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UNIVERSITY OF FIRST CHOICE AND THE NATION'S PRIDE

OUTLINE OF COURSE

- Introduction to metabolism and bioenergetics
- Breakdown of Biological molecules and their uses as fuel
- Biological oxidation: Electron transport chain
- Oxidative phosphorylation

Bioenergetics : Biochemical thermodynamics

FREE ENERGY IS THE USEFUL ENERGY IN A SYSTEM

Gibbs change in free energy (ΔG) is that portion of the total energy change in a system that is available for doing work—ie, the useful energy, also known as the chemical potential.

Enthalpy, *H, is the heat content of the reacting* system.

Entropy is the extent of disorder or randomness of the system and becomes maximum as equilibrium is approached.

Biologic Systems Conform to the General Laws of Thermodynamics.

The first law of thermodynamics states that the total energy of a system, including its surroundings, remains constant.

The second law of thermodynamics states that the total entropy of a system must increase if a process is to occur spontaneously.

Under conditions of constant temperature and pressure, the relationship between the free energy change (ΔG) of a reacting system and the change in entropy (ΔS) is expressed by the following equation, which combines the two laws of thermodynamics:

$$\Delta G = \Delta H - T\Delta S$$

If ΔG is negative, the reaction proceeds spontaneously with loss of free energy; ie, it is **exergonic.**

If, in addition, ΔG is of great magnitude, the reaction goes virtually to completion and is essentially irreversible.

On the other hand, if ΔG is positive, the reaction proceeds only if free energy can be gained; ie, it is **endergonic.**

If, in addition, the magnitude of ΔG is great, the system is stable, with little or no tendency for a reaction to occur.

If ΔG is zero, the system is at equilibrium and no net change takes place.

Cells are isothermal systems—they function at essentially constant temperature (they also function at constant pressure).

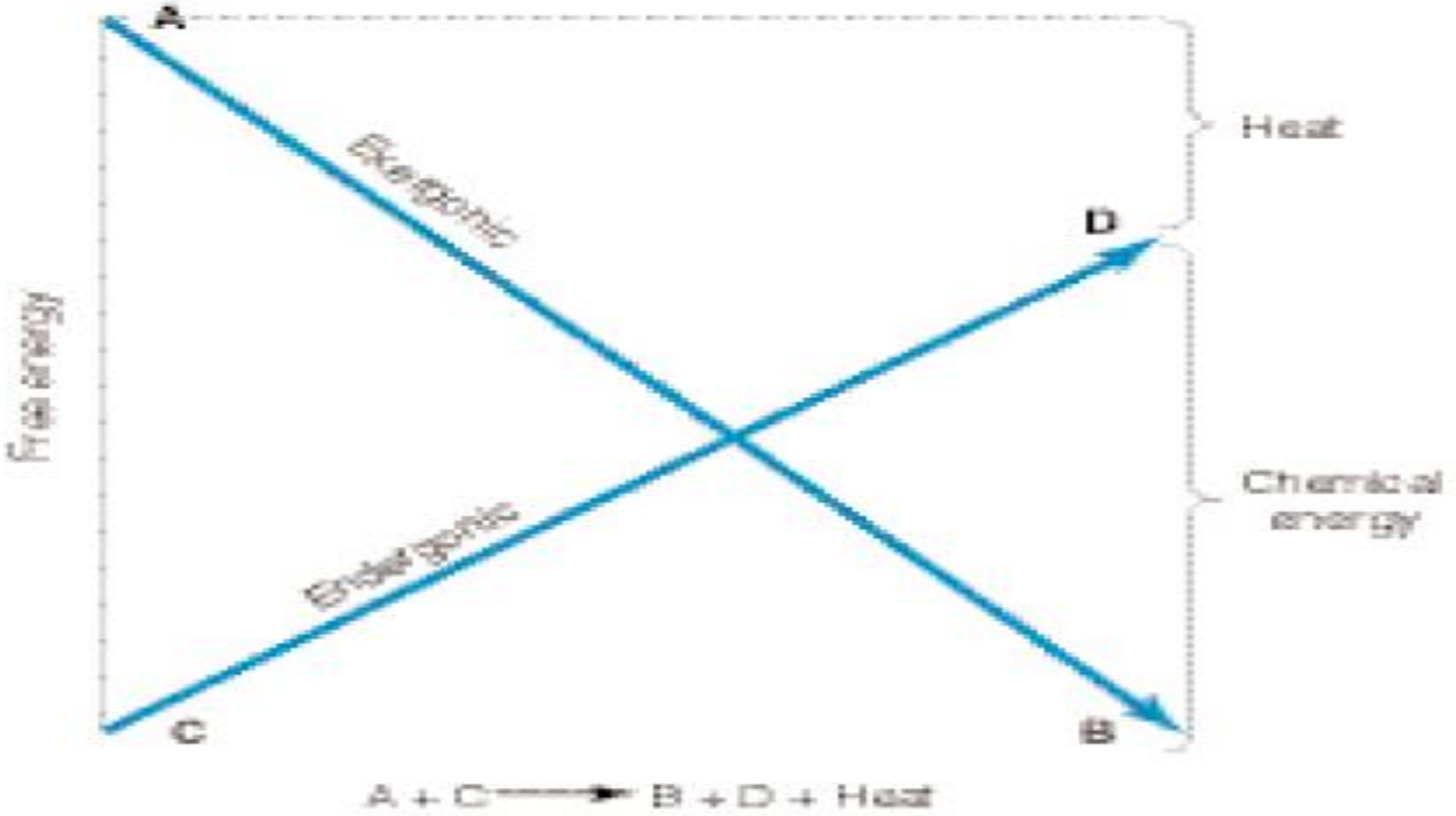
Heat flow is not a source of energy for cells, because heat can do work only as it passes to a zone or object at a lower temperature.

The energy that cells can and must use is free energy, described by the **Gibbs free-energy function** ***G****, which allows prediction* of the direction of chemical reactions, their exact equilibrium position, and the amount of work they can in theory perform at constant temperature and pressure.

- In practice, an endergonic process cannot exist independently but must be a component of a coupled exergonic- endergonic system where the overall net change is exergonic.

- The exergonic reactions are termed **catabolism** (generally, the breakdown or oxidation of fuel molecules), whereas the synthetic reactions that build up substances are termed **anabolism.**

- **The combined** catabolic and anabolic processes constitute **metabolism.**



Coupling of an exergonic to an endergonic reaction.

HIGH-ENERGY PHOSPHATES PLAY A CENTRAL ROLE IN ENERGY CAPTURE AND TRANSFER

Standard free energy of hydrolysis of some organophosphates of biochemical importance.[1,2]

Compound	$\Delta G^{0\prime}$ kJ/mol	$\Delta G^{0\prime}$ kcal/mol
Phosphoenolpyruvate	−61.9	−14.8
Carbamoyl phosphate	−51.4	−12.3
1,3-Bisphosphoglycerate (to 3-phosphoglycerate)	−49.3	−11.8
Creatine phosphate	−43.1	−10.3
$\boxed{ATP \rightarrow ADP + P_i}$	−30.5	−7.3
$ADP \rightarrow AMP + P_i$	−27.6	−6.6
Pyrophosphate	−27.6	−6.6
Glucose 1-phosphate	−20.9	−5.0
Fructose 6-phosphate	−15.9	−3.8
AMP	−14.2	−3.4
Glucose 6-phosphate	−13.8	−3.3
Glycerol 3-phosphate	−9.2	−2.2

[1] P_i, inorganic orthophosphate.
[2] Values for ATP and most others taken from Krebs and Kornberg (1957). They differ between investigators depending on the precise conditions under which the measurements are made.

Metabolism

Metabolism is the sum total of chemical transformations taking place in a cell or organism which occurs through a series of enzyme-catalyzed reactions.

These series of enzyme-catalyzed reaction constitutes METABOLIC PATHWAYS.

Each of the consecutive steps in a metabolic pathway brings about a specific, small chemical change.

This change is usually the removal, transfer or addition of a particular atom or functional group.

The precursor is converted into a product through a series of metabolic intermediates called METABOLITES.

TWO PHASES OF METABOLISM

CATABOLISM

- Is the degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats and proteins) are converted into smaller, simpler end products (e.g lactic acid, CO_2 , NH_3).

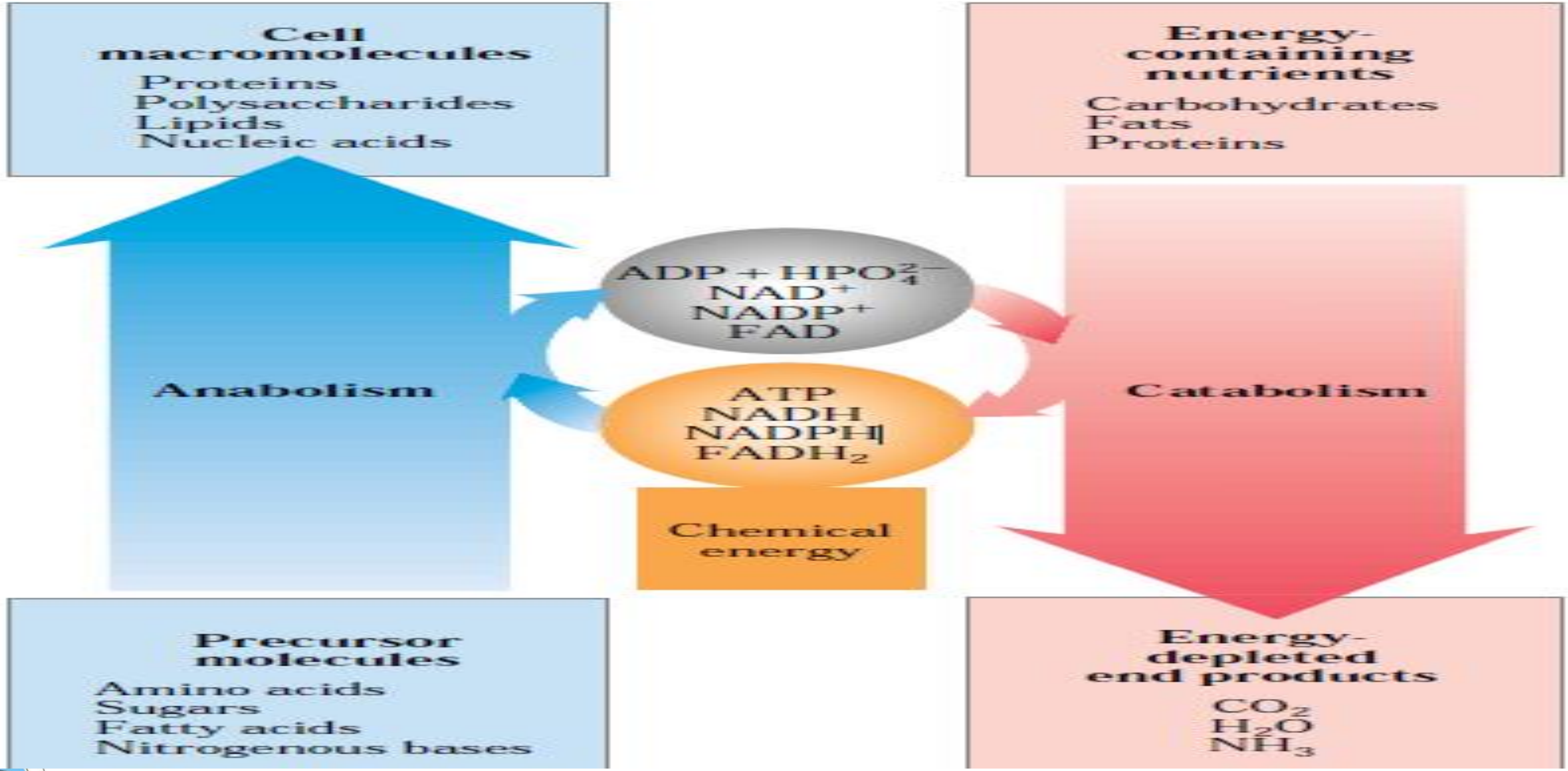
- Catabolic pathways release energy, some of which is conserved in the formation of ATP and reduced electron carriers (NADH, NADPH & $FADH_2$).

ANABOLISM

- Is the biosynthetic phase in which small, simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins and nucleic acids.

- Anabolic reactions require an input of energy, generally in the form of ATP or NADH/NADPH and $FADH_2$

ANABOLISM AND CATABOLISM



STRATEGY OF METABOLISM

1. TO PRODUCE ATP.

2. TO GENERATE NADPH (REDUCING EQUIVALENTS).

3. SYNTHESIZE AND DEGRADE BIOMOLECULES REQUIRED IN SPECIALIZED CELLULAR FUNCTIONS.

4. TO ALTERNATE DEGRADATIVE AND BIOSYNTHETIC PATHWAY.

METABOLIC PATHWAYS

LINEAR

NON-LINEAR (BRANCHED)

CONVERGING CATABOLISM

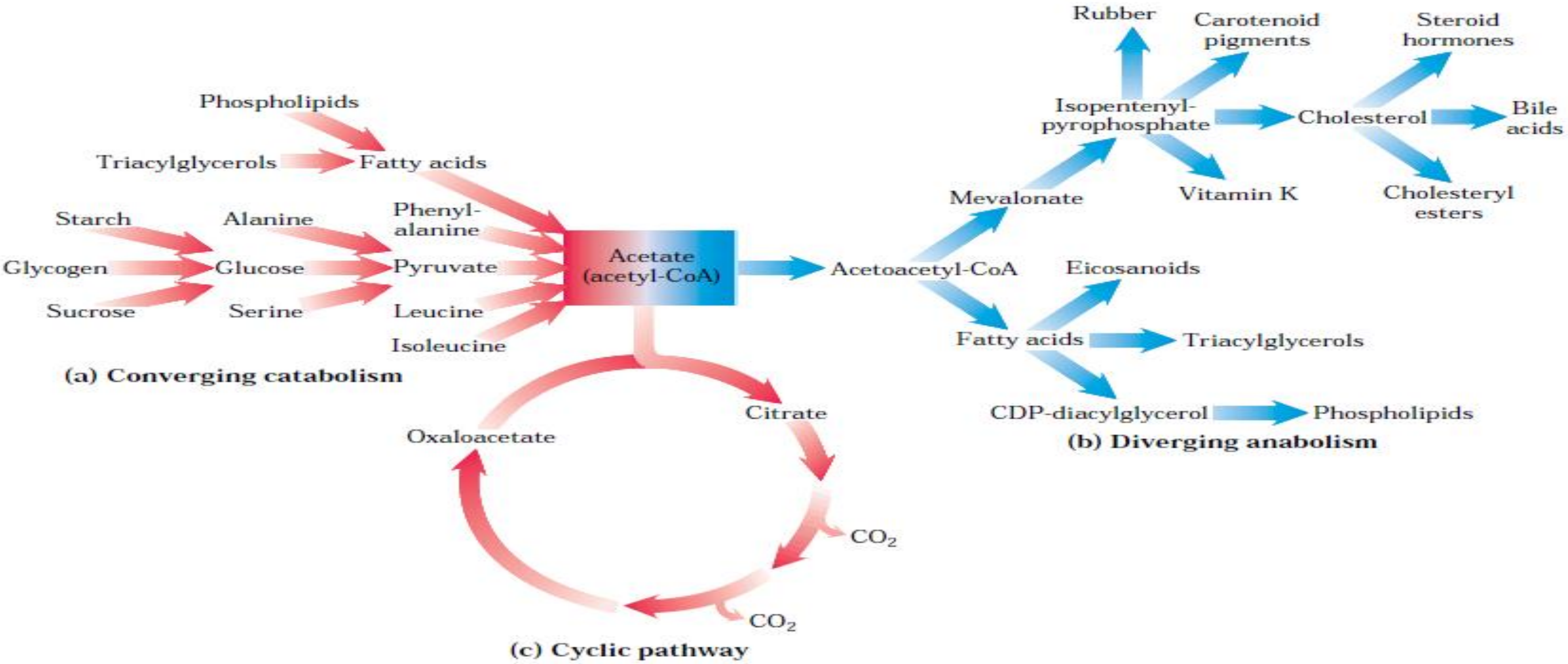
(CONVERTING SEVERAL STARTING MATERIALS INTO A SINGLE PRODUCT)

