COURSE CODE: **BCH 301**

COURSE TITLE: **Metabolism of Carbohydrates**

NUMBER OF UNITS: 2 Units

COURSE DURATION: **Two hours per week**

COURSE DETAILS:

Course Coordinator: Prof. (Mrs) E. A. Balogun
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Office Location: Room 17, COLNAS Phase 2
Other Lecturers:

COURSE CONTENT:

- Digestion and degradation of carbohydrates- sugars, storage polysaccharides and cell walls.
- Reactions of sugars-Glycolysis, the tricarboxylic acid clcle, the pentose phosphate pathway, the Cori cycle, the Calvin pathway, Gluconeogenesis and the disorders of carbohydrate metabolism.

COURSE REQUIREMENTS:

READING LIST:

LECTURE NOTES

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 → L Lactate

$C_6H_{12}O_6 \longrightarrow 2\ HO-COO-H\ (CH_3) + 2H^+$

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) → 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 triose PO_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' group from ATP to some acceptor molecule.

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

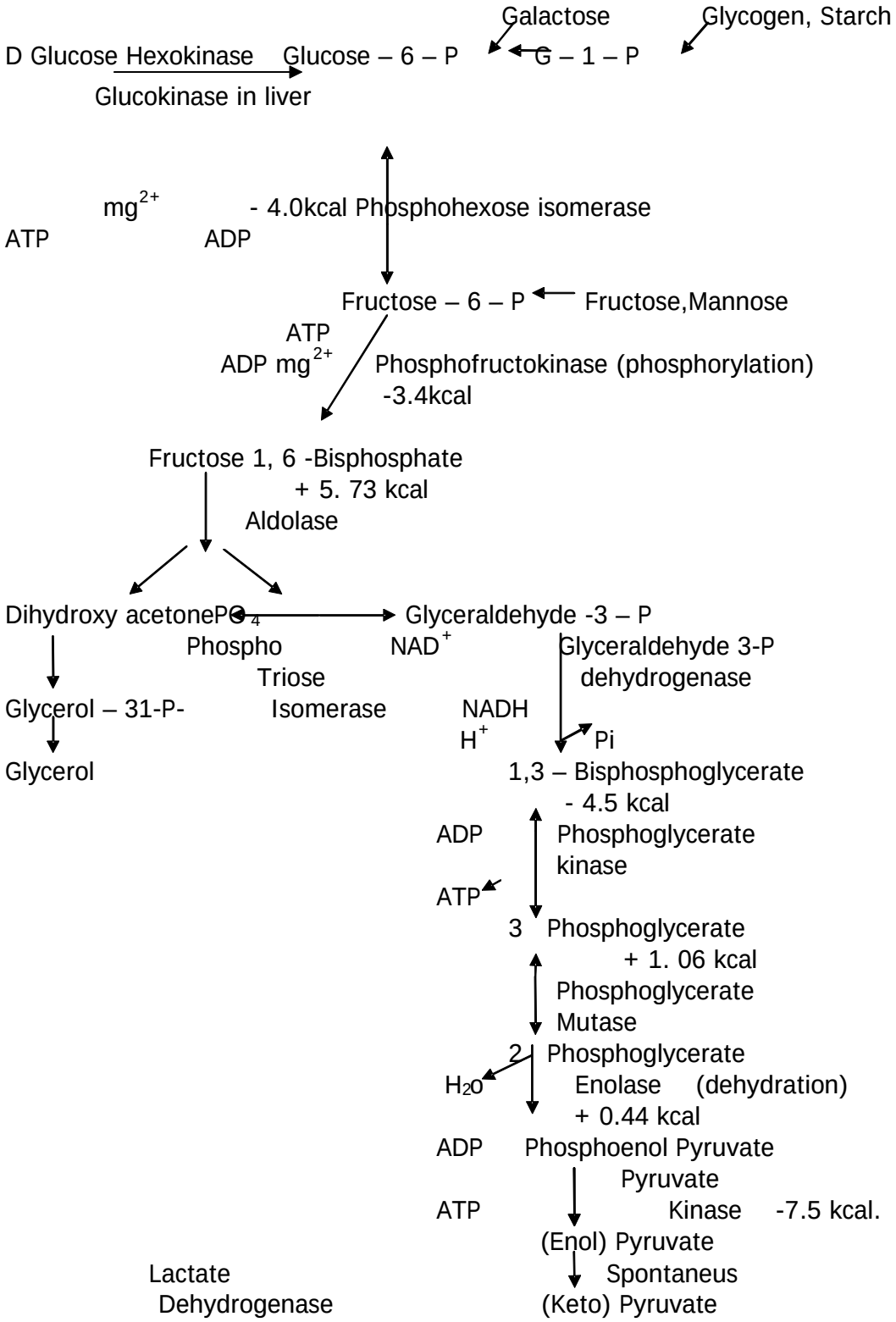
   These 2 require mg^{2+} ions.

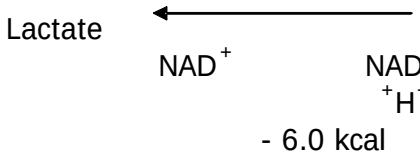
3. Isomerases: Catalyze the isomerization of aldose sugars to ketose sugars.
4. Dehydrogenases: Perform oxidation

   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.

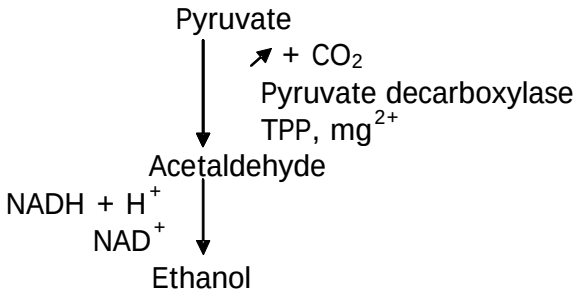
Sequence of reactions:





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

$$CH_3C\ CO\ H_2 \quad + \quad 2½\ O_2 \longrightarrow 3\ CO_2 \ + \ 2H_2O$$

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).

