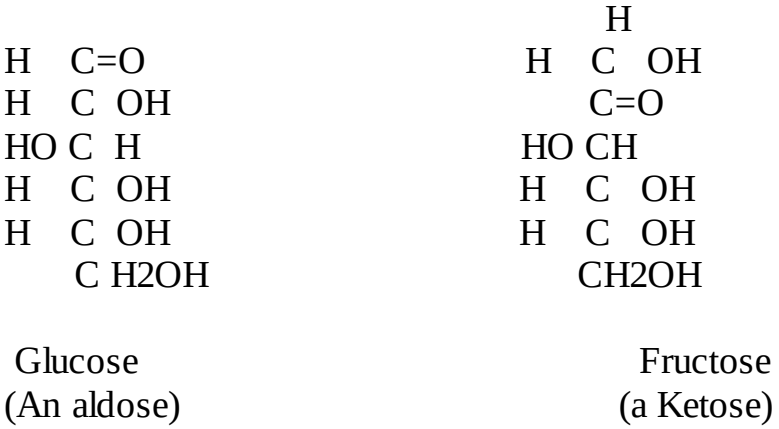
Carbohydrate metabolism

Introduction

Carbohydrates are an important source of energy for the human beings as well as a means by which chemical energy can be storage. Catabolism of carbohydrates provides the major share of the requirements for maintains of life.

Carbohydrate may be defined as polyhydroxy aldehydes or ketones, or as substance that yield one of these compounds on hydrolysis. Glucose C6H12O6 and fructose C6H12O6 are examples, respectively, of aldose and ketose as shown in figure-1.



Glucose (An aldose)

Fructose (a Ketose)

Classification of carbohydrate:

Carbohydrate may be classified in three main groups

1. Monosaccharides: the simple sugar that have only four to seven or eight carbon atoms and contain only one aldehyde or ketone functional groups.

2. Oligosaccharide: compound sugars that yield two to six molecules of simple sugar on hydrolysis.

3. Polysaccharides: groups of compounds that yield a large number monosacchrides on hydrolysis (starch and glycogen).

Importance of Glucose:

1. Glucose is the preferred source of energy for most of the body tissues. Brain cells derive energy mainly from glucose.
2. When the glucose metabolism is deranged, life- threatening conditions may occur. A minimum amount of glucose is always required for normal functioning.
3. Normal fasting plasma glucose level is 70 to 110 mg/dl. After a heavy carbohydrate meal, in a normal person, this level is below 150 mg/dl.

Carbohydrate metabolism:

Sucrose, lactose, maltose, and isomaltose are the principle source of carbohydrate in the diet of the western world. Less than 3 % of the ingested carbohydrates is free glucose. Carbohydrate must be broken down to monosaccharides before they can be absorbed into the intestinal mucosal cells.

Sucrose ⟶ Fructose + Glucose

Lactose ⟶ Galactose + Glucose

Maltose ⟶ Glucose + Glucose

Disaccharide Monosacchride

In the digestive process, salivary amylase mix with food , hydrolyzed starch to starch dextrin, maltose and maltotriose. The digestion by the enzyme continuos until it inactivated by gastric HCl. Further hydrolysis occurs by the pancreatic amylase in the intestine.

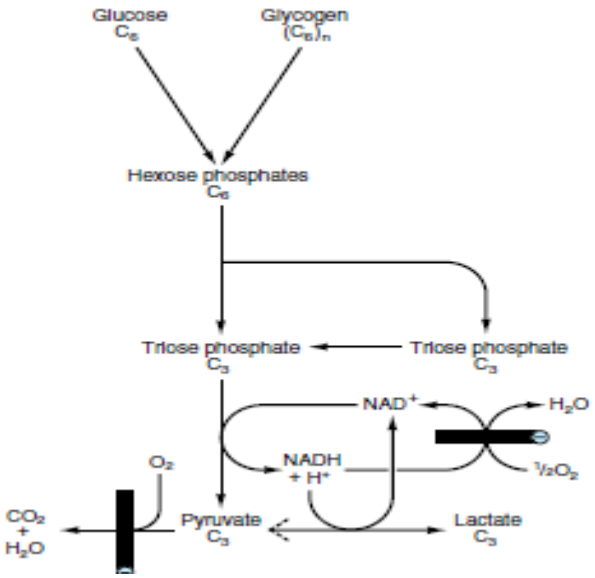
Sucrose, lactose, maltose and isomaltose ingested in the diet or formed from amalase hydrolyzes, are further broken down into monosacchride by enzymes are attached to the brush border of the intestine cells. Monosacchrides are than transported to the liver via portal circulation.

In the liver, fructose and galactose are mainly converted to glucose. Some glucose is released into circulating blood to supply energy to the tissues, or stored in form of glycogen in the liver and muscles. The

catabolism of glucose of glucose to pyruvic acid or lactic acid for production of energy *via* ATP production is called **glycolysis.**

Glycoltic enzymes are present in the extra-mitochondrial compartment of the cell. Although aerobic glycolysis occurs in most tissues like liver, kidney, and erthrocytes, anaerobic glycolysis occures only in muscle.

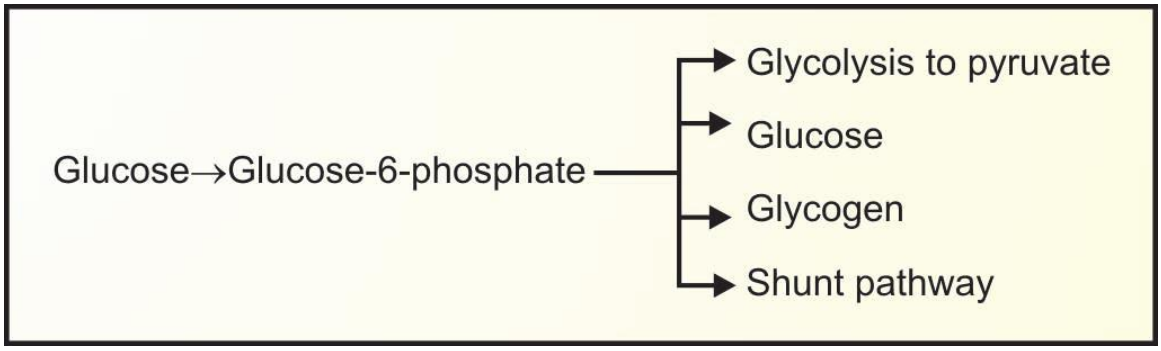
Plasma glucose is derived from from the hydrolysis of the dietry starch and polysacared from the conversion of the other dietry hexose into glycose by the liver and the synthesis of glucose from the amino acids or pyruvate.