DIVERGING ANABOLISM

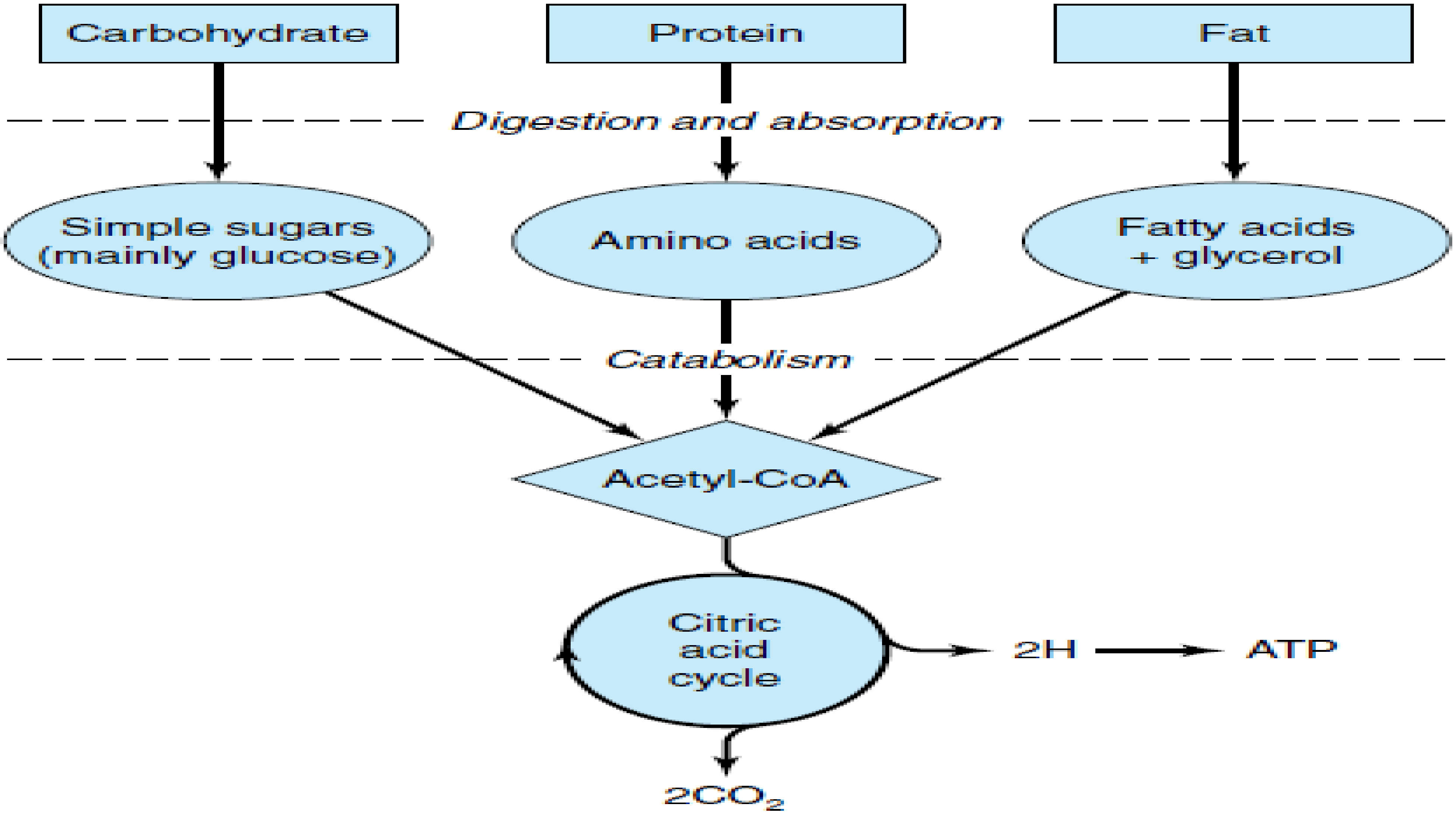
(YIELDING MULTIPLE USEFUL END PRODUCTS FROM A SINGLE PRECURSOR)

CYCLIC

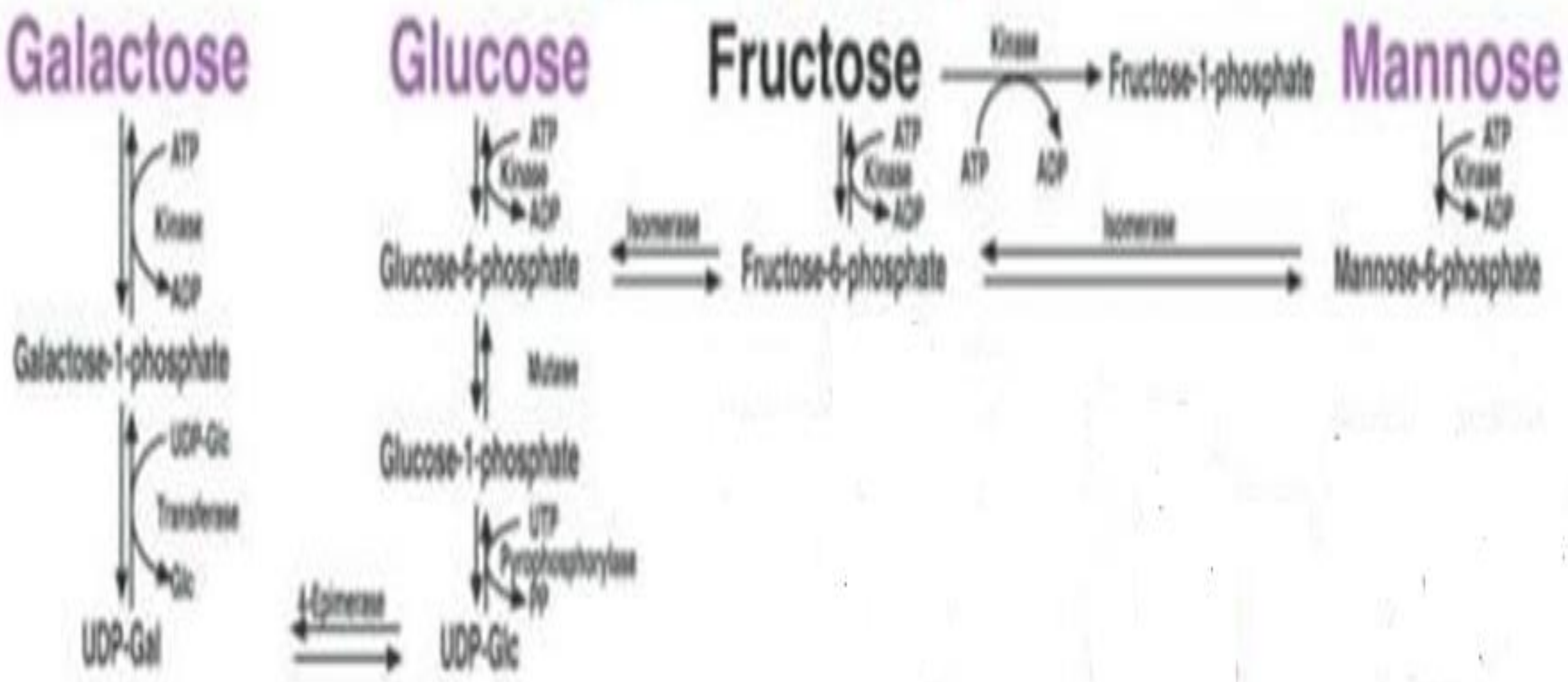
(A STARTING COMPONENT OF THE PATHWAY IS REGENERATED IN A SERIES OF REACTION THAT CONVERTS ANOTHER STARTING COMPONENT INTO A PRODUCT)


Phospholipids
Triacylglycerols
Fatty acids
Starch
Glycogen
Sucrose
Alanine
Glucose
Serine
Phenyl-alanine
Pyruvate
Leucine
Isoleucine
Acetate (acetyl-CoA)
(a) Converging catabolism
Citrate
Oxaloacetate
CO_2
CO_2
(c) Cyclic pathway
Acetoacetyl-CoA
Mevalonate
Isopentenyl-pyrophosphate
Rubber
Carotenoid pigments
Vitamin K
Cholesterol
Steroid hormones
Bile acids
Cholesteryl esters
Eicosanoids
Fatty acids
Triacylglycerols
CDP-diacylglycerol
Phospholipids
(b) Diverging anabolism

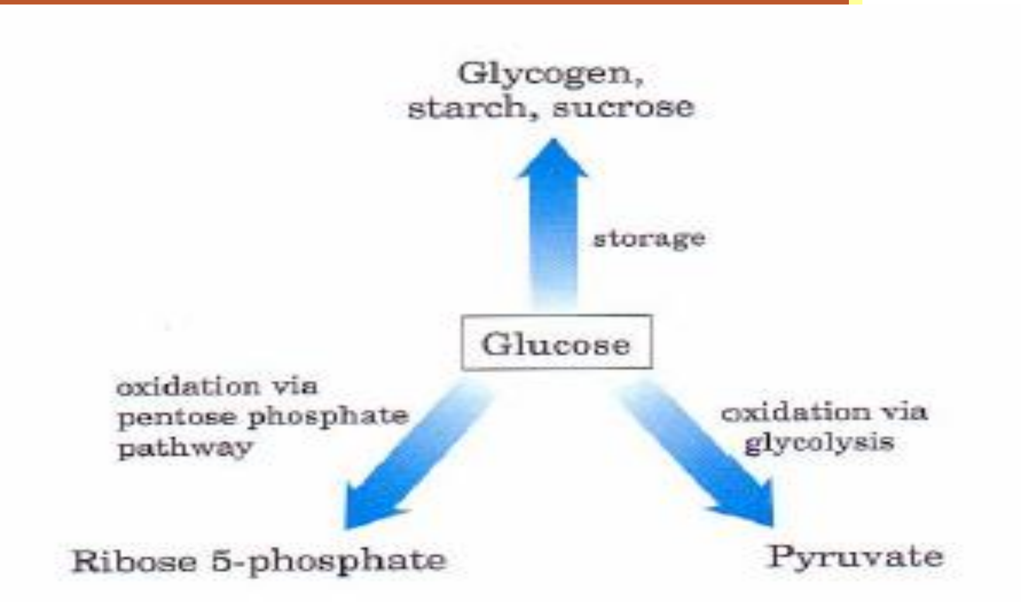
Overview of metabolism

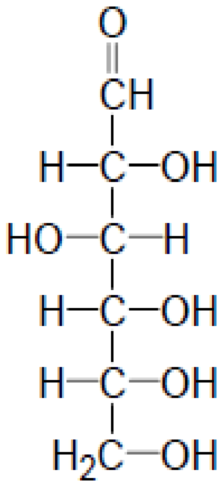


Monosaccharide Interconversion

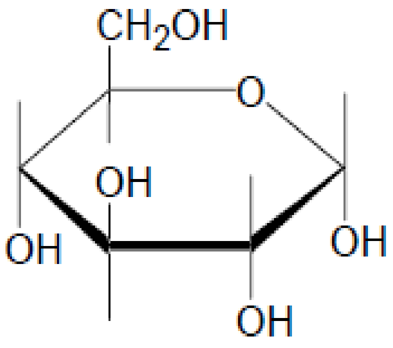


GLYCOLYSIS

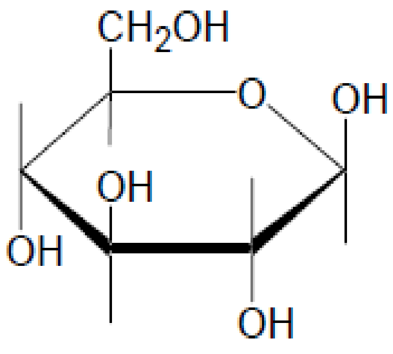




D-glucose



α-D-glucose



β-D-glucose

D-Glucose is a major fuel for most organisms.

For higher plants and animals there are three major metabolic fates for glucose

Nearly every living cell catabolizes glucose and other simple sugars by a process called glycolysis.

Glycolysis differs from one species to another only in the details of regulation and the fate of pyruvate.

Glycolysis is the metabolic pathway that catabolizes glucose into two molecules of pyruvate.

Glycolysis occurs in the cytosol of cells and is essentially an anaerobic process since the pathway's principle steps do not require oxygen.

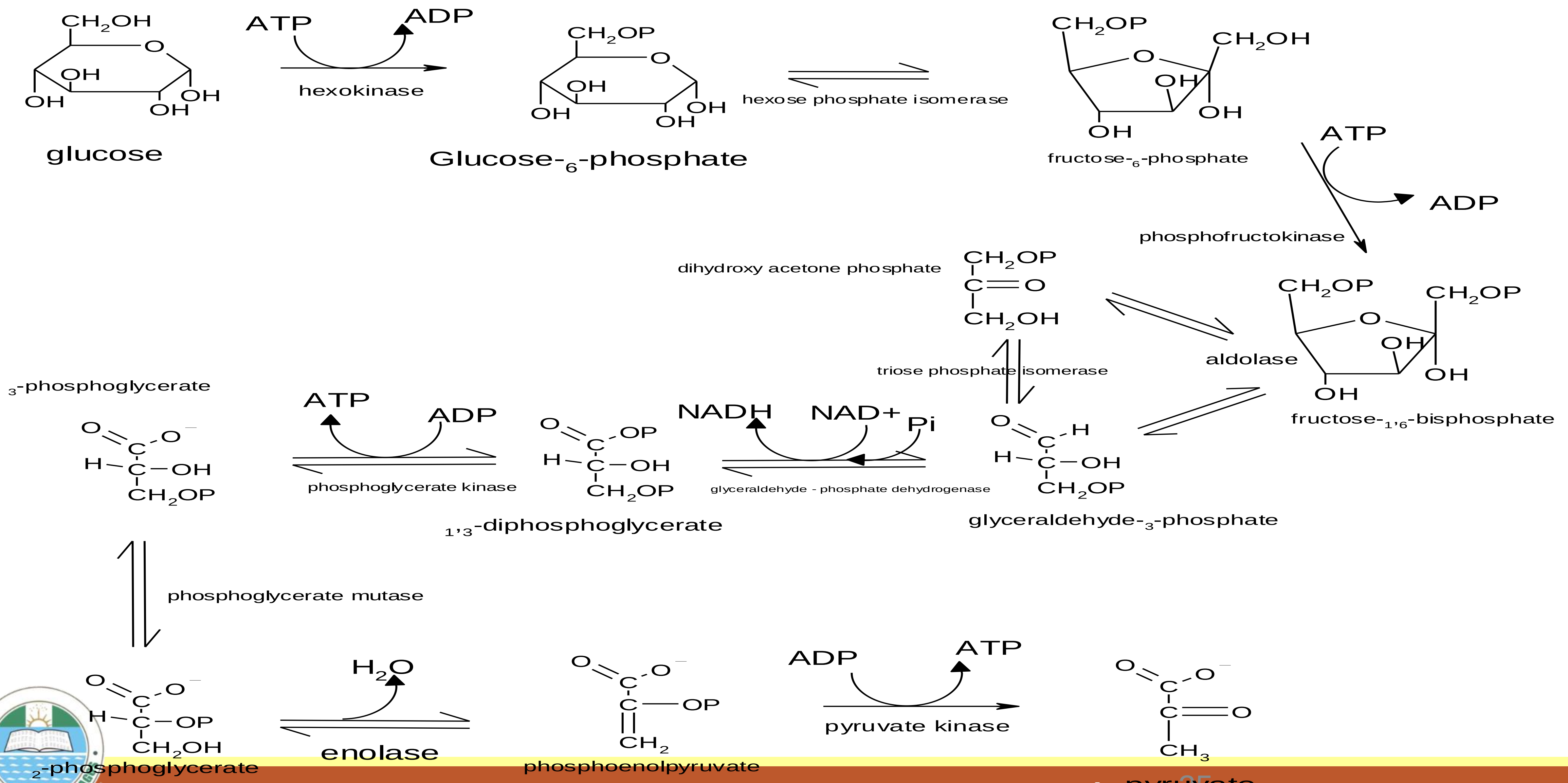
Glycolysis consists of 10 enzyme catalyzed reactions.

