BCH 301
CARBOHYDRATE METABOLISM

The carbohydrate used by the cells for fuel are the monosaccharides; glucose, fructose, galactose and mannose.

The latter two are converted to glucose. Subdivisions of carbohydrate metabolism:-

1. Glycolysis, Citric acid cycle.
2. Gluconeogenesis, Glycogenesis, Glycogenolysis, Hexose monophosphate shunt, Uronic acid pathway, Fructose metabolism, Galactose metabolism and Amino sugar metabolism.

Glycolysis (Embden – meyerhof pathway)

This is the anaerobic process by which glucose is degraded to 2 moles of lactic acid

D Glucose $\longrightarrow$ L Lactate

$C_6H_{12}0_6 \longrightarrow {}_2\,HO - COO^- H + 2H^+$

CH_3

Site: Occurs in virtually all tissues. Enzymes are found in the cytoplasm.

Importance: It provides a device for generating ATP without using O_2. Used in place of the combustion of glucose to $CO_2 + H_2O$.

Glucose + 2 (ADP + Pi) $\longrightarrow$ 2 lactate + $2H^+$ + 2ATP

If glycogen is used 3ATP is formed.

The overall reactions can be divided into two.

(1) Activation: Glucose is converted to a triose PO_4 by phosphorylation

(2) Energy Producing:- Oxidation of triosePO_4 to lactate

The enzymes with the exception of enolase and pyruvate decarboxylase can be classified into (1) Kinases which catalyse the transfer of a 'PO'$_4$ group from ATP to some acceptor molecule.

2. Mutases which catalyze the transfer of a 'PO'$_4$ group of a low energy level from one position to another on the same molecule

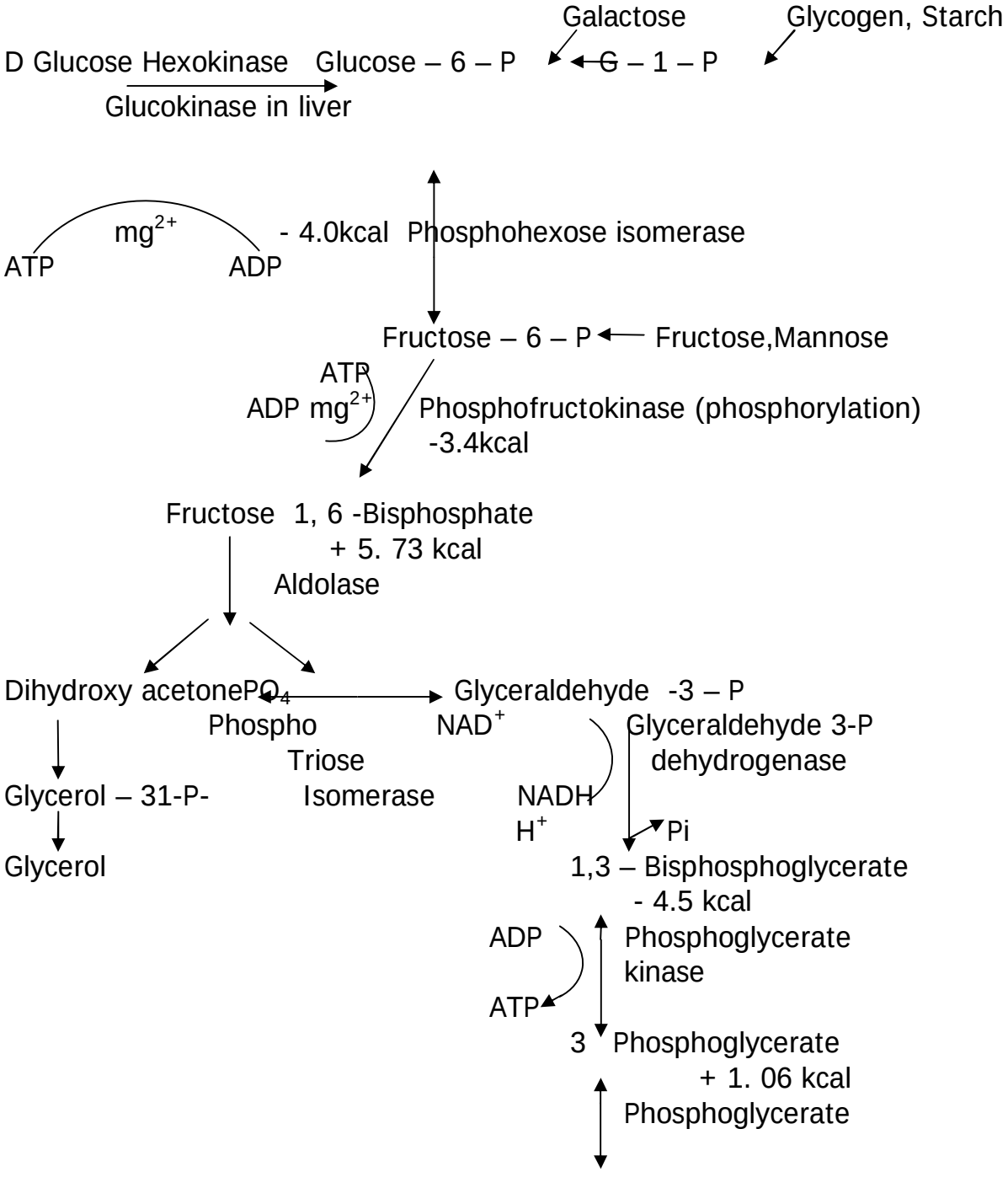
These 2 require mg^{2+} ions.

