Glycogen Metabolism

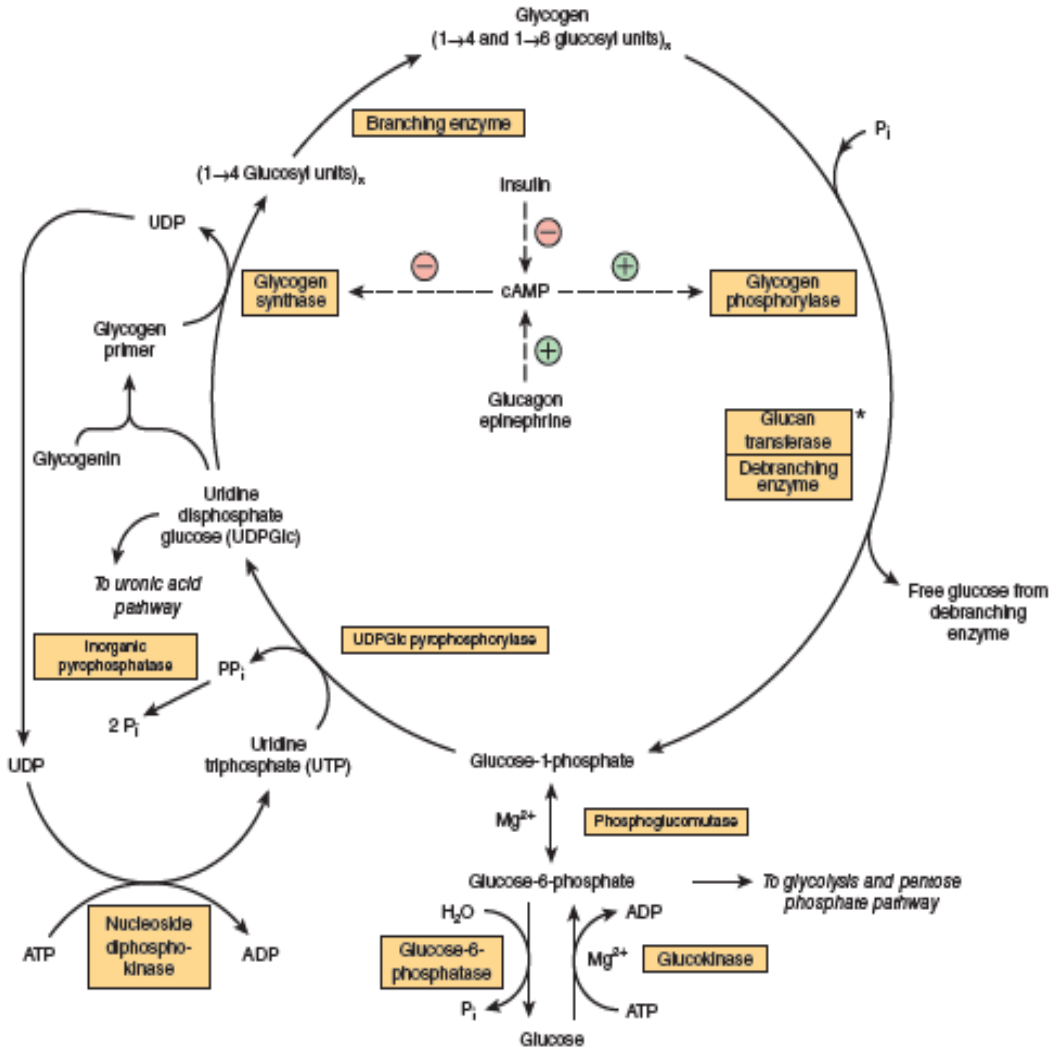
Glycogen is the major storage carbohydrate in animals, corresponding to starch in plants; it is a branched polymer of D-glucose. Muscle glycogen is a readily available source of glucose for glycolysis within the muscle itself. Liver glycogen functions to store and export glucose to maintain blood glucose between meals. After 12–18 hours of fasting, the liver glycogen is almost totally depleted. Glycogen storage diseases are a group of inherited disorders characterized by deficient mobilization of glycogen leading to muscular weakness or even death. Glycogen is the major storage form of glucose mainly in the liver and muscle. The concentration of liver glycogen (up to 6%) is greater than in muscle (1%) tissues. However, because muscle tissue comprises a large mass, its total capacity to storage is three to four times that of the liver. The synthesis, **glycogenesis** and degradation, **glycogenolysis** occur via different pathways. Glycogenesis and glycogenolysis are both cytosolic processes.

