

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)

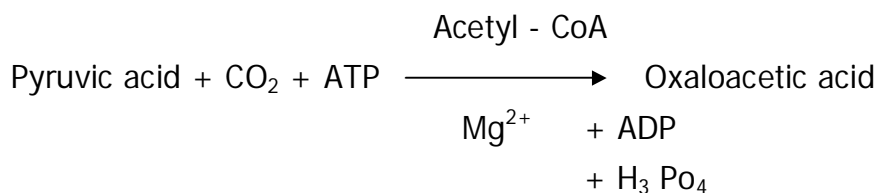
During starvation, from amino acids of tissue protein (4) In diabetic states.

Importance:

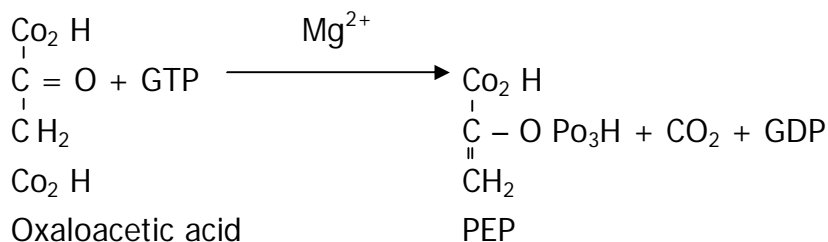
- (1) Glucose is required in adipose tissue as a source of glyceride - glycerol
- (2) It maintains the level of intermediates of the citric acid cycle in many tissues.
- (3) It is the only fuel which supplies E to skeletal muscle under anaerobic conditions.
- (4) It is the precursor of milk sugar (lactose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

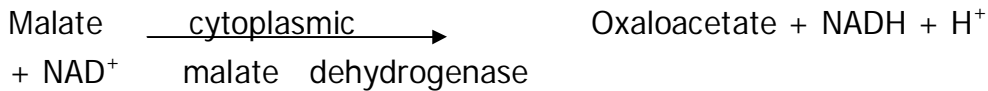
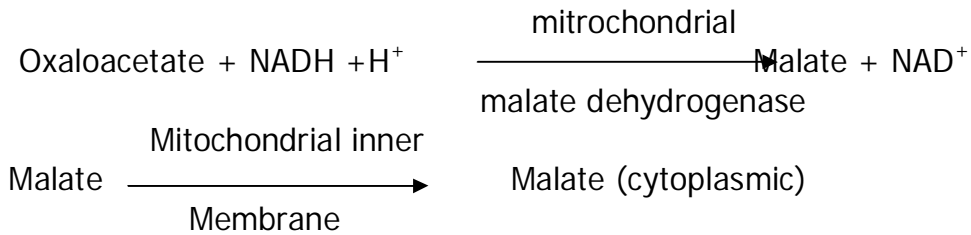
1. The enzyme pyruvate carboxylase used is produced in the mitochondria therefore the pyruvic acid must enter the mitochondria for the reaction to occur.



