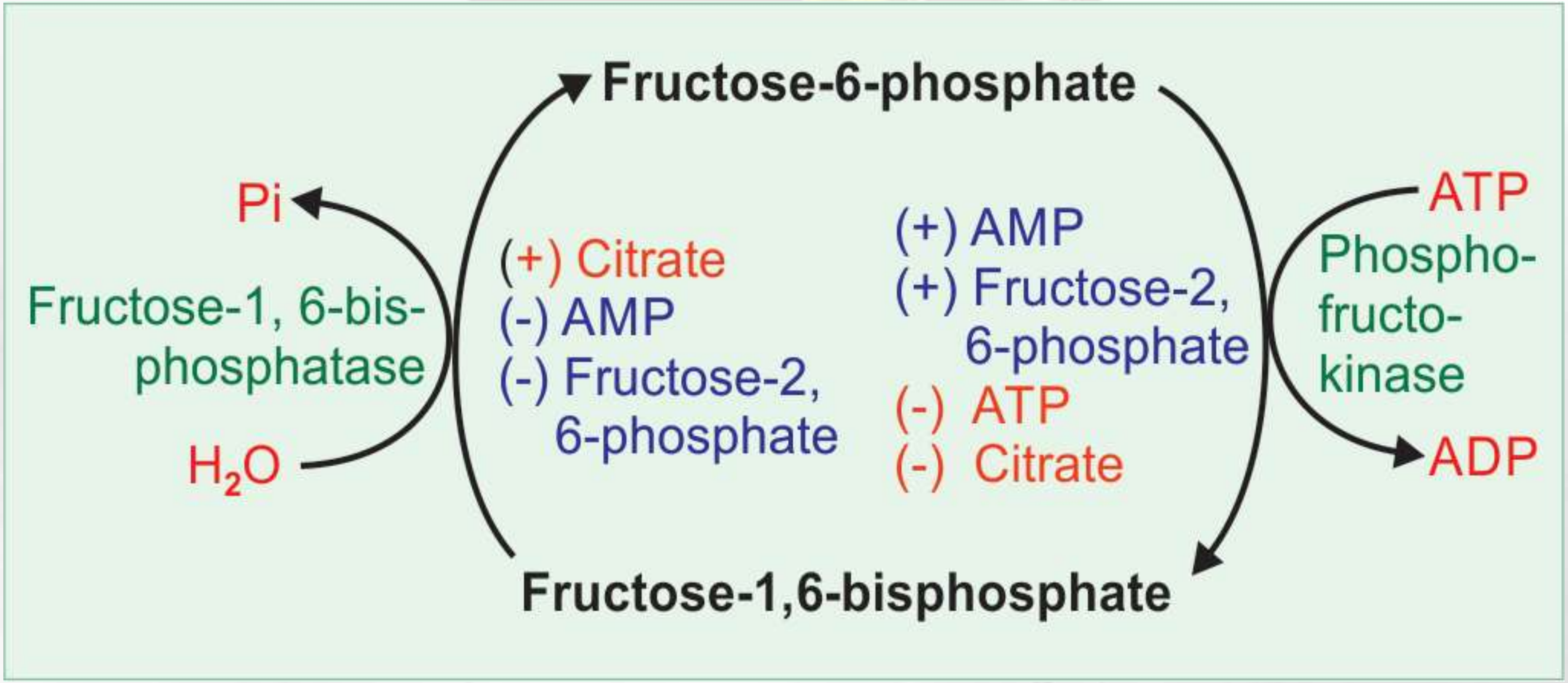
Glucose

Gluconeogenesis ↑ | ↓ **Glycolysis**

Gluconeogenesis	Glycolysis
Glucagon (+)	(--)glucagon
Glucocorticoids (+)	
Insulin (--)	(+) Insulin

Pyruvate

Reciprocal Regulation of Enzymes



Physiological Significance of Gluconeogenesis

Maintenance of blood glucose level especially under conditions of starvation.

The brain has a minimum need of 120 grams of glucose per day.

The body stores of glycogen are depleted within the first 12-18 hours of fasting.