Glycogenesis & Glycogenolysis

Glycogenesis is the pathway for the formation of glycogen from glucose. This process requires energy, supplied by ATP and uridine triphosphate (UTP). It occurs in muscle and liver. **Glycogenesis** is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage, As in glycolysis, glucose is phosphorylated to glucose- 6-phosphate, catalyzed by hexokinase in muscle and glucokinase in liver, Glucose-6-phosphate is isomerized to glucose-1-phosphate by phosphoglucomutase. Next, glucose-1-phosphate reacts with uridine triphosphate (UTP) to form the active nucleotide uridine diphosphate glucose (UDPGlc) and pyrophosphate , catalyzed by UDPGlc pyrophosphorylase. The initial steps in glycogen synthesis involve the protein Glycogenin catalyzes the transfer of a further seven glucose residues from UDPGlc, in α (1-4) linkage, to form a glycogen primer that is the substrate for glycogen synthase. The glycogenin remains at the core of the glycogen granule .

Glycogen synthase catalyzes the formation of a glycoside bond between C-1 of the glucose of UDPGlc and C-4 of a terminal glucose residue of glycogen, liberating uridine diphosphate (UDP). The addition of a glucose residue to a preexisting glycogen chain, or "primer," When a growing chain is at least 11 glucose residues long, branching enzyme transfers a part of the 1 - 4chain (at least six glucose residues) to a neighboring chain to form a 1 -6 linkage, establishing a branch point. The branches grow by further additions of 1-4-glucosyl units and further branching.

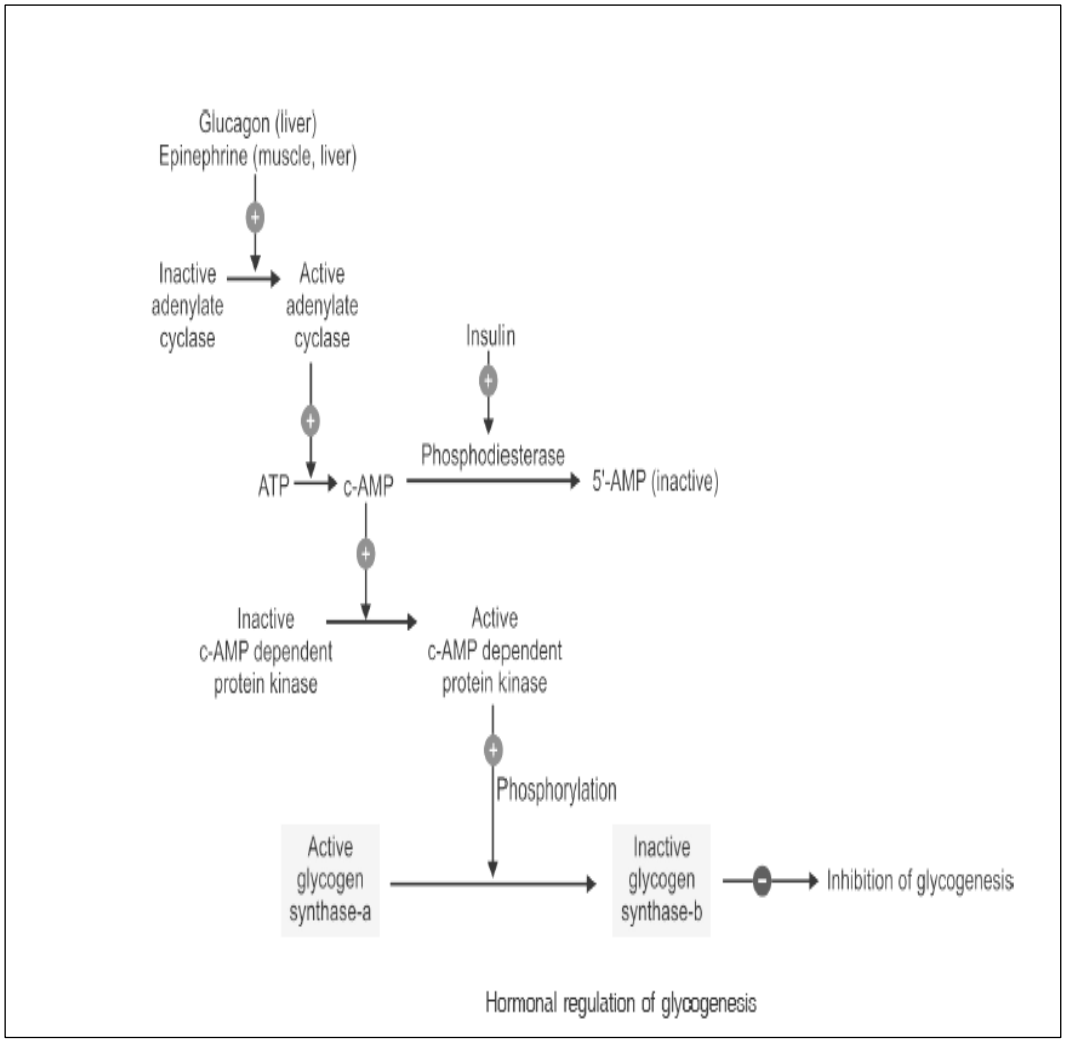
In glycogenolysis Glycogen phosphorylase catalyzes to yield glucose 1-phosphate . Glycogen phosphorylase requires pyridoxal phosphate as its coenzyme. The terminal glucosyl residues from the outermost chains of the glycogen molecule are removed sequentially until approximately four glucose residues remain on either side of a 1- 6 branch .The debranching enzyme has two catalytic sites in a single polypeptide chain. The other is a 1-6-glycosidase that catalyzes hydrolysis of the 1-6 glycoside bond to liberate free glucose. The combined action of phosphorylase and these other enzymes leads to the complete breakdown of glycogen. The reaction catalyzed by phosphoglucomutase is reversible, so that glucose-6-phosphate can be formed from glucose 1-phosphate. In liver, but not muscle, glucose-6-phosphatase catalyzes hydrolysis of glucose-6-phosphate, yielding glucose that is exported, leading to an increase in the blood glucose concentration. **Cyclic AMP** integrates the regulation of glycogenolysis and glycogenesis by promoting the simultaneous activation of phosphorylase and inhibition of glycogen synthase. Insulin acts reciprocally by inhibiting glycogenolysis and stimulating glycogenesis.