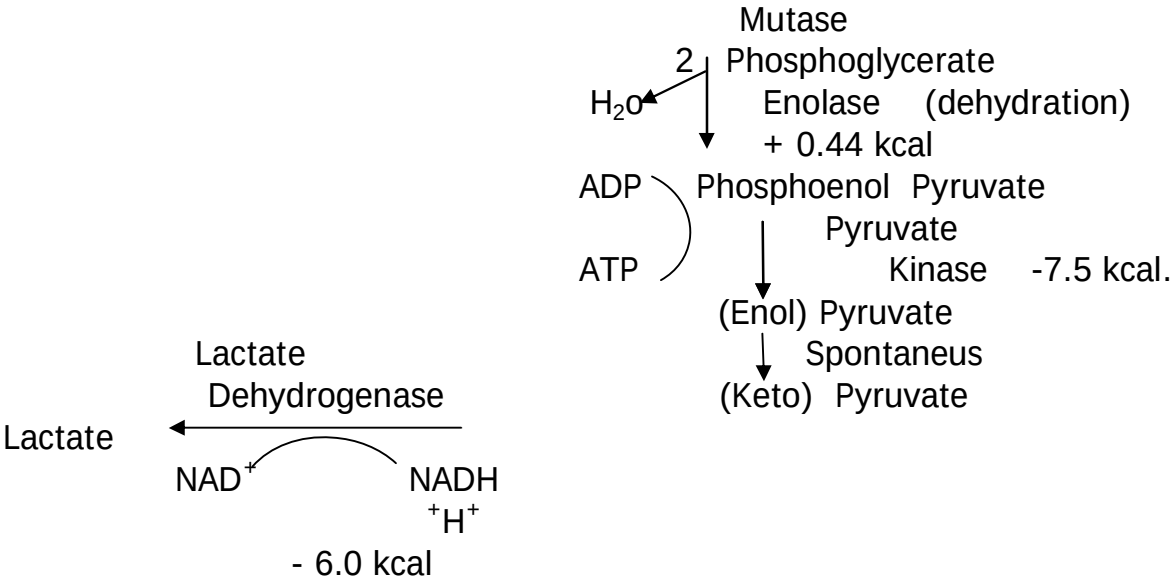
3. Isomerases: Catalyze the isomerization of aldose sugars to ketose sugars.
4. Dehydrogenases: Perform oxidation

Pyruvate is the end product of glycolysis in aerobic condition, under anaerobic, pyruvate is reduced by NADH to lactate.

Since 2 molecules of triose P are formed per mole of glucose, 2 moles of ATP are generated.

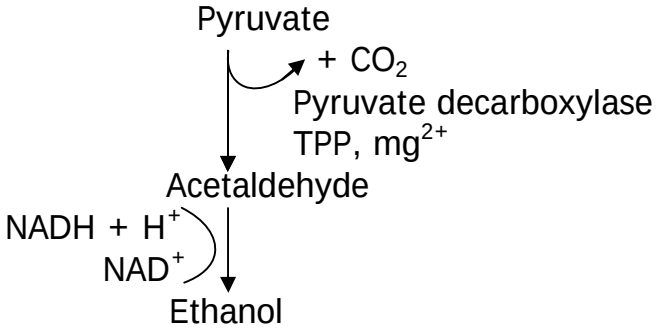
Sequence of reactions:





Alcoholic fermentation:- eg. Yeast

The reactions are identical except for the manner in which pyruvic acid is metabolized



NB: Ethanol + CO_2 cannot be converted to glucose because the decarboxylation reaction is exergonic and irreversible unlike the last stage of glycolysis.

