Carbohydrates

Carbohydrates may be defined as polyhydroxy aldehydes or ketones or compounds which produce them on hydrolysis

Functions of carbohydrate

Carbohydrates participate in a wide range of functions

1. They are the most abundant dietary source of energy (4cal per gram) for all organism.

2. Carbohydrates are precursors for many organic compounds (fats, amino acids)

3. Carbohydrates as (glycoproteins and glycolypids) participate in the structure of cell membrane and cellular functions such a cell growth adhesion and fertilization.

4. They are structural components of many organism. these include the fibre (cellulose) of plants, exoskeleton of some insects and the cell wall of microorganism.

5. Carbohydrates also serve as the storage form of energy (glycogen)to meet the immediate energy demands of the body.

6. Carbohydrates are utilised as raw materials for several industries ex :paper ,plastic ,Textiles, alcohol etc.

Classification of carbohydrates

Carbohydrates are often referred to as saccharides means sugar

They are broadly classified into

- Monosaccharides
- Oligosaccharides
- Polysaccharides

Monosaccharides

Monosaccharides are the simplest group of Carbohydrates and are often referred as simple sugars.

They have a general formula $Cn(H_2O)n$.

They cannot be further hydrolysed.

Monosaccharides are divided into different categories based on

1. Functional group 2. Number of carbon atom

Functional group

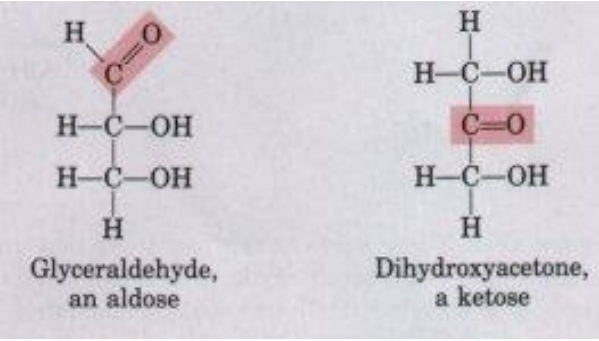
- Aldoses or Aldose sugar - when the functional group in the monosaccharide is an aldehyde, they are known as aldose sugar. Ex :glyceraldehyde, glucose.
- Ketosis or Keto sugar - when the function group in the monosaccharide is a keto group, they are referred as ketosis .Ex: dihydroxy acetone, fructose.

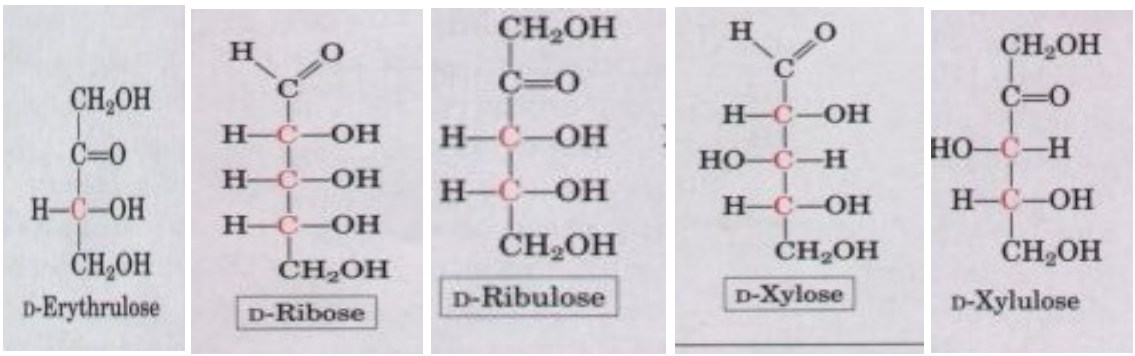
Number of carbon atom

Based on the number of carbon atom the monosaccharides are regarded

Number of carbons	**Name**	**Aldose**	**Ketose**
3	Triose	Glyceraldehyde	Dihydroxy acetone
4	tetrose	Erythrose	Erythrulose
5	pentose	Xylose, Ribose	Xylulose, Ribulose
6	hexose	Glucose, Galactose, Mannose	Fructose
7	heptose	-	Sedoheptulose

- GLUCOSE is a Aldohexoses while FRUCTOSE is a ketohexose.





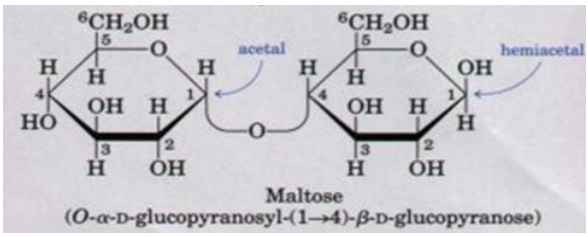
Oligosaccharides

Oligosaccharides contain 2 to 10 monosaccharide molecules which are liberated on hydrolysis

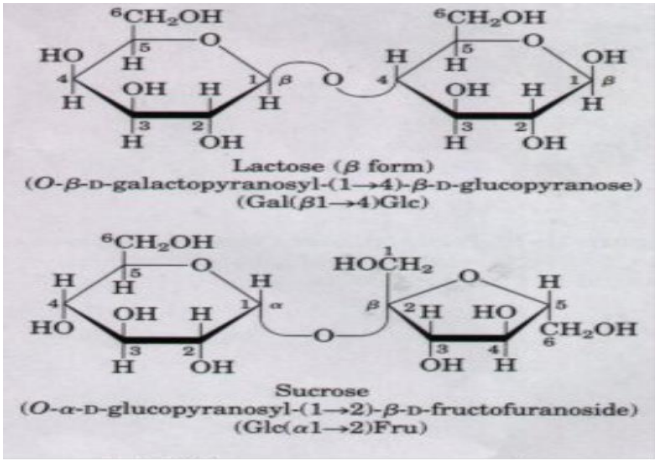
1.Disaccharides

Disaccharides on hydrolysis produces two molecules of the same or different monosaccharides the general formula is$Cn(H_2O)n-1$.

Maltose - glucose and glucose



Lactose - glucose and galactose



. Sucrose- glucose and fructose

2.Trisaccharides

Ex: Raffinose - fructose +galactose +Glucose

3.Tetrasaccharides

Ex: stachyose: -2moles of galactose +glucose + fructose.

Polysaccharides

Polysaccharides contain more than 10 monosaccharide molecules on hydrolysis

They are of two types

- **Homopolysaccharides**(homoglycans): They contain monosaccharide unit of a single type and may be represented by general formula $(C_6H_{10}O_5)n$.

  Example- Starch, Glycogen, Inulin, Cellulose

- **Heteropolysaccharides**(heteroglycans):They posess 2 or more different types of monosaccharides units or their derivatives .

  Example – Mucopolyssacharide, Heparin, Chondroitin sulphate.

HOMO POLYSACCHARIDES (HOMOGLYCANS)

1. **Starch**

- Starch is the carbohydrate reserve of plants , which is the most important dietary source for higher animals, including man.
- High content of starch is found in cereals, roots, tubers, vegetables
- Starch is a polymer composed of a D-glucose units held by glycosidic bonds.
- It is known as glucosan or glucan
- Starch consists of two polysaccharide components-water soluble amylose (15-20%) and a water insoluble amylopectin 80-85%
- Chemically, amylose is a long unbranched chain with 200 1,000 D-glucose units held by (α-1,4) glycosidic linkages.
- Amylopectin, on the other hand, is a branched chain with a (α,1→ 6 glycosidic bonds at the branching points and a (α-1→ 4) linkages everywhere else. Amylopectin molecule containing a few thousand glucose units locks like a branched tree (20-30 glucose units per branch).
- Starches are hydrolysed by amylase (pancreatic or salivary) to liberate dextrins and finally maltose and glucose units.

- Amylase acts specifically on (α-1,4) glycosidic bonds.

2.Dextrins

- Dextrins are the breakdown products of starch by the enzyme amylase or dilute acids.
- Starch is sequentially hydrolysed through different dextrins and, finally, to maltose and glucose.
- The various intermediates (identified by iodine colouration) are soluble starch (blue), amylodextrin (violet), erythrodextrin (red) and achrodextrin (no colour).

3.Inulin

- Inulin is a polymer of fructose i.e., fructosan.
- It occurs in dahlia bulbs, garlic, onion etc.
- It is a low molecular weight (around 5,000) polysaccharide easily soluble in water.
- Inulin is not utilized by the body.
- It is used for assessing kidney function through measurement of glomerular filtration rate (GFR).

4.Glycogen

- Glycogen is the carbohydrate reserve in animals, hence often referred to as animal starch
- It is present in high concentration in liver, followed k by muscle, brain etc.
- Glycogen is also found in plants, that do not possess chlorophyll (eg yeast, fungi).

- The structure of glycogen is similar to that of amylopectin with more number of branches.
- Glucose is the repeating unit in glycogen joined together by (α1-4) glycosidic bonds, and (α1-6) glycosidic bonds at branching points.
- The molecular weight (up to 1 x 10") and the number of glucose units (up to 25,000) vary in glycogen depending on the source glycogen is obtained.