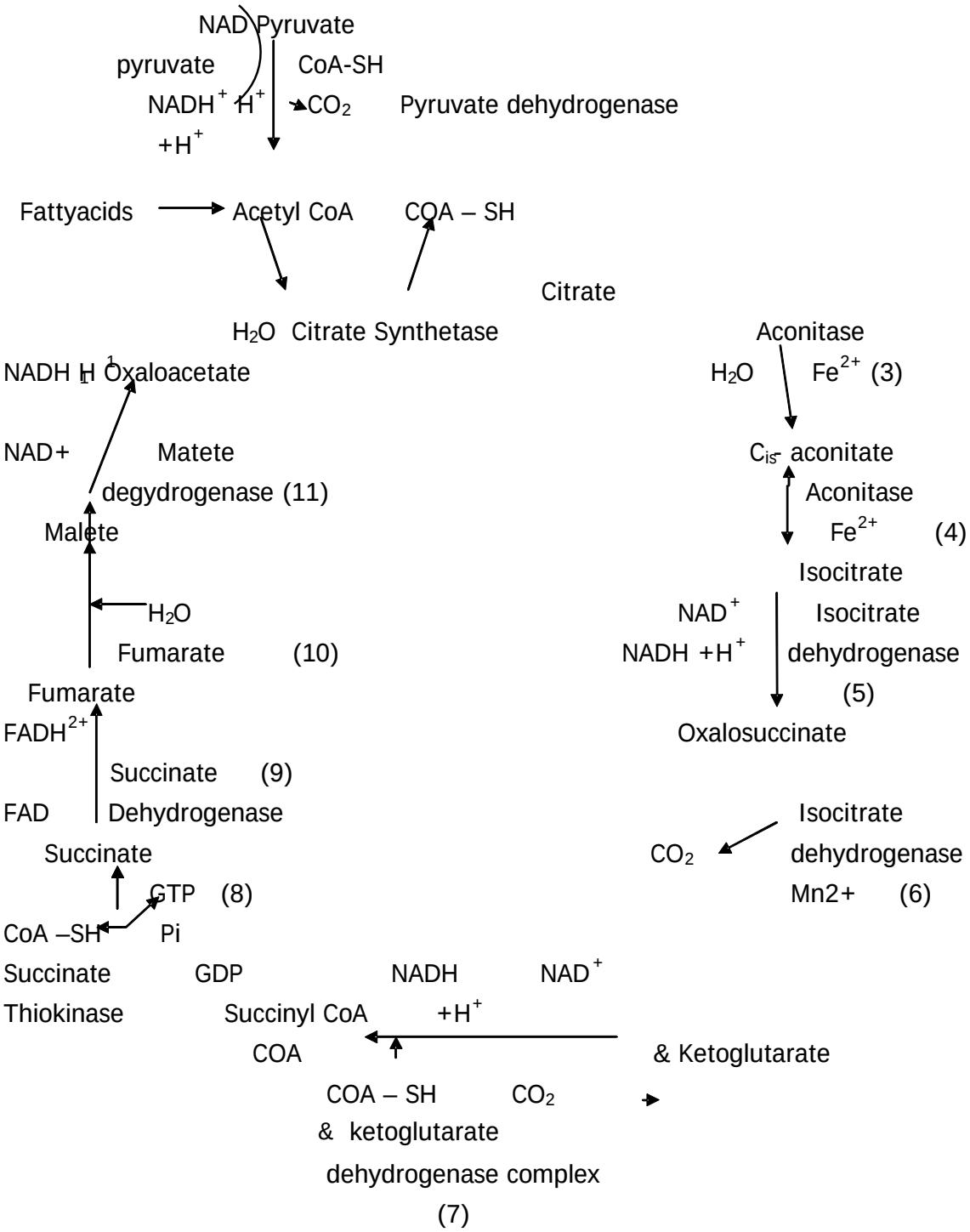
11. The last reaction that completes the cycle involves the oxidation of L malate to oxaloacetic acid. Oxidizing agent = NAD^+