Pathway of Glycogenesis and glycogenolysis in the liver

Regulation of glycogenesis

• **Glycogen synthase** is the regulatory enzyme of glycogenesis. It exists in two forms: Glycogen synthase-a, an active or dephosphorylated form and Glycogen synthase-b, an inactive or phosphorylated form.

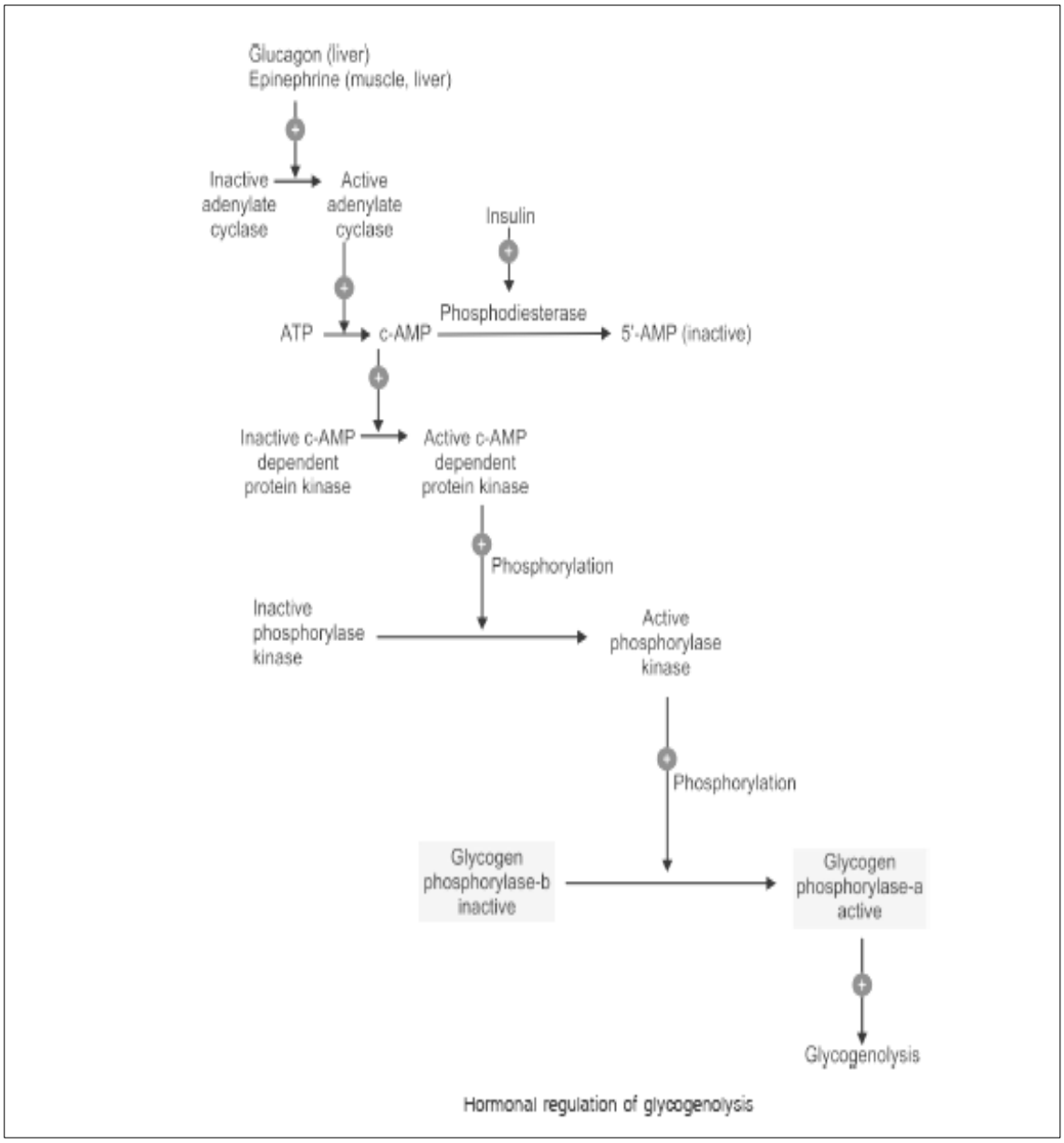


Hormonal regulation of glycogenesis

Regulation of glycogenolysis

• **Glycogen phosphorylase** is the regulatory enzyme of glycogenolysis. It exists in two forms: Glycogen phosphorylase-a, an active or phosphorylated form and Glycogen phosphorylase-b, an inactive or dephosphorylated form.

• Degradation of glycogen is stimulated by epinephrine in the muscle and by glucagon in the liver via activation of adenylate cyclase that catalyzes the synthesis of c-AMP**.**