5.Cellulose

- Cellulose occurs exclusively in plants.
- It the most abundant organic substance in plant kingdom.
- It is a predominant constituent of plant cell wall.
- Cellulose is totally absent in animal body.
- Cellulose is composed of β-D-glucose units of linked by β(1,4) glycosidic bonds.
- Cellulose cannot be digested by mammals-including man due to lack of the enzyme that cleaves β-glycosidic bonds (α amylase breaks α bonds only).
- Certain ruminants and herbivorous animals contain microorganisms in the gut which produce enzymes that can cleave β-glycosidic bonds. Hydrolysis of cellulose yields a disaccharide cellobiose, followed by β-D-glucose.

- Cellulose, though not digested, has great importance in human nutrition.
- It is a major constituent of fiber, the non-digestable carbohydrate.
- The functions of dietary fiber include decreasing the absorption of glucose and cholesterol from the intestine, besides increasing the bulk of feces.

6.Chitin

- Chitin is composed of N-acetyl D-glucosamine units held together by β (1→4) glycosidic bonds.
- It is a structural polysaccharide found in the exoskeleton of some invertebrates e.g. insects &crustaceans.

HETEROPOLYSACCHARIDES

When the polysaccharides are composed of different types of sugars or their derivatives, they are referred to heteropolysaccharides or as heteroglycans.

1. **Mucopolysaccharides**

- These are heteroglycans made up of repeating units of sugar derivatives, namely amino sugars and uronic acids.
- Mucopolysaccharides are more commonly known as glycosaminoglycans (GAG).

2. **Hyaluronic Acid**

- Hyaluronic acid is an important GAG found in the ground substance of synovial fluid of joints and vitreous humor of eyes.
- It is also present as a ground substance in connective tissues and forms a gel around the ovum.
- Hyaluronic acid serves as a lubricant and shock absorbant in joints.

- Hyaluronic acid is composed of alternate units of D-glucuronic acid and N-acetyl D-glucosamine.
- These two molecules form disaccharide units held together by β(13) glycosidic bonds.

3.Chondroitin Sulfates

- Chondroitin 4-sulfate (Greek: chondros cartilage) is a major constituent of various mammalian tissues (bone, cartilage, tendons, heart, valves, skin, cornea etc.).
- Structurally, it is comparable with hyaluronic acid.
- Chondroitin 4-sulfate consists of repeating disaccharide units composed of D-glucuronic acid and N-acetyl D-galactosamine 4-sulfate .

- Chondroitin 6-sulfate is also present in many tissues. As evident from the name, the sulfate group is found on C6 instead of C4.

4.Heparin

- Heparin is an anticoagulant (prevents blood clotting) that occurs in blood, lung, liver, kidney, spleen etc.
- Heparin helps in the release of the enzyme lipoprotein lipase which causes clearing the turbidity of lipemic plasma.

- Heparin is composed of alternating units of N-sulfo D-glucosamine 6-sulfate and glucuronate 2-sulfate.

The fasting blood glucose level in normal individuals is 60-100 mg/dl.

Major pathways of carbohydrate metabolism

The important pathways of carbohydrate metabolism are listed

1. **Glycolysis (Embden-Meyerhof pathway) -** The oxidation of glucose to pyruvate and lactate

2**. Citric acid cycle (Krebs cycle or tricarboxylic acid cycle) -** The oxidation of acetyl CoA to carbon dioxide and water.

Krebs cycle is the final common oxidative pathway for carbohydrates, fats or amino acids, through acetyl CoA.

3. **Gluconeogenesis -** The synthesis of glucose from non-carbohydrate precursors (e.g. amino acids, glycerol etc.).

4**. Glycogenesis** - The formation of glycogen from glucose.

5. **Glycogenolysis** - The breakdown of glycogen to glucose and then to lactate and pyruvate.

6. **Hexose monophosphate shunt (pentose phosphate pathway, HMP Shunt or direct oxidative pathway)** - This pathway is an alternative to glycolysis and TCA cycle for the oxidation of glucose. Here, glucose is directly oxidized to carbon dioxide and water.

7. **Uronic acid pathway** - Glucose is converted to glucuronic acid, pentoses and, in some animals, to ascorbic acid (not in man). This pathway is also an alternative oxidative pathway for glucose.

8. **Galactose metabolism -** The pathways concerned with the conversion of galactose to glucose and the synthesis of lactose.

9. **Fructose metabolism** - The oxidation of fructose to pyruvate and the relation between fructose and glucose metabolism.

10. **Amino sugar and mucopolysaccharide metabolism** - The synthesis of amino sugars and other sugars for the formation of mucopoly saccharides and glycoproteins.

Entry of glucose into cells

Glucose concentration is very low in the cells compared to blood dor humans < 100 mg/dl). However, glucose does not enter the cells by simple diffusion. Two specific transport systems are recognized for the entry of glucose into the cells

1. Insulin-independent transport system of glucose: This is a carrier mediated uptake of glucose which is not dependent on the hormone L insulin. This is operative in hepatocytes, erythro cytes and brain

2. Insulin-dependent transport system: This occurs in muscle and adipose tissue

Glucose transporters: In recent years, at least five glucose transporters (GLUT-1 to GLUT-5) in the cell membranes have been identified. They exhibit tissue specificity, for instance, GLUT-1 is abundant in erythrocytes whereas GLUT-4 is abundant in muscle and adipose tissue. Insulin increases the number and promotes the activity of GLUT-4 is skeletal muscle and adipose tissue

1.GLYCOLYSIS

Glycolysis is derived from the Greek words (glycose-sweet or sugar; lysis-dissolution).

This pathway is often referred to as Embden-Meyerhof pathway (E.M. pathway) in honour of the two biochemists who made a major contribution to the knowledge of glycolysis.

Glycolysis is defined as the sequence of reactions converting glucose (or glycogen) to pyruvate or lactate, with the production of ATP

Salient features

1. Glycolysis takes place in all cells of the body. The enzymes of this pathway are present in the cytosomal fraction of the cell.

2. Glycolysis occurs in the absence of oxygen (anaerobic) or in the presence of oxygen (aerobic) Lactate is the end product under anaerobic condition. In the aerobic condition, pyruvate i formed, which is then oxidized to $CO_2$and H_2O

3. Generally, Embden-Meyerhof pathway is a emergency energy-yielding pathway for cells in th absence of oxygen.

4. The occurrence of glycolysis is a pre- requisite for the aerobic oxidation of carbohydrate the latter takes place in the cells possess mitochondria

5. Glycolysis is a major pathway for ATP synthesis in tissues lacking mitochondria, e.g erythrocytes, cornea, lens etc.

6. In some other tissues which have relatively few mitochondria (e.g. testes, leucocytes and kidney medulla), glycolysis is significant for ATP production.

7. Glycolysis is very essential for brain which is dependent on glucose for energy. The glucose in brain has to undergo glycolysis before it is oxidized to CO_2 and H_2O.

8. Glycolysis (anaerobic) may be summarized by the net reaction

Glucose + 2ADP+ 2Pi→→→→ 2Lactate + 2ATP

9. The intermediates formed in glycolysis are useful for the synthesis of non-essential amino acids and glycerol, the latter used for fat formation.

10. Reversal of glycolysis along with the alternate arrangements made at the irreversibie steps will result in the synthesis of glucose (gluconeogenesis).

REACTIONS OF GLYCOLYSIS

The sequence of reactions of glycolysis are given .The pathway can be divided into three distinct phases