The pathway can be broken down into 2 phases.

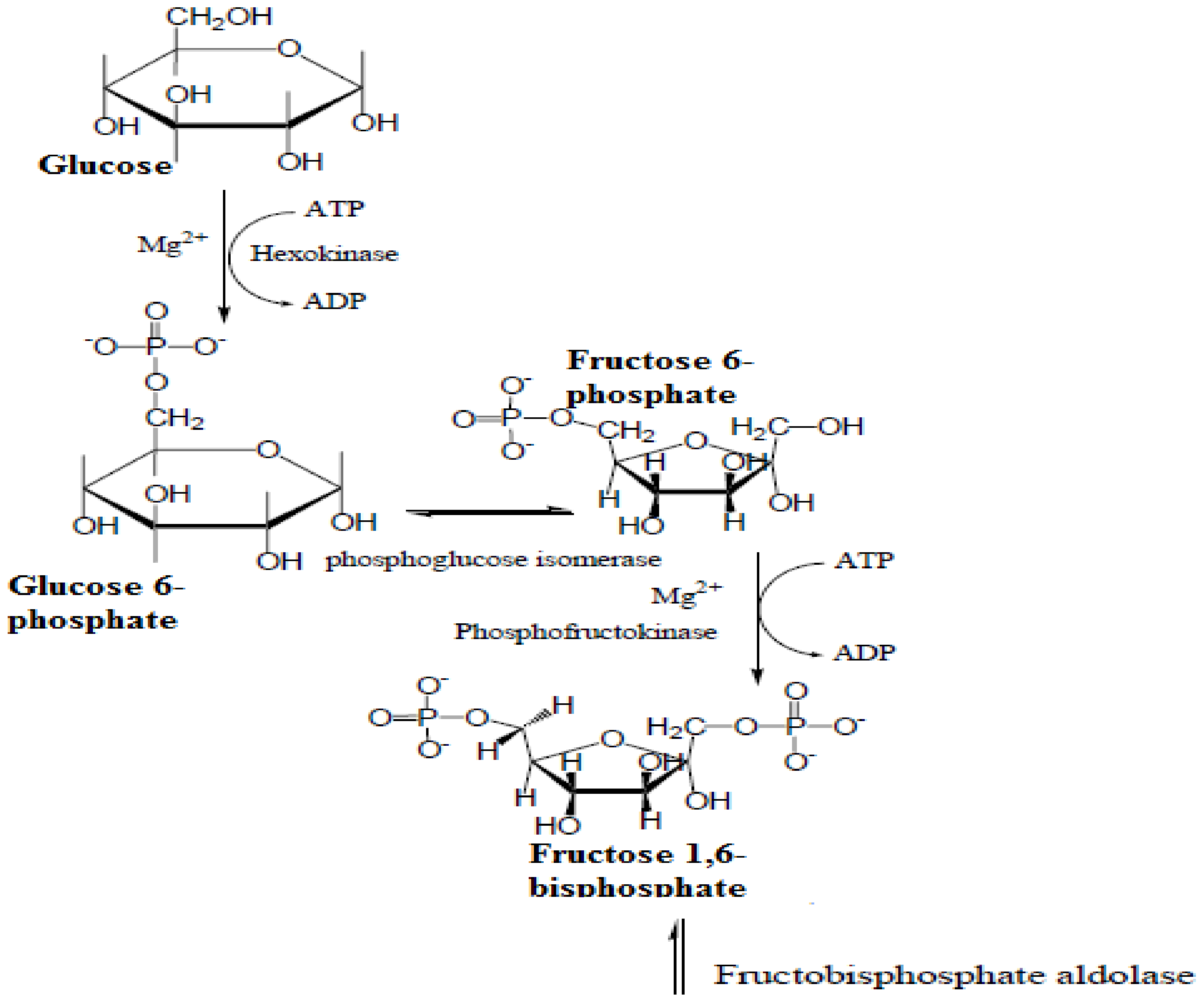
The net reaction produces 2 molecules of NADH, 2 molecules of ATP, 2 molecules of Pyruvate per molecule of glucose.

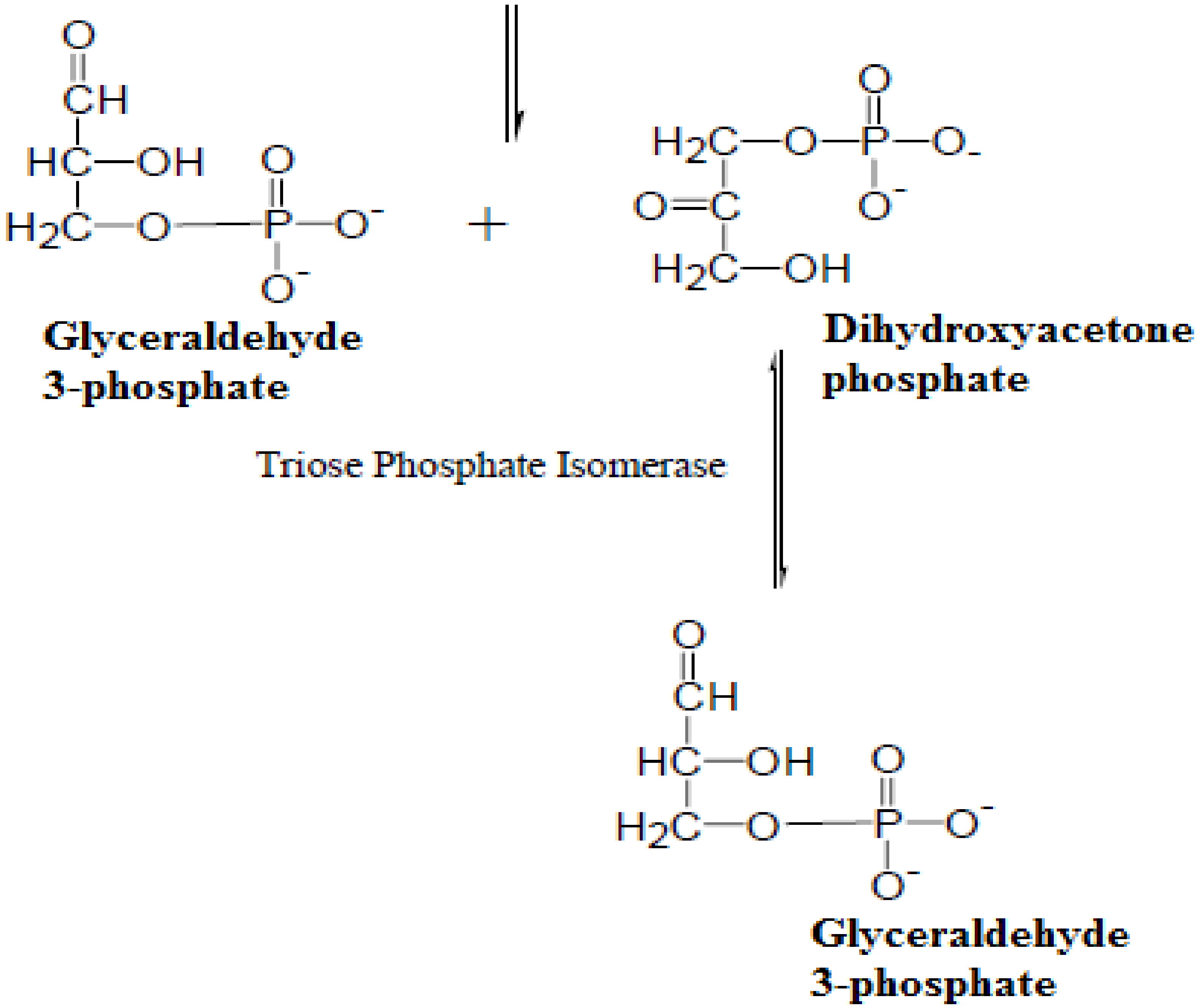
2 Glucose + 2 ADP + 2 Pi + 2 NAD^+ $\longrightarrow$ 2 Pyruvate + 2ATP + 2 NADH + H^+

Schematic of Glycolysis

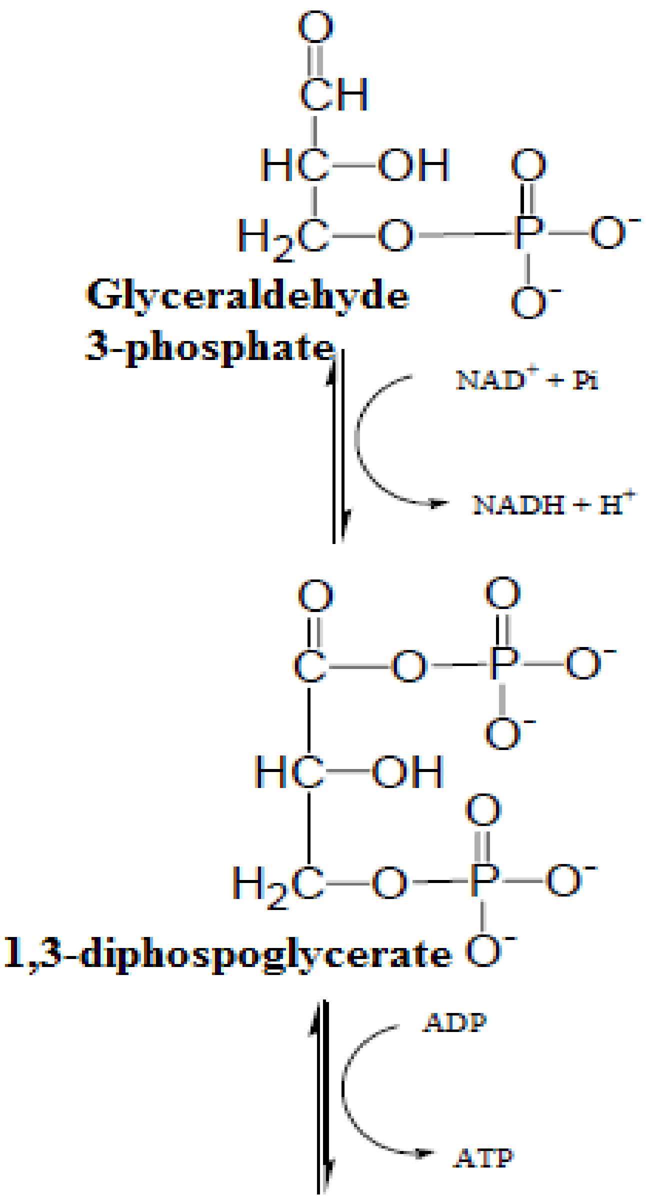


Phase 1: Preparatory phase



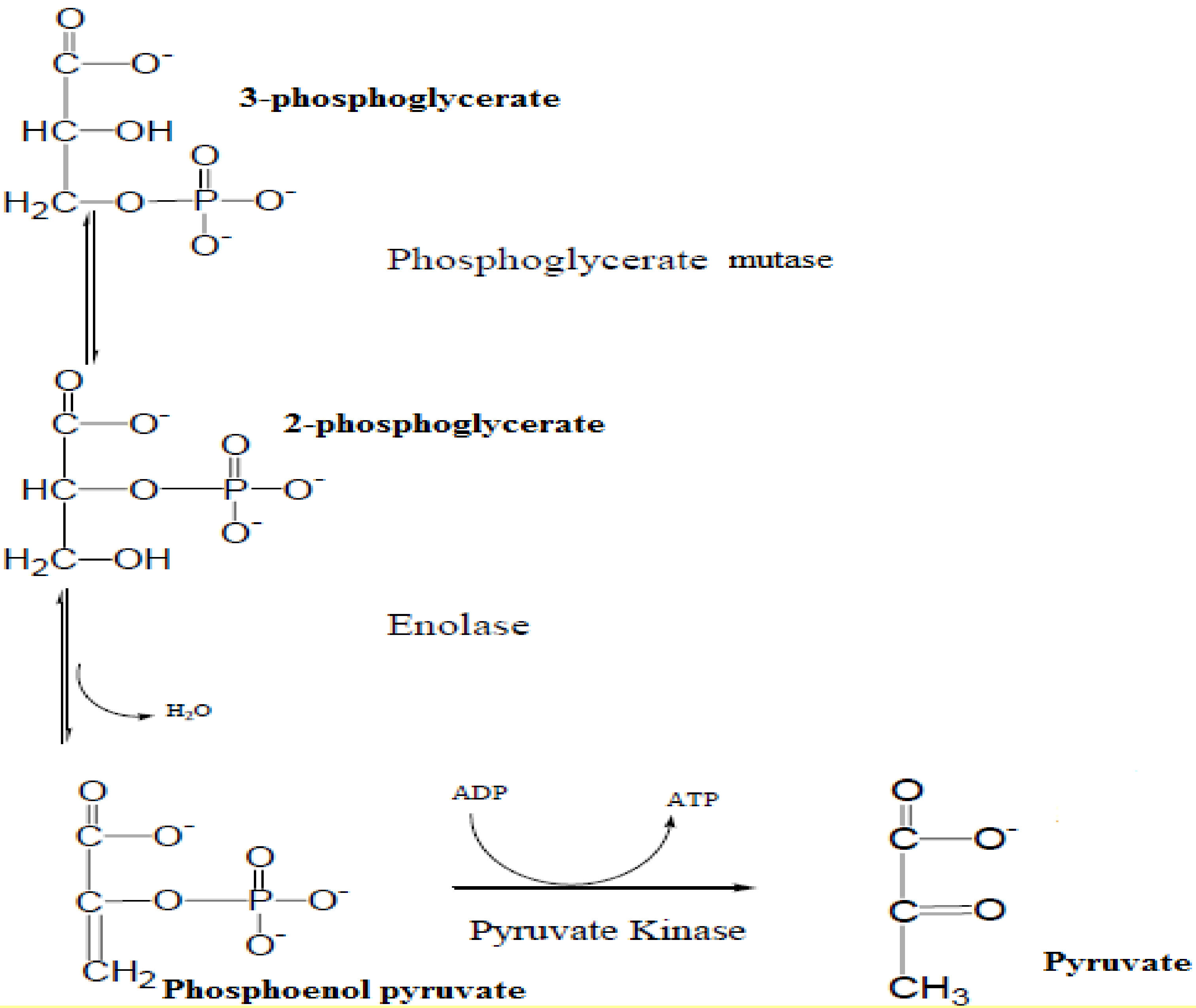

Glyceraldehyde
3-phosphate
+
Dihydroxyacetone
phosphate
Triose Phosphate Isomerase
Glyceraldehyde
3-phosphate