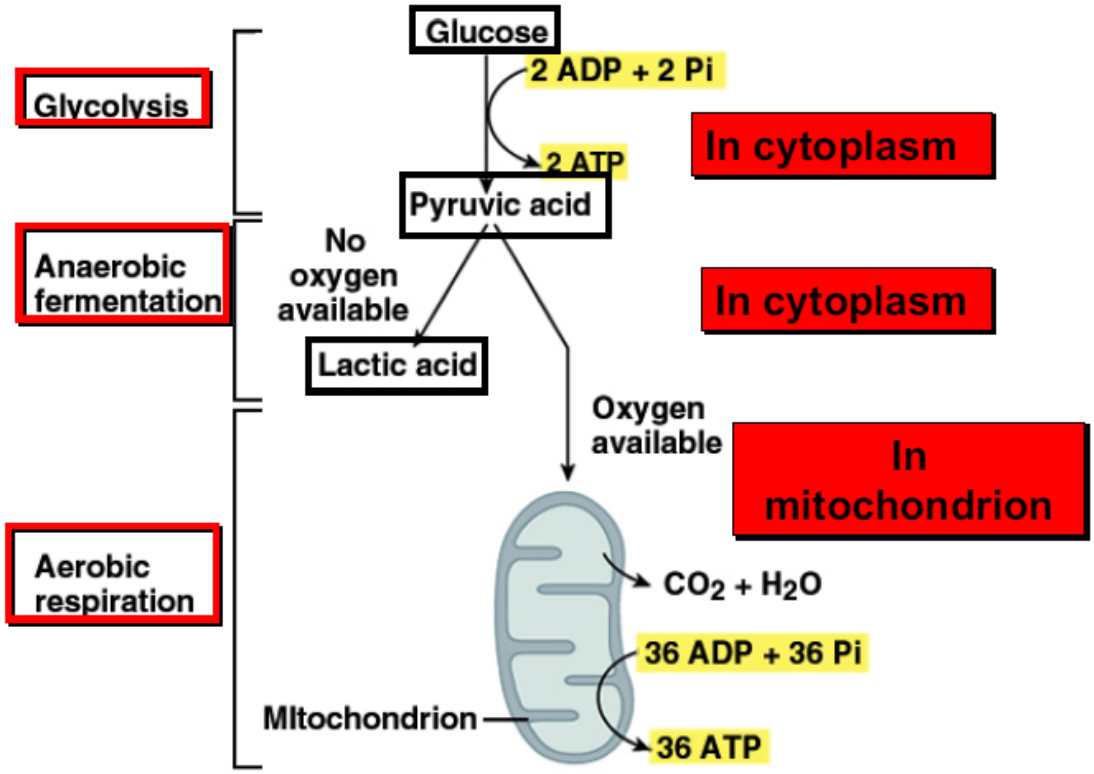
The general conversion of glucose and glycogen to energy

in times of glucose excess (elevation of blood glucose after the meal), glucose is enzematically polymerized in the liver to form glycogen (glycogenesis). When the glucose drops, glycogen is converted to glucose (glycogenolysis) by a defferent set of the enzymes thus, indepdent mechaanisms exits for regulation the blood glucose level by means of glycogenesis - glycogenolysis reactions.

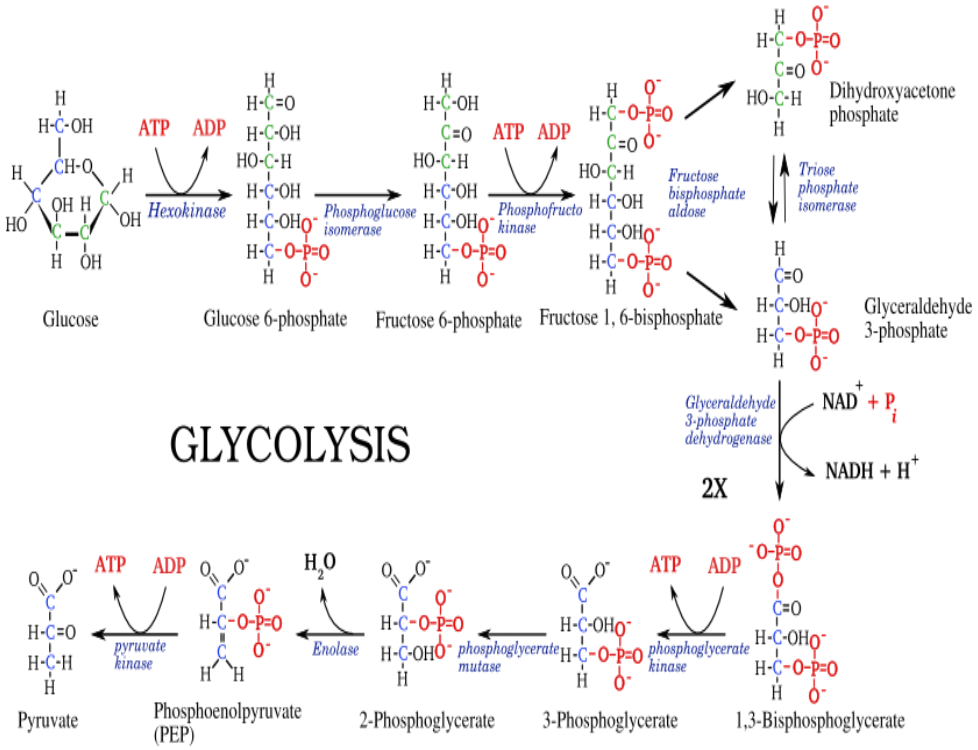
The liver is the main orgain for the storage of excess carbohydrate as glycogen, although skeletal and the heart muscles can store minor amount. Excess glucose is converted to fat by the adipose cells where it stored.