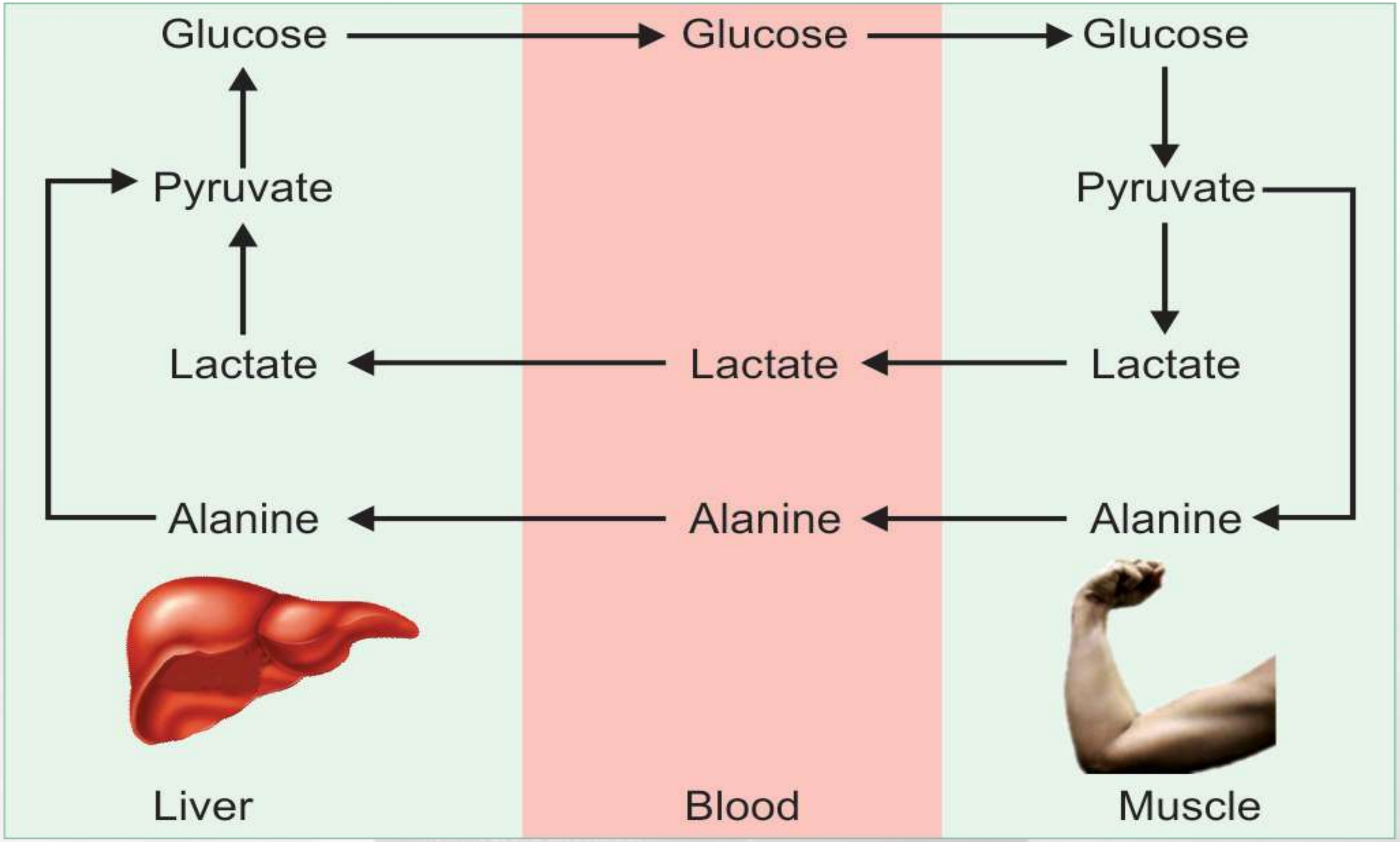
On prolonged starvation

gluconeogenesis is speeded up

Protein catabolism provides the substrates, glucogenic amino acids for gluconeogenesis

Clinical Significance of Gluconeogenesis

1. **Pyruvate carboxylase deficiency**: It is a rare inborn error of metabolism manifested with neurological symptoms and mental retardation, due to deficient fuel supply to the nervous system. Accumulation of lactic acid and keto acids leads to metabolic acidosis. Hyperammonemia is also seen. It is an autosomal recessive condition
2. **Malignant hyperthermia**: This may occur when halothane is given as an anesthetic to certain persons. There is inappropriate release of calcium from sarcoplasmic reticulum. This results in uncontrolled heat generation, damage of muscle cells
3. **Ethanol (Ethyl alcohol)**: It inhibits gluconeogenesis. During the metabolism of ethanol the level of cytoplasmic NADH is raised. Thus, the Pyruvate → Malate → Oxaloacetate reactions are reversed. So, excessive ingestion of alcohol results in hypoglycemia. Lactate also accumulates as NADH level is high.



Cori's cycle (upper circle) and Glucose-alanine cycle (lower circle)