KREB'S OR TRICARBOXYLIC ACID CYCLE

This cycle acts as the final pathway for the oxidation of Carbohydrate, lipids and proteins from their acetyl residues to CO_2 and water in the mitochondria.

All the necessary components of the cycle including the enzymes are in the mitochondria.

Overall reaction:-

Pryuvate

$$CH_3\,C\,CO_2\,H + 2½\,O_2 \longrightarrow 3\,CO_2 + 2H_2\,O$$

Importance:

1. Through the cycle, energy liberated during respiration is made available.
2. It is involved in the synthesis of glucose
3. Provides the raw materials for the synthesis of several amino acids eg. aspartate and glutamate
4. Blood pigments also arises from succinyl CoA.

Sequence of Reaction:-

Prelim: Oxidative decarboxylation involving 6 cofactors ; CoA – SH, NAD, lipoic acid FAD, Mg^{2+} and TPP. TPP is more involved in the decarboxylation process while the Co enzyme A combines with the acetyl residue to form an ester of CoA – acetyl - CoA.

2. Condensation reaction between acetyl- CoA and oxaloacetic acid. Coenzyme A is liberated and citrate is formed.

3,4 Isomerisation of citric acid into Cis- aconitate, then into isocitric acid. Req. Fe^{2+} as a cofactor. Which suggest its role in the formation of carbonium by promoting the dissociation of the hydroxyl group.

5&6 Oxidative decarboxylation of isocitrate to & - ketoglutarate. Oxalosuccinate is not released as a free intermediate, it is firmly bound to the enzyme. Mg^{2+} or Mn^{2+} is a cofactor. The oxidant is NAD.

The regulation of TCA centres on this enzyme. High concentration of ATP decreases its activity while AMP concentration stimulates the reaction.

7. Formation of succinyl CoA by oxidative decarboxylation reaction. TPP, Mg^{2+}, NAD, lipoic acid serve as cofactors the mechanism is analogous to that of Pyruvate dehydrogenases. Arsenite is an inhibitor of the enzyme.
8. Formation of high energy PO_4 at the expense of the thioester formed in reaction 7.
9. The enzyme catalyzes the removal of 3 H atoms from succinic acid to form fumarate

   Inhibitor = Malonic acid

   Oxidizing agent is FAD

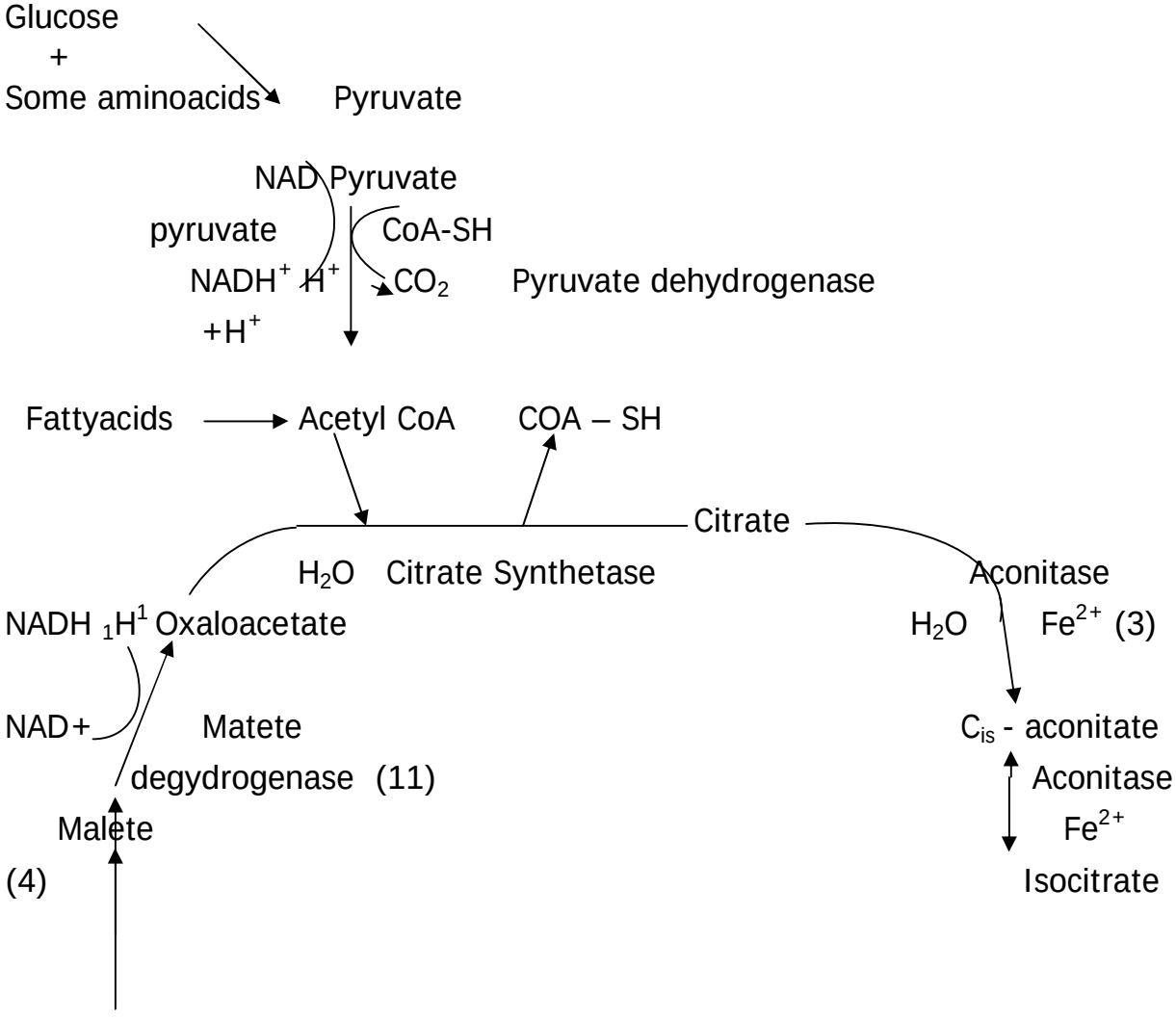
10. Addition of H_2O to fumarate to form malic acid (malate).