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



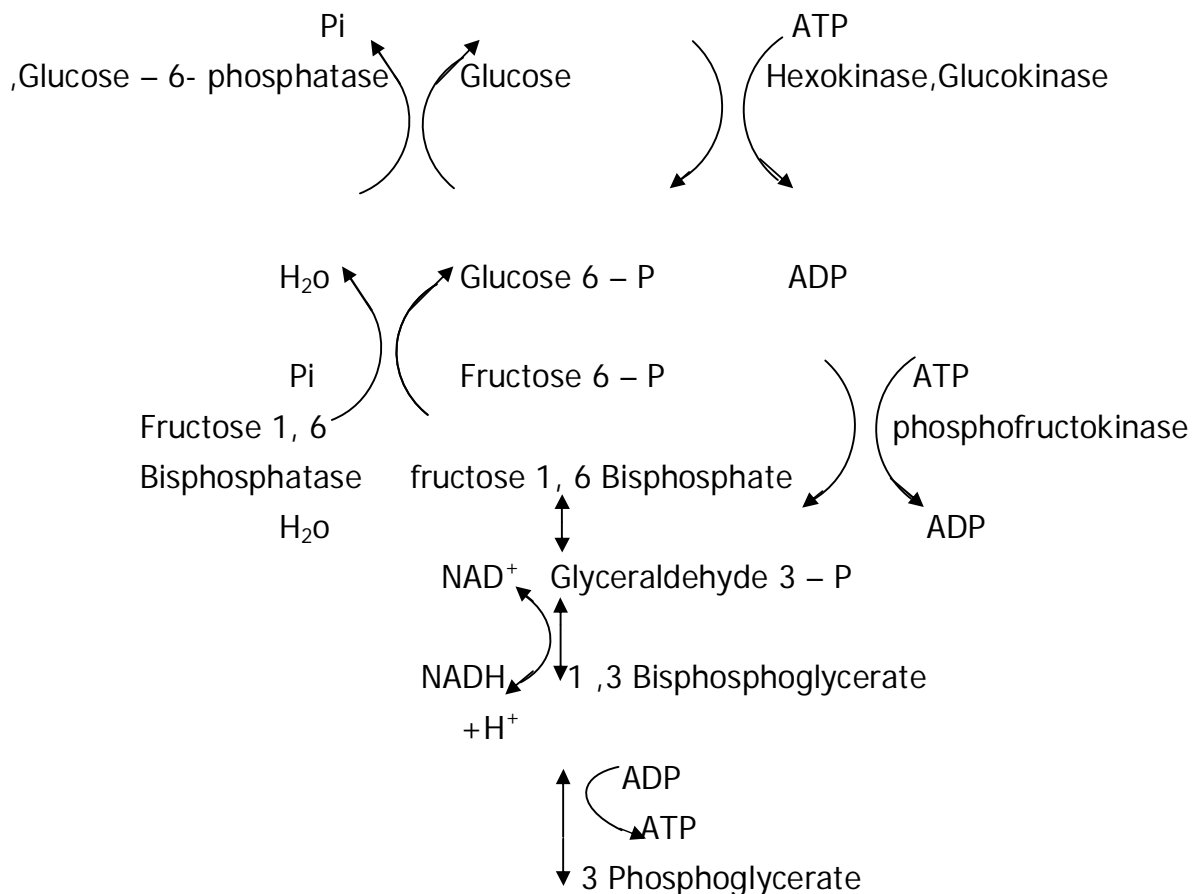
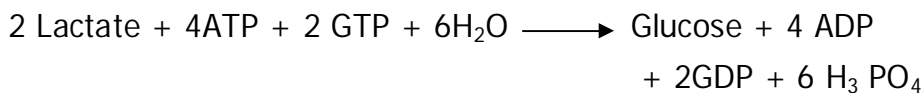
The carboxykinase is present only in the cytoplasm, but the oxaloacetate is not able to pass through the mitochondrial membrane therefore it is first reduced to malic acid.