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

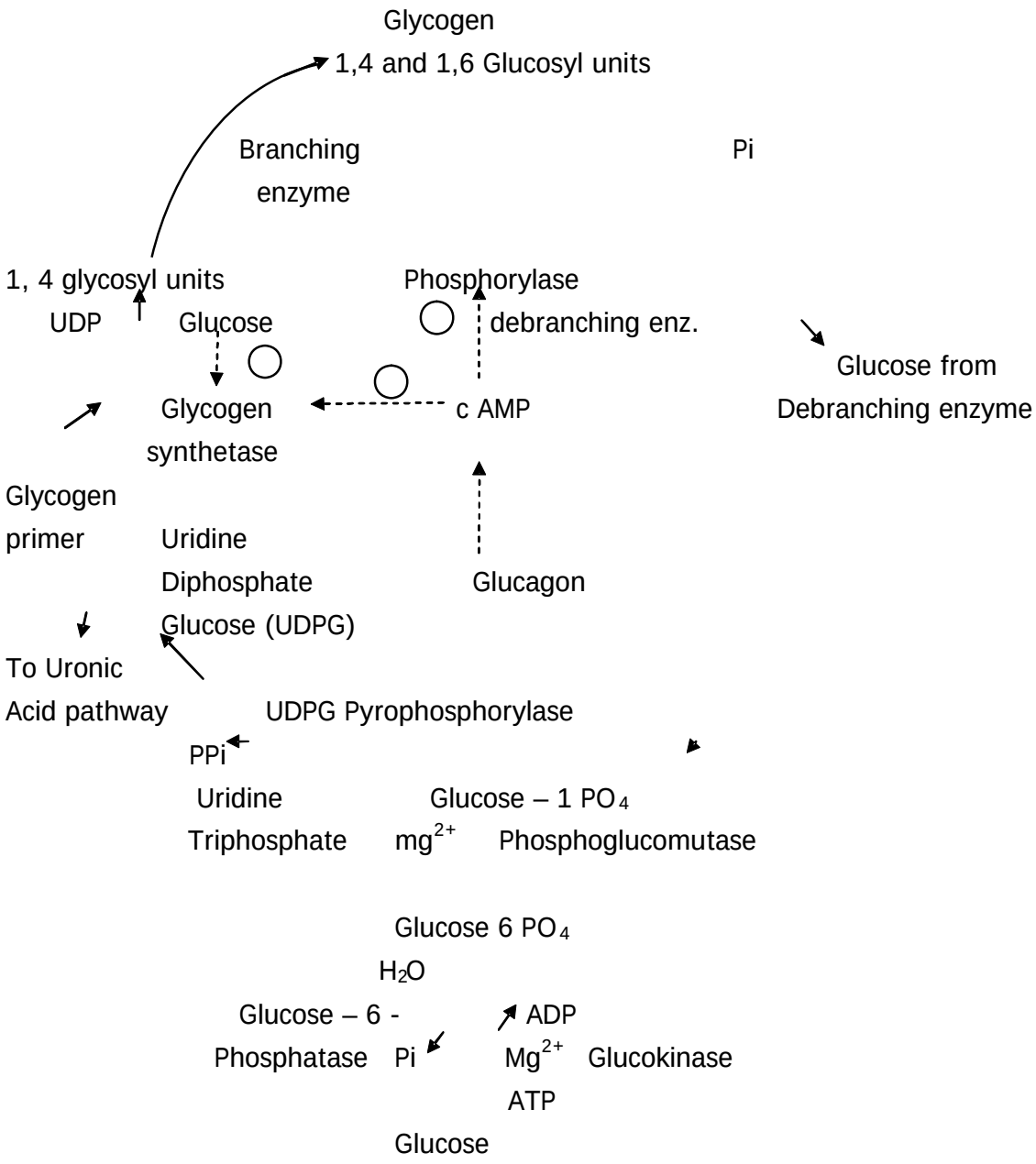
		No of ATP
Isocitrate dehydrogenase	NAD	3
& - ketoglutaratee dehydrogenase	NADH	3
Succinate Thiokinase		1
Succinate	$FAHD_2$	2
Malate dehydrogenase	NADH	3
		12

Sequence of Reactions:-

Glucose
+
Some aminoacids → Pyruvate


NAD Pyruvate
pyruvate
CoA-SH
NADH + H+
CO2
Pyruvate dehydrogenase
+H+
Fattyacids
Acetyl CoA
COA – SH
Citrate
H2O Citrate Synthetase
Aconitase
NADH H 1
Oxaloacetate
H2O
Fe2+ (3)
NAD+
Matete
degydrogenase (11)
Cis- aconitate
Aconitase
Malete
Fe2+ (4)
Isocitrate
H2O
NAD+
Isocitrate
Fumarate (10)
NADH +H+
dehydrogenase
(5)
Fumarate
Oxalosuccinate
FADH2+
Succinate (9)
FAD
Dehydrogenase
Isocitrate
Succinate
CO2
dehydrogenase
Mn2+ (6)
GTP (8)
CoA –SH
Pi
Succinate
GDP
NADH
NAD+
Thiokinase
Succinyl CoA
+H+
COA
& Ketoglutarate
COA – SH
CO2
& ketoglutarate
dehydrogenase complex
(7)

Pathway of glycogenesis and glycogenolysis in the liver



(+) Stimulation

(-) Inhibition

Glycogen Storage Disorders

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 $\longrightarrow$ 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 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 of 4 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 $\longrightarrow$ 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 PHOSPHATEPATHWAY