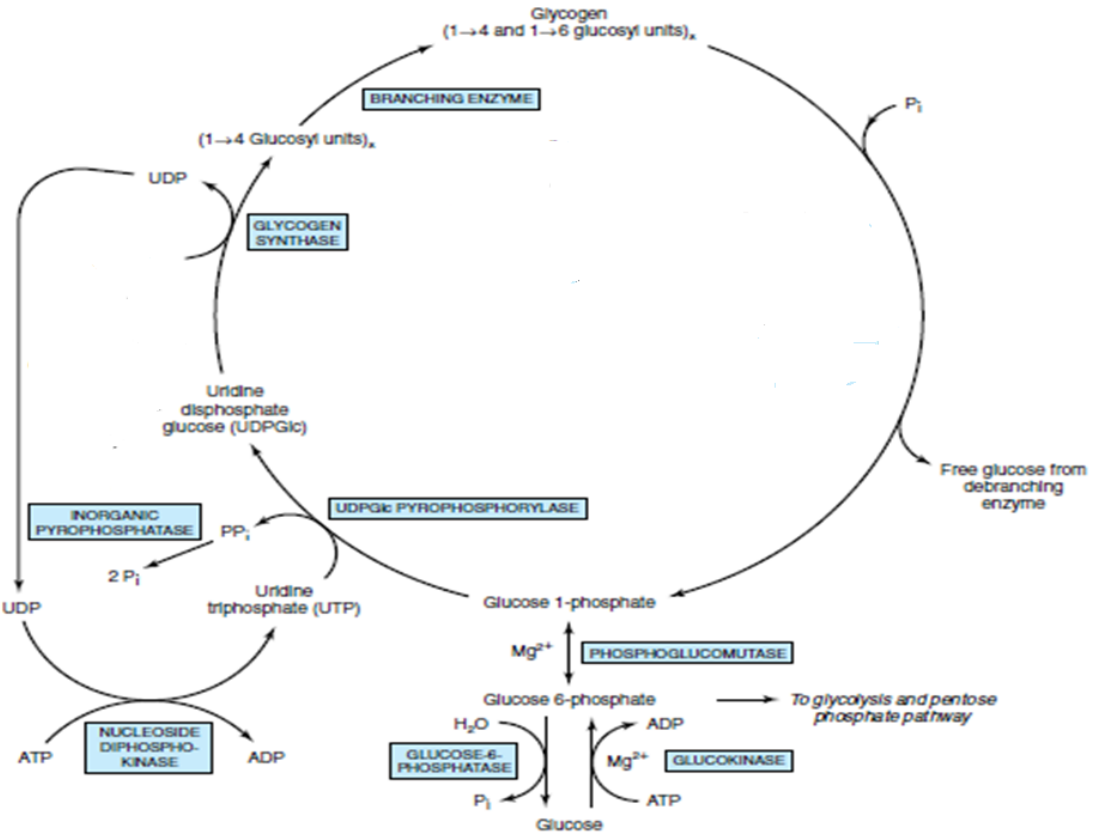


Fate of glucose 6- phosphate



The aerobic and anaerobic pathyways of carbohydrate metabolism


GLYCOLYSIS
Glucose
ATP
ADP
Hexokinase
Glucose 6-phosphate
Phosphoglucose isomerase
Fructose 6-phosphate
ATP
ADP
Phosphofructo kinase
Fructose 1, 6-bisphosphate
Fructose bisphosphate aldose
Dihydroxyacetone phosphate
Triose phosphate isomerase
Glyceraldehyde 3-phosphate
Glyceraldehyde 3-phosphate dehydrogenase
NAD+ + Pi
NADH + H+
2X
1,3-Bisphosphoglycerate
ATP
ADP
phosphoglycerate kinase
3-Phosphoglycerate
phosphoglycerate mutase
2-Phosphoglycerate
H2O
Enolase
Phosphoenolpyruvate (PEP)
ATP
ADP
pyruvate kinase
Pyruvate



Glycogen synthesis and degredation pathways

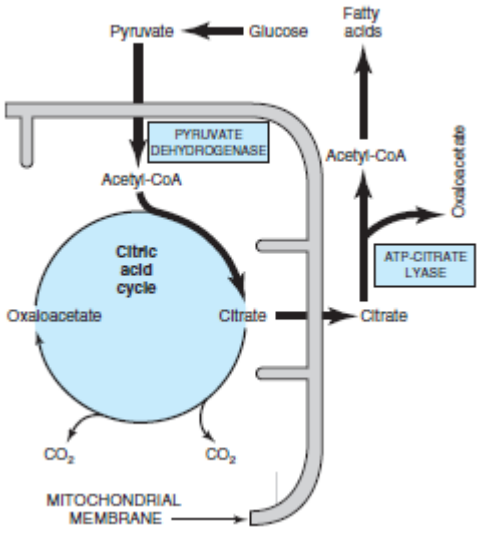
The energy stored in the glucose molecules is made available to the organism through several catabolic bathways that maiunly generate adenosine triphosphate (ATP).