Phase II: Pay Off Phase

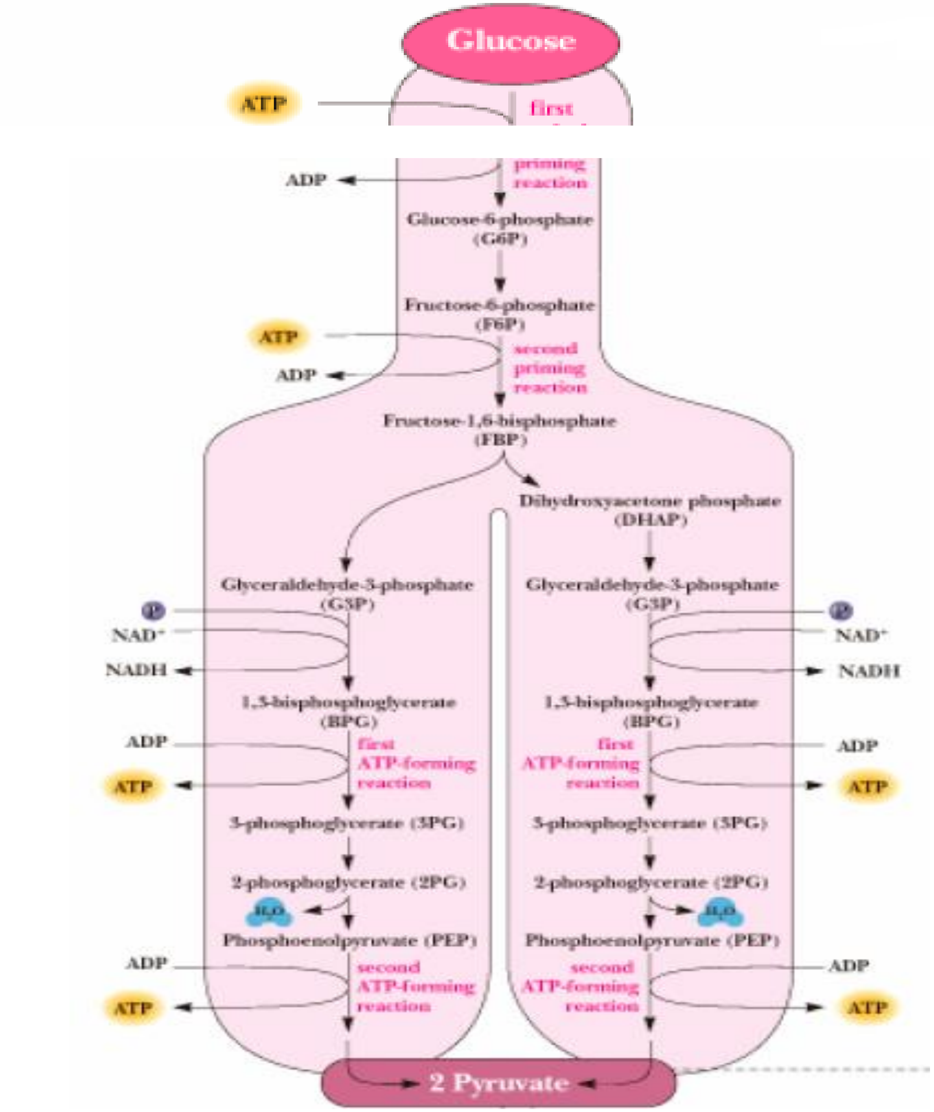


Glyceraldehyde 3-phosphate dehydrogenase

Phosphoglycerate kinase


3-phosphoglycerate
Phosphoglycerate mutase
2-phosphoglycerate
Enolase
H_2O
ADP
ATP
Pyruvate Kinase
Phosphoenol pyruvate
Pyruvate

Bioenergetics of Glycolytic Pathway



Efficiency of the Glycolytic pathway

Glucose + NAD^+ $\longrightarrow$ 2 Pyruvate + 2NADH + $2H^+$

ΔG_1^{i0} = -146 KJ/mol.

2ADP + 2Pi $\longrightarrow$ 2ATP

ΔG_2^{i0} = 2 (30.5 KJ/mol)= 61.0 KJ/mol

Overall ΔG^{01} = -146 + 61.0 = -85 KJ/ mol.

and

Efficiency of Glycolysis = (-85/-2870) × 100 = 2.96%

Where -2870 KJ/mol is the energy liberated as heat when 1 mol of Glucose is combusted.

Inhibitors of Glycolytic Pathway

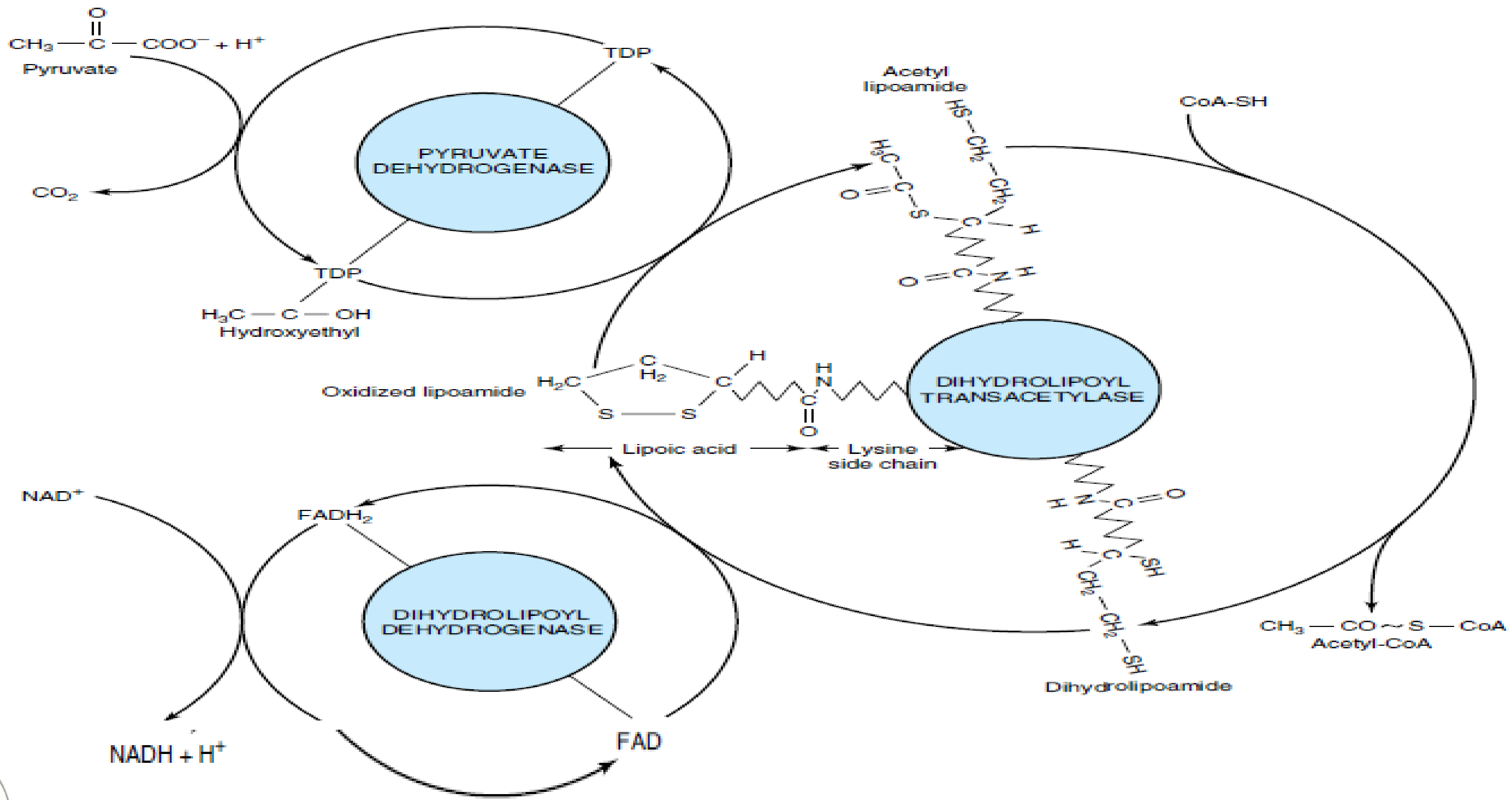
Iodoacetate inhibits the Glyceraldehyde 3-phosphate dehydrogenase step.

Fluoride inhibits the Enolase step.

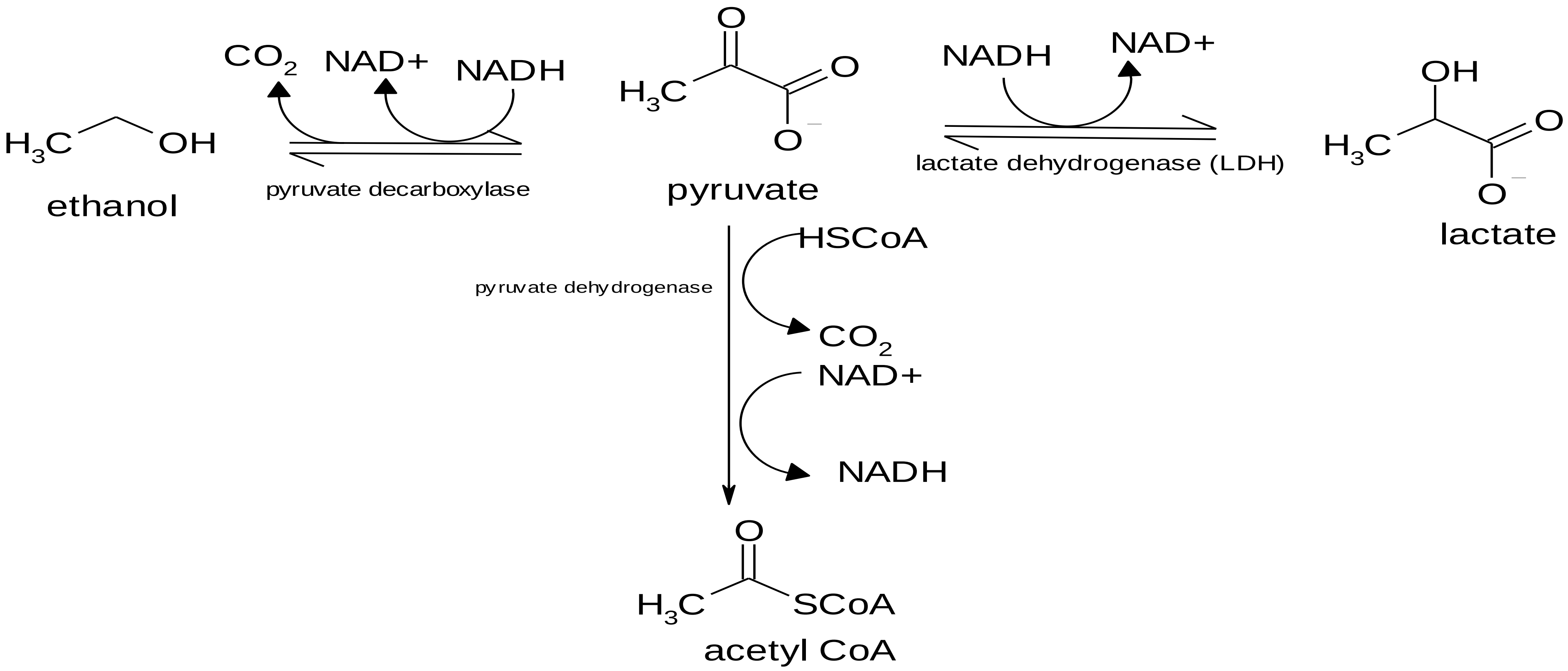
FATES OF PYRUVATE

- AEROBIC CONDITIONS
- ANAEROBIC CONDITIONS

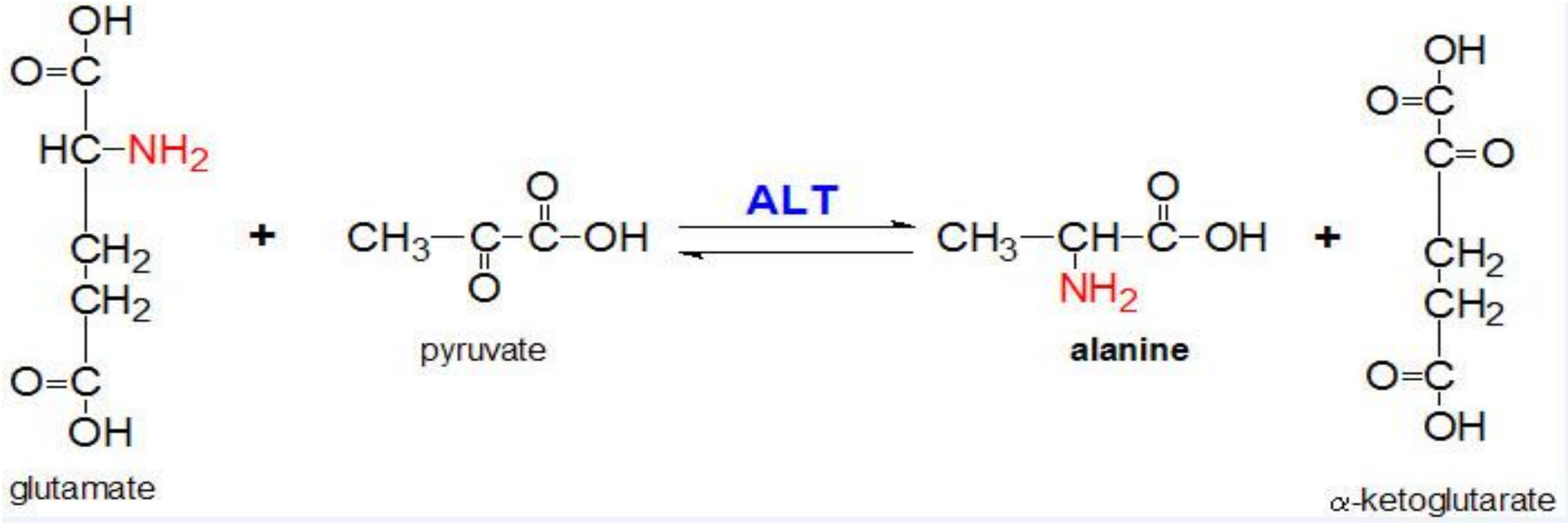
Oxidative Decarboxylation of Pyruvate to Acetyl CoA



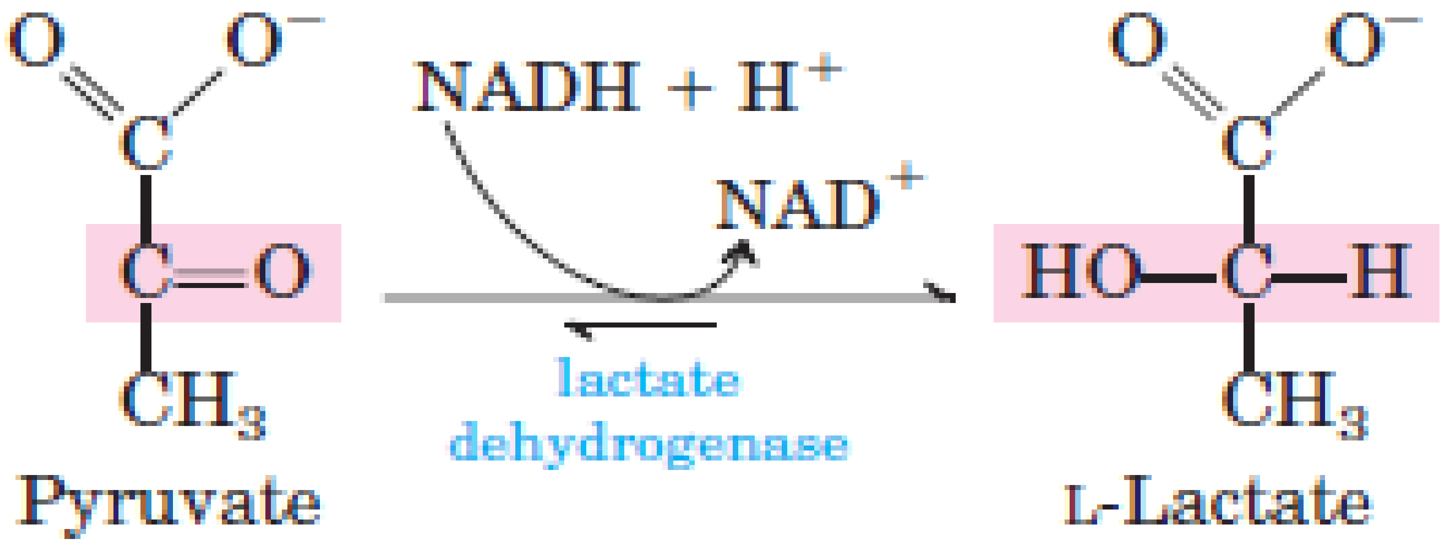
Conversion of pyruvate to ethanol and lactate under anaerobic conditions