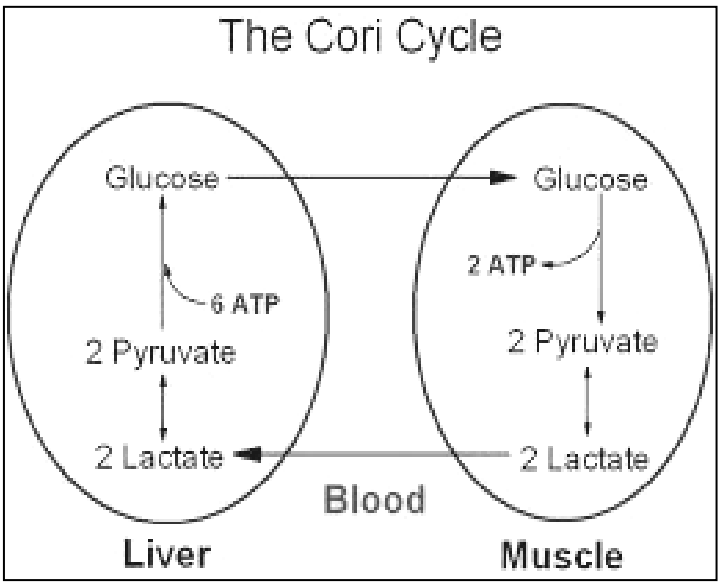


Hormonal regulation of glycogenolysis

Gluconeogenesis

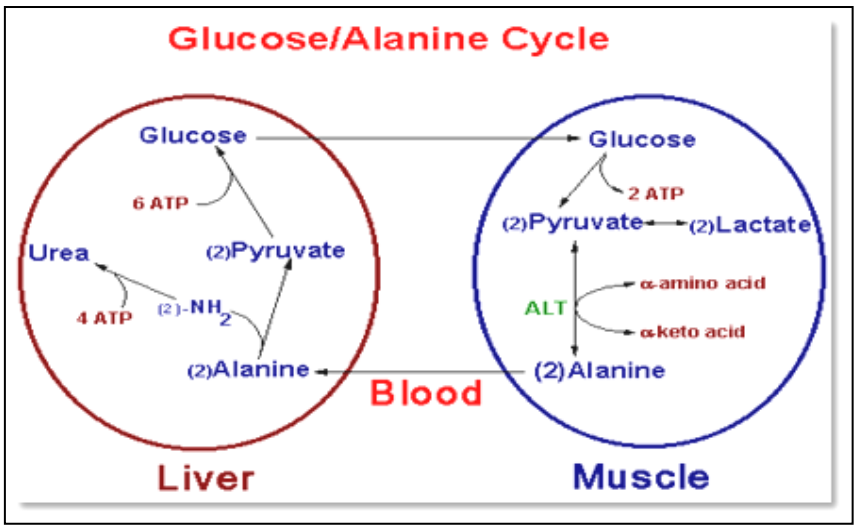
Gluconeogenesis is the term used to include all pathways responsible for converting noncarbohydrate precursors to glucose or glycogen. Liver and kidney are the major gluconeogenic tissues. Gluconeogenesis meets the needs of the body for glucose when carbohydrate is not available in sufficient amounts from the diet or from glycogen reserves. A supply of glucose is necessary especially for the nervous system, kidney and erythrocytes. Failure of gluconeogenesis is usually fatal. Hypoglycemia causes brain dysfunction, which can lead to coma and death. The major substrates are the glucogenic amino acids, pyruvate, and lactate, glycerol, and propionate. Glycerol produced by adipose tissue also Propionate, the principal glucogenic fatty acid is a major substrate for gluconeogenesis in these species.

Gluconeogenesis clears lactate produced by muscle and erythrocytes. In lactate, formed by glycolysis in skeletal muscle and erythrocytes, is transported to the liver and kidney where it re-forms glucose, which again becomes available via the circulation for oxidation in the tissues. This process is known as the **Cori cycle,** or **lactic acid cycle** as shown in figure:



Lactic acid (Cori) cycle

The **glucose- alanine cycle** transports glucose from liver to muscle with formation of pyruvate, followed by transamination to alanine, then transports alanine to the liver, followed by gluconeogenesis back to glucose.



Glucose-Alanine cycle

Regulation of Gluconeogenesis

• The hormones **glucagon** and **epinephrine** stimulate gluconeogenesis by inducing the synthesis of the key enzymes, while **insulin inhibits** the gluconeogenesis by repressing their synthesis.

• During starvation and in diabetes mellitus, a high level of glucagon stimulates gluconeogenesis. However in well-fed state, insulin suppresses the gluconeogenesis.

Alcohol inhibits gluconeogenesis