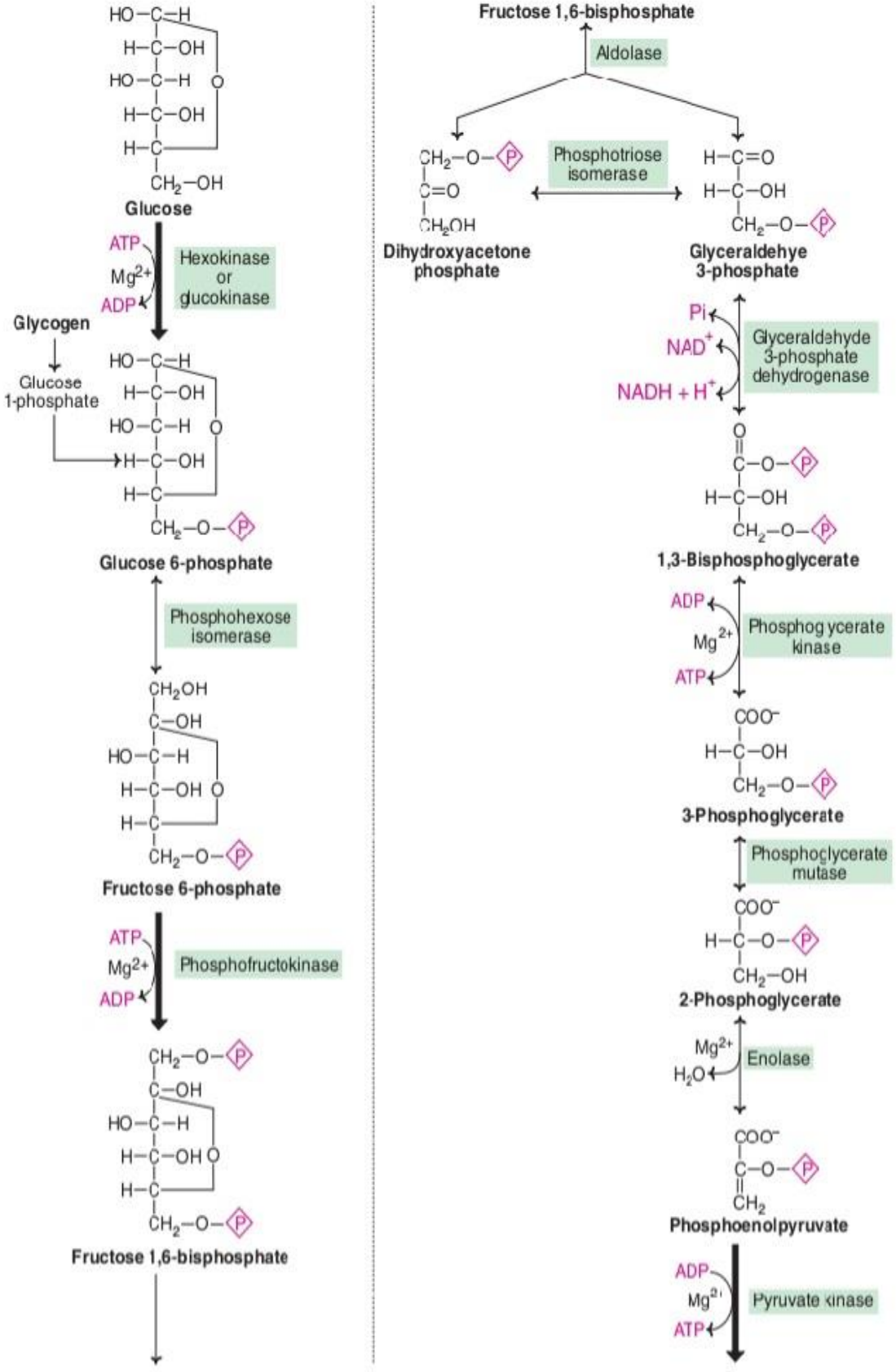
A. Energy investment phase or priming stage
B. Splitting phase
C. Energy generation phase.

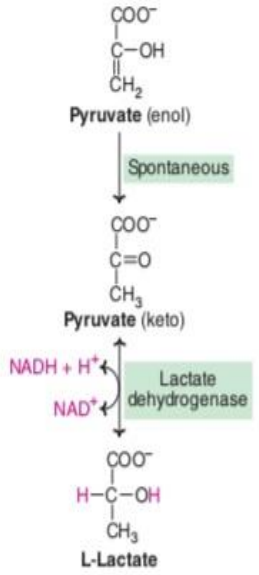
- Energy investment phase or priming stage

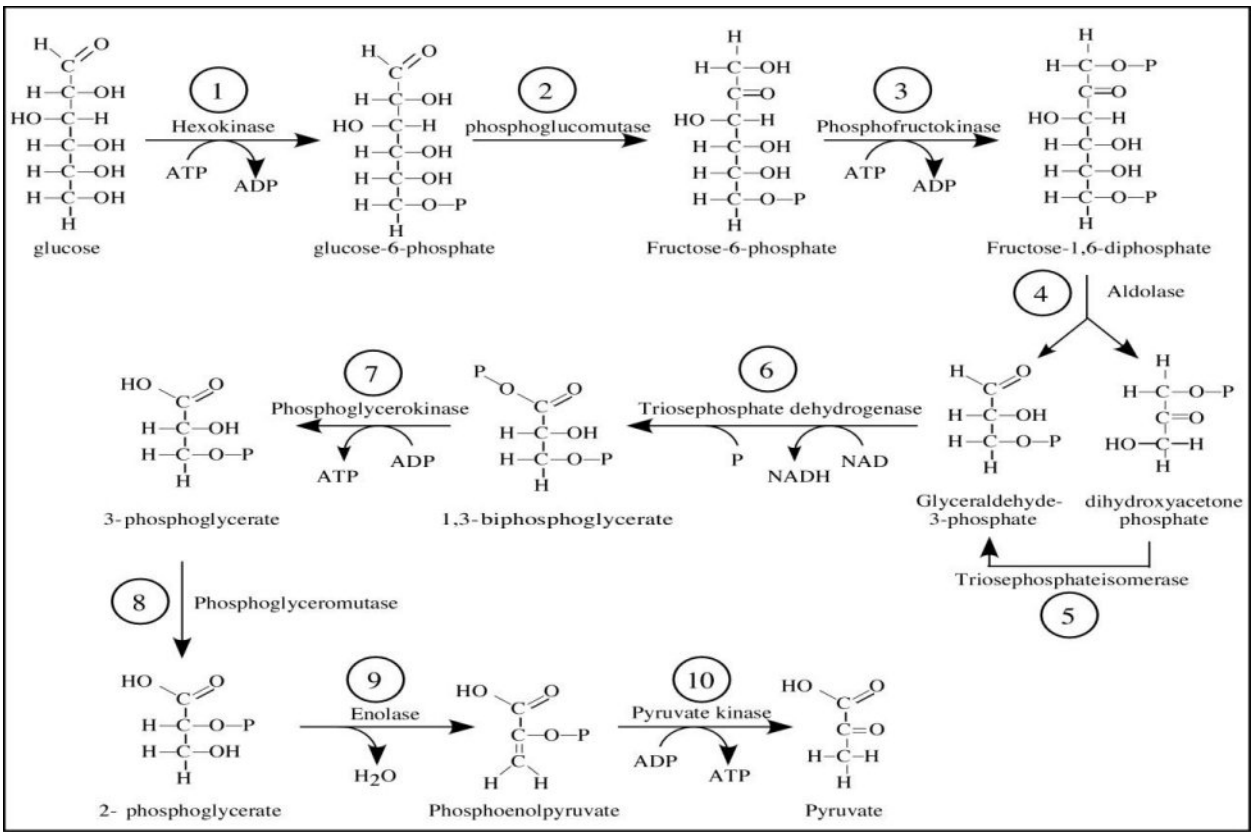
- Glucose is phosphorylated by ATP to form Glucose6-phosphate and is catalyzed by hexokinase.

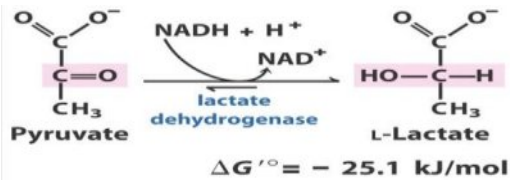
- Glucose6-phosphate gives Fructose-6-phoshphate by the enzyme phospho hexose isomerase

- Fructose-6-phosphate is phosphorylated by ATP to fructose-1,6-bisphosphate and is catalyzed by phosphofructokinase enzyme.


Glucose
ATP
Mg2+
ADP
Hexokinase or glucokinase
Glycogen
Glucose 1-phosphate
Glucose 6-phosphate
Phosphohexose isomerase
Fructose 6-phosphate
ATP
Mg2+
ADP
Phosphofructokinase
Fructose 1,6-bisphosphate
Fructose 1,6-bisphosphate
Aldolase
Phosphotriose isomerase
Dihydroxyacetone phosphate
Glyceraldehye 3-phosphate
Pi
NAD+
NADH + H+
Glyceraldehyde 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
ADP
Mg2+
ATP
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Mg2+
H2O
Enolase
Phosphoenolpyruvate
ADP
Mg2+
ATP
Pyruvate kinase


Pyruvate (enol)
Spontaneous
Pyruvate (keto)
NADH + H+
NAD+
Lactate dehydrogenase
L-Lactate


glucose
1
Hexokinase
ATP
ADP
glucose-6-phosphate
2
phosphoglucomutase
Fructose-6-phosphate
3
Phosphofructokinase
ATP
ADP
Fructose-1,6-diphosphate
4
Aldolase
Glyceraldehyde-3-phosphate
dihydroxyacetone phosphate
Triosephosphateisomerase
5
6
Triosephosphate dehydrogenase
P
NADH
NAD
1,3-biphosphoglycerate
7
Phosphoglycerokinase
ATP
ADP
3-phosphoglycerate
8
Phosphoglyceromutase
2- phosphoglycerate
9
Enolase
H2O
Phosphoenolpyruvate
10
Pyruvate kinase
ADP
ATP
Pyruvate


NADH + H+
NAD+
lactate dehydrogenase
Pyruvate
L-Lactate
ΔG'°= − 25.1 kJ/mol

- Splitting phase

- fructose-1,6-bisphosphate forms glyceradldehyde-3-phosphate (GAP) & dihydroxyacetone phosphate(DHAP). • This reaction is catalyzed by Aldolase.