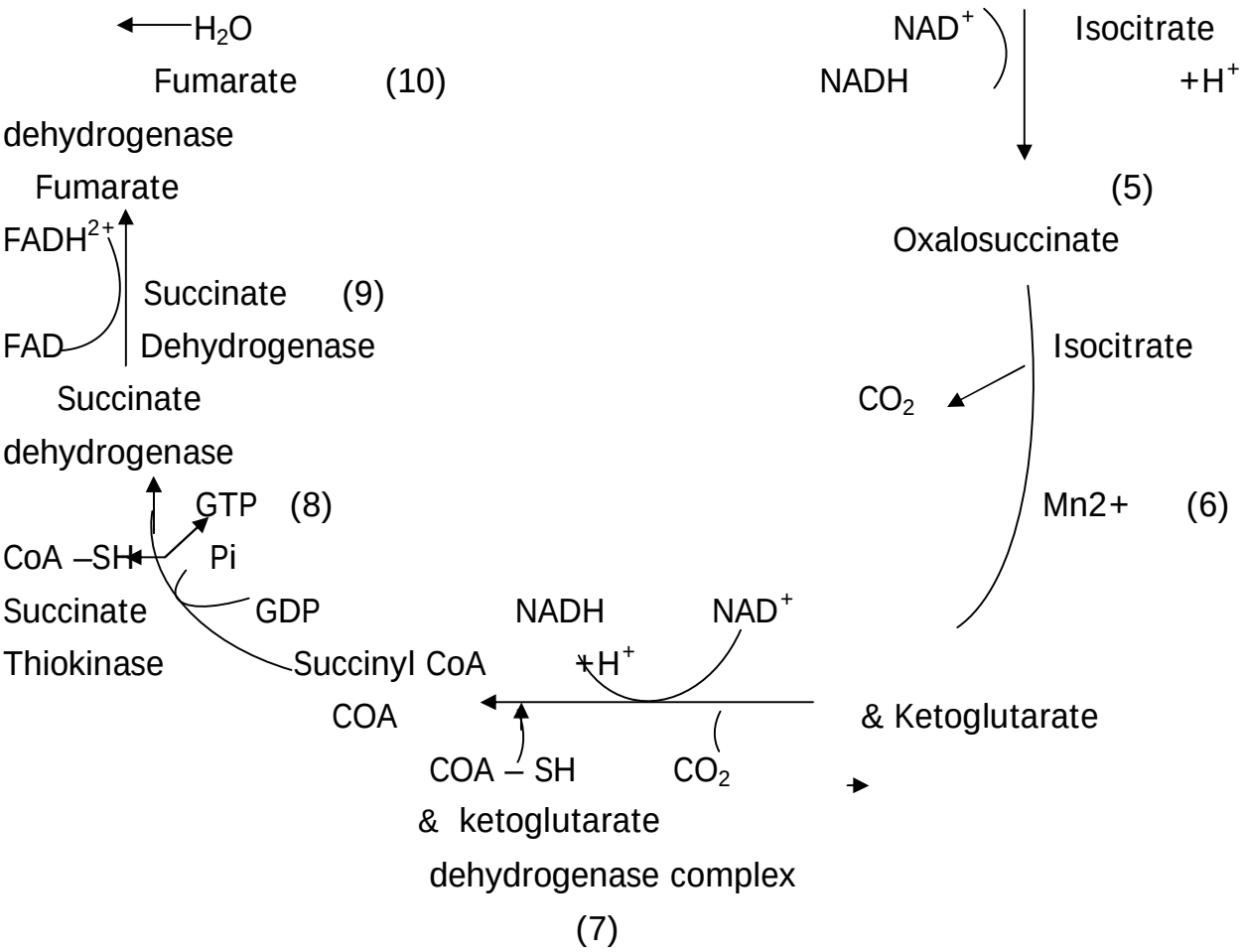
11. The last reaction that completes the cycle involves the oxidation of L malate to oxaloacetic acid. Oxidizing agent = NAD^+