Ethanol oxidation in the liver to acetaldehyde by the enzyme alcohol dehydrogenase utilizes NAD+. The increase NADH produced in the liver interferes with gluconeogenesis as illustrated below:

$$\text{Ethanol} + NAD^+ \longleftrightarrow \text{Acetaldehyde} + NADH + H^+$$

When NADH increased produced the following reactions:

$$\text{Pyruvate} + NADH + H^+ \longleftrightarrow \text{Lactate} + NAD^+$$

$$\text{Oxaloacetate} + NADH + H^+ \longleftrightarrow \text{Malate} + NAD^+$$

It is evident from the above reactions that pyruvate and oxaloacetate, the predominant substrates for gluconeogenesis, are made unavailable by alcohol intoxication. This happens due to over consumption of NAD+ and excessive production of NADH by alcohol. Alcohol consumption increases the risk of hypoglycemia (reduced plasma glucose) due to reduced gluconeogenesis.

Many factors play role in regulating blood glucose

In addition to the direct effects of hyperglycemia in enhancing the uptake of glucose into the liver, the hormone insulin plays a central role in regulating blood glucose. It is produced by the B cells of the islets of Langerhans in the pancreas in response to hyperglycemia.

Glucose transporters are a wide group of membrane proteins that facilitate the transport of glucose over a plasma membrane. Because glucose is a vital source of energy for all life, in another hand enzymes play vital role of glucose metabolism, Hexokinase has a low Km (higher affinity) for glucose and acting even at low concentrations. Glucokinase has a considerably higher Km (lower affinity) for glucose, so that its activity increases in high concentration of glucose. It promotes hepatic uptake of large amounts of glucose at the high concentrations found in the hepatic portal vein after a carbohydrate meal. It is absent from the liver of ruminants, which have little. Glucagon is the hormone produced by the A cells of the pancreatic islets. Its secretion is stimulated by hypoglycemia. In the liver, it stimulates glycogenolysis by activating phosphorylase. Glucagon also enhances gluconeogenesis from amino acids and lactate. In all these actions, glucagon acts via generation of cAMP.