- Dihydroxyacetone phosphate is oxidized to form Glyceraldehyde-3-phosphate. • This reaction is catalyzed by triose phosphate isomerase enzyme.

- Energy generation phase

- Glyceraldehyde-3-phosphate dehydrogenase catalyzes the conversion of Glyceraldehyde3-phosphate into 1,3-bisphosphoglycerate.

- 1,3-bisphosphoglycerate (1,3-BPG) forms 3-phosphoglycerate by phospho glycerate kinase.

- 3- phosphoglycerate forms 2- phosphoglycerate by phospho glycerate mutase.

- 2- phosphoglycerate to phosphoenolpyruvate(PEP) by enolase enzyme.

- Phosphoenolpyruvate to pyruvate by pyruvate kinse. This compound is the phosphate ester of the enol tautomer of pyruvate.

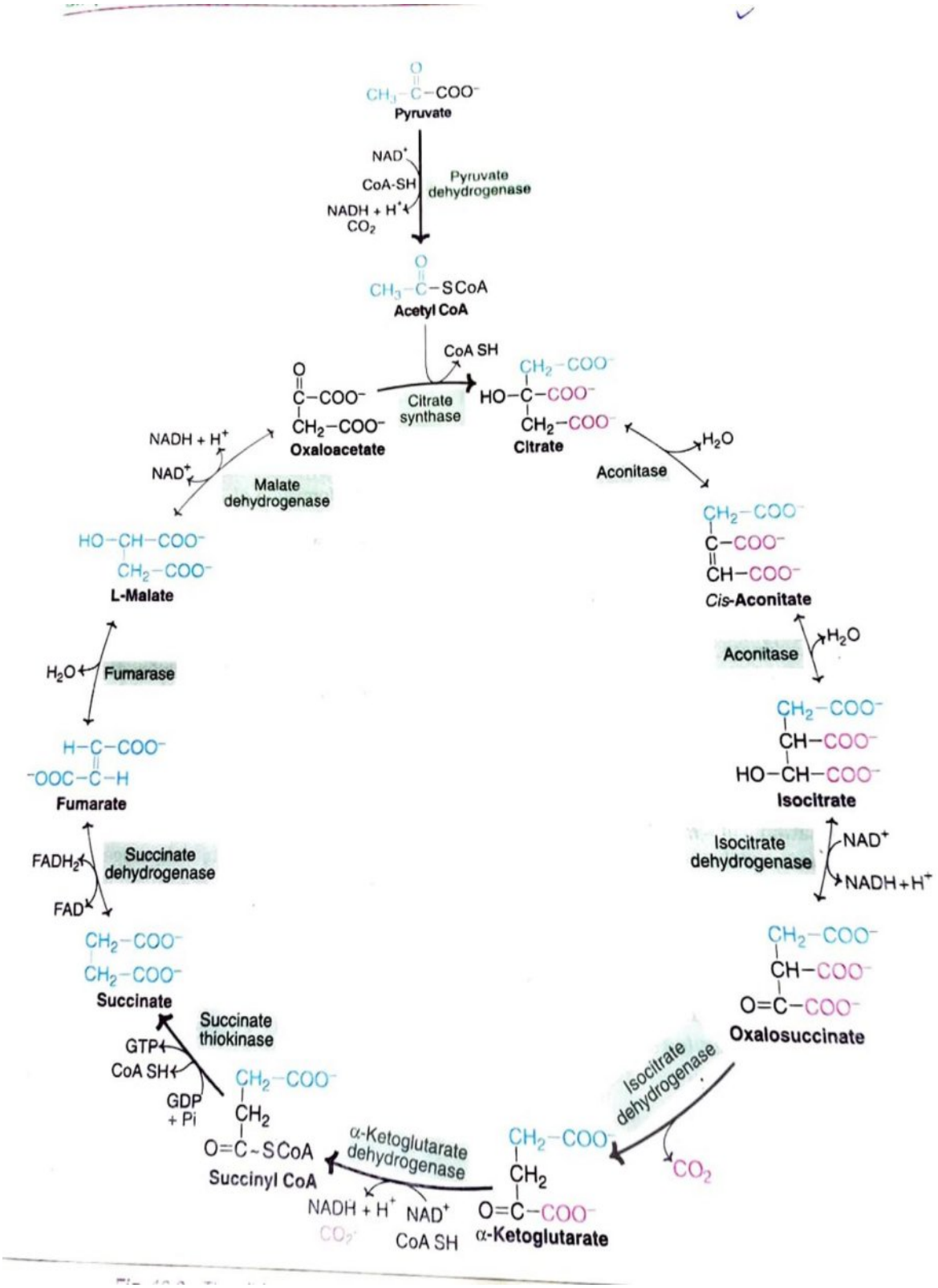
- pyruvate converted to lactate by lactate dehydrogenase

Significance of glycolysis

- All tissues utilise the glycolytic pathway to break down glucose into energy in the form of ATP
- Significant pathway for energy production, particularly in anaerobic circumstances
- It is critical for energy synthesis in cells without mitochondria
- It produces intermediates for subsequent metabolic processes
- Glycolysis is involved in glycogen metabolism, the pentose phosphate pathway, amino sugar synthesis, triglyceride synthesis (by glycerol 3-phosphate), lactate synthesis (a dead-end reaction), and transamination with alanine

2.Citric acid cycle (Krebs cycle or tricarboxylic acid cycle)

The Krebs cycle or Citric acid cycle is a series of enzyme-catalyzed reactions occurring in the mitochondrial matrix, where acetyl-CoA is oxidized to form carbon dioxide and coenzymes are reduced, which generate ATP in the electron transport chain.


Pyruvate
NAD+
CoA-SH
NADH + H+
CO2
Pyruvate dehydrogenase
Acetyl CoA
CoA SH
Citrate synthase
Oxaloacetate
Citrate
NADH + H+
NAD+
Malate dehydrogenase
Aconitase
H2O
L-Malate
Cis-Aconitate
Aconitase
H2O
Fumarase
Isocitrate
Fumarate
Isocitrate dehydrogenase
NAD+
NADH+H+
FADH2
FAD
Succinate dehydrogenase
Oxalosuccinate
Succinate
Succinate thiokinase
GTP
CoA SH
GDP + Pi
Isocitrate dehydrogenase
CO2
α-Ketoglutarate dehydrogenase
Succinyl CoA
NADH + H+
CO2
NAD+
CoA SH
α-Ketoglutarate

Pathway	Enzymes	No.of ATP
Glycolysis	Glyceraldehyde 3-phosphate dehydrogenase (2 NADH ETC oxidative phosphorylation)	6
	Phosphoglycerate kinase (substrate level phosphorylation)	2
	Pyruvate kinase (substrate level phosphorylation)	2
	Two ATP are consumed in the reactions catalysed by hexokinase and phosphofructokinase	2
	Net ATP synthesis in glycolysis in aerobic condition	8
	Pyruvate dehydrogenase (2 NADH, ETC, oxidative phosphorylation)	6
Citric acid cycle	Iso citrate dehydrogenase (2 NADH, ETC. oxidative phosphorylation)	6
	Ketoglutarate dehydrogenase	6
	Succinate thickinase (substrate level phosphorylation)	2
	Succinate dehydrogenase (2 FADH, ETC, oxidative phosphorylation)	4
	Malate dehydrogenase (2 NADH ETC, oxidative phosphorylation)	6
	Total ATP per mole of glucose under aerobic condition	38
	Total ATP per mole of glucose under anaerobic condition	2

Significance of TCA cycle

- The Krebs cycle or Citric acid cycle is the final pathway of oxidation of glucose, fats, and amino acids.
- Many animals are dependent on nutrients other than glucose as an energy source.
- Amino acids (metabolic product of proteins) are deaminated and get converted to pyruvate and other intermediates of the Krebs cycle. They enter the cycle and get metabolized e.g. alanine is converted to pyruvate, glutamate to α-ketoglutarate, aspartate to oxaloacetate on deamination.
- Fatty acids undergo β-oxidation to form acetyl CoA, which enters the Krebs cycle.
- It is the major source of ATP production in the cells. A large amount of energy is produced after the complete oxidation of nutrients.