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

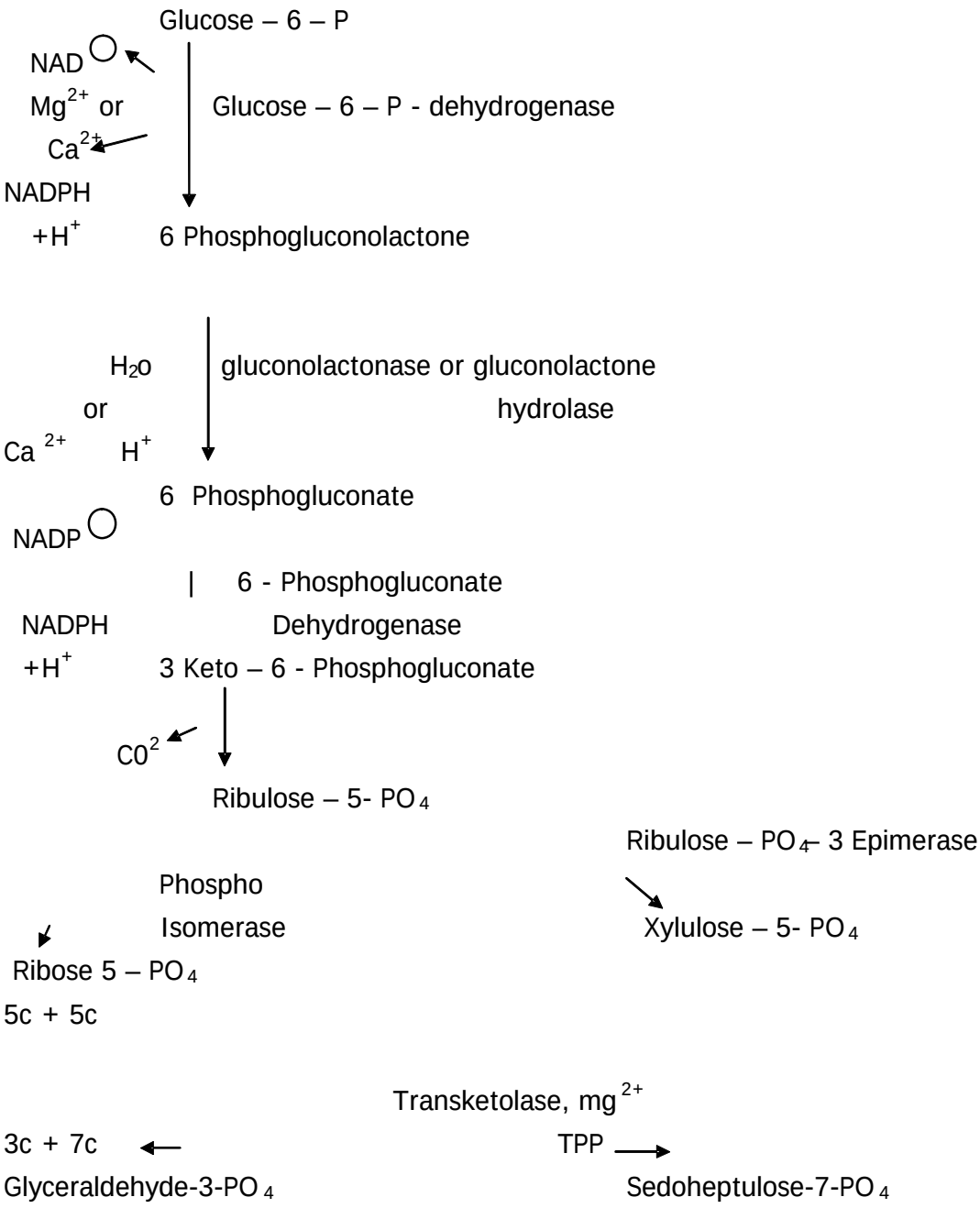
2: The glucose 5 – PO$_4$ is converted back to triose sugar then into glucose 6 – PO_4.

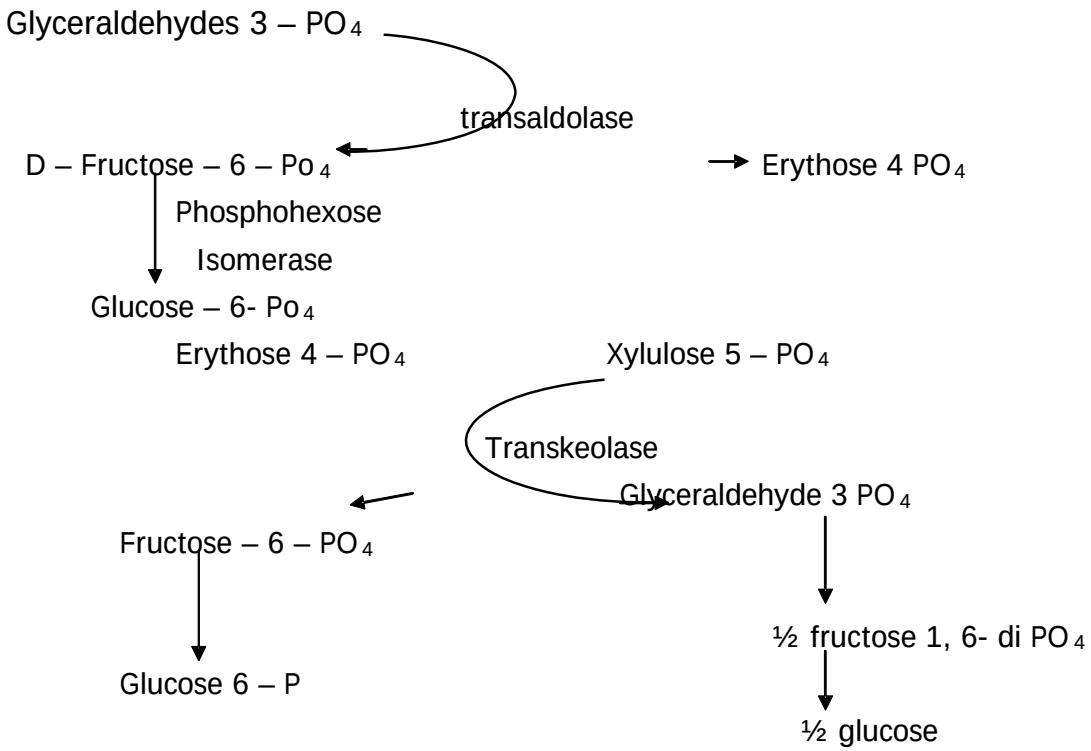
3 Glucose – 6 – Po$_4$ + 6 $NADP^+$ ⟶ $3CO_2$ + 2 Glucose – 6 – Po_4 + Glyceraldeyde 3 – PO_4 + 6 NADPH + 6 H^+

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:-





GLUCONEOGENESIS

This is the way in which the body meets its needs of glucose when carbohydrate is not available in sufficient amounts from the diet. The body then converts non glucose substances into glucose.

Site:- Major site is the liver, kidneys have limited capacity.

Rate:1). Is increased on high protein diets.

(2) During exercise when large amounts of lactic and pyruvic acids escape from the working muscles and there is no need to replenish the muscle glycogen supply therefore the liver acts to return to them sources of energy lost by the muscles. (3) During starvation, from amino acids of tissue protein (4) In diabetic states.