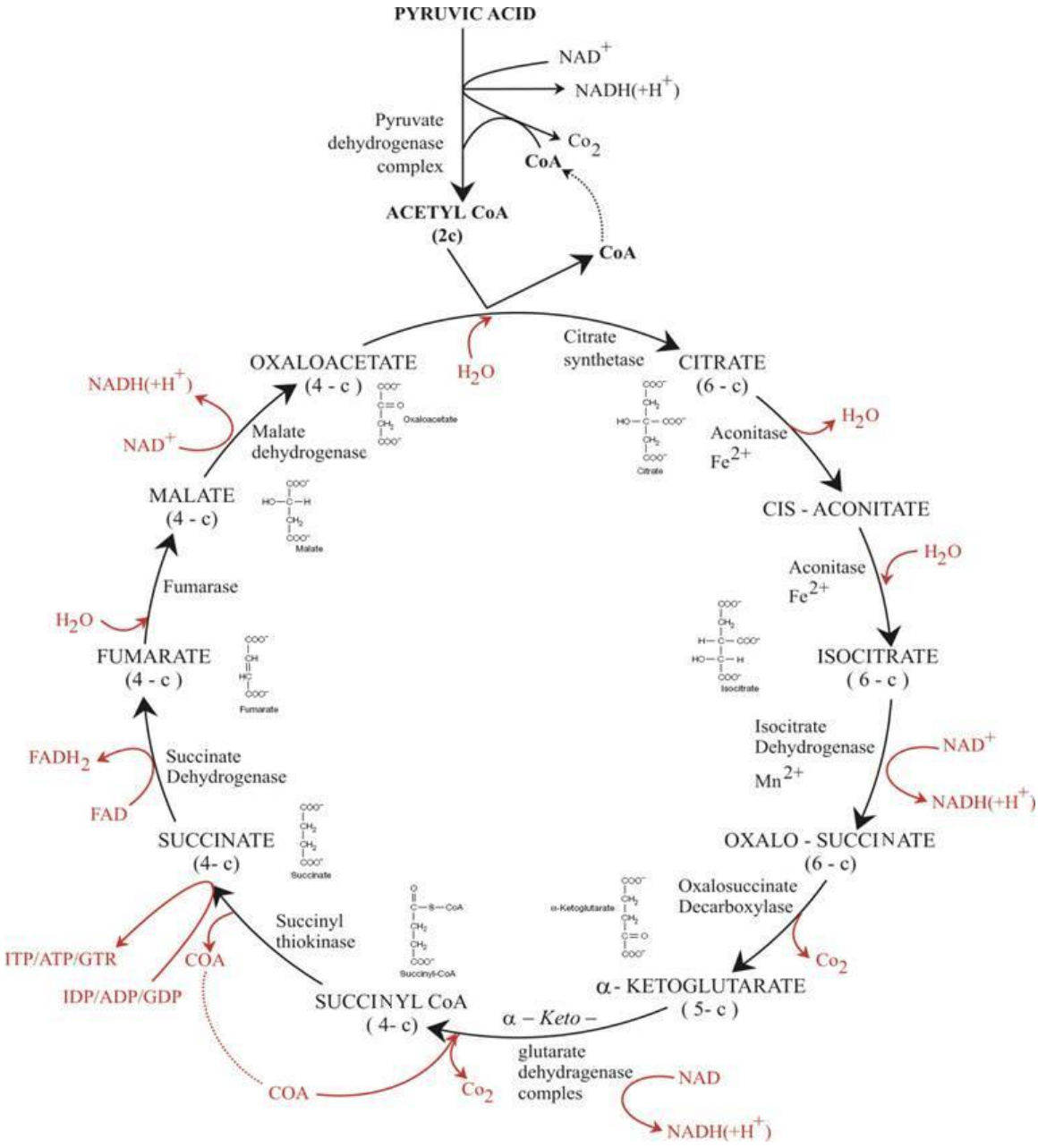
The principal pathway of glucose oxidation consists of two phases, anaerobic and aerobic oxidation (oxidative phosphorylation), both of which are made up of many different enzymatic steps. The anaerobic phase beter known as glycolysis.

The glucose – 6 - phosphaate (G-6-P) is converted through several steps to triose phosphate and then to pyruvate. All these reaction take place in the cytoplasm. Glycolysis can be revered, that is, pyruvate can be converted back to G-6-P, but by partly different pathway. Some of the pyruvate is converted into lactate by the enzyme lactate dehydrogenase, but the bulk of it enters the tricarboxylic acid (TCA) cycle. When sufficent oxygen is present, the aerobic phase of glucose utilization begins with the decarboxylation of pyruvate. pyruvate is converted in the mitochondria to acetyl Co, which oxidized to CO2 and H2O to generate many molecules of ATP the energy derived from the aerobic oxidation of glucose is about 19 times as great as that obtained by anaerobic glycolysis alone.

Formation of the acetylCo-A is common to the catabolism of the glucose, fatty acids, and some amino acids*

*** Acetyl Co-A is the compound formed fromed by transfer of an acetyl group to coenzyme A(Co-A) . Co-A is a comples of adenosine with panathenic acid (a member of vitamine B complex and β-mercaptoethylamine. CoA functions as a cofactor in enzymatic acyl transfer reactions.**