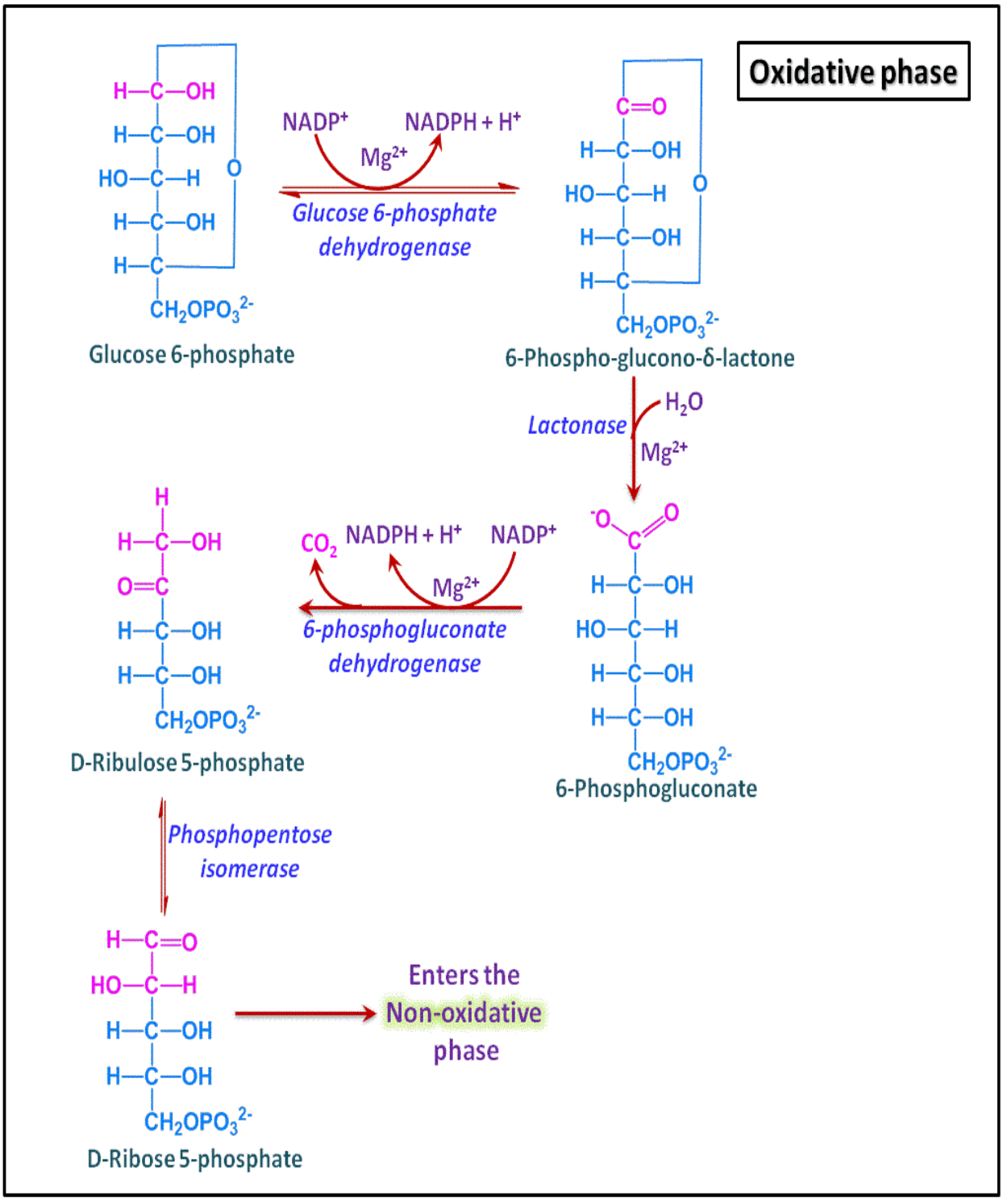
- It plays an important role in gluconeogenesis lipogenesis and interconversion of amino acids.
- Many intermediate compounds are used in the synthesis of amino acids, nucleotides, cytochromes, chlorophylls, etc.
- Vitamins play an important role in the citric acid cycle. Riboflavin, niacin, thiamin, and pantothenic acid a part of various enzymes cofactors (FAD, NAD) and coenzyme A.
- Regulation of the Krebs cycle depends on the supply of NAD+ and the utilization of ATP in physical and chemical work.
- The genetic defects of the Krebs cycle enzymes are associated with neural damage.
- As most of the processes occur in the liver to a significant extent, damage to liver cells has a lot of repercussions. Hyperammonemia occurs in liver diseases and leads to convulsions and coma. This is due to reduced ATP generation as a result of the withdrawal of α-ketoglutarate and the formation of glutamate, which forms glutamine.

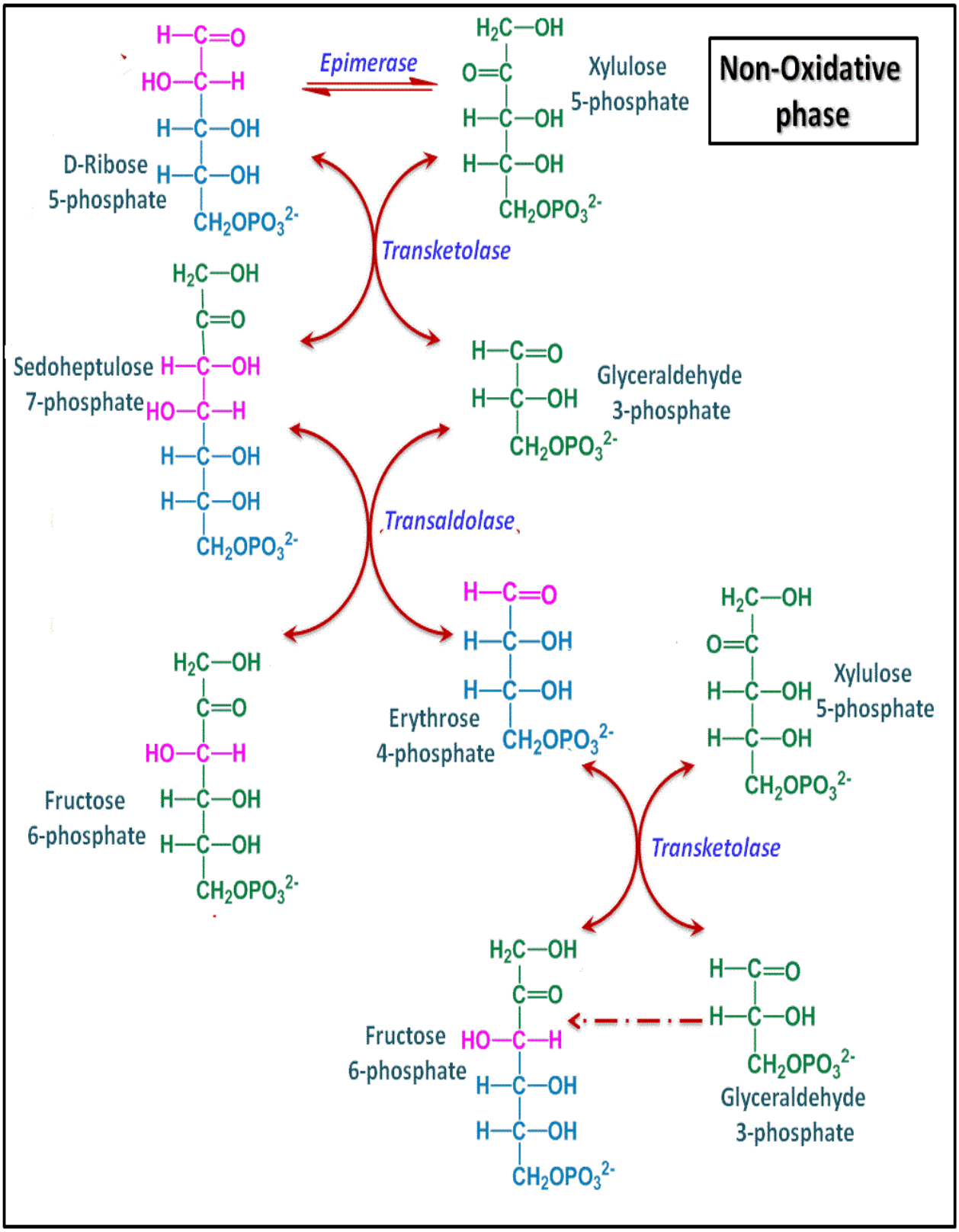
3.HEXOSE MONO PHOSPHATE SHUNT (HMP Shunt)

- Hexose monophosphate pathway or HMP shunt is also called pentose phosphate pathway or phosphogluconate pathway.
- This is an alternative pathway to glycolysis and TCA cycle for the oxidation of glucose.
- However, HMP shunt is more anabolic in nature, since it is concerned with the biosynthesis of NADPH and pentoses.
- The enzymes of HMP shunt are located in the cytosol.
- The tissues such as liver, adipose tissue, adrenal gland, erythrocytes, testes and lactating mammary gland, are highly active in HMP shunt.
- Most of these tissues are involved in the biosynthesis of fatty acids and steroids which are dependent on the supply of NADPH.