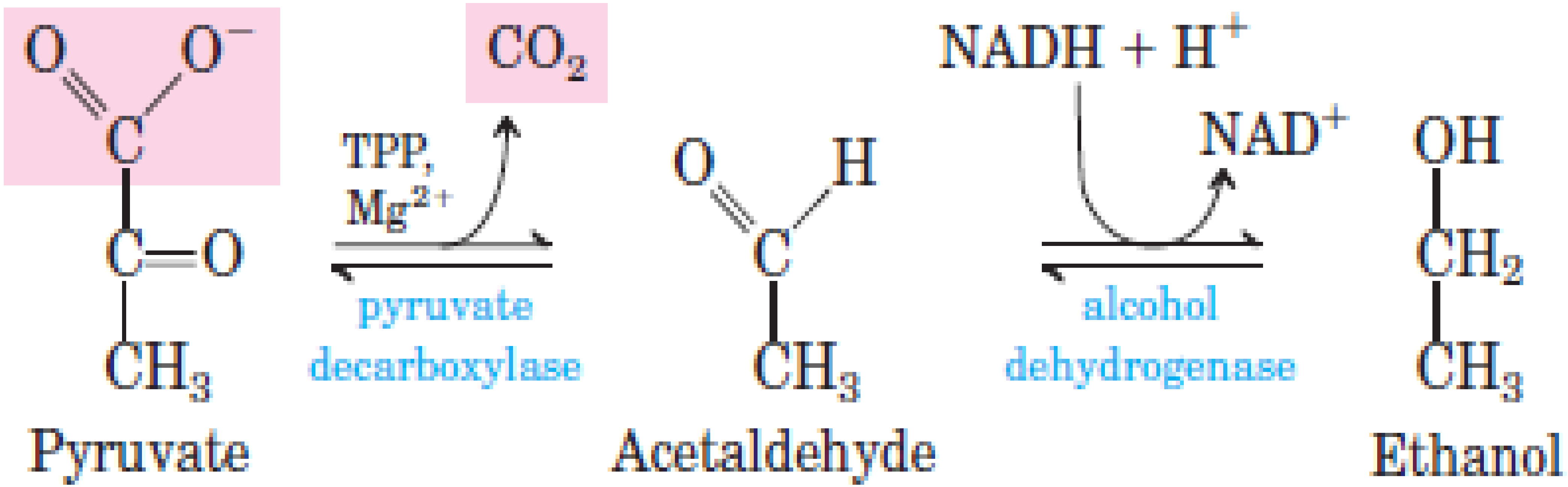
Conversion of Pyruvate to Alanine by an Aminotransferase (transaminase)



Conversion of Pyruvate to Lactate



Conversion of pyruvate to Ethanol



TRICARBOXYLIC ACID (TCA) CYCLE

The citric acid cycle is the final common pathway for the aerobic oxidation of carbohydrate, lipid and protein.

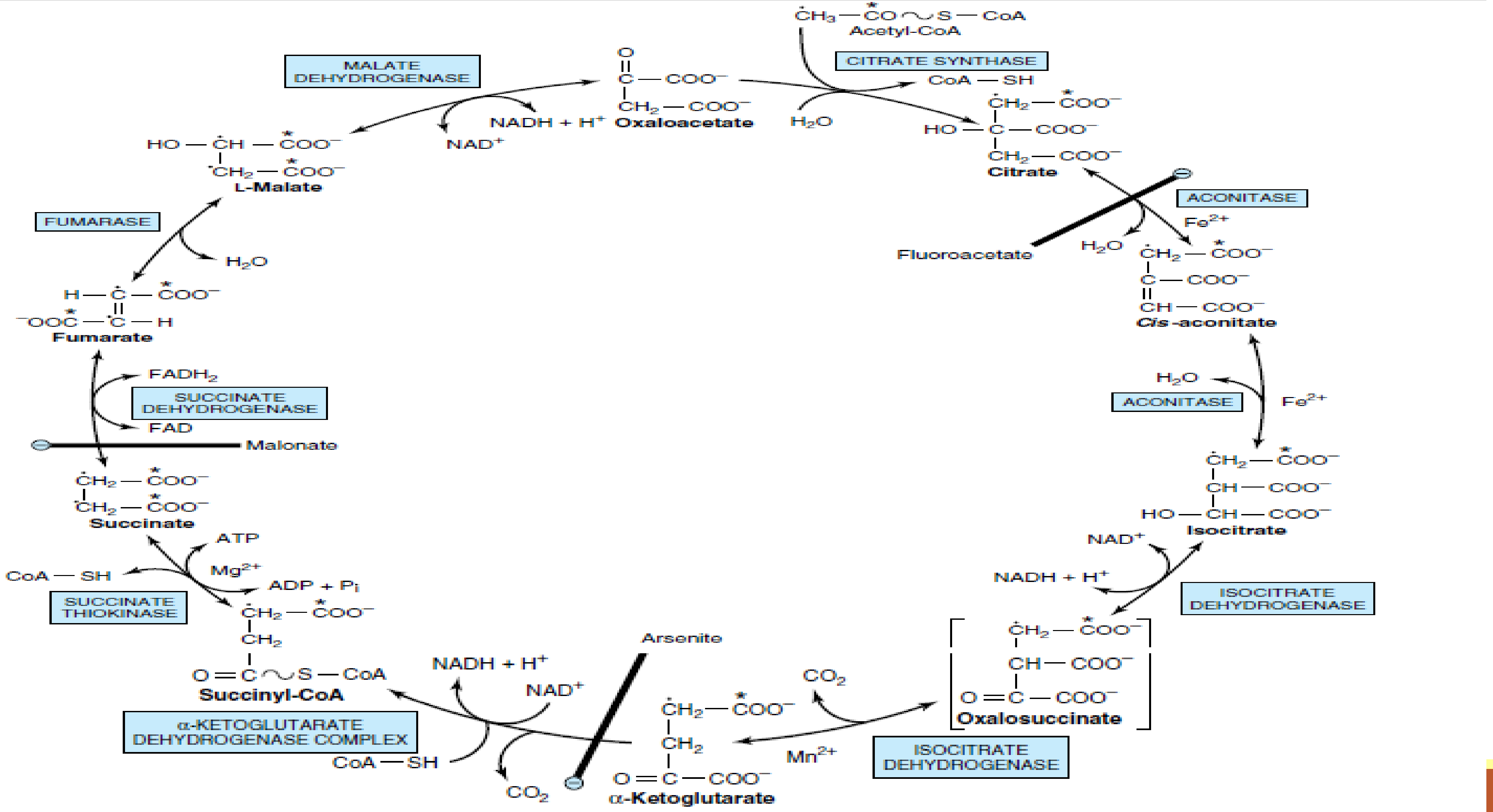
The tricarboxylic acid cycle (TCA cycle) is a series of enzyme-catalyzed chemical reactions that form a key part of aerobic respiration in cells.

Glucose, fatty acids and most amino acids are metabolized to acetyl-CoA or intermediates of the cycle.

This cycle is also called the Krebs cycle and the citric acid cycle.

The process takes place in the matrix of the mitochondria.

CITRIC ACID CYCLE



Energetics of TCA cycle

Produces 1 molecule of $FADH_2$ and 3 of NADH and one GTP directly.

3 NADH = 3 X 3 = 9 ATP

1 FADH = 1 X 2 = 2 ATP

1 GTP = 1 ATP

i.e 12 moles of ATP per cycle.

2 Acetyl CoA from 2 Pyruvate = 2 Cycles

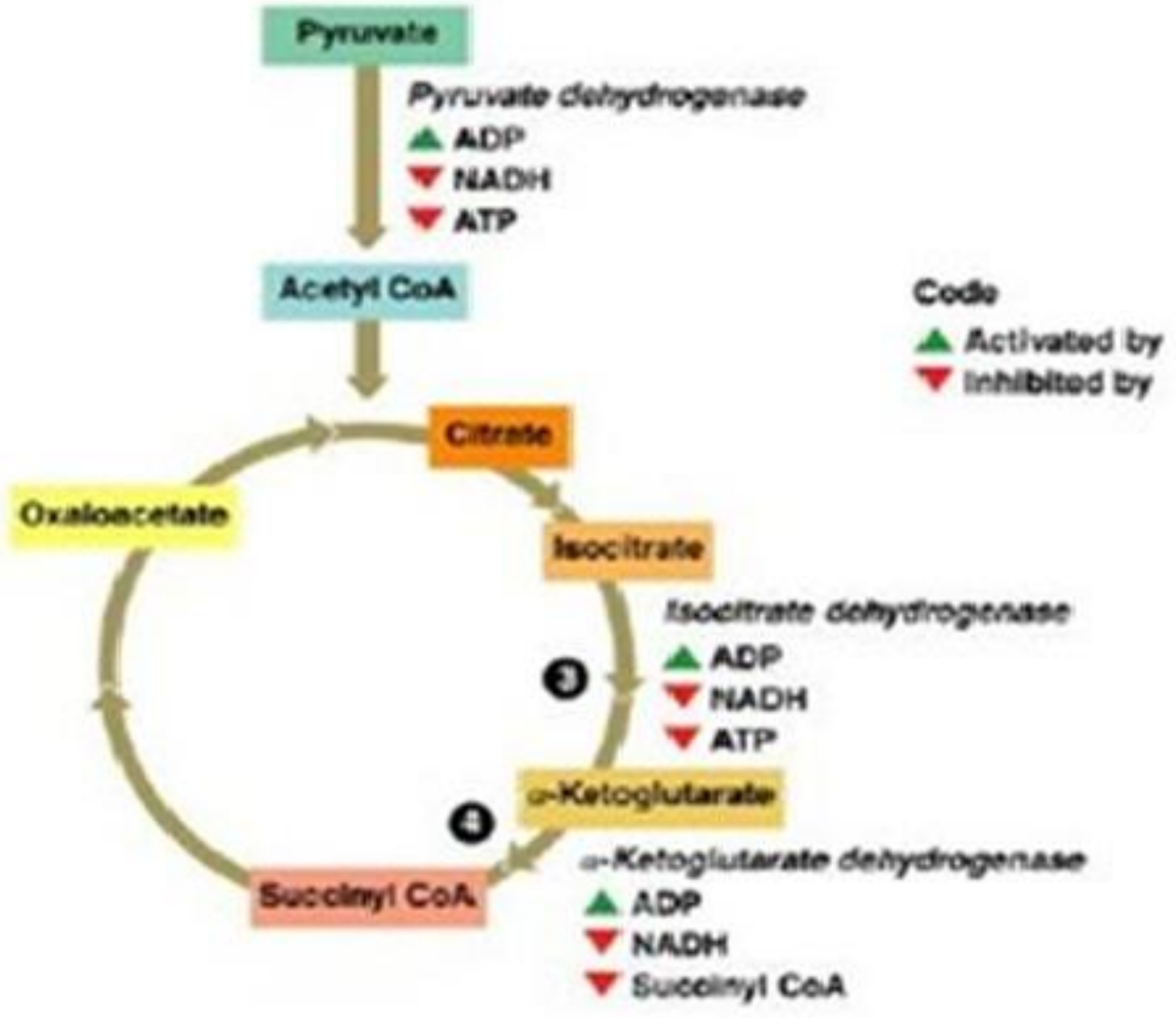
2 cycles = 2 x 12 = 24 ATP

Oxidative Decarboxylation of 2 Pyruvate to 2 Acetyl CoA yields 2 NADH = 6 ATP

i.e oxidation of Pyruvate in the mitochondria yields 24 + 6 = 30 ATP.

Regulation of the Citric acid cycle

- Low levels of ATP stimulate the formation of acetyl CoA for the citric acid cycle.
- High ATP and NADH levels decrease the formation of acetyl CoA and slow down the citric acid cycle.



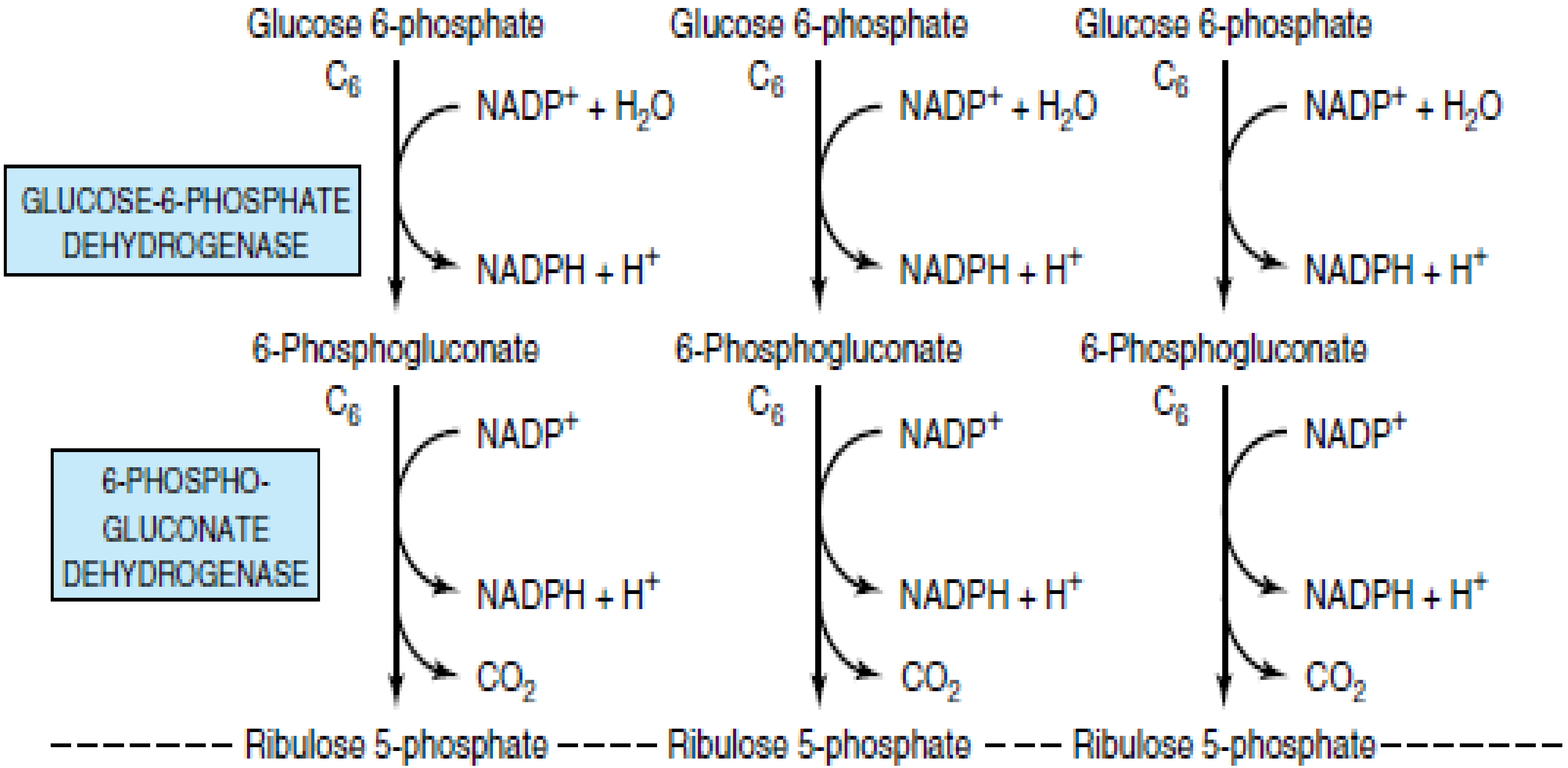
Pentose Phosphate Pathway

- The pentose phosphate pathway is an alternate route for the oxidation of glucose without direct consumption or generation of ATP.