The tricarboxylic cycle (TCA) with all enzymes and co- factors

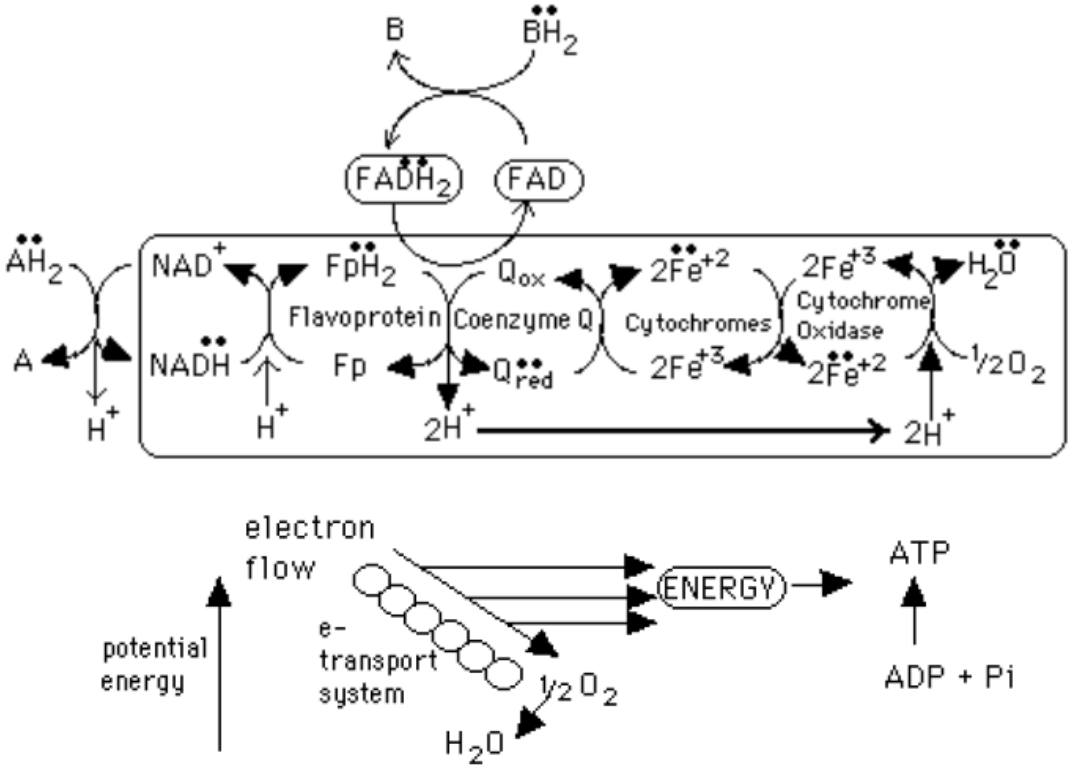
Energy produced by the TCA cycle

Two carbone atoms enter the cycle as acytyl CoA and leave as CO2. the cycle dosnt involve net consuption or production of oxaloacetate or any other intermediate. Four pairs of electrons are transferred during one turn of the cycle three paris of electrons reducing NAD^+ to NADH by and one pair reducing FAD to FADH2. oxidation of one NADH by the electron transport chain lead to formation of approximately three ATP, whereas the oxidation of FADH2 yeild approximatly two ATP. The total yeild of energy is shown in bellow table.

Energy producing reaction	Number of ATP produced
3NADH to $3NAD^+$	9
FADH to FAD	2
GDP+Pi to GTP	1
	Total 12 ATP /acetyl CoA oxidized

Oxidative Phosphorylation & The Electron Transport Chain:

• OXIDATIVE PHOSPHORYLATION is the indirect way of generating ATP from ADP and Pi using the energy released from REDOX REACTIONS on the ELECTRON TRANSPORT (RESPIRATORY) CHAIN.
• The ELECTRON TRANSPORT CHAIN is a series of compounds on the INNER MITOCHONDRIAL MEMBRANE which transfers H2 or electrons from one compound to another in a series of REDOX REACTIONS.



The Oxidative Phosphorylation & The Electron Transport Chain

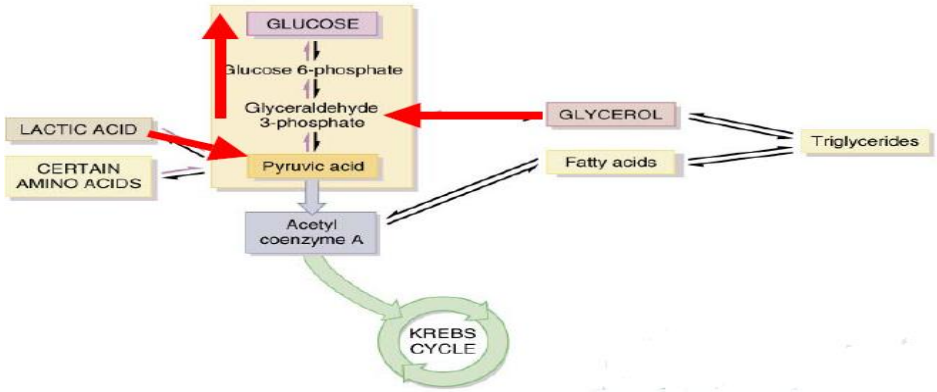
Gluconeogenesis

The liver has enzymes to reverse glycolysis, forming glucose from pyruvate or from oxaloacetate of the Krebs cycle.

• This process is called gluconeogenesis and converts lactic acid, glycerol & glucogenic amino acids to glucose.

- During exercise it converts LACTIC ACID back to glucose. which is sent back to the muscles to reenter glycolysis

- When carbohydrates are unavailable as in starvation or diabetes mellitus gluconeogenesis maintains the blood glucose level (especially for brain cells). **Gluconeogenesis** is stimulated by **Glucocorticoids** (mainly **cortisol**) released in times of stress via **ACTH** and by glucagon (both hyperglycemic hormones).



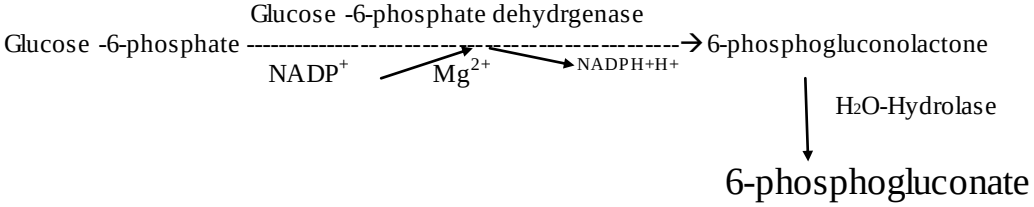
Gluconeogenis pathways

Pentose phosphate pathway

Pentose phosphate pathway, also called hexose monophosphate shunt (HMP) is the second major pathway for the metabolism of glucose. Enzymes for this pathway are localized in the cytosol, while reducing eqiuivalents are accepted by the $NADP^+$ instead of NAD^+. This pathway is operative in many tissues , such as liver, erthrocytes, lacting mammary glands. Testes, and adipose tissue.