The sequences Of reactions of HMP SHUNT is divided into two PHASE

1. OXIDATIVE
2. NON OXIDATIVE


Oxidative phase
Glucose 6-phosphate
NADP+
NADPH + H+
Mg2+
Glucose 6-phosphate dehydrogenase
6-Phospho-glucono-δ-lactone
Lactonase
H2O
Mg2+
6-Phosphogluconate
CO2
NADPH + H+
NADP+
Mg2+
6-phosphogluconate dehydrogenase
D-Ribulose 5-phosphate
Phosphopentose isomerase
D-Ribose 5-phosphate
Enters the Non-oxidative phase


Non-Oxidative phase
Epimerase
D-Ribose 5-phosphate
Xylulose 5-phosphate
Transketolase
Sedoheptulose 7-phosphate
Glyceraldehyde 3-phosphate
Transaldolase
Erythrose 4-phosphate
Xylulose 5-phosphate
Fructose 6-phosphate
Transketolase
Fructose 6-phosphate
Glyceraldehyde 3-phosphate

Significance of HMP shunt:

- HMP shunt is unique in generating two important products—pentoses and NADPH—needed for the biosynthetic reactions and other functions.

Importance of pentoses:

- In the HMP shunt, hexoses are converted into pentoses, the most important being ribose 5-phosphate. This pentose or its derivatives are useful for the synthesis of nucleic acids (RNA and DNA) and many nucleotides such as ATP, NAD^+, FAD and CoA.
- Skeletal muscle is capable of synthesizing pentoses, although only the first few enzymes of HMP shunt are active. It, therefore, appears that the complete pathway of HMP shunt may not be required for the synthesis of pentoses.

Importance of NADPH:

- NADPH is required for the reductive biosynthesis of fatty acids and steroids, hence HMP shunt is more active in the tissues concerned with lipogenesis, e.g. adipose tissue, liver etc.
- NADPH is used in the synthesis of certain amino acids involving the enzyme glutamate dehydrogenase.
- There is a continuous production of H_2O_2 in the living cells which can chemically damage unsaturated lipids, proteins and DNA. This is, however, prevented to a large extent through antioxidant reactions involving NADPH. Glutathione mediated reduction of H_2O_2.Glutathione (reduced, GSH) detoxifies H_2O_2, peroxidase catalyses this reaction. NADPH is responsible for the regeneration of reduced glutathione from the oxidized one.
- Microsomal cytochrome P_{450} system (in liver) brings about the detoxification of drugs and foreign compounds by hydroxylation reactions involving NADPH.
- Phagocytosis is the engulfment of foreign particles, including microorganisms, carried out by white blood cells. The process requires the supply of NADPH.
- Special functions of NADPH in RBC: NADPH produced in erythrocytes has special functions to perform. It maintains the concentration of reduced glutathione which is essentially required to preserve the integrity of RBC membrane. NADPH is also necessary to keep the ferrous iron (Fe^{2+}) of hemoglobin in the reduced state so that accumulation of met hemoglobin (Fe^{3+}) is prevented.

4. GLUCONEOGENESIS

- The synthesis of glucose from non-carbohydrate compounds is known as gluconeogenesis.
- The major substrates/precursors for gluconeogenesis are lactate, pyruvate, glucogenic amino acids, propionate and glycerol.

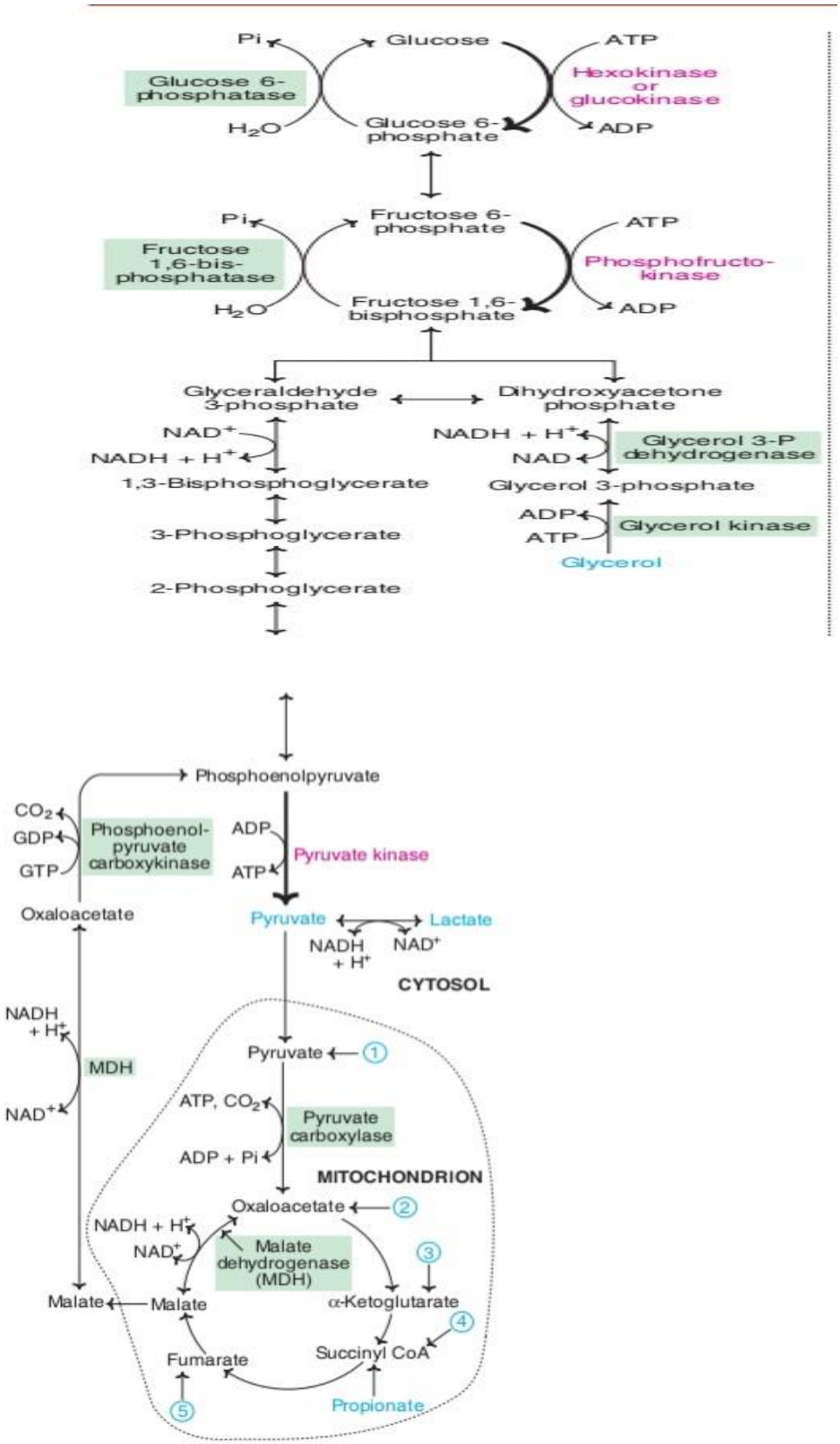
Location of gluconeogenesis:

- Gluconeogenesis occurs mainly in the cytosol, although some precursors are produced in the mitochondria.
- Gluconeogenesis mostly takes place in liver (about 1 kg glucose synthesized everyday) and, to some extent, in kidney matrix (about one-tenth of liver capacity).

Significance:

- The gluconeogenesis cycle is crucial for controlling blood sugar levels during deprivation.
- Glucose occupies a key position in the metabolism and its continuous supply is absolutely essential to the body for a variety of functions

- RBCs, neurons, skeletal muscle, the medulla of the kidney, the testes, and embryonic tissue are just a few of the cells and tissues that need glucose to function.
- In fasting even more than a day, gluconeogenesis must occur to meet the basal requirements of the body for glucose and to maintain the intermediates of citric acid cycle. This is essential for the survival of humans and other animals.
- Glucose is the only source that supplies energy to the skeletal muscle, under anaerobic conditions
- Certain metabolites produced in the tissues accumulate in the blood, e.g. lactate, glycerol, propionate etc. Gluconeogenesis effectively clears them from the blood.