ENERGY PRODUCTION:- The oxidation of each molecule of acetate (a complete turn of the cycle) generates 12 moles of ATP which is equivalent to about 84 kcal

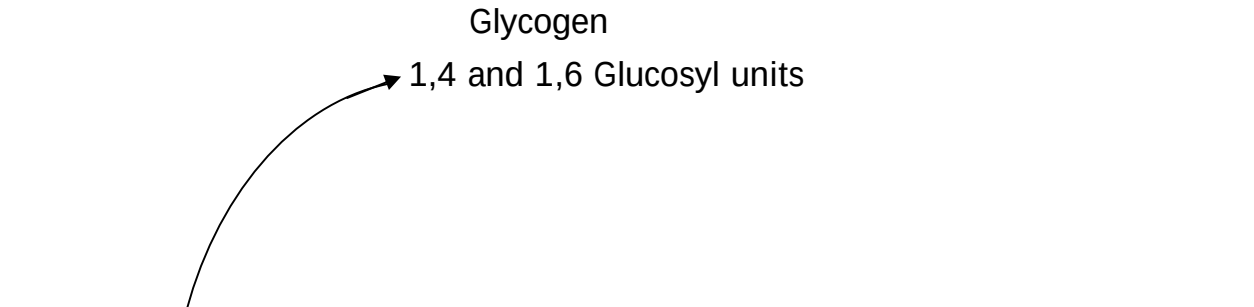
		No of ATP
Isocitrate dehydrogenase	NAD	3
& - ketoglutaratee dehydrogenase	NADH	3
Succinate Thiokinase		1
Succinate	$FAHD_2$	2
Malate dehydrogenase	NADH	3
		12