Significance of Gluconeogenesis

• Gluconeogenesis maintains blood glucose level when carbohydrate is not available in sufficient amounts from the diet.

• During starvation when hepatic glycogen reserve is totally depleted, glucose is provided by gluconeogenesis to the brain and other tissues like erythrocytes, lens, cornea of the eye and kidney medulla. They require a continuous supply of glucose as a source of energy.

• Gluconeogenesis is used to clear the products of the metabolism of other tissues from the blood, for example:

– Lactate, produced by muscle and erythrocytes

– Glycerol produced by adipose tissue

– Propionyl-CoA produced by oxidation of odd carbon number fatty acids and carbon skeleton of some amino acids.

Other Hormones Affect Blood Glucose

The anterior pituitary gland secretes hormones that tend to elevate the blood glucose and therefore antagonize the action of insulin. These are growth hormone, ACTH (adrenocorticotropic hormone), these glucocorticoids hormone are secreted by the adrenal cortex and increase gluconeogenesis. This is a result of enhanced hepatic uptake of amino acids and increased activity of aminotransferases and key enzymes of gluconeogenesis. In all these actions, glucocorticoids act in a manner antagonistic to insulin.

In addition of that, Epinephrine is secreted by the adrenal medulla as a result of stressful stimuli (fear, excitement, hemorrhage, hypoxia, hypoglycemia, etc) and leads to glycogenolysis in liver and muscle owing to stimulation of phosphorylase enzyme. In muscle, glycogenolysis results in increased glycolysis, whereas in liver glucose is the main product leading to increase in blood glucose.

Glucosuria

When the blood glucose increased to relatively high levels, this case effect on kidney function. Glucose is continuously filtered by the glomerular but is normally completely reabsorbed in the renal. The capacity of the tubular system to reabsorb glucose is limited to a rate of about 350 mg/min, and in hyperglycemia (poorly controlled diabetes mellitus) the glomerular filtrate may contain more glucose than can be reabsorbed, resulting in **Glucosuria.**

Hypoglycemia May Occur During Pregnancy

Premature and low birth- weight babies are more susceptible to hypoglycemia, since they have little adipose tissue to generate enough fuels such as free fatty acids or ketone and the enzymes of gluconeogenesis may not be completely functional at this time also Glycerol, which would normally be released from adipose tissue, but is less available for gluconeogenesis. Also in pregnancy, when the fetal need to nutrition from Maternal with related to having too much of the insulin in the blood along with not enough food that lead to Low blood sugar (hypoglycemia).

Glucose Tolerance

Glucose tolerance is the ability to regulate the blood glucose concentration after the administration of a test dose of glucose (normally 1 g/kg body weight). In diabetes mellitus (type 1, or insulin-dependent diabetes mellitus; IDDM) is characterized by decreased glucose tolerance due to decreased secretion of insulin in response to the glucose challenge. Glucose tolerance is also impaired in type 2 diabetes mellitus (NIDDM), which is often associated with obesity and increased levels of free fatty acids. Poor glucose tolerance can also be expected due to hyperactivity of the pituitary or adrenal cortex because of the antagonism of the hormones secreted by these glands to the action of insulin. Administration of insulin (as in the treatment of diabetes mellitus type 1) lowers the blood glucose and increases its utilization and storage in the liver and muscle as glycogen.

Pentose Phosphate Pathway Metabolism

Significance of Pentose Phosphate Pathway

• The pentoses (ribose-5-phosphate) required for the biosynthesis of nucteotide and nucleic acids (RNA and DNA) are provided by pentose phosphate pathway.

• It provides a route for the interconversion of pentoses and hexoses.