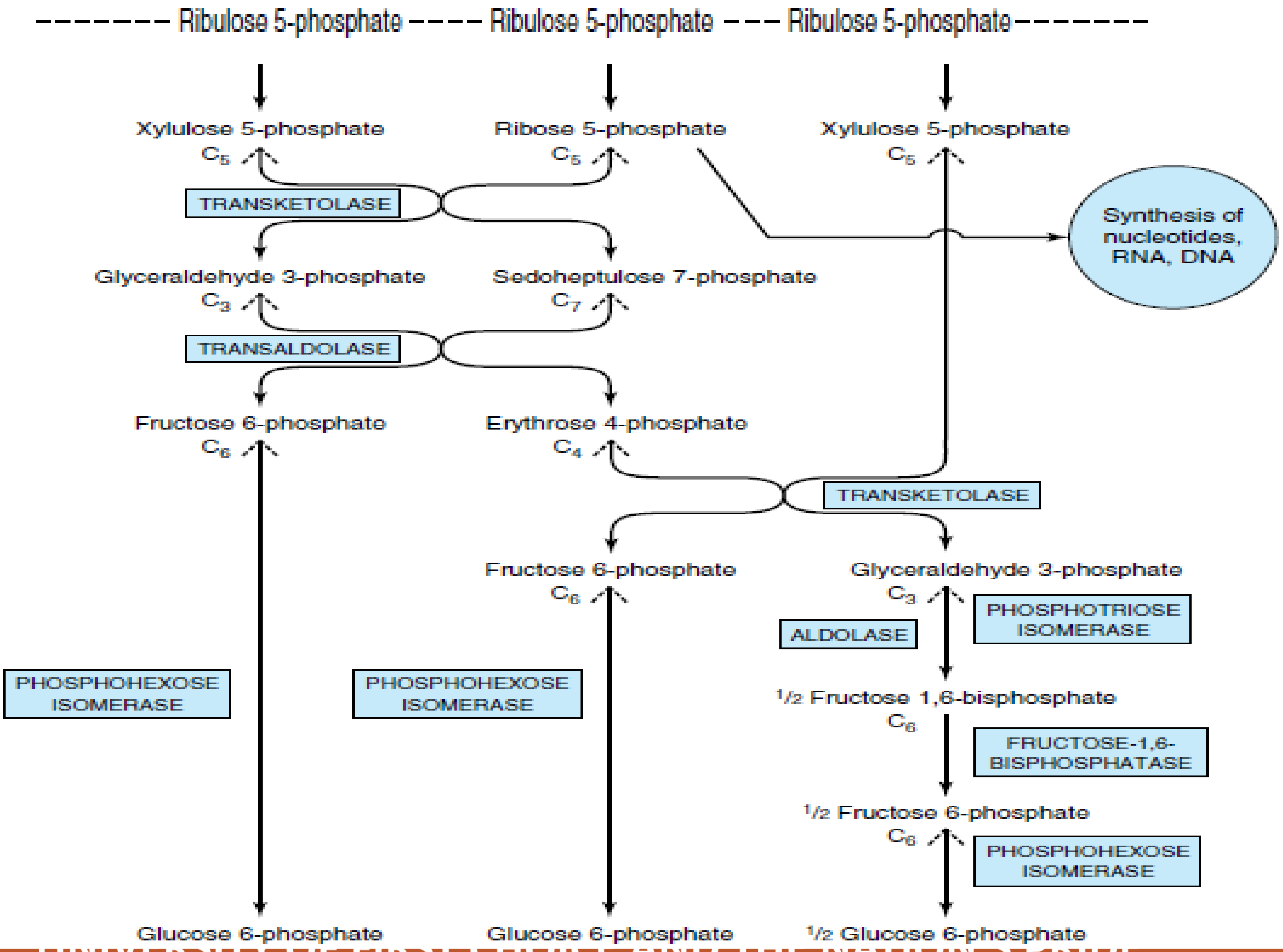
- The pentose phosphate pathway takes place entirely within the cytoplasm (because $NADP^+$ is used as a hydrogen acceptor) and is also known as the hexose monophosphate shunt or phosphogluconate pathway.

- It is basically used for the synthesis of NADPH and D-ribose.