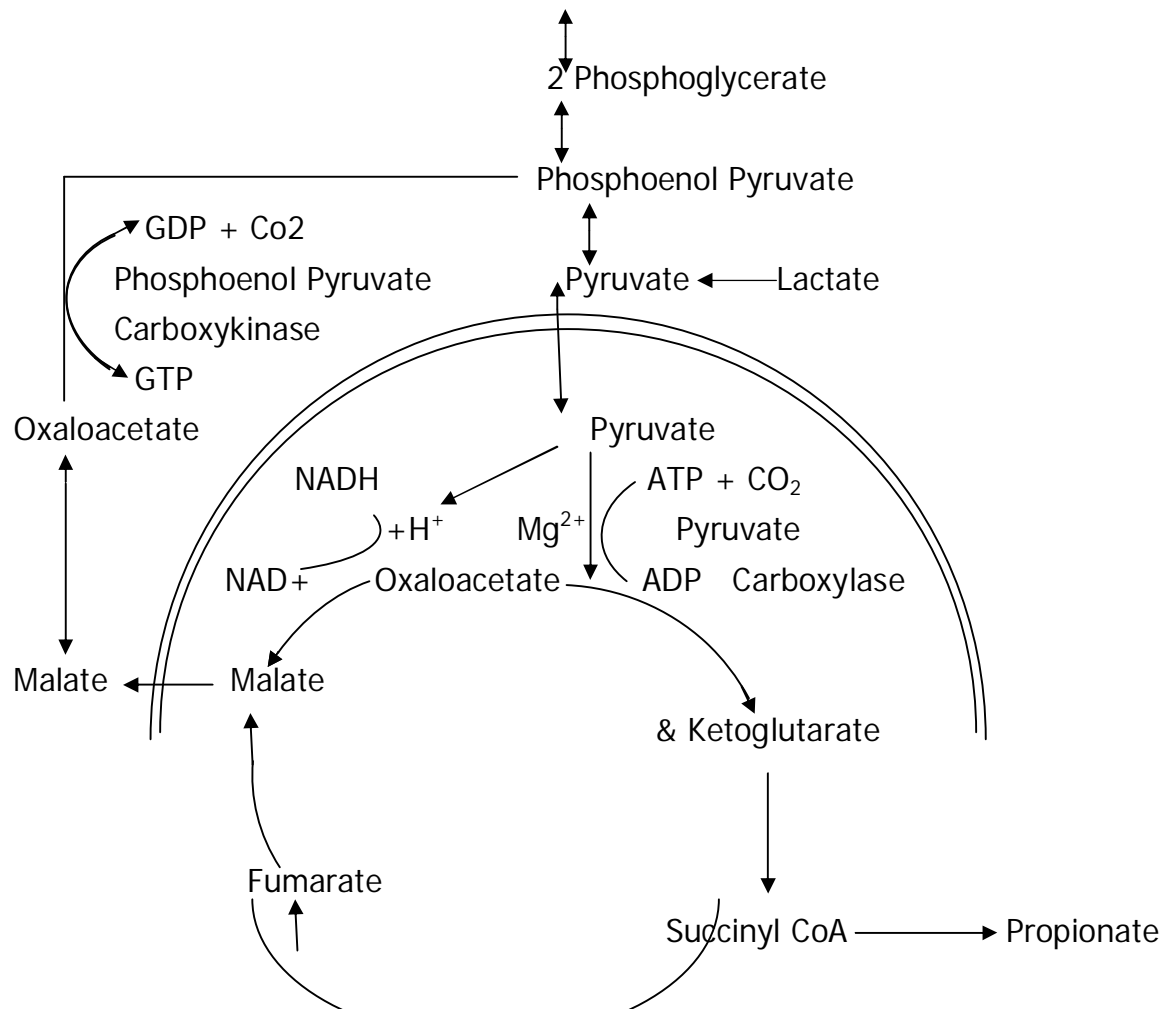


3. Action of phosphatase which (a) catalyzes the hydrolysis of fructose – 1,6 bisphosphate to form fructose – 6 – PO₄ by the enzyme fructose 1,6 bisphosphatase

(b) Production of glucose from glucose 6 – PO₄ also requires another enzyme – Glucose 6 – phosphatase.

Overall reaction:





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 I-PO₄ 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 uridy 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 absent or very low in the liver, kidney and intestinal tissue.

Type II (Pompe's disease) due to deficiency of lysosomal α - 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

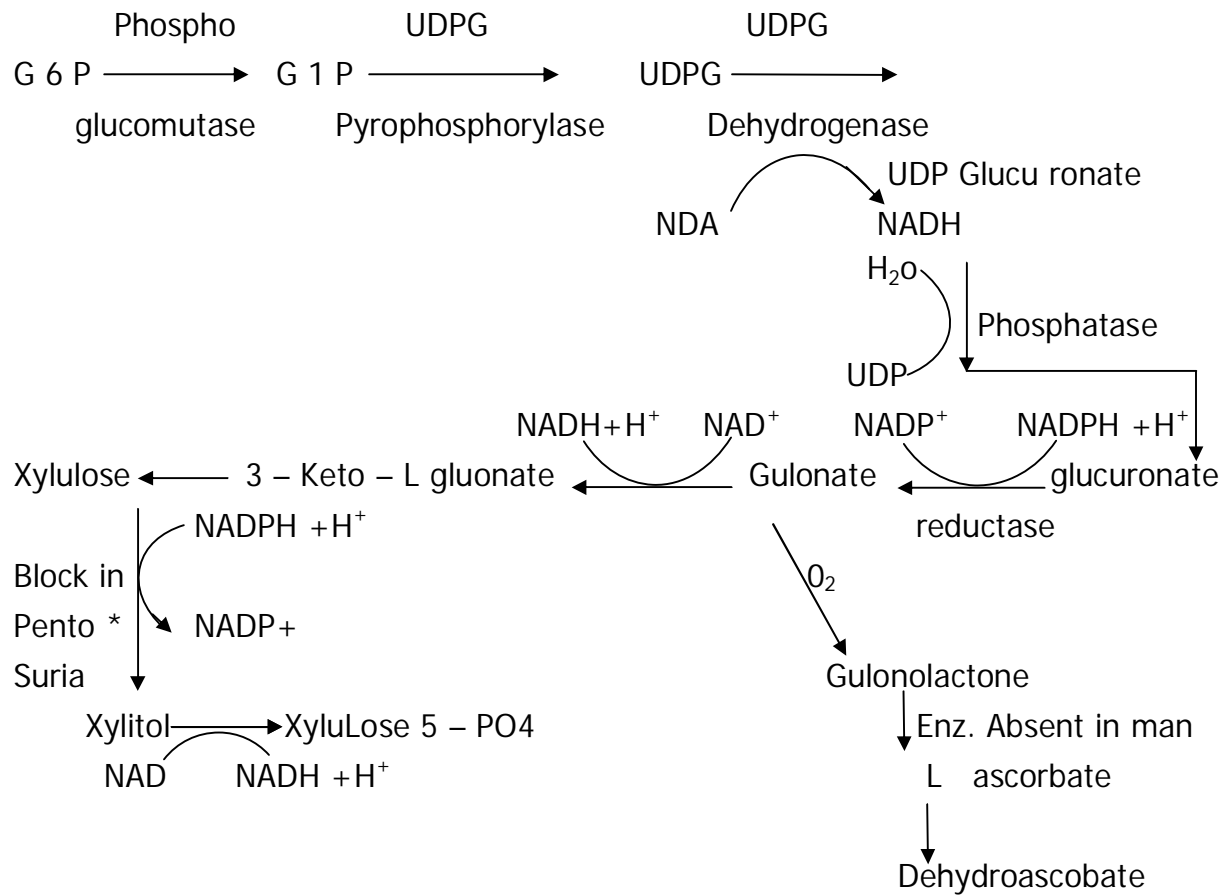
1. Formation of NADPH is very important in the HMP pathway in red blood cells. There is high correlation between G 6 phosphate dehydrogenase and the fragility of red cells (susceptibility to hemolyses). Especially when the cells are subjected to the toxic effects of certain drugs e. g. primaquine etc. 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 inability 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- PO_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.