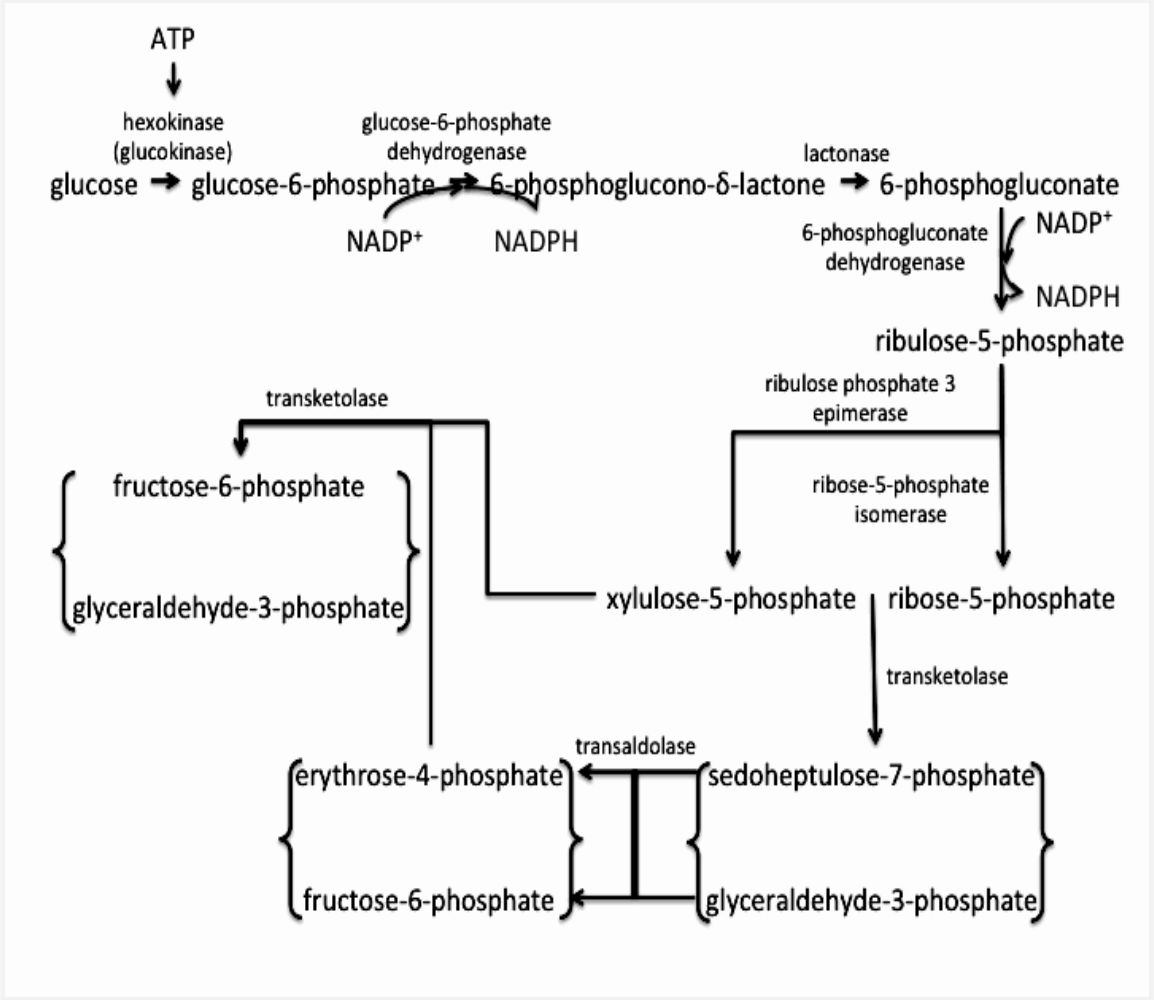
• It generates NADPH which plays important role in several other biological processes,

Regulation of Pentose Phosphate Pathway

• The first step in the pathway, catalyzed by glucose- 6-phosphate dehydrogenase (G-6-PD) is the rate limiting step.

• The activity of G-6-PD is regulated by cellular concentration of NADPH. NADPH is a competitive inhibitor of the enzyme G-6-PD.

- Insulin is also involved in the regulation of pentose phosphate pathway. It enhances the pathway by inducing the enzyme G-6-PD