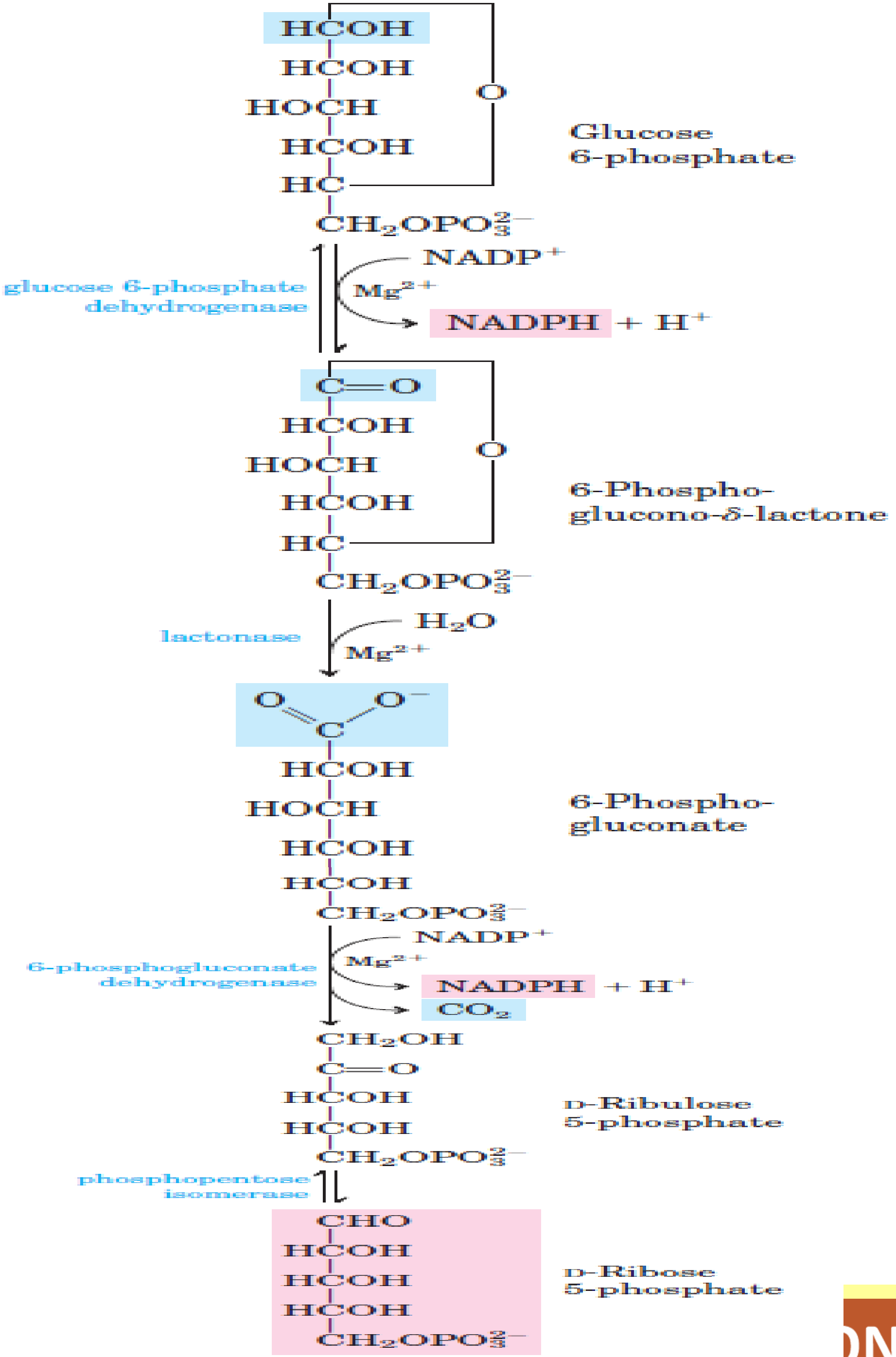
Oxidative Phase

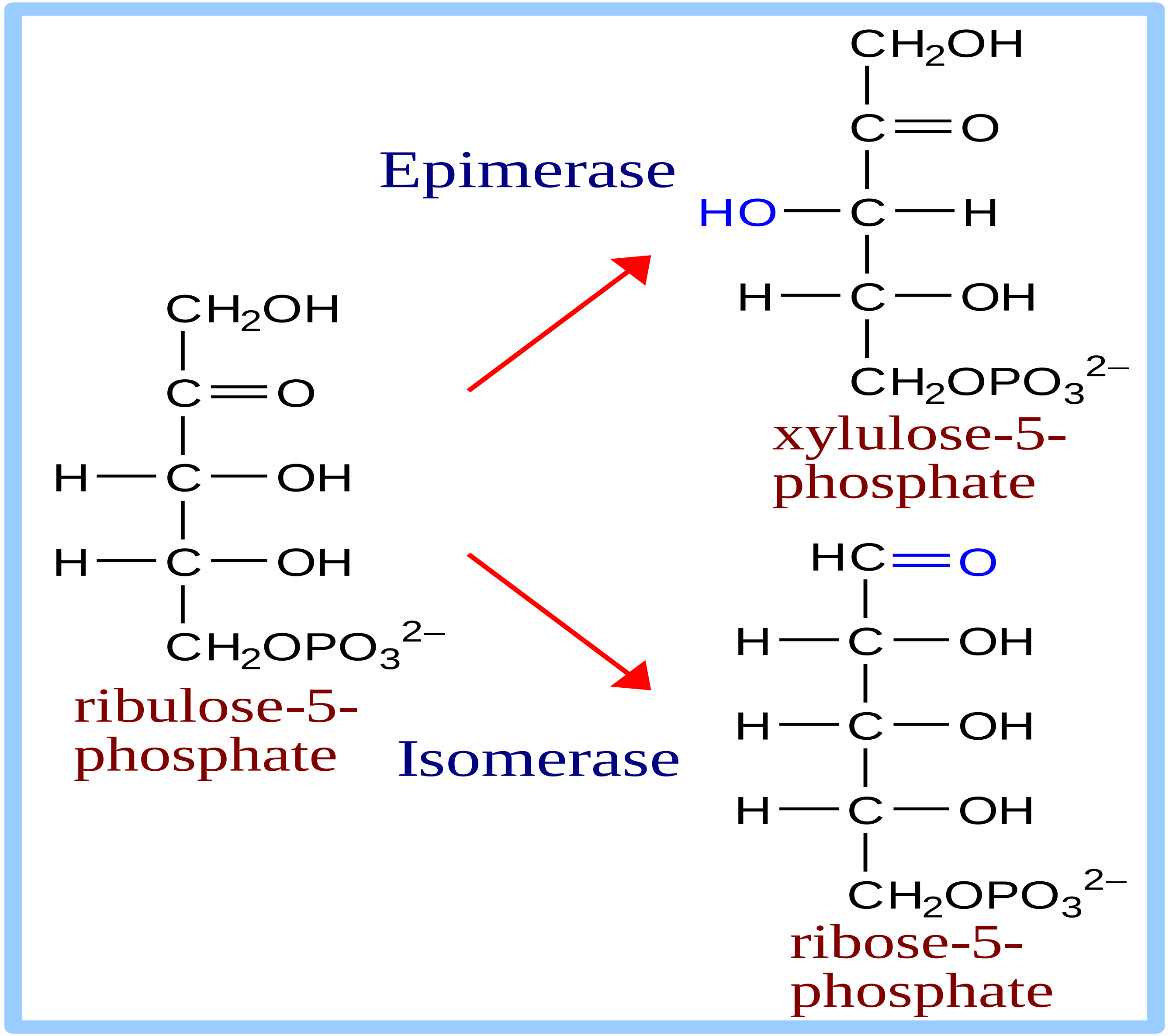


Non-oxidative Phase



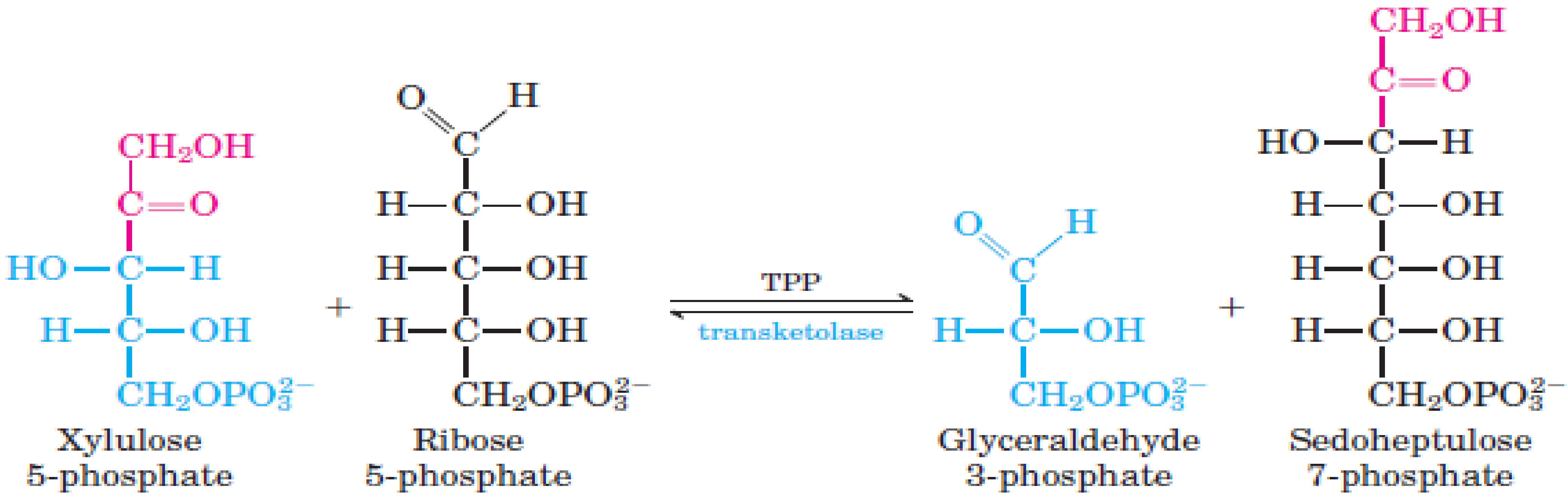
Oxidative Phase

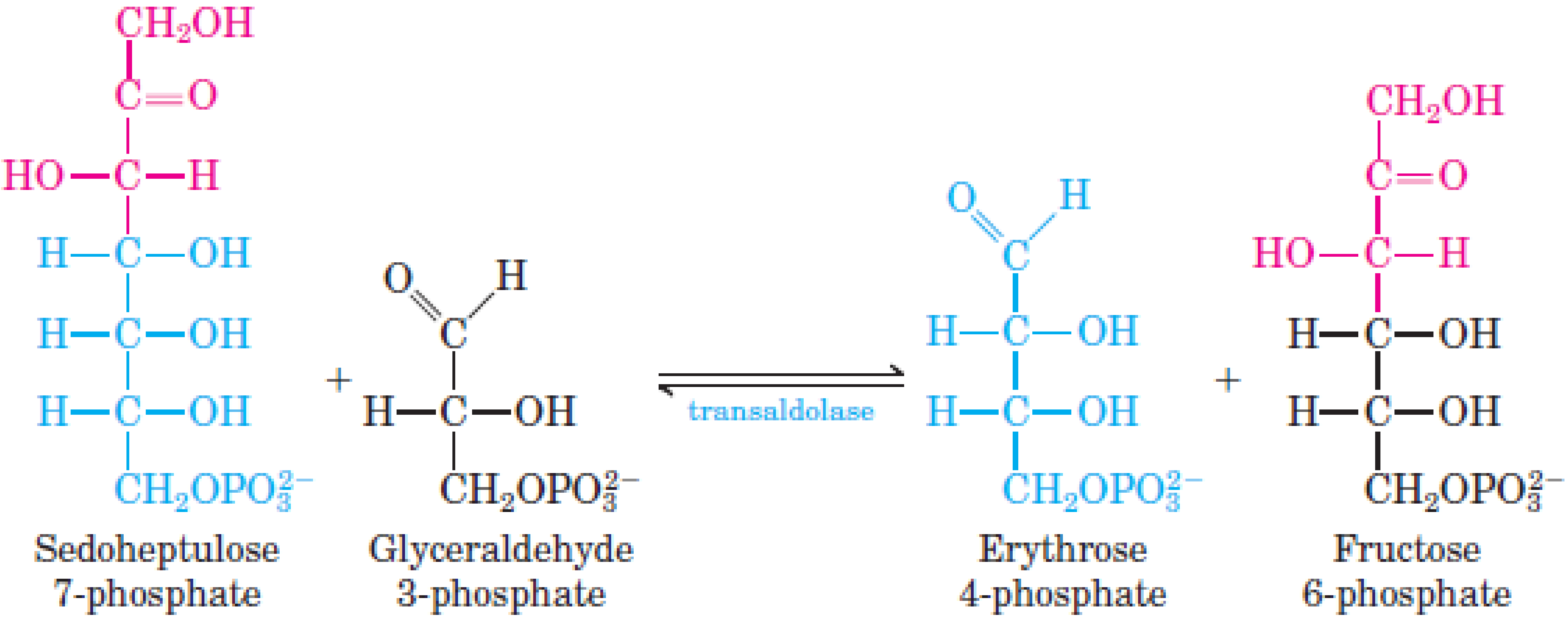


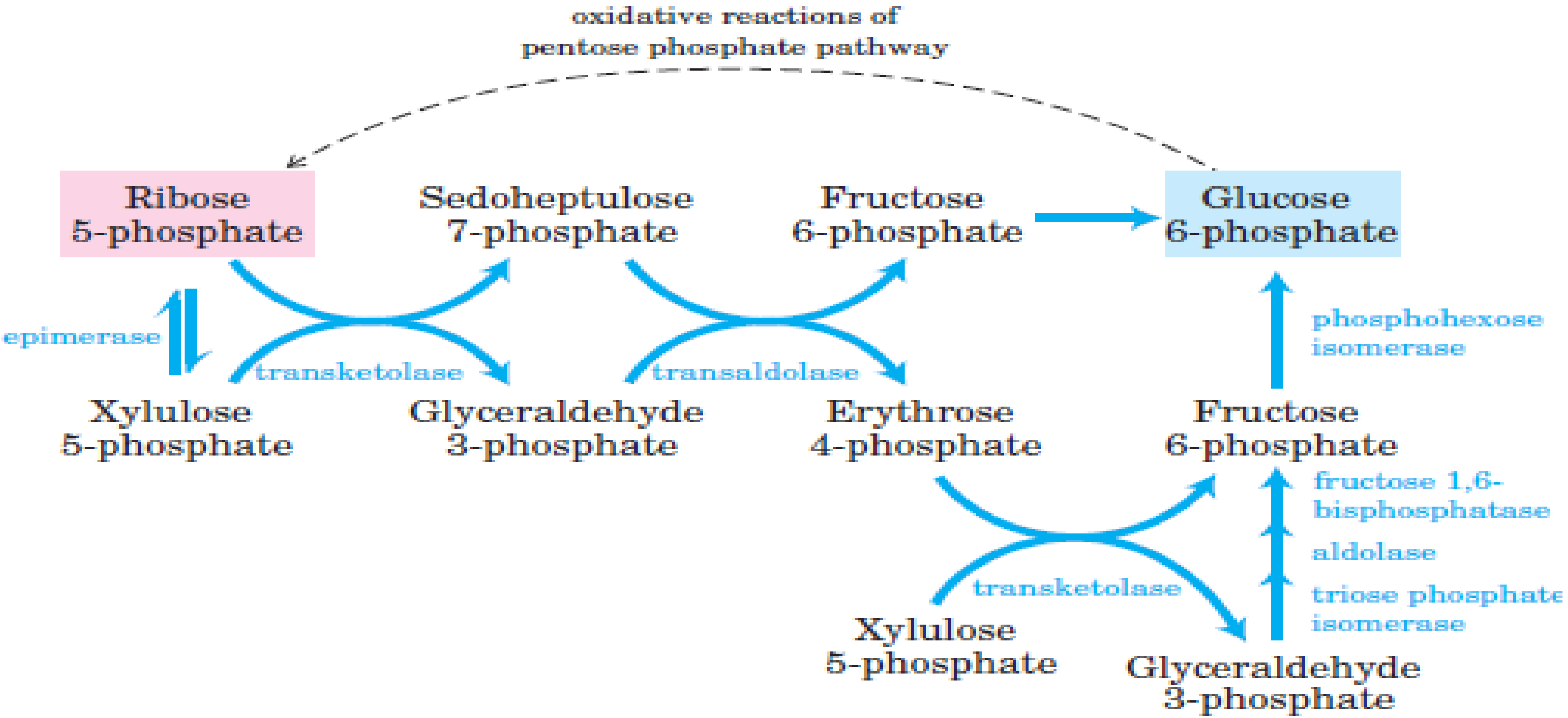


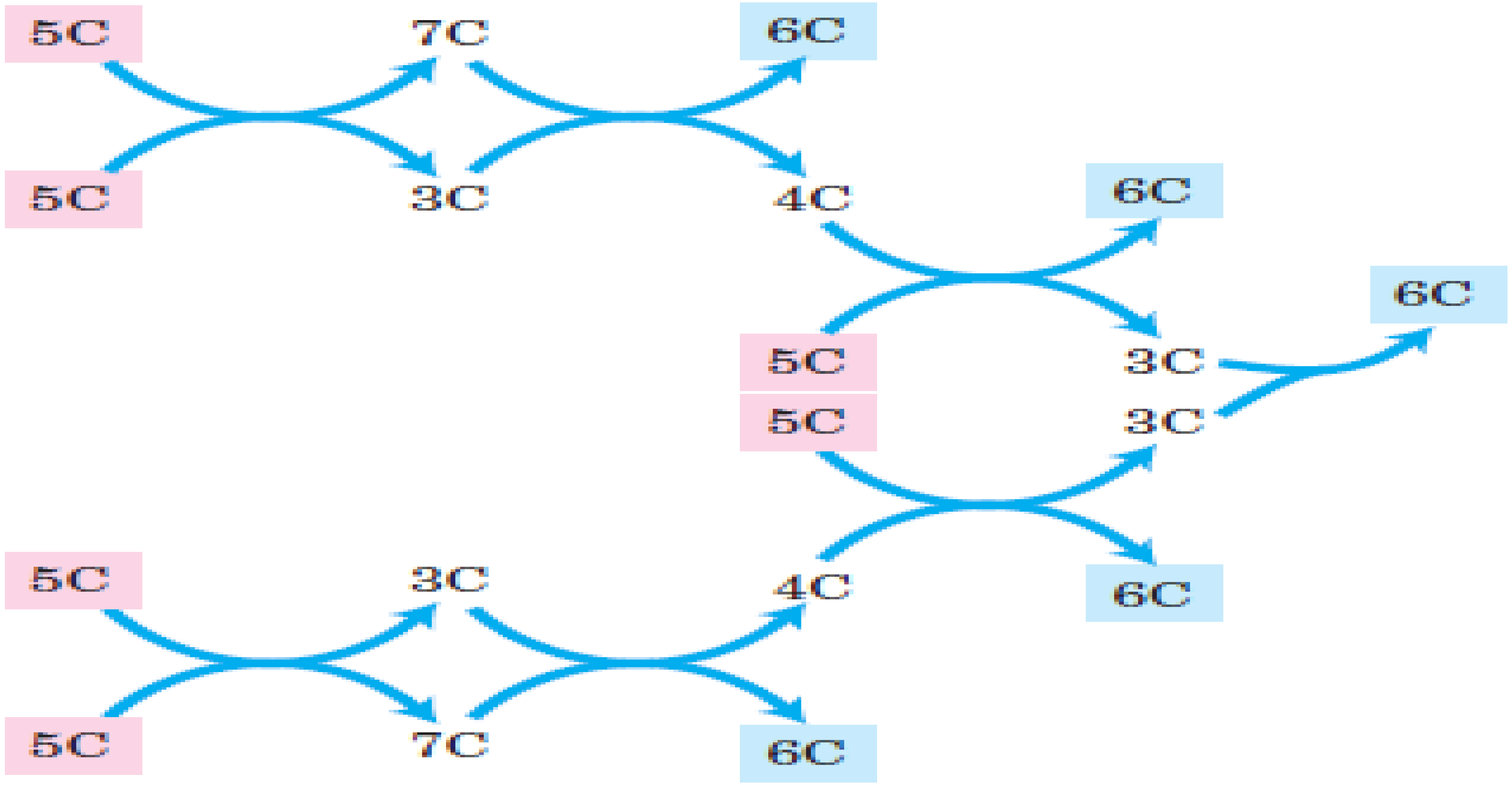
Epimerase
Isomerase
ribulose-5-phosphate
xylulose-5-phosphate
ribose-5-phosphate

Non-oxidative phase




transaldolase
Sedoheptulose 7-phosphate
Glyceraldehyde 3-phosphate
Erythrose 4-phosphate
Fructose 6-phosphate


oxidative reactions of
pentose phosphate pathway
Ribose
5-phosphate
Sedoheptulose
7-phosphate
Fructose
6-phosphate
Glucose
6-phosphate
epimerase
transketolase
transaldolase
phosphohexose
isomerase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate
Erythrose
4-phosphate
Fructose
6-phosphate
fructose 1,6-
bisphosphatase
aldolase
transketolase
triose phosphate
isomerase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate


5C
7C
6C
5C
3C
4C
6C
6C
5C
3C
5C
3C
5C
3C
4C
6C
5C
7C
6C

Regulation of the Pentose phosphate pathway

Regulation of Glucose-6-phosphate Dehydrogenase:

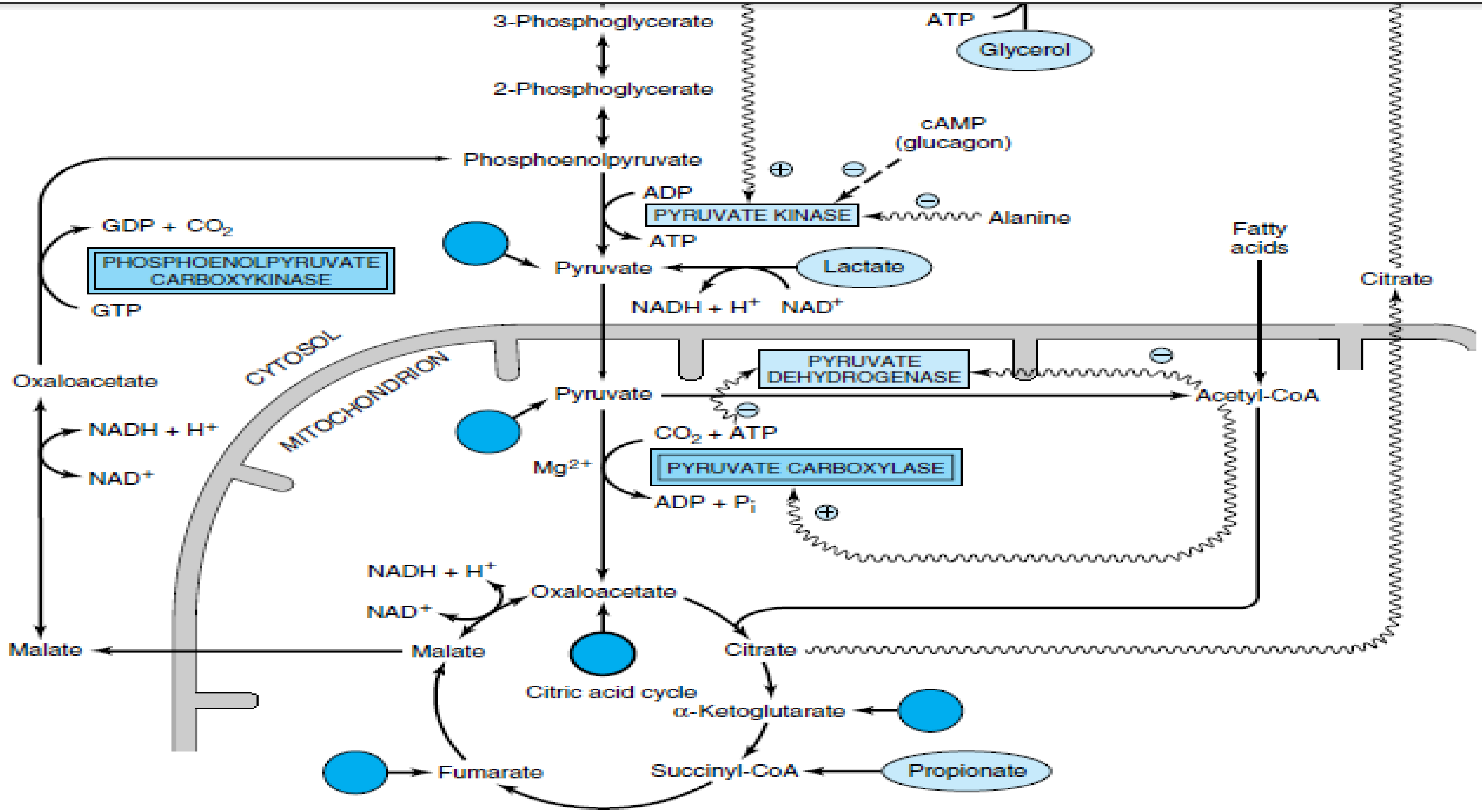
- Glucose-6-phosphate Dehydrogenase is the **committed step** of the Pentose Phosphate Pathway.
  This enzyme is regulated by availability of the substrate **$NADP^+$**.