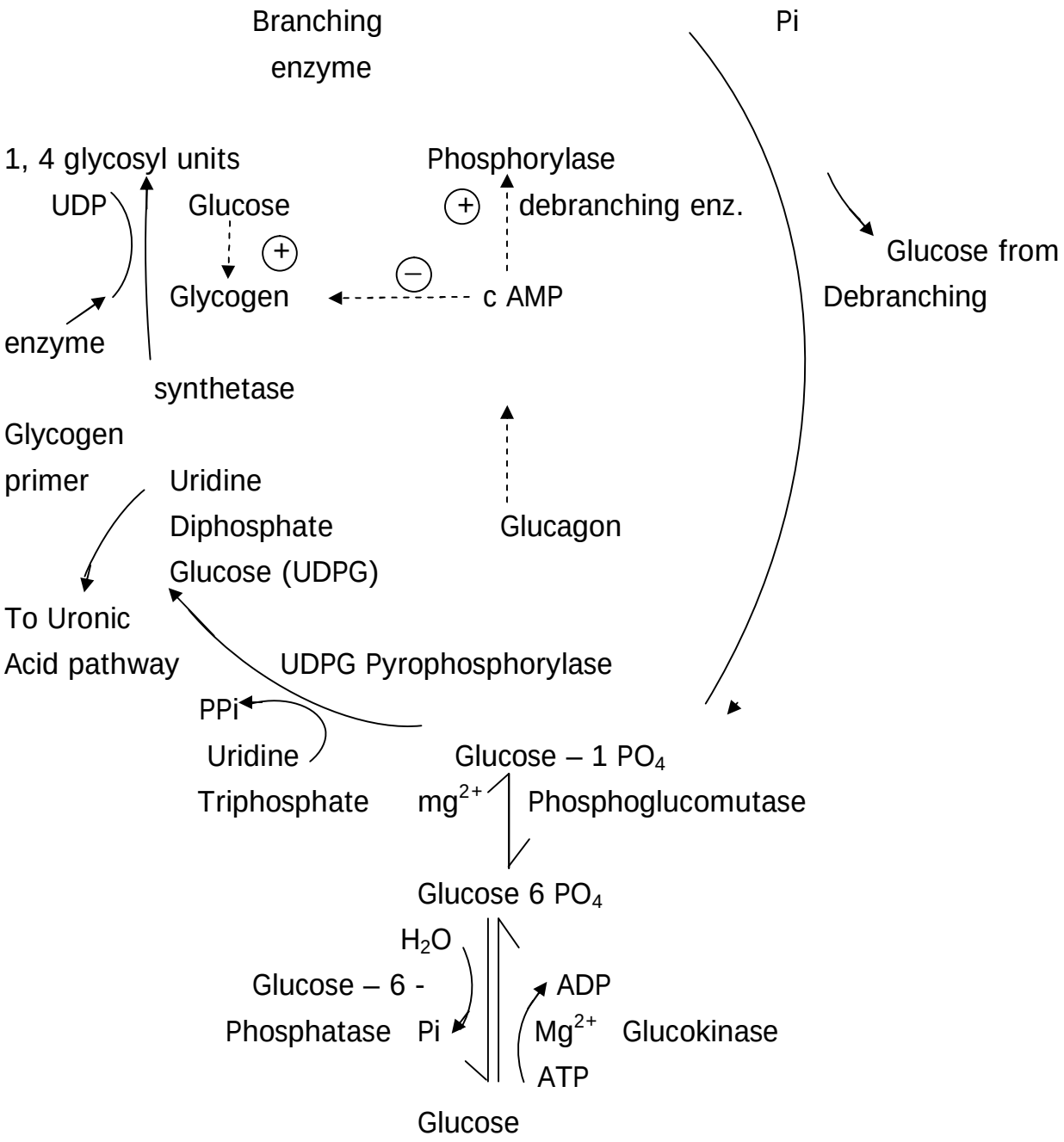
Sequence of Reactions:-





Pathway of glycogenesis and glycogenolysis in the liver





(+) Stimulation

(-) Inhibition

<u>Glycogen Storage Disorders</u>

1. Type 1 (von gierke's disease) due to deficiency of Glucose 6 – phosphatase in the cell of the liver and renal convoluted tubules.

Hypoglycemia lack of glycogenolysis under the stimulus of epinephrine or glucagon.

2. Pompe's disease: due to deficiency of liposomal & - 1, 4 – glycosidase.
3. Type III:- Cori's disease (limit dextrinosis) – amylo -1, 6 – glucosidase. Glycogen structure is abnormal, increased number of branched points
4. Type II = Andersens disease - glycogen structure abnormal very long inner and outer unbranched chain due to deficiency of 1, 4 1,6 transglucosylase.
5. Type V:- Mc Aidles syndrome – due to deficiency of muscle glycogen phosphornylase Has high muscle glycogen content.
6. Hers disease – due to liver glycogen phosphorylose.

GLYCOGEN

Glycogen is a branched polysaccharide composed entirely of & –D- glucose units. The molecular weight may vary from 1 million to 4 million

Formation of glycogen occur mostly in the liver and muscles and in small traces in every tissue of the body. Liver glycogen replenishes blood glucose when it is lowered while muscle glycogen acts as a readily available source of hexose units for glycolysis within the muscle itself.

Glycogenesis:

Glucose is phosphorylated to glucose 6 PO_4 this is then converted to glucose 1 – PO_4 in a reaction catalyzed by phosphoglucomutase. Glucose – 1-PO4 then react with uridine triphosphate to form UDPG the reaction being catalysed by UDPG pyrophosphorylase, inorganic pyrophosphate is released.

Glycogen synothetase or glucosyl transferase catalyses the reaction in which the C_1 of the activated glucose of UDPG forms a glycosidic bond with the C_4 of a terminal glucose residue of glycogen liberating UDP when the chair has been lengthened to between 6 and 11 glucose residue, the branching enzyme (amylo - 1,4 1,6 – transglucosidase acts on the glycogen. The enz transfers a part of the – 1, 4 – chain to a neighbouring chain to form a 1- 6 linkage thus establishing a branch point in the molecule.

G – 6 - phosphatase is absent in the muscle but present in liver and kidney where it allows the tissues to add glucose to the blood.

Glycogenolysis

Is the breakdown of glycogen. First the debranching enzyme breaks 1 -6, bond, the enzyme phosphorylase breaks down the 1 – 4 linkage of glycogen to yield glucose 1 – PO_4 this is converted to G-6-P then to glucose by G-6 phosphatase enzyme.

In the muscle phosphorylase is present both in the active form phosphorylase a (active in the absence of 5^1 AMP and phosphorylase be active only in the presence of 5^1 AMP).