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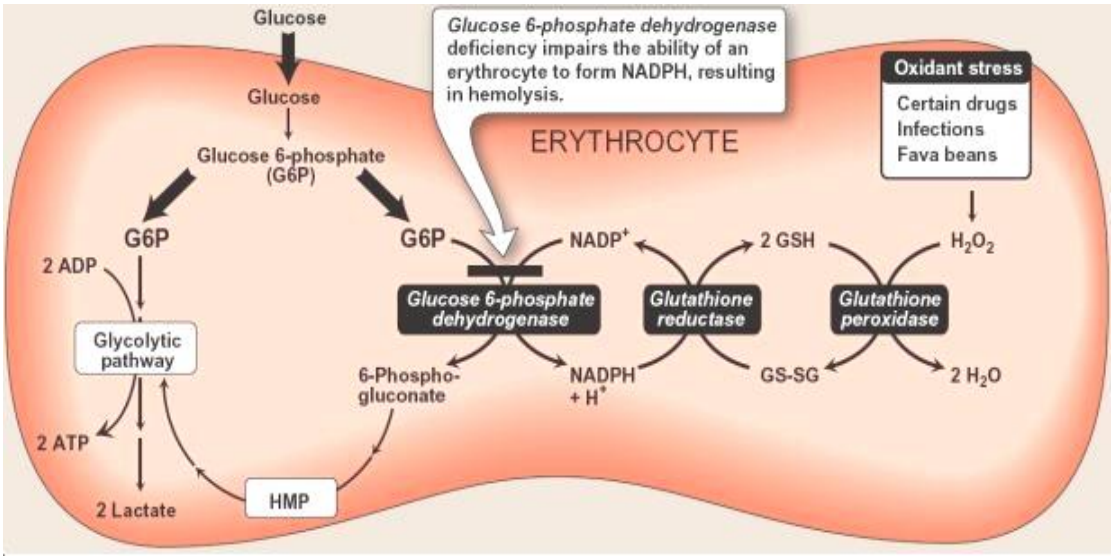
Pentose Phosphate Pathway (PPP)

Genetic deficiency of glucose 6-phosphate dehydrogenase, the first enzyme of the pentose phosphate pathway, is a major cause of hemolysis of red blood cells, resulting in hemolytic anemia and affecting approximately 100 million people worldwide. The G6PD / NADPH pathway is the only source of reduced glutathione in red blood cells (erythrocytes).



Role of G6PD as antioxidant enzyme

The role of red cells as oxygen carriers puts them at substantial risk of damage from oxidizing free radicals except for the protective effect of G6PD/NADPH/glutathione. The pentose phosphate pathway is active in liver, adipose tissue, adrenal cortex, thyroid, erythrocytes, testis, and lactating mammary gland. Its activity is low in non lactating mammary gland and skeletal muscle.

Hereditary Fructose Intolerance (HFI)

Hereditary Fructose Intolerance (HFI) is an inborn error of fructose metabolism. Fructose is converted to fructose-1-phosphate by the liver by fructokinase. Deficiencies of fructokinase cause essential fructosuria, a clinically benign condition characterized by the excretion of unmetabolized fructose in the urine. Symptoms of Hereditary Fructose include kidney failure.

Sorbitol (polyol) pathway

The sorbitol (polyol) pathway (not found in liver) is responsible for fructose formation from glucose and increases in activity as the glucose concentration rises in diabetes in those tissues that are not insulin-sensitive, ie, the lens, peripheral nerves, and renal glomerular. Both fructose and sorbitol are found in the lens of the eye in increased concentrations in diabetes mellitus and may be involved in the pathogenesis of diabetic cataract**.**

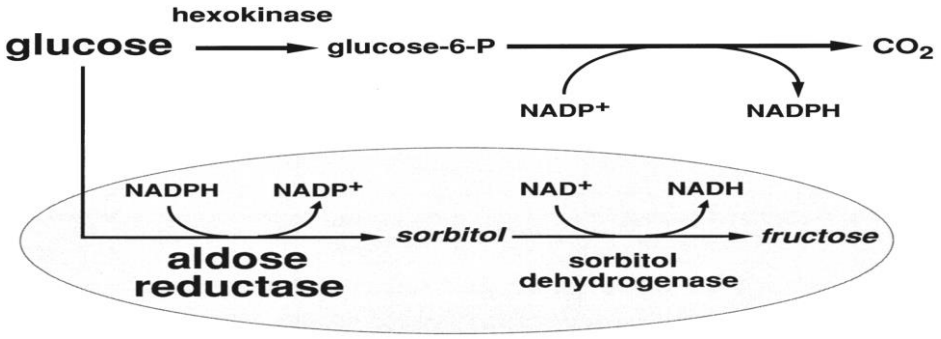


Figure: Polyol pathway

Galactosemias

Inability to metabolize galactose occurs in the Galactosemias, which may be caused by inherited defects in galactokinase so galactose can't convert to galactose-6-phosphate. galactose concentration which increased in the blood and in the eye is reduced by aldose reductase to galactitol, which accumulates, causing cataract