URONIC ACID PATHWAY

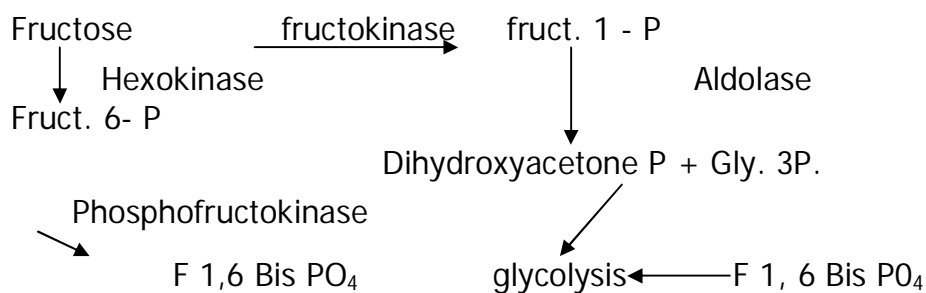


Importance

- 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 PO₄ to form UDPG which is now oxidized at C₆ by a 2 step process to UDP – glucuronate by inversion around C₄.

- 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 oxidized 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 accomplished 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 barbitol or of chlorobutanol to rat.

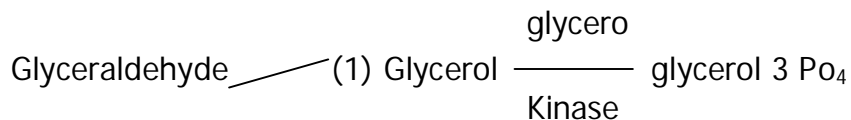
Fructose Catabolism



Metabolism of fructose

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

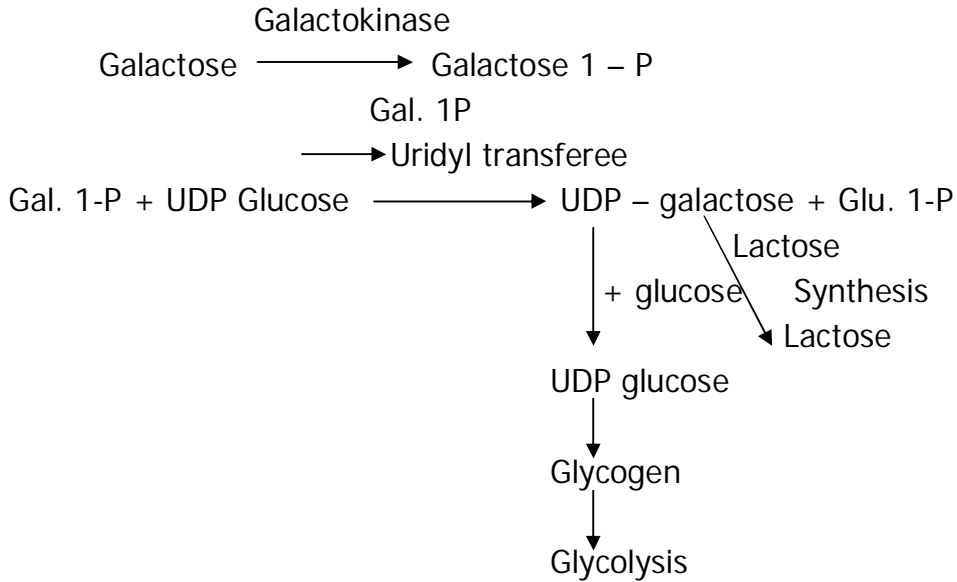
Fructose is phosphorylated by hexokinase to form Fruct. 6-PO₄ or fructokinase in the liver converts fructose to fructose 1-PO₄. This is split into D- Glyceraldehyde and dihydroxyacetone Po₄ by aldolase B. Absence of enzymes leads to hereditary fructose intolerance