HEXOSE MONO PHOSPHATE SHUNT.
OR PENTOSE PHOSPHATE PATHWAY

This is an alternative pathway for the degradation of glucose via 5C sugar other than the hexose.

Site:- It is active in the liver, adipose tissue, adrenal cortex, thyroid, testis, erythrocytes and lactating mammary glands.

Importance:- It is a device for generating NADPH (Dihydronicotinamide adenine dinucleotide phosphate). By the oxidation of Glucose 6 Po_4 to ribulose - 5 - PO_4 and CO_2. 2 moles of NADPH is produced for each mole of glucose ester oxidized.

Function of NADPH: It is an electron carrier. It plays a special role in biosynthetic processes within the cell. e.g . long chain and unsaturated fatty acids.

It is the reducing agent for the reduction of glucose to sorbitol also for the reduction of glucuronic acid to L gluconic acid.

Also reductive carboxylation of pyruvate to malate. It plays a role in the hydroxylation reaction involved in the formation of steroids and in the conversion of phenylalanine to tyrosine.

2. Ribose – 5 -PO_4 produced is an essential component of nucleotides and RNA

Sequence of Reactions

The main reactions can be divided into two. 1: Glucose 6 Po_4 undergoes two oxidations to form a pentose ribulose – 5 – PO_4.

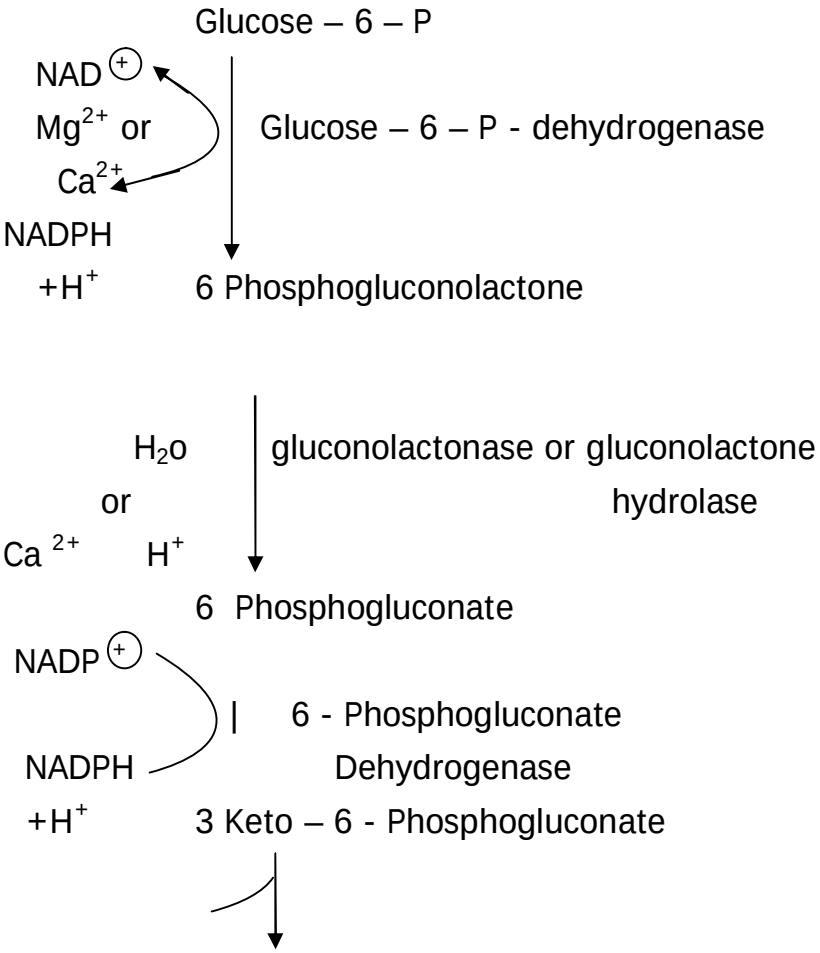
2: The glucose 5 – PO_4 is converted back to triose sugar then into glucose 6 – PO_4.