Pi
Glucose
ATP
Glucose 6-phosphatase
Hexokinase or glucokinase
H_2O
Glucose 6-phosphate
ADP
Fructose 6-phosphate
Fructose 1,6-bis-phosphatase
Phosphofructo-kinase
Fructose 1,6-bisphosphate
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
NAD^+
$NADH + H^+$
Glycerol 3-P dehydrogenase
1,3-Bisphosphoglycerate
Glycerol 3-phosphate
3-Phosphoglycerate
Glycerol kinase
Glycerol
2-Phosphoglycerate
Phosphoenolpyruvate
CO_2
GDP
GTP
Phosphoenol-pyruvate carboxykinase
Pyruvate kinase
Oxaloacetate
Pyruvate
Lactate
CYTOSOL
MDH
Pyruvate carboxylase
MITOCHONDRION
Malate dehydrogenase (MDH)
α-Ketoglutarate
Malate
Succinyl CoA
Fumarate
Propionate

Gluconeogenesis from amino acids:

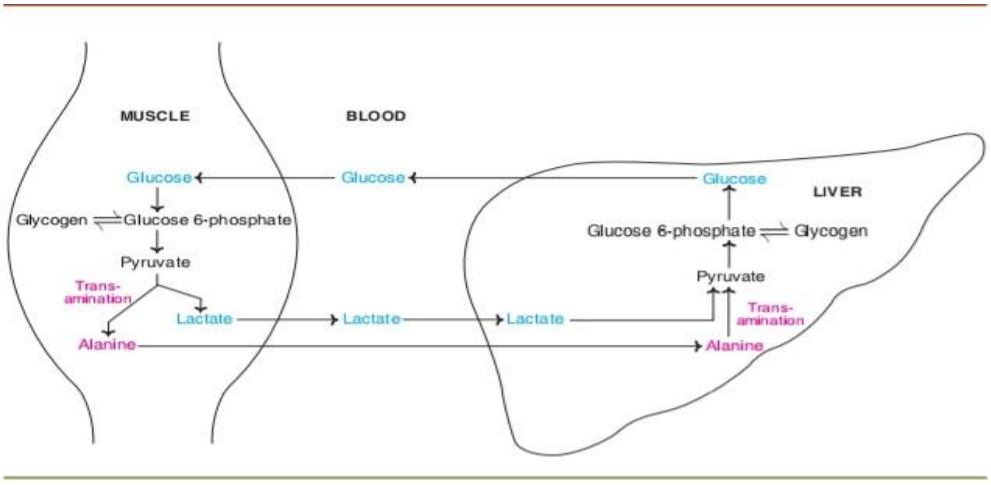
- The carbon skeleton of glucogenic amino acids (all except leucine and lysine) results in the formation of pyruvate or the intermediates of citric acid cycle which, ultimately, result in the synthesis of glucose.

Gluconeogenesis from glycerol:

- Glycerol is liberated mostly in the adipose tissue by the hydrolysis of fats (triacylglycerols).
- The enzyme glycerokinase (found in liver and kidney, absent in adipose tissue) activates glycerol to glycerol 3-phosphate.
- The latter is converted to dihydroxyacetone phosphate by glycerol 3-phosphate dehydrogenase.
- Dihydroxyacetone phosphate is an intermediate in glycolysis which can be conveniently used for glucose production.

Gluconeogenesis from lactate (Cori cycle):

- Lactate produced by active skeletal muscle is a major precursor for gluconeogenesis.
- Under anaerobic conditions, pyruvate is reduced to lactate by lactate dehydrogenase (LDH)



Gluconeogenesis from propionate:

- Oxidation of odd chain fatty acids and the breakdown of some amino acids (methionine, isoleucine) yield a three carbon propionyl CoA.
- Propionyl CoA carboxylase acts on this in presence of ATP and biotin and converts to methyl malonyl CoA which is then converted to succinyl CoA in presence of B_{12} coenzyme.
- Succinyl CoA formed from propionyl CoA enters gluconeogenesis via citric acid cycle

GLYCOGEN METABOLISM

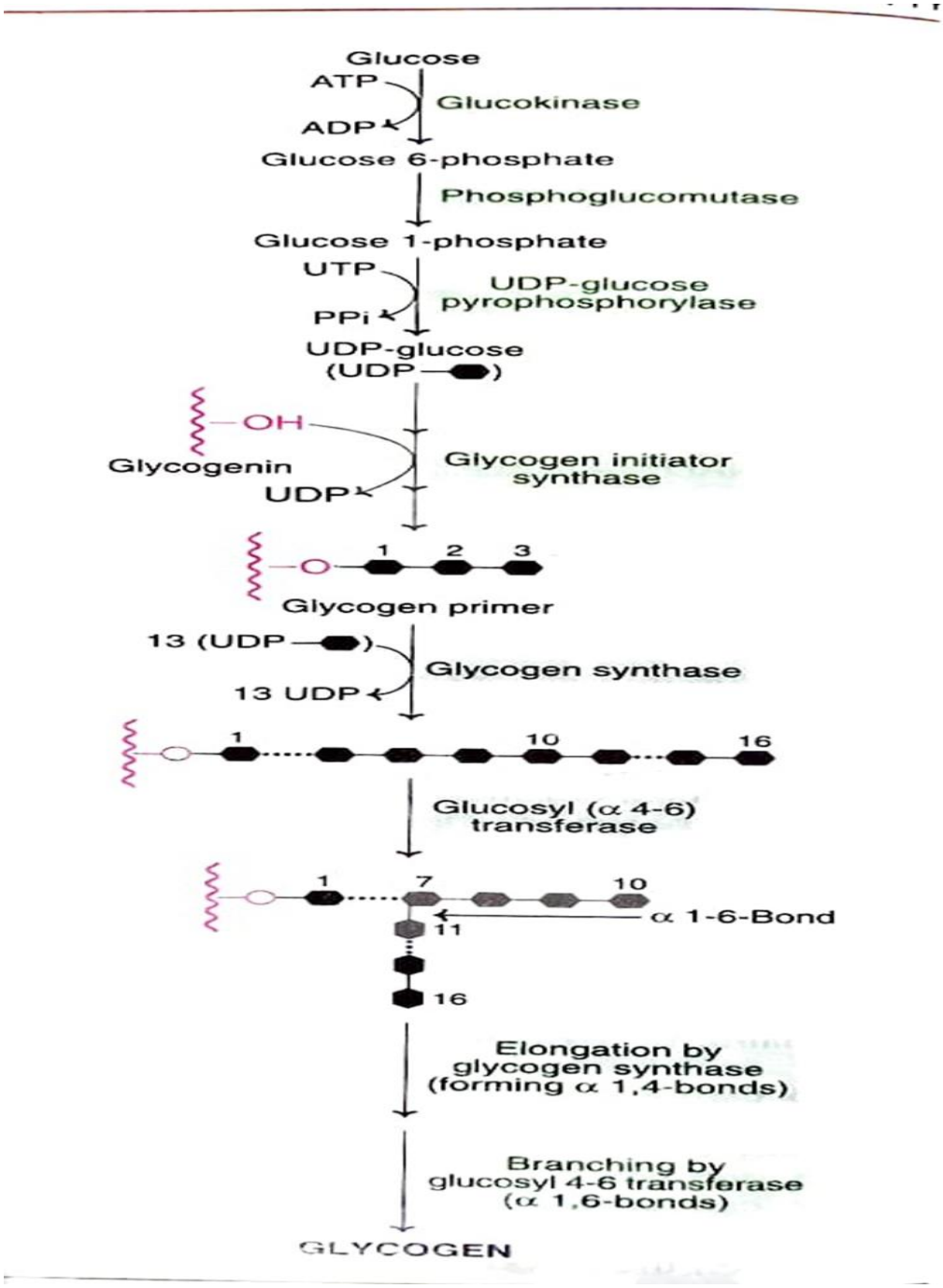
- Glycogen is the storage form of glucose in animals, as is starch in plants.
- It is stored mostly in liver (6-8%) and muscle (1-2%).
- Due to more muscle mass, the quantity of glycogen in muscle (250 g) is about three times higher than that in the liver (75 g).
- Glycogen is stored as granules in the cytosol, where most of the enzymes of glycogen synthesis and breakdown are present.

Functions of glycogen:

- The prime function of liver glycogen is to maintain the blood glucose levels, particularly between meals.
- Liver glycogen stores increase in a well-fed state which is depleted during fasting.
- Muscle glycogen serves as a fuel reserve for the supply of ATP during muscle contraction.
- Glycogenis a homopolysaccharide composed of alpha D glucose.
- The glucose units are held together by alpha 1,4 linkages.
- After 8-10 residues of glucose, abranch is formed with alpha 1,6 glycosidic linkage.
- Glycogen can generate energy in the absence of oxygen

GLYCOGENESIS:

- The synthesis of glycogen from glucose is glycogenesis **.**
- Glycogenesis takes place in the cytosol.
- Requires ATP,UTP besides glucose.
- Glucose is converted to glucose 6 phosphate with enzyme hexokinase (muscles) and glucokinase (liver)
- Glucose 6 phosphate is converted to glucose 1 phosphate with phospo glucomutase enzyme
- Uridine di phosphate glucose(UDPG) is synthesized from glucose 1phosphate and UTP by UDPG pyrophosphorylase
- A small fragment of Pre existing glycogen act as primer
- In absence of glycogen a specific protein glycogenin can accept glucose from UDPG
- The hydroxyl group of the amino acid tyrosine of glycogenin, where initial glucose unit is attached .
- Enzyme glycogen initiator synthase transfers the first molecule of glucose to glycogenine