Importance:

(1) Glucose is required in adipose tissue as a source of glyceride - glycerol
(2) It maintains the level of intermediates of the citric acid cycle in many tissues.
(3) It is the only fuel which supplies E to skeletal muscle under anaerobic conditions.
(4) It is the precursor of milk sugar (lactose in mammary gland).
(5) Gluconeogenic mechanism clear the products of the metablolism of other tissues from the blood eg. lactate and glycerol.

Metabolic Pathway:- It occurs by reversal of each step of the glycolytic pathway, but the 3 irreversible reactions must be bypassed in this case.

1. The enzyme pyruvate carboxylase used is produced in the mitochondria therefore the pyruvic acid must enter the mitochondria for the reaction to occur.

$$\text{Pyruvic acid} + CO_2 + ATP \xrightarrow[Mg^{2+}]{\text{Acetyl - CoA}} \text{Oxaloacetic acid} + ADP + H_3PO_4$$

2. Phosphoenol pyruvate carboxykinase converts oxaloacetate to phosphoenol p pyruvate.

$$\begin{array}{l} Co_2H \\ C=O + GTP \\ CH_2 \\ Co_2H \\ \text{Oxaloacetic acid} \end{array} \xrightarrow{Mg^{2+}} \begin{array}{l} Co_2H \\ C-O\,PO_3H + CO_2 + GDP \\ CH_2 \\ \text{PEP} \end{array}$$

The carboxykinase is present only in the cytoplasm, but the oxaloacetate is not able to pass through the mitochordrial membrance therefore it is first reduced to malic acid.

$$\text{Oxaloacetate} + NADH + H^+ \xrightarrow[\text{malate dehydrogenase}]{\text{mitrochondrial}} \text{Malate} + NAD^+$$

$$\text{Malate} \xrightarrow[\text{Membrane}]{\text{Mitochondrial inner}} \text{Malate (cytoplasmic)}$$

$$\text{Malate} + NAD^+ \xrightarrow[\text{malate dehydrogenase}]{\text{cytoplasmic}} \text{Oxaloacetate} + NADH + H^+$$

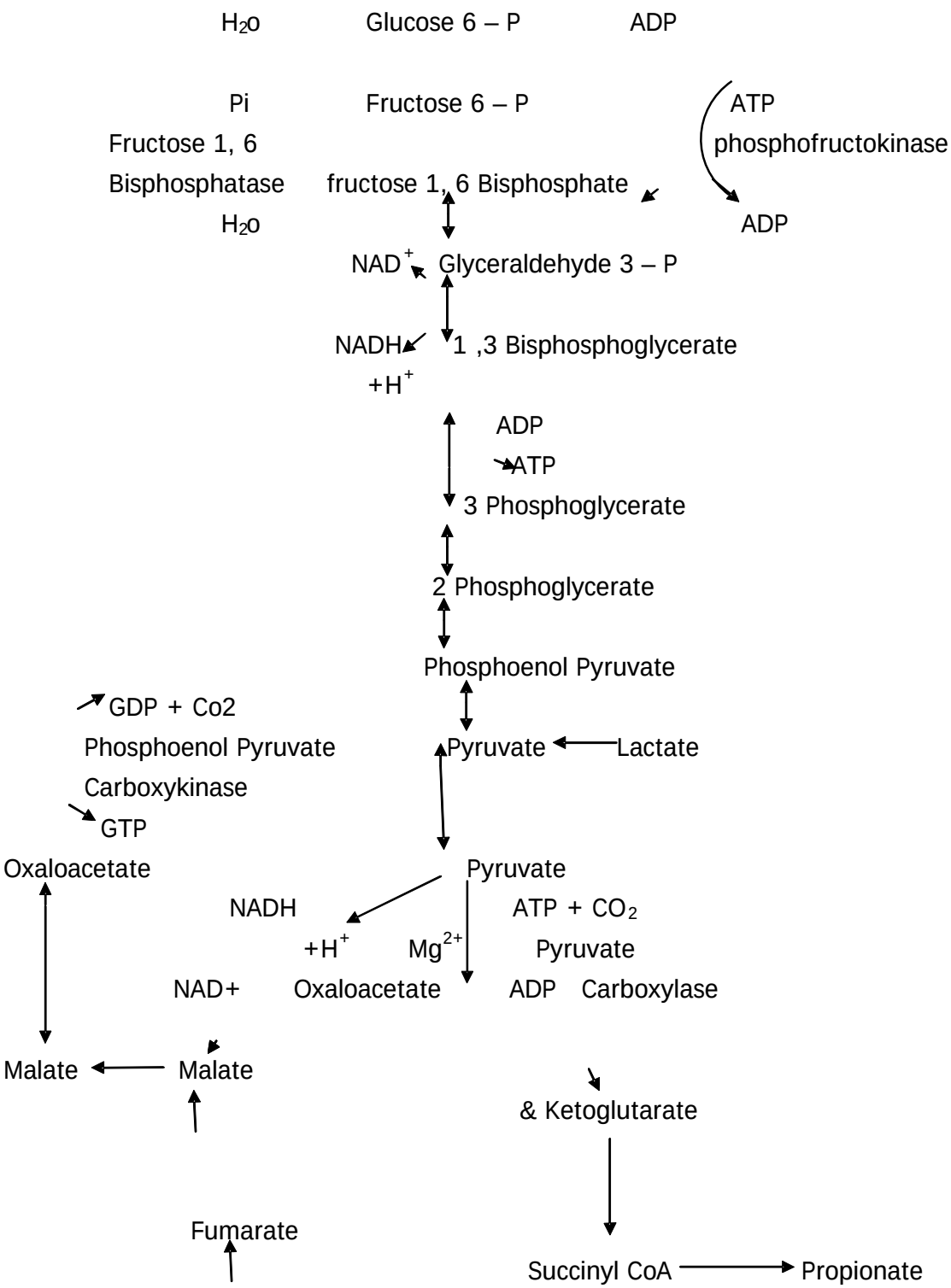
3. Action of phosphatase which (a) catalyzes the hydrolysis of fructose – 1,6 bisphosphate to form fructose – 6 – PO_4 by the enzyme fructose 1,6 bisphosphatase

(b) Production of glucose from glucose 6 – PO_4 also requires another enzyme – Glucose 6 – phosphatase.