In overall process, six molecules of glucose are utilized to give six molecules of CO2 and six molecules of pentose. The pentoses are subsequently, rearranged to give four molecules of fructose -6-phosphate and two molecules of glyceraldeehyde -3-phosphate. Two trioses can also form a hexose by the reversal glycolysis.

1. Firstly, glucose is activated to glucose -6-phosphate, by enzyme hexokinase.
2. Thereafter, glucose-6-phospate is changed to 6-phosphogluconolactone and subsequently , to 6-phosphogluconate , by the enzyme glucose-6-phosphate dehydrogenase. This enzyme is induced by insulin. During this process $NADP^+$ is reduced to $NADPH + H^+$.

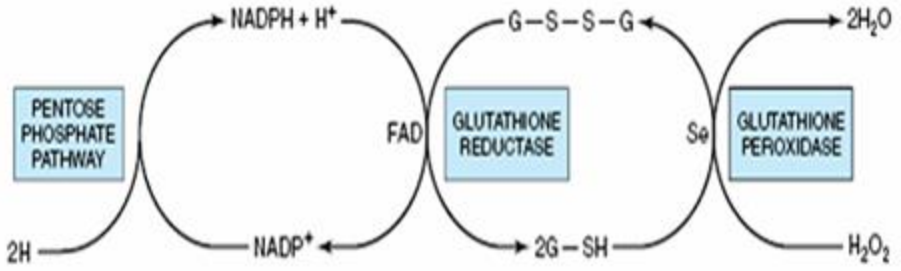


Glucose -6-phosphate dehydrogenase deficicency

Glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency is an X-linked inherited disease. Characterized by hemolytic anemia, cased by the inability to detoxify oxidizing agent. The life span of many individuals with G6PD deficiency is somewhat shortened as a result of complications arising from chronic hemolysis.

Babies with G6PD deficiency may experience neonatal jaundice, appearing one to four days after birth, which may result from impaired hepatic catabolism of heme or increased production of bilirubin.

Diminshed G6PD activity impairs the ability of the red blood cells to form the NADPH, which is essential for the maintenance of the reduced glutathione pool. The results in a decrease in the cellular detoxification of free radicals and peroxidase formed within cell. Reduced level of glutathione result in oxidation of sulfhydryl group in protein including hemoglbin and lead to the formation of denatured protein that form insluble masses, called Heinz bodies, which gets attached to the red cell membrane



Glutathione role in RBCs

Factors determining blood glucose level:

Under normal conditions of nutritional intake and balance, the blood glucose concentration of the adults is usually between 80-100 *mg/dl* (4.44-5.56 *mmol/L*). After a meal high in carbohydrate content, it may rise to 130 to 160 *mg/dl* (7.22-8.89 *mmol/L*).

1. The plasma glucose level at an instant depends on the balance between glucose entering and leaving the extra cellular fluid.
2. Hormones will make this balance possible
3. The major factors which cause entry of glucose into blood are:
a) Absorption from intestines
b) Glycogenolysis (breakdown of glycogen)
c) Gluconeogenesis
d) Hyperglycemic hormones (glucagon, steroids)
4. Factors leading to depletion of glucose in blood are:
a) Utilisation by tissues for energy
b) Glycogen synthesis
c) Conversion of glucose into fat (lipogenesis)
d) Hypoglycemic hormone (insulin).

Hormonal factors:

Insulin:

Insulin is a polypeptide hormone produced by beta cells of the islets of **Langerhans** in the pancreas. Its synthesis from precursor called proinsulin.

Insulin is the only hormone that produces a decrease in blood glucose levels. It increases the uptake of glucose by muscle and fat cells, by increasing the cellular cell permeability to glucose. It is also increases the up take of glucose by the liver, promoting glycogenesis and lipogenesis (formation of fat). Overall this hormone stimulated anabolic processes.

Glucagon:

Glucagon is a linear polypeptide hormone secreted by the alpha cells of pancreatic islets. Its stimulated by:

- *Breakdown of glycogen*
- *Liver gluconeogenises*
- *Hepatic lipolysis*

Thus, the blood glucose and free fatty acid levels rise when the hormone secreted.

Epinephrine:

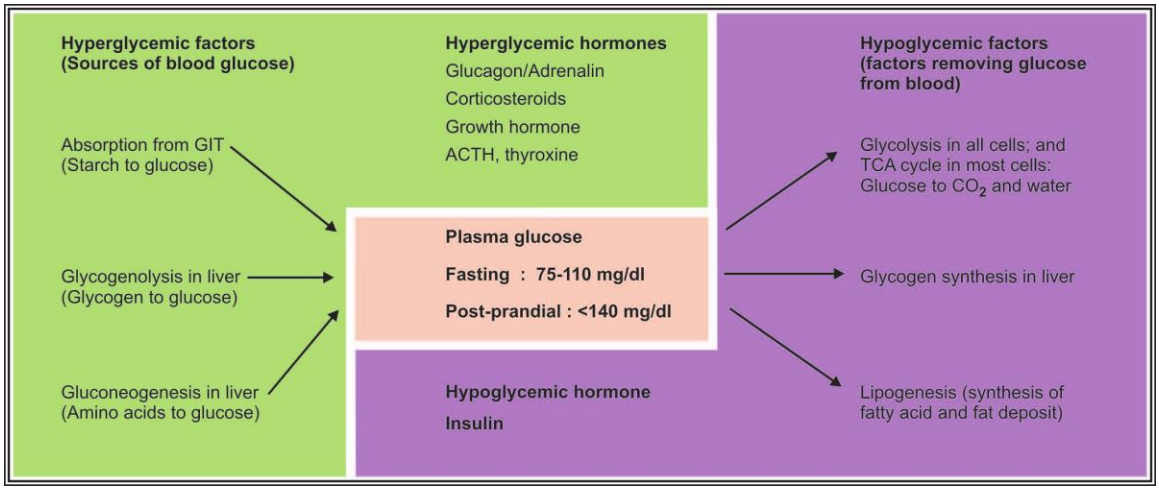
The adrenal medulla produced and secreted the hormone epinephrine (adrenaline). By activation the enzyme adenylate cyclase. Its increase the synthesis of cyclic 3,5 AMP in a number of body tissues. Its leads to the activation of phosphrylase in hepatic cells and thus, to increase breakdown of glycogen and elevation of blood glucose level.

