CARBOHYDRATE METABOLISM

Metabolism

Metabolism is defined as a set of life-sustaining chemical reactions in organisms. The main purposes of metabolism are: ***the conversion of food to energy to run cellular processes; the conversion of food/food articles to building block unit for proteins, lipids, nucleic acids, and some carbohydrates; and the elimination of nitrogenous wastes.***

These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. (The word metabolism can also state the sum of all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the above described set of reactions within the cells is called intermediary metabolism or intermediate metabolism).

IMPORTANCE OF METABOLISM

1. Metabolic paths are required for conversion of food to energy to run cellular processes; the conversion of food/food articles to building block unit for proteins, lipids, nucleic acids, and some carbohydrates; and the elimination of nitrogenous wastes.
2. For detoxification of various xenobiotics, accumulation of these substances within the body may be harmful to human being.
   For example degradation of drugs.

Types of metabolic reactions:-

1. Catabolism
2. Anabolism

Catabolism:-

The word "catabolic" means the same as "degradative," but it is Greek and therefore sounds a whole lot more intellectual and studious. A large share of the substrates broken down in **catabolism** is used for **producing ATP**, the **"Electric energy"** of the cell. Just as electricity can be used to drive just about any domestic job, ATP is used for almost every energy-driven job in cell biology. Because of its key role in the life of the cell, we will study metabolism of carbohydrates, lipids and proteins for generation of ATP (stored form of energy).

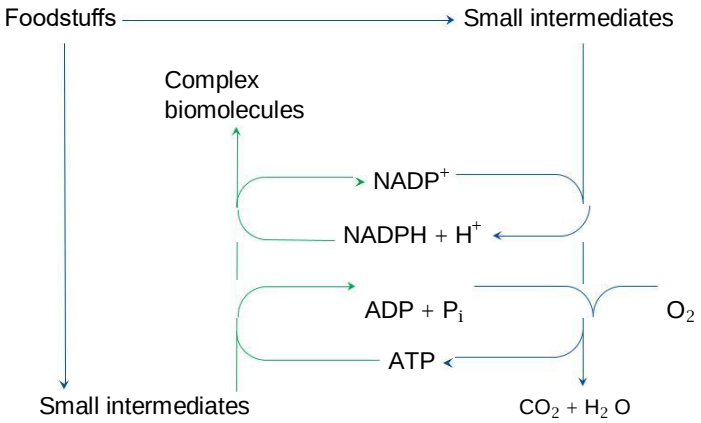
Anabolism

The word "**anabolic**" might explain as "**productive**." *Anabolic pathways are the opposite of catabolic paths, that is, they generate new biomolecules.* They produce ***small molecules*** and ***building blocks*** that are not sufficiently available in the food, as well as ***macromolecules,*** in particular ***proteins*** and ***nucleic acids***. Apart from building block

elements and ATP, anabolic pathways also require a good deal of ***decreasing power***, mostly in the form of **NADPH**. One major pathway that supplies NADPH is the hexose monophosphate shunt, which will be covered in later section.

Some pathways can perform both in catabolic and anabolic activities. An example is the Citric Acid Cycle, which breaks down Acetyl-CoA but also contributes in the synthesis of amino acids. Such pathways are sometimes to as ***Amphibolic.***

Flow chart representing the Catabolic and Anabolic path:



Abnormal Metabolism:

Most of the chemical reactions occurs/ catalyzed by enzymes. Deficiency of an enzyme leads to disturbance in metabolism. Enzyme deficiency may be due to following

1. Dietary deficiency
2. Disease
3. Genetic defects

Dietary deficiency:

Deficiency of *Iron* in diet leads to decrease *Hemoglobin* synthesis which leads to *Iron deficiency anemia*. Deficiency of Iodine leads to defective synthesis of *Thyroid hormone*. It results in *hypothyroidism*.

Disease :

Metabolism is disturbed in certain diseases. In liver disease there is decrease synthesis of drug metabolizing enzymes. So drugs may produce toxic effects in liver diseases.

Genetic defects:

Some enzymes deficiencies occur due to genetic defects. These defects are called as inborn errors of metabolism. For example disease like frucosuria and galactosemia occurs due to inborn errors of carbohydrates metabolism.