Overall reaction:

$$2\,\text{Lactate} + 4ATP + 2\,GTP + 6H_2O \longrightarrow \text{Glucose} + 4\,ADP + 2GDP + 6\,H_3PO_4$$

$$\text{Glucose} \xrightarrow[\text{Hexokinase, Glucokinase}]{ATP} \text{Glucose – 6 – phosphate} \xrightarrow{Pi}$$


H2o
Glucose 6 – P
ADP
Pi
Fructose 6 – P
ATP
Fructose 1, 6
Bisphosphatase
fructose 1, 6 Bisphosphate
phosphofructokinase
H2o
ADP
NAD+
Glyceraldehyde 3 – P
NADH
+H+
1 ,3 Bisphosphoglycerate
ADP
ATP
3 Phosphoglycerate
2 Phosphoglycerate
Phosphoenol Pyruvate
GDP + Co2
Phosphoenol Pyruvate
Carboxykinase
GTP
Pyruvate
Lactate
Oxaloacetate
Pyruvate
NADH
+H+
Mg2+
ATP + CO2
Pyruvate
NAD+
Oxaloacetate
ADP
Carboxylase
Malate
Malate
& Ketoglutarate
Fumarate
Succinyl CoA
Propionate

Diseases of Carbohydrate Metabolism

1. Essential Pentosuria: Here considerable quantities of L – Xylulose appear in the urine. This is due to the absence of the enzyme necessary to accomplish reduction of L – xylulose to xylitol and hence inability to convert the L-isomer to the D form.
2. Hereditary fructose intolerance due to the absence of aldolase B
3. Fructose induced hypoglycemia:- Despite the presence of a high glycogen reserve. May be due to accumulation of fructose l-PO and F-1,6-BIP which inhibit the activity of liver phosphorylase.
4. Galactosemia:- Inherited metabolic disease in which galactose accumulates in the blood and spills over into the urine when this sugar or lactose is ingested. Also there is marked accumulation of Gal-I-P in the red blood cells. An inherited lack of gal IP uridyl transferase in the liver and red blood cells.

Diseases of glycogen storage

Type 1 Glycogenosis (von Gierke's disease):

Both the liver cells and the cells of the renal convoluted tubules are loaded with glycogen which are metabolically unavailable. Ketosis and hyperlipemia also occurs. The activity of Gluc 6 – phosphatase enzyme is abscent or very low in the liver, kidney and intestinal tissue.

Type II (Pompe's disease) due to deficiency of lysosomal & - 1,4 – glucosidase (acid maltase whose function is to degrade glycogen which otherwise accumulates in the lysosomes.

Type III (limit dextrinosis) Due to the absence of debranching enzyme which causes the accumulation of a polysaccharide of the limit dextrin type.

Type IV (Amylopectinosis) – Due to the absence of branching enzyme with the result that a polysaccharide having few branch points accumulates.

Type V glycogenosis (myophosphorylase deficiency glycogenosis, Mc Ardies syndrome) Patients with this disease exhibit a diminished tolerance to exercise although the skeletal muscles have an abnormally high content of glucogen. Little or no lactate is detectable in their blood after exercise.

Type VI glycogenosis: Due to phosphoglucomutase deficiency in the liver.

Type VII glycogenosis: Due to deficiency of phosphofructokinase in the muscles.

Diseases associated with HMP

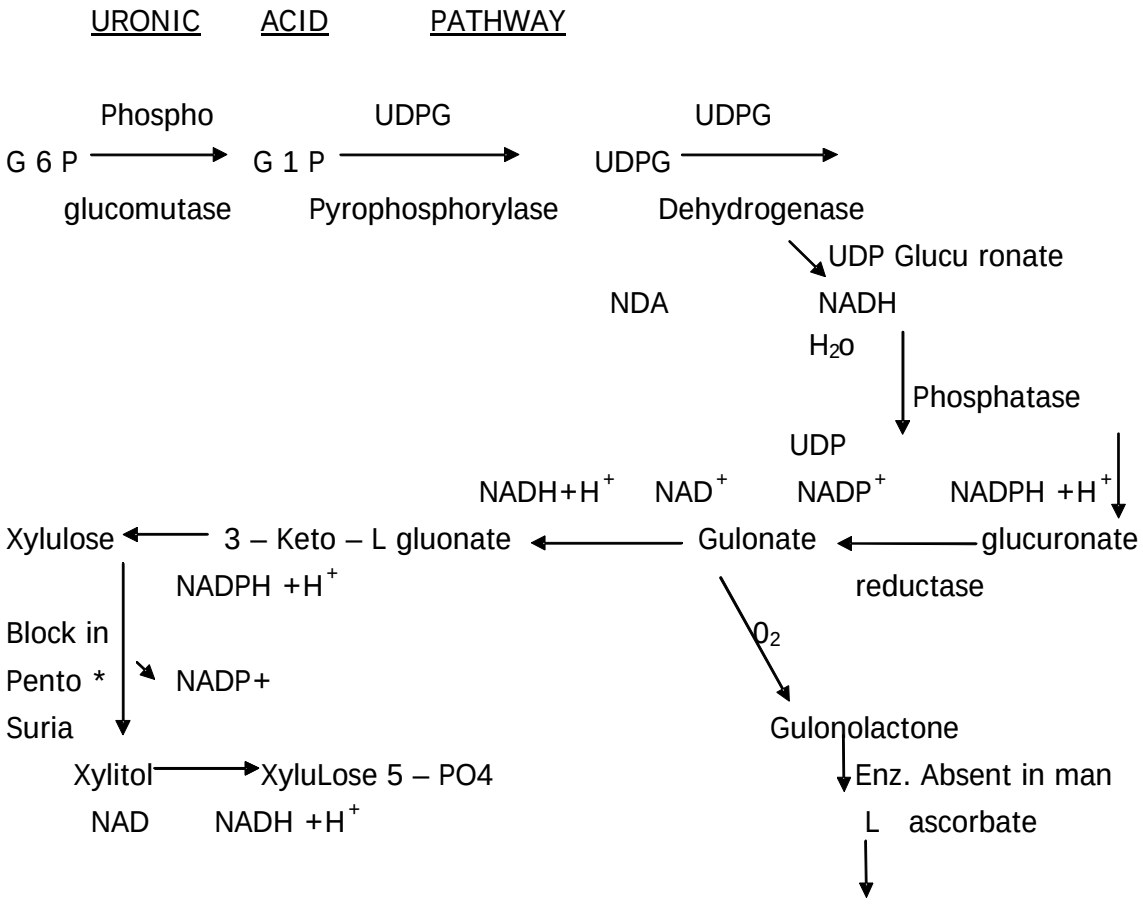
1. Formation of NADPH is very important in the HMP pathway in red blood cells.