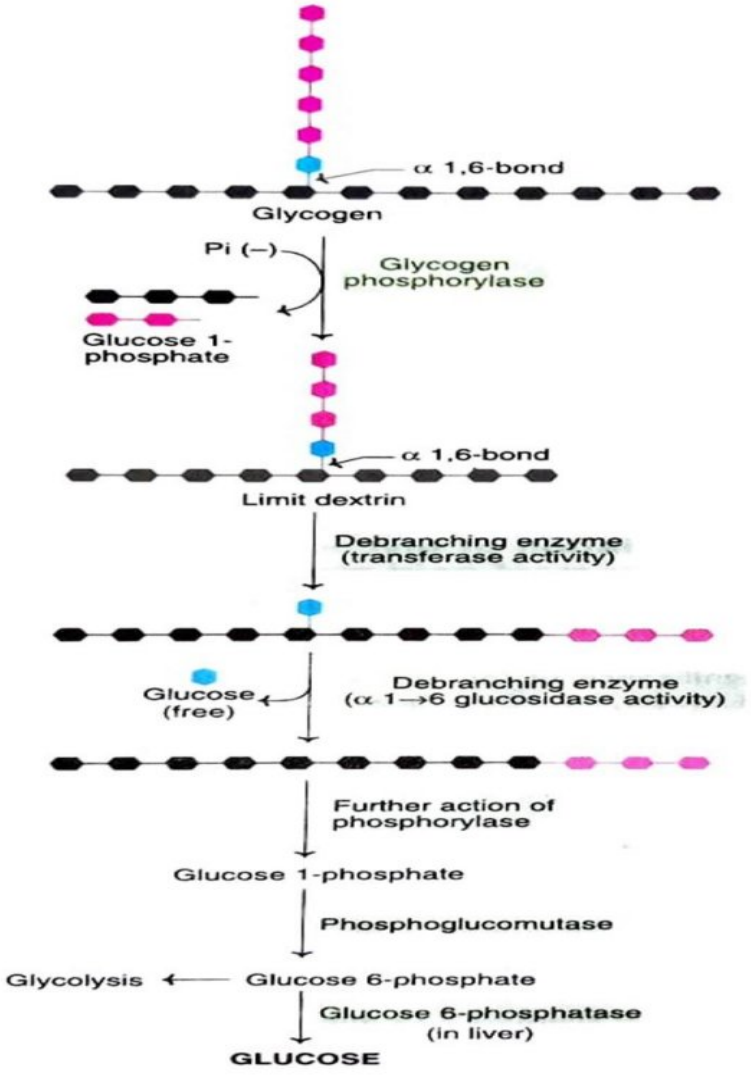
- Glycogenine itself takes a few glucose residues to form a fragment of primer.
- Glycogen synthase is responsible for the formation of Alpha 1,4 glycosidic linkage
- Branches are formed by the enzyme Glucosyl Alpha 4,6- transferase.
- Between 5 to 8 glucose residue, another residue is linked by Alpha 1,6 Bond

- Glycogen is furthur elongated and branched by glycogen synthase and glucosyl 4,6 transferase enzyme

The overall reaction of the glycogen synthesis for the addition of each glucose residue is
(Glucose)$_n$ + Glucose + 2ATP ——» (Glucose)$_{n+1}$ + 2 ADP + Pi
Of the two ATP utilized, one is required for the phosphorylation of glucose while the other is needed for conversion of UDP to UTP

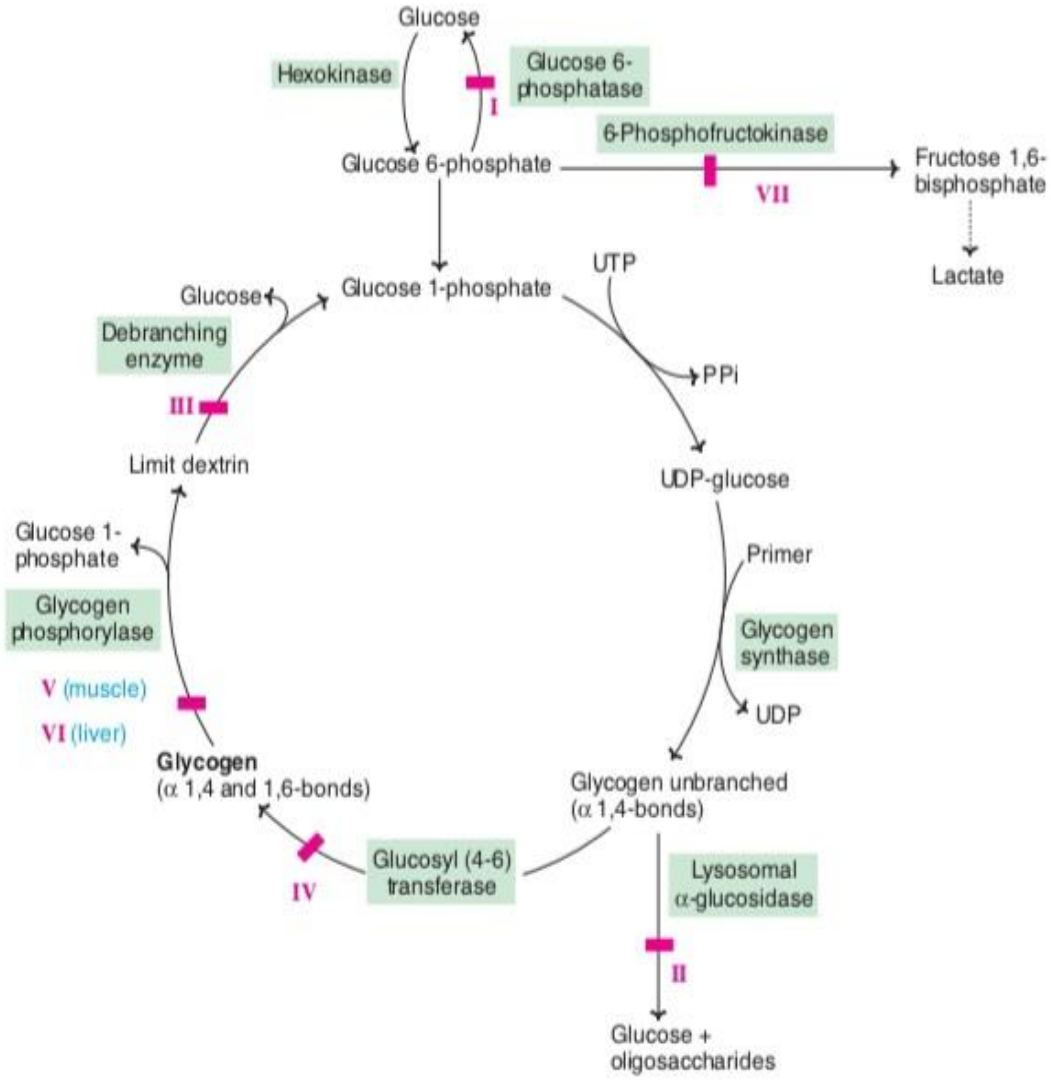
GLYCOGENOLYSIS:

- **The degradation of stored glycogen** in liver and muscle constitutes glycogenolysis.
- The pathways for the synthesis and degradation of glycogen are not reversible.
- An independent set of enzymes present in the cytosol carry out glycogenolysis.
- Glycogen is degraded by breaking a-1, 4- and a-1, 6-glycosidic bonds.



- Glycogen is converted to limit dextrin with enzyme glycogen phosphorylase.
- Limit dextrin with the help of debranching enzymes is converted to glucose 1 phosphate.
- Phosphogluconamutase converts glucose 1 phosphate to glucose 6phosphate.
- Glucose 6 phosphate is converted to glucose with glucose phosphatase enzyme.

GLYCOGEN STORAGE DISEASE



Type	Name	Enzyme defect	Organ(s) involved	Characteristic features
I	von Gierke's disease (type I glycogenosis)	Glucose 6-phosphatase	Liver, kidney and intestine	Glycogen accumulates in hepatocytes and renal cells, enlarged liver and kidney, fasting hypoglycemia, lactic acidemia; hyperlipidemia; ketosis; gouty arthritis.
II	Pompe's disease	Lysosomal α-1,4 glucosidase (acid maltase)	All organs	Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
III	Cori's disease (limit dextrinosis, Forbe's disease)	Amylo α-1,6-glucosidase (debranching enzyme)	Liver, muscle, heart, leucocytes	Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar but milder compared to von Gierke's disease.
IV	Anderson's disease (amylopectinosis)	Glucosyl 4-6 transferase (branching enzyme)	Most tissues	A rare disease, glycogen with only few branches accumulate; cirrhosis of liver, impairment in liver function.
V	McArdle's disease (type V glycogenosis)	Muscle glycogen phosphorylase	Skeletal muscle	Muscle glycogen stores very high, not available during exercise; subjects cannot perform strenous exercise; suffer from muscle cramps; blood lactate and pyruvate do not increase after exercise; muscles may get damaged due to inadequate energy supply.
VI	Her's disease	Liver glycogen phosphorylase	Liver	Liver enlarged; liver glycogen cannot form glucose; mild hypoglycemia and ketosis seen.
VII	Tarui's disease	Phosphofructokinase	Skeletal muscle, erythrocytes	Muscle cramps due to exercise; blood lactate not elevated; hemolysis occurs.

Rare glycogen disorders VIII, IX, X and XI have been identified. They are due to defects in the enzymes concerned with activating and deactivating liver phosphorylase.