Thyroid hormones:

The hormones thyroxin (T*3*) and triiodothyronine (T3) are secreted by the thyroid gland. Its increase the absorption of glucose from the Gastrointestinal tracts and accelerated the degradation of insulin (***hyperglycemic***). A person diagnosed as having hyperthyroidism may have symptoms of mild diabetes.

Regulation of glucose in Fasting State:

i) Normally, 2 to 2½ hours after a meal, the blood glucose level falls to near fasting levels. It may go down further; but this is prevented by processes that contribute glucose to the blood.
ii) For the next 3 hours, hepatic glycogenolysis will take care of the blood sugar level.
iii) Thereafter, gluconeogenesis will take charge of the situation.
iv) Liver is the major organ that supplies the glucose for maintaining blood glucose level.
v) Hormones like glucagon, epinephrine, glucocorticoids, growth hormone, ACTH and thyroxine will keep the blood glucose level from falling. They are referred to as anti-insulin hormones or hyperglycemic hormones.



Overview of regulation of blood sugar

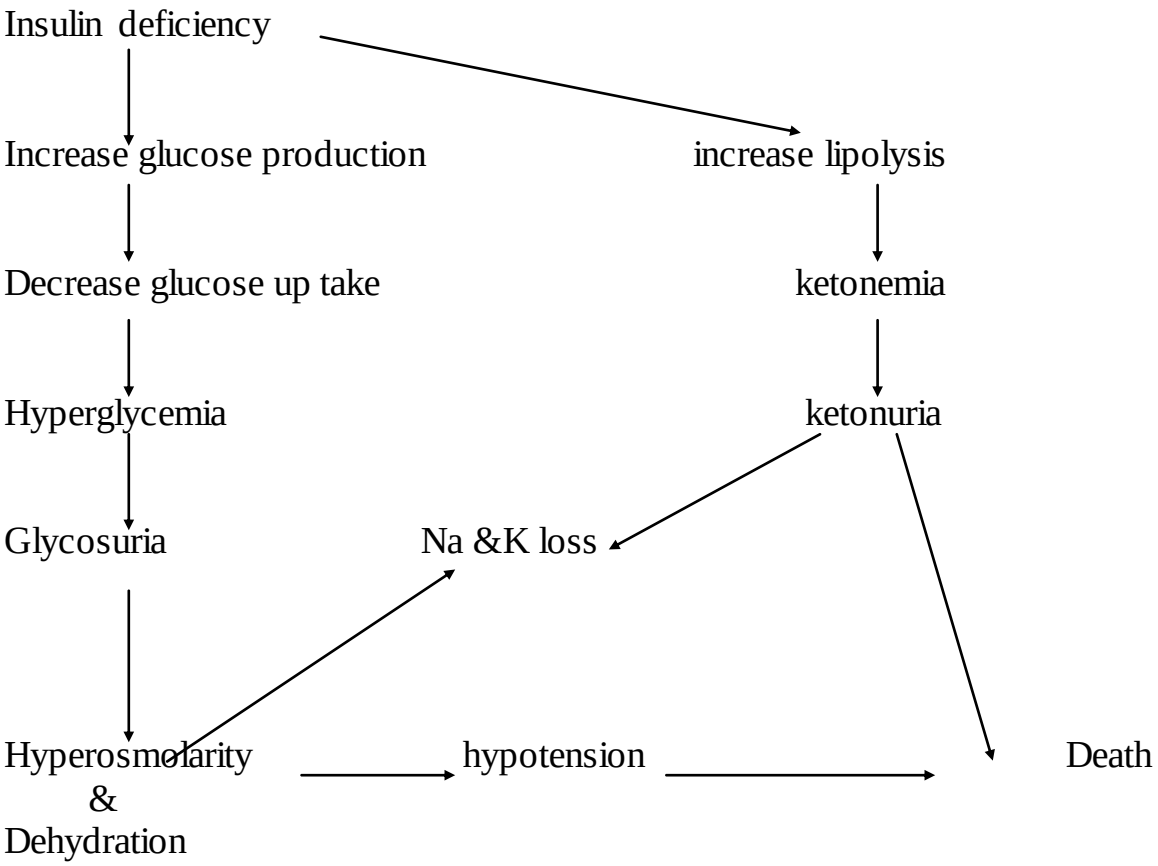
Diabetes mellitus:

Diabetes mellitus may be defined as genetically heterogeneous group of disorders manifested ultimately by insulin deficiency and loss of carbohydrate tolerance. This disease may be idiopathic or secondary to such disordered as pancreatic carcinoma, cushings syndrome and acromegaly. The idiopathic type is the most common in the united state, where it is estimated that there are 10 million case of diabetes.

Two general classification of idiopathic diabetes mellitus have been identified:

- **Type 1** (insulin–dependent diabetes mellitus (IDDM).
- **Type 2** (non-insulin dependents diabetes mellitus (NIDDM).

The pathophysiology of insulin deficiency is shown bellow:



Ketone bodies are produced when excessive amount of fatty acids are catablized and availablity of glucose islimted. these condition occurs most commonly in diabetes mellitus and prolonged fasting.