There is high correlation between G 6 phosphate dehydrogenase and the fragility of red cells (susceptibility to hemolyses). Especially when the cells are subjected to the toxic effects of certain drugs e. g. primaquine etc. the majority of patients whose red cells are hemolysed by these toxic agents have been found to possess a hereditary deficiency in the oxidative enzyme of the HMP pathway of the red blood cell.

2. Developments of cataracts sometimes occurs as a complication of galactosemia an inherited inability disease associated with the mobility to convert galactose to glucose.

Galactose inhibits the activity of G - 6 - P Dehydrogenase of the lens when fed to experimental animals and in in vitro when galactose. 1-P0 $_4$ is added to a homogenate of lens tissue.

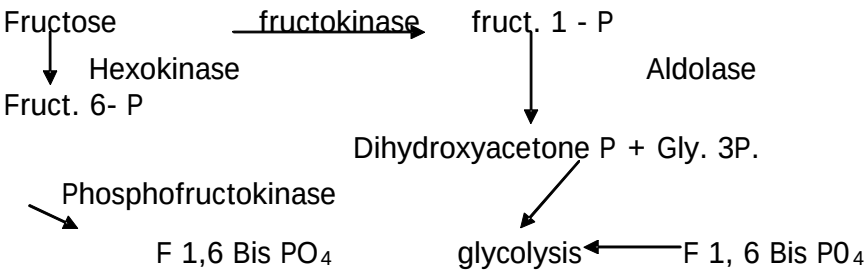
F-1,6- bisphosphatase deficiency causes lactic acidosis and hypoglycemia because lactate and glucogenic amino acid are prevented from being converted to glucose.



Dehydroascobate

Importance

- Galacturonate is an important constituent of pectins
- UDPG – is the active form of glucuronate for reactions involving incorporation of glucuronic acid into chondroitin sulfate.
- Xylulose – used in HMP pathway
- The enzyme which convert L gulonolactone to 2 keto – L- gulonate before its conversion to L ascorbate is absent in man.
  - Uronic acid pathway is for the conversion of glucose to glucuronic acid, ascorbic acid and pentoses. It is also an alternative oxidative pathway for glucose.
  - Sequence of Reaction: Glucose is converted to G-6-P which is converted to G 1 P. this then react with uridine tri PO_4 to form UDPG which is now oxidized at C_6 by a 2 step process to UDP – glucuronate by inversion around C . 4
  - UDPglucuronate is useful in the conversion of glucuronic acid into chondroitin sulphate or steroid hormones etc. Gulonate is the precursor of ascorbate in animals capable of synthesising the vitamin except man, and other primates eg guinea pigs rather gulonate is oxidize to 3 – keto – L – gulonate. . Xylulose is a constituent of the HMP but here L –xylulose is formed. To make it useful for HMP the L isomer must be converted to D xylulose.
  - This is acoomplished by an NADPH dependent reduction to xylitol which is then oxidized in an NAD – dependent reaction to D- xylulose.
  - Various drugs increase the rate of this reaction e.g administration
  - of barbital or of chlorobutanol to rat.



Metabolism of fructose

This is found only in seminal vesicles and the placenta of ungulates and whales.

Fructose is phosphorylated by hexokinase to form Fruct. 6-PO_4 or fructokinase in the liver converts fructose to fructose 1-PO . Thi4s is split into D-Glyceraldehyde and dihydroxyacetone Po by aldolase B. Absence of enzymes leads to hereditary fructose intolerance

Glyceraldehyde (1) Glycerol glycero glycerol 3 Po_4 Kinase

(2) → Glyceraldehyde Aldehyde DH Glycerate

(3) Triokinase in liver catalyses the phosphorylation of D glyceradehyde to gly 3 $P0_4$.

Glyceralde and dihydroxyacetone PO_4 → glycolysis OR may combine in the presence of aldolase to form glucose.