Carbohydrate Metabolism

1. INTRODUCTION

All living cells require energy to carry out various cellular activities. This energy is stored in the chemical bonds of organic molecules (e.g. carbohydrates, fats, proteins) that we eat as food. These organic molecules are broken down by enzymatic reactions in cells to generate energy in the form of adenosine triphosphate (ATP). The ATP generated by these pathways in cells is used to drive fundamental cellular processes. The food we consume is mainly comprised of proteins, polysaccharides (carbohydrates) and fats. These are first broken down into smaller units: proteins into amino acids, polysaccharides into sugars, and fats into fatty acids and glycerol. This process of digestion occurs outside the cell. The amino acids, simple sugars and fatty acids then enter the cell and undergo oxidation by glycolysis (in the cytosol) and the citric acid cycle (in the mitochondria) to generate ATP (from ADP and P_i).

OBJECTIVES

After reading the notes student will be able to…….

- Describe glycolysis, Citric Acid Cycle
- Explain Glycogenesis and Glycogenolysis
- Describe the Hormonal regulation of blood sugar level

GLYCOLYSIS (EMBDEN-MEYERHOF PATHWAY)

Definition

In glycolysis pathway glucose is converted to pyruvate (aerobic condition) or lactate (anaerobic condition), along with production of a small quantity of energy.

Site of reaction: All the reactions are take place in the cytoplasm.

Importance of the glycolysis pathway:

- It is the only pathway that is taking place in all the cells of the body.
- Glycolysis is the only source of energy in erythrocytes.
- In vigorous exercise, when muscle tissue lacks enough oxygen, anaerobic glycolysis forms the major source of energy for muscles.
- The glycolytic pathway may be considered as the preliminary step before complete oxidation.
- The glycolytic pathway provides carbon skeletons for synthesis of non-essential amino acids as well as glycerol part of fat.
- Most of the reactions are reversible.

Steps of glycolytic pathway

1. Glucose is phosphorylated to glucose -6-phosphate. The enzyme is hexokinase, which splits ATP into ADP and the Pi is added on to the glucose. The energy released by hydrolysis of

ATP is utilized for the forward reaction. Hexokinase is the key glycolytic enzyme and the reaction is irreversible.

2. Glucose-6-phosphate is isomerised to fructose-6-phosphate by phosphohexose isomerase.
3. Fructose-6-phosphate is further phosphorylated to fructose-1,6-bisphosphate. The enzyme is phosphofructokinase, it is an important key enzyme and the reaction is irreversible.
4. Fructose-1, 6-bisphosphate is cleaved into two 3 carbon atoms; one glyceraldehyde-3-phosphate and another molecule of dihydroxyacetone phosphate. The enzyme is aldolase. Dihydroxyacetone phosphate is isomerised to glyceraldehyde-3-phosphate by the enzyme phophotriose isomerase.
5. Glyceraldehyde-3-phosphate is dehydrogenated and simultaneously phosphorylated to 1,3-bis-phosphoglycerate with the help of NAD^+. The enzyme is glyceraldehyde-3-phosphate dehydrogenase.
6. 1, 3-bis-phosphoglycerate is converted to 3-phosphoglycerate by the enzyme 1, 3-bis-phosphoglycerate kinase. Here one molecule of ATP is formed and this reaction is an example for Substrate level phosphorylation.
7. 3-phosphoglycerate is isomerised to 2-phosphoglycerate by shifting the phosphate group from 3^{rd} to 2^{nd} carbon atom. The enzyme is phosphoglucomutase.
8. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. One water molecule is removed. A high energy phosphate bond is produced. This enzyme requires $Mg^{++}$and inhibited by fluoride.
9. Phosphoenol pyruvate is dephosphorylated to pyruvate, by pyruvate kinase. One molecule of ATP is generated. This step is irreversible.
10. In anaerobic condition pyruvate is reduced to lactate by lactate dehydrogenase.In aerobic conditions pyruvate enters citric acid cycle for complete oxidation. The lactate from anaerobic cycle enters cori's cycle.

Energy produce from glycolysis