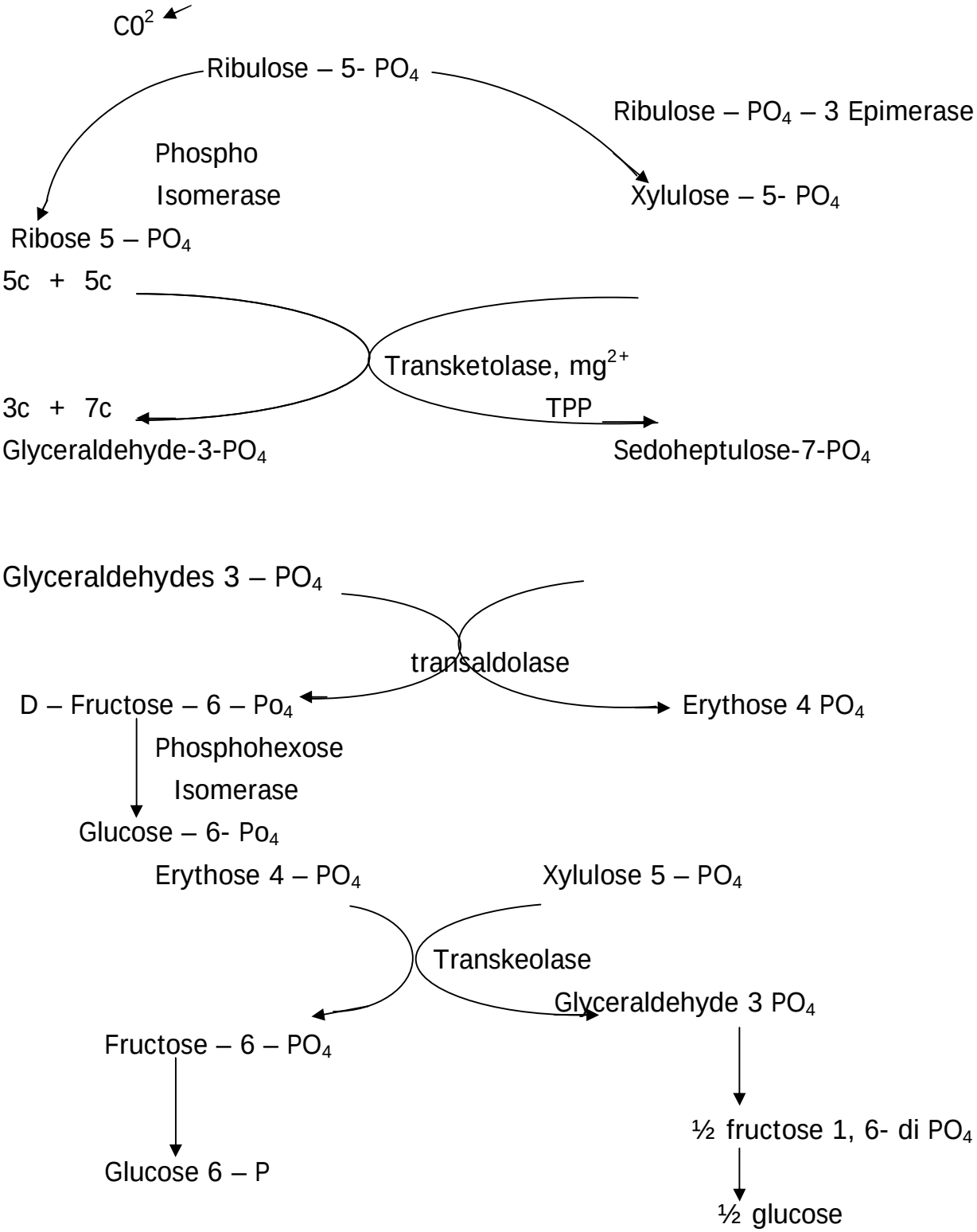
3 Glucose – 6 – Po_4 + 6 $NADP^+$ ⟶ $3C0_2$ + 2 Glucose – 6 – Po_4 + Glyceraldeyde 3 – PO_4 + 6 NADPH + 6 H^+

Transketolase catalyses the transfer of a ketol gp (i.e 2C unit) from xylulose 5-P to an aldehyde acceptor.

Transaldolase catalyses the transfer of a dihydroxyacetone unit from sedoheptulose 7-P to glyceraldehyde 3-P.

Sequence of Reactions:-




$C0^2$
Ribulose – 5- PO_4
Ribulose – PO_4 – 3 Epimerase
Phospho
Isomerase
Xylulose – 5- PO_4
Ribose 5 – PO_4
5c + 5c
Transketolase, mg^{2+}
3c + 7c
TPP
Glyceraldehyde-3-PO_4
Sedoheptulose-7-PO_4
Glyceraldehydes 3 – PO_4
transaldolase
D – Fructose – 6 – Po_4
Erythose 4 PO_4
Phosphohexose
Isomerase
Glucose – 6- Po_4
Erythose 4 – PO_4
Xylulose 5 – PO_4
Transkeolase
Glyceraldehyde 3 PO_4
Fructose – 6 – PO_4
½ fructose 1, 6- di PO_4
Glucose 6 – P
½ glucose