Galactose Metabolism:-

Galactose —Galactokinase→ Galactose 1 – P

Gal. 1P —Uridyl transferee→ Gal. 1-P + UDP Glucose → UDP – galactose + Glu. 1-P

UDP – galactose + glucose → Lactose Synthesis → Lactose

UDP glucose

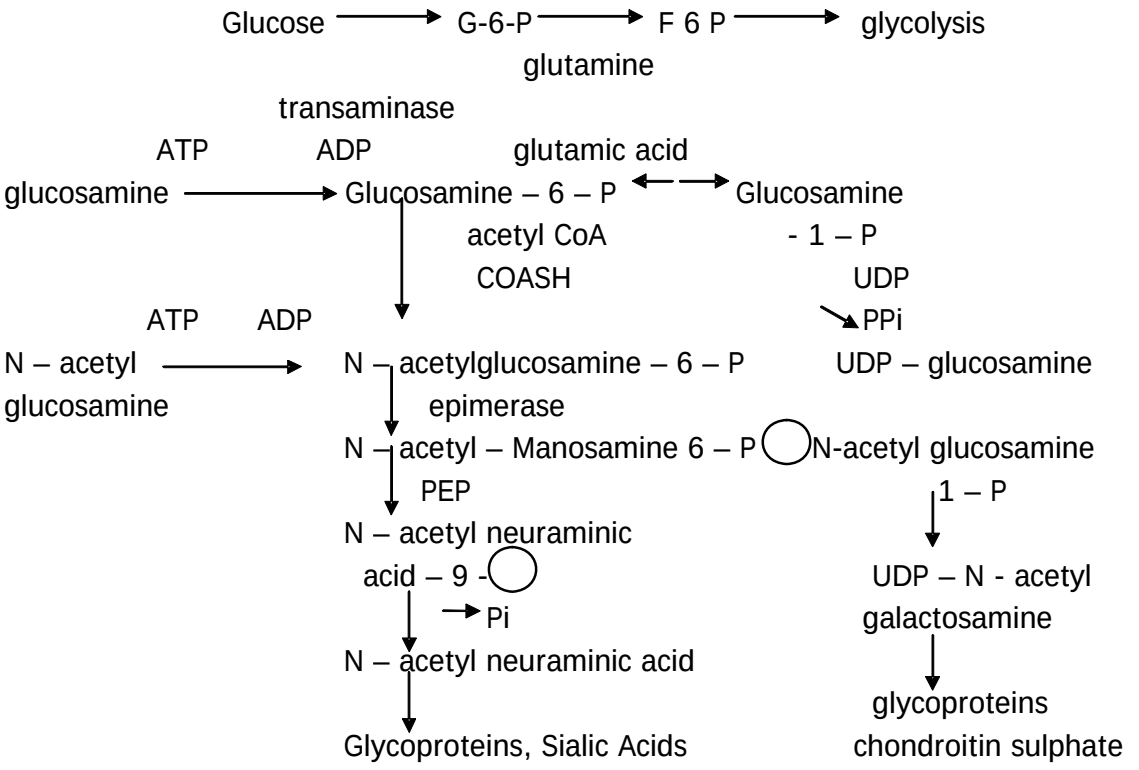
Glycogen

Glycolysis

Metabolism of Amino Sugars (eg. Glucosamine –6 –P, N acetyl glucosamine).

They are important components in many complex polysaccharides.

Glycogen



Digestion and Absorption of Carbohydrate

The principal dietary carbohydrate are polysaccharide, disaccharides, and monosaccharides. Starches and their derivatives are the only polysaccharides that are digested in man. The disacchandes lactose and sucrose are also ingested along with the monosaccharides, fructose and glucose. Digestion is the disintegration of the naturally occurring foodstuffs into assimilable forms.

First reaction takes place in the mouth. Saliva contain salivary amylase (ptyalin) which hydrolysis starch and glycogen to maltose. Because of the short time it acts on food, digestion is not much. Mastication subdivides the food increasing its solubility and surface area for enzyme attack. In the acid environment of the stomach digestion of carbohydrate stops.

The stomach contents (chyme) is introduced into the duodenum through the pyloric valve. The pancreatic and bile duct. open into the duodenum, their alkaline content neutralizes the pH of the chyme as a result of the influence of the hormones secretin which stimulates flow of pancreatic juice and cholecystokinin which stimulate the production of enzymes.

For carbohydrate it contains pancreatic & amylase (similar to salivary amylase) hydrolyzing starch and glycogen to maltose, maltrotriose and a mixture of branched (1:6) oligosaccharides (&limit dextrins) and some glucose.

Intestinal secretion also contain digestive enzymes specific for disaccharide and oligosaccharides i.e & glucosidase maltase which removes single glucose residues from & (1→4) linked oligosaccharides and disaccarides starting from the non reducing ends isomaltase (& - dextrinase) which hydrolyses 1 → 6 bonds in & limit dextrins B – galactosidase (lactase) for removing galactose from lactose, sucrase for hydrolyzing sucrose and trehalase for hydrolyzing trehalose.

sucrase on sucrose → fructose + glucose
Maltase on Maltose → glucose
Lactase on lactose → glucose+ galactose
Trelalase on Trelalose → glucose

Absorption:

90% of ingested foodstuffs is absorbed in the course of the passage through the small intestine. The product of carbohydrate digestion are absorbed from the jejunum into the blood of the portal venous system in the form of monosaccharides (the hexoses) glucose, fructose, mannose and galactose although the pentose sugars if present in the food ingested will also be absorbed. Glucose and galactose are actively transported. Fructose is absorbed more slowly than these two it is by simple diffusion. A carrier transports glucose across membrane into the cytosol, it binds both Na^+ and glucose at different sites of the molecule. The energy required is obtained from the hydrolysis of ATP linked to Na /P$^+$ pump. The active transport of glucose is inhibited by ouabain (also Na $^+$pump) and phlorhizin a plant glycoside.