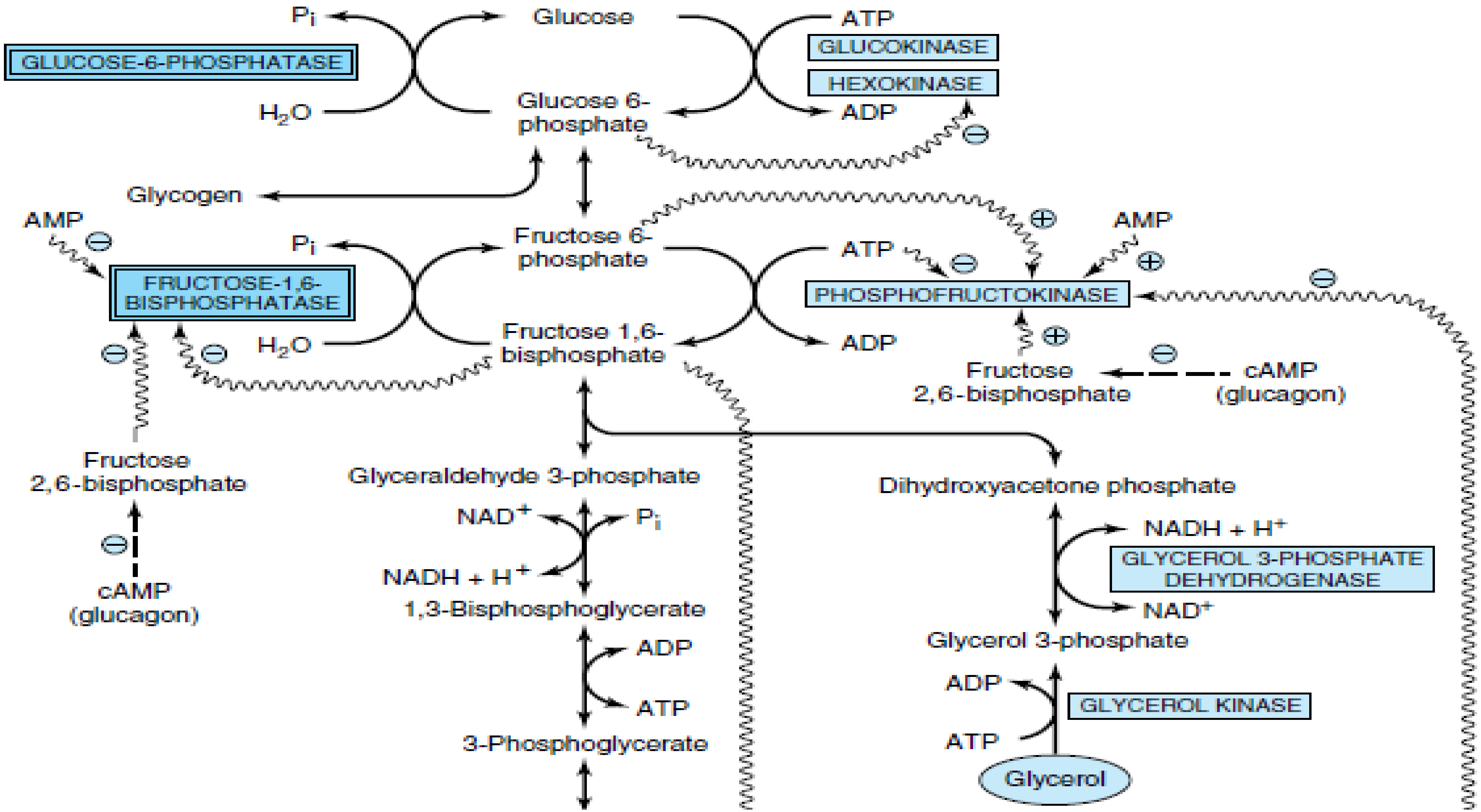
- As NADPH is utilized in reductive synthetic pathways, the increasing concentration of $NADP^+$ stimulates the Pentose Phosphate Pathway, to replenish NADPH.

Differences between the Glycolytic pathway and PPP

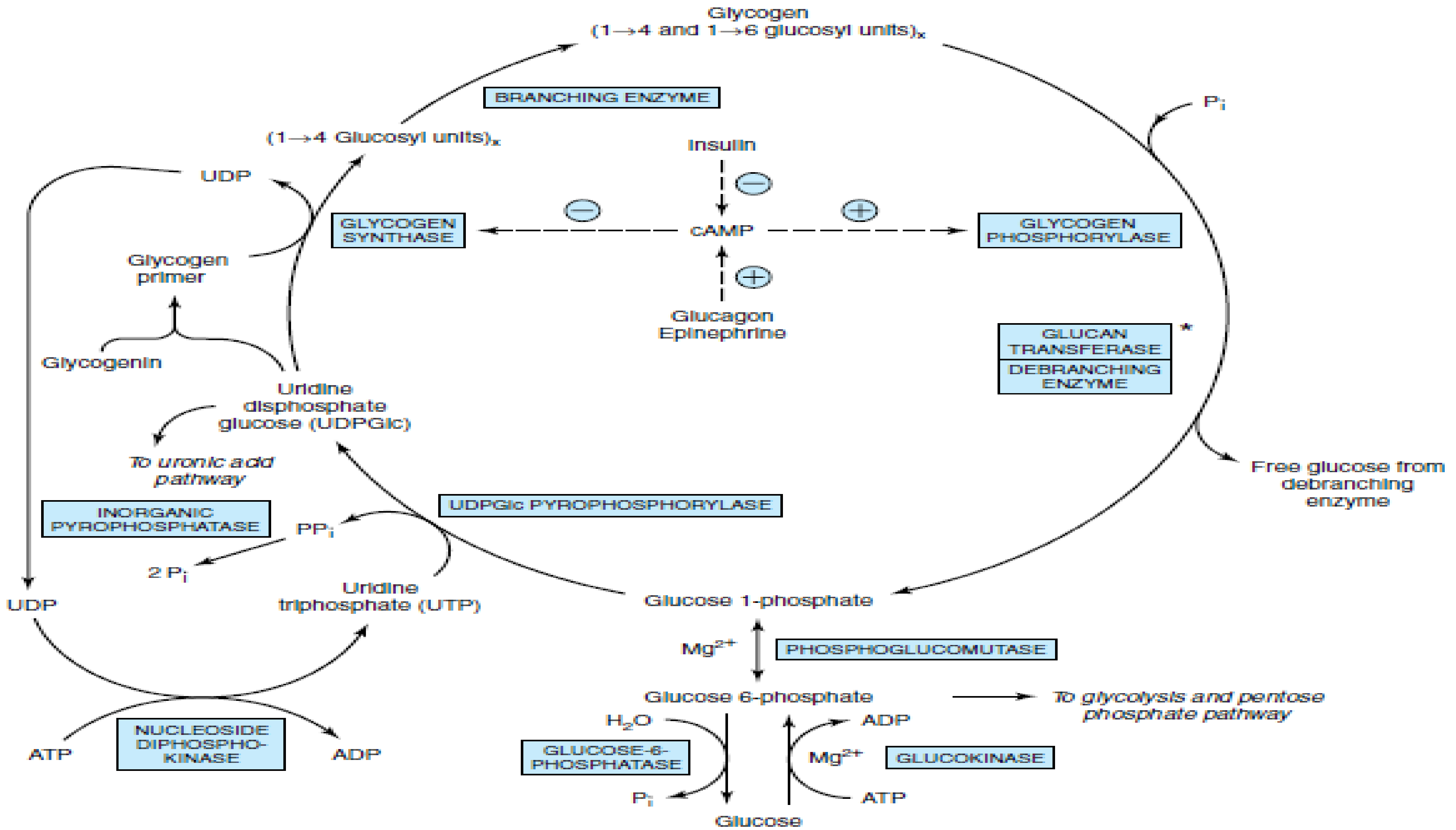
	Glycolysis	Pentose Phosphate Pathway
ATP	ATP	No ATP
CO_2	Not Generated	Generated
Reducing Equivalents	NAD^+	$NADP^+$

Gluconeogenesis




Glucose
Pi
GLUCOSE-6-PHOSPHATASE
H2O
ATP
GLUCOKINASE
HEXOKINASE
ADP
Glucose 6-phosphate
Glycogen
AMP
Fructose 6-phosphate
FRUCTOSE-1,6-BISPHOSPHATASE
Pi
H2O
ATP
AMP
PHOSPHOFRUCTOKINASE
ADP
Fructose 1,6-bisphosphate
Fructose 2,6-bisphosphate
cAMP (glucagon)
Fructose 2,6-bisphosphate
cAMP (glucagon)
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
NAD+
Pi
NADH + H+
1,3-Bisphosphoglycerate
ADP
ATP
3-Phosphoglycerate
NADH + H+
GLYCEROL 3-PHOSPHATE DEHYDROGENASE
NAD+
Glycerol 3-phosphate
ADP
ATP
GLYCEROL KINASE
Glycerol

Glycogen synthesis and glycogenolysis



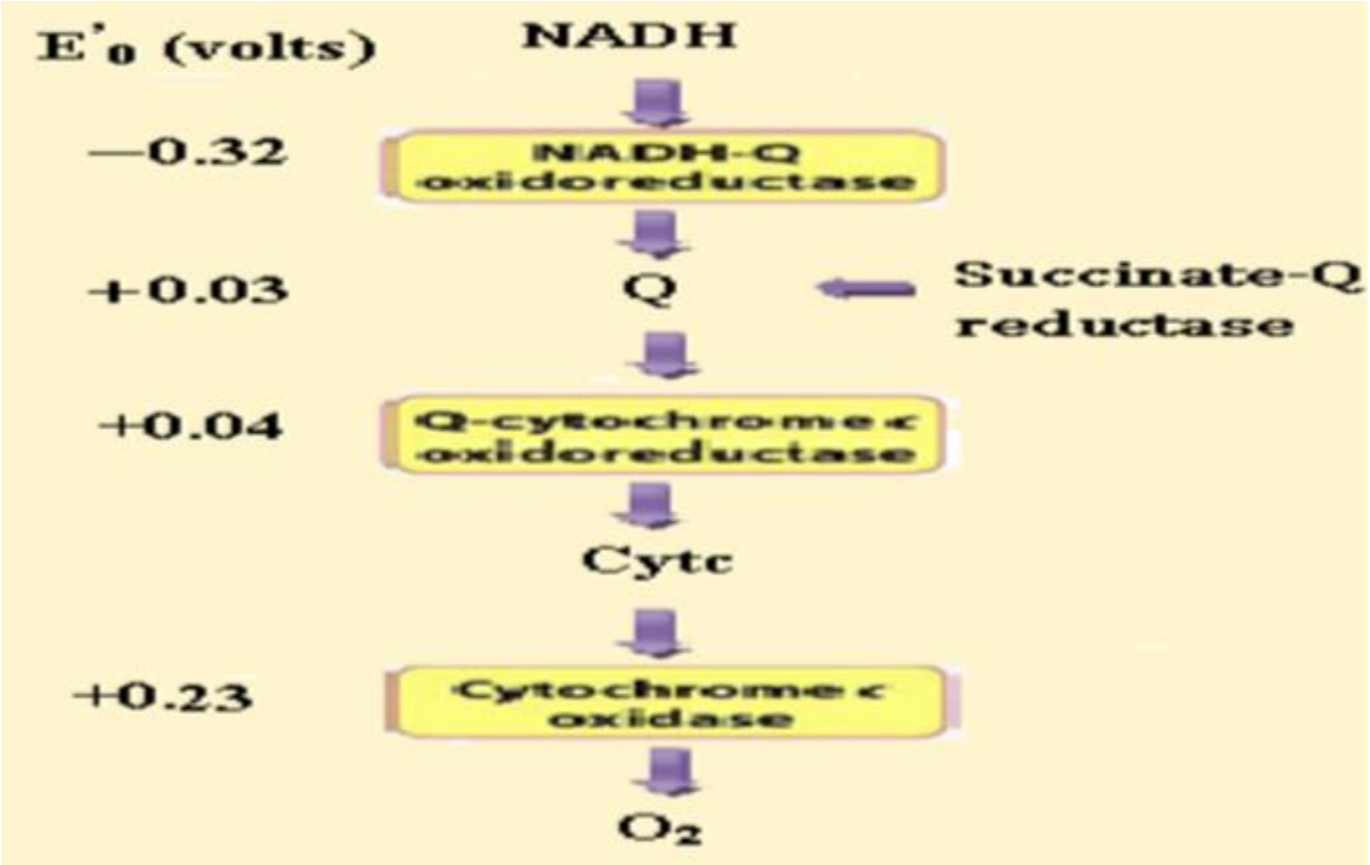
Electron Transport Chain

- NADH oxidation and ATP synthesis → not occur in a single step.

- Electrons → not transferred from NADH → oxygen directly.

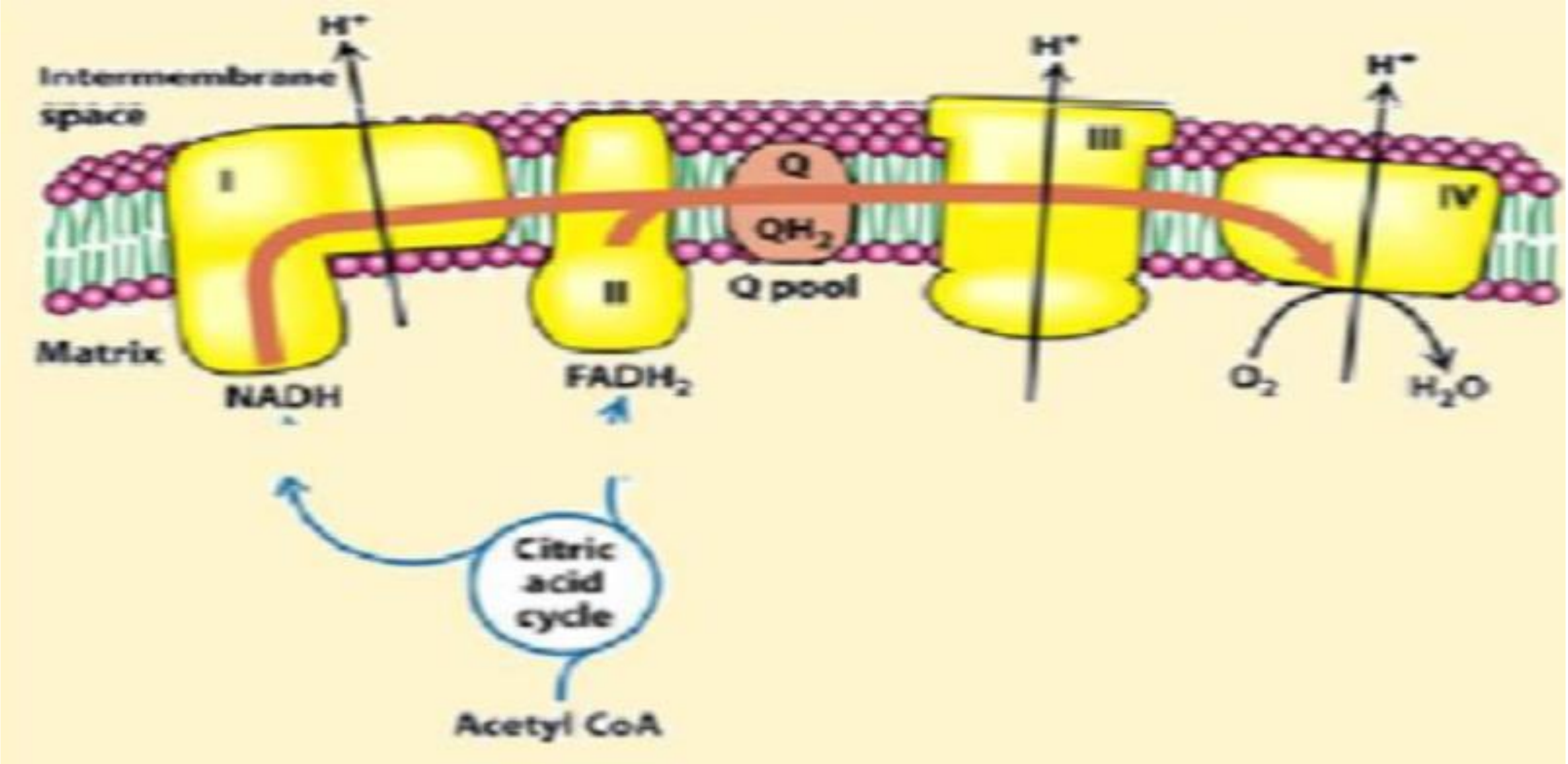
- Electrons are transferred from NADH → oxygen → along a chain of electron carriers → called **electron transport chain** (**respiratory chain**).

Electron Transport Chain



- NADH and FADH2 are **oxidized** by electron transport through → respiratory chain → Synthesis of ATP.

- Energy liberated by electron transport => used to create a proton gradient across the mitochondrial inner membrane => that is used to drive ATP synthesis (chemiosmotic hypothesis)→ in presence of ATP synthase .



H⁺
Intermembrane space
I
II
Q
QH_2
Q pool
III
IV
H⁺
H⁺
Matrix
NADH
$FADH_2$
O_2
H_2O
Citric acid cycle
Acetyl CoA

THANK YOU