(3) Triokinase in liver catalyses the phosphorylation of D glyceradehyde to gly 3 PO₄.

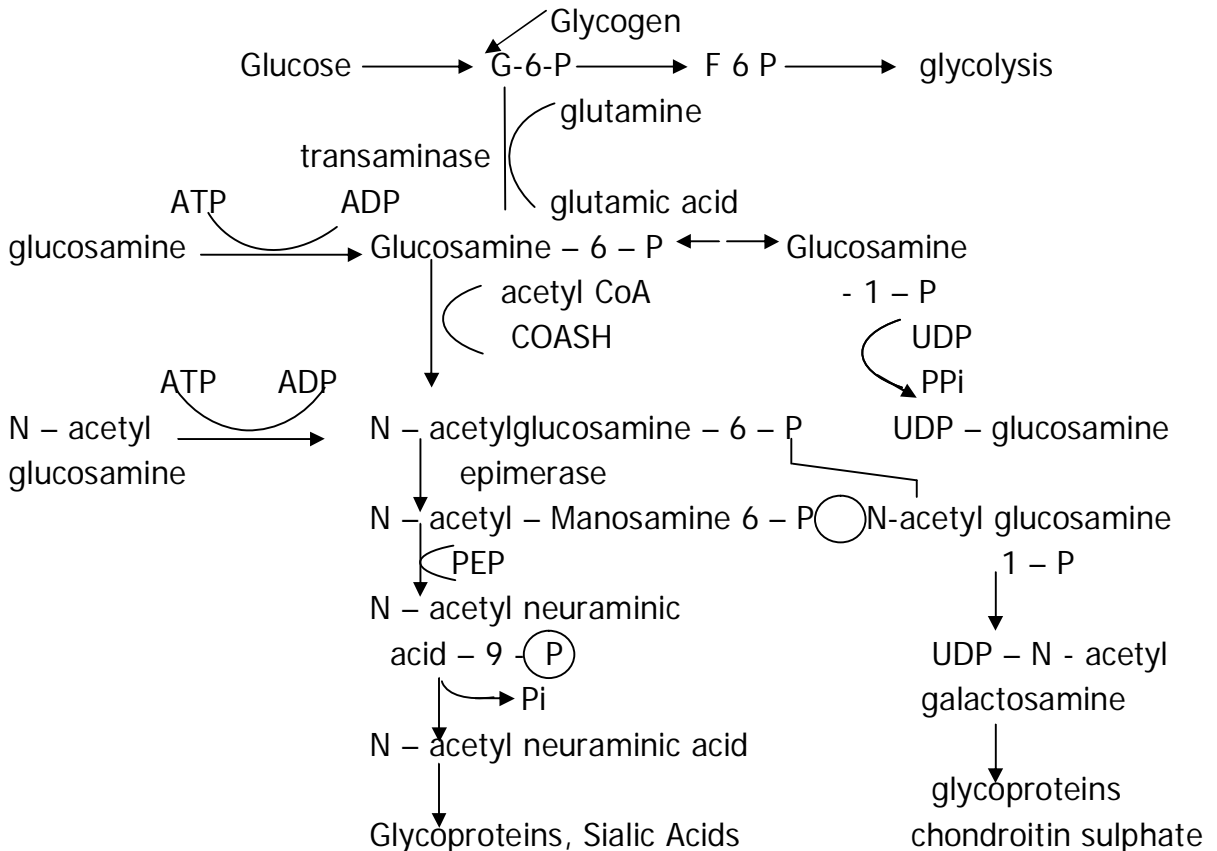
Glyceralde and dihydroxyacetone PO₄ \rightarrow glycolysis OR may combine in the presence of aldolase to form glucose.

Galactose Metabolism:-



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

They are important components in many complex polysaccharides.



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, maltotriose 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.