The main differents between type 1 and type 2 diabetes

	Type 1	Type 2
Age of onset	Usally during chilhood ar puberty	Frequently after age symptoms develop gradually
Prevelance	900.000 =10% of dignosed diabetes	10 milion =90% of dignised diabetes
Nutritioal status at time of disease onset	Frequently undernoished	Obesity usally present
Gentic predisposition	Moderate	Very strong
Defect or deficiency	B cells are destroyed , elimination production of insulin	Insulin resistance with inabilty of b cells to produce appropriate quantity of insulin
Plasma insulin	Low to absent	High early in disease low in disease of long duration
Acute complication	Ketoacidosis	Hyperomolar coma
Treatment with oral hypoglycemic drugs	Unresponsive	Responsive
Treatment	Insulin is always necessary	Diet + exercise No response /-- Oral hypoglycemic drugs No response/-- Insuline

Physiology:

The brain:

The brain cells are the most sensitive organ to hypoglycemia, they derive their energy from aerobic metabolism of glucose and they cannot:

- Storage glucose in significant amount.
- Synthesis of glucose.

The liver:

The liver is the most important single organ in ensuring a constant energy supply for other tissues, including the brain, under a wide variety of conditions. The hepatic cells are in a key position to buffer the hyperglycemic effect of a high carbohydrate meal. Liver can adapted different roles like:

- **Converted glucose to glycogen (glycogenesis)**
- **Converted glucose to fatty acid, which are ultimately stored as triglyceride in adipose tissue.**
- **During fasting, liver can converted fatty acid to glucose when there is short supply.**
- **Break down of glycogen to glucose (glycogenolysis).**

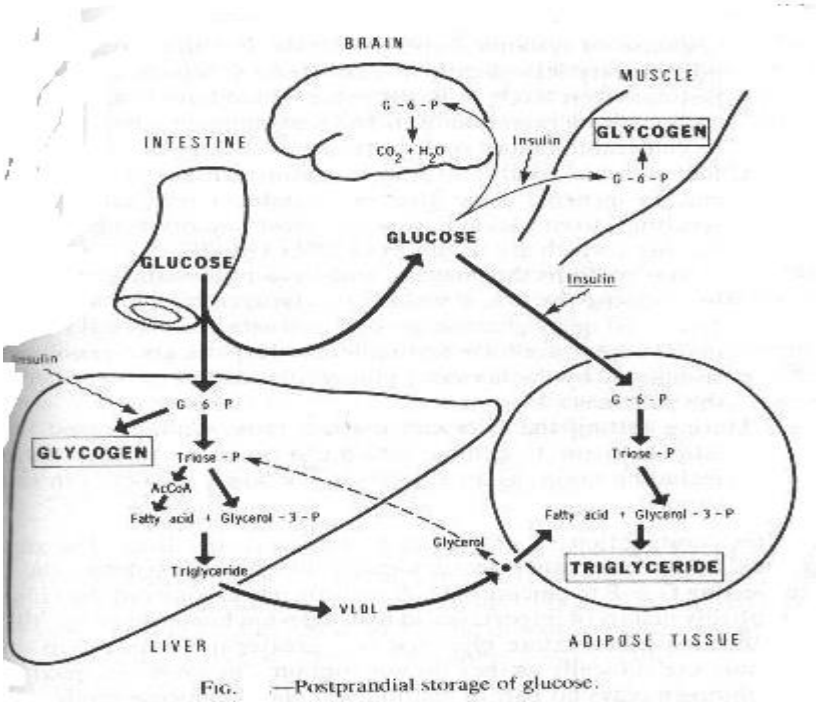


FIG. —Postprandial storage of glucose.

in muscles :

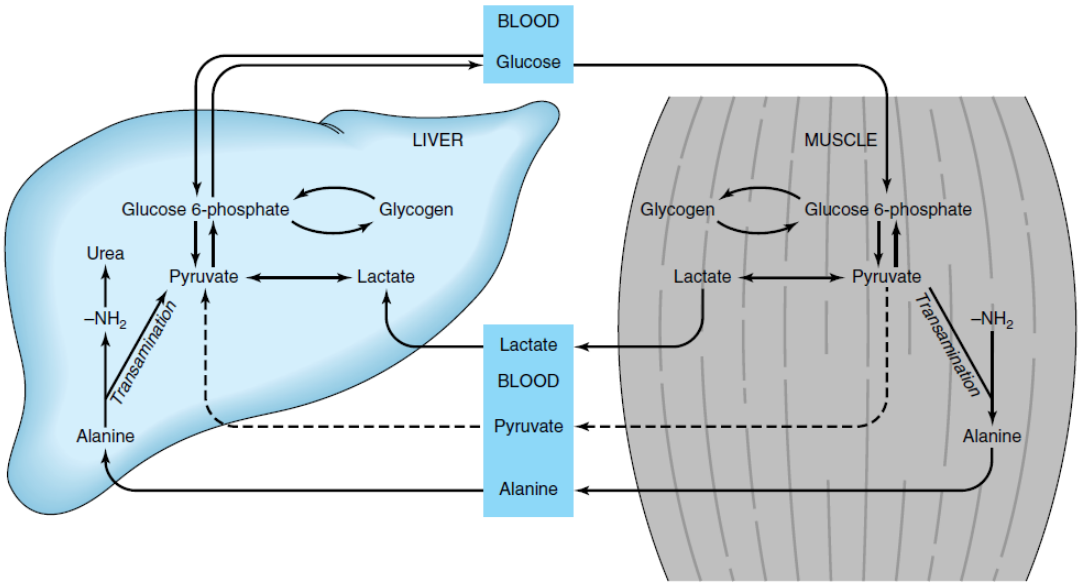


Figure 19–4. The lactic acid (Cori) cycle and glucose-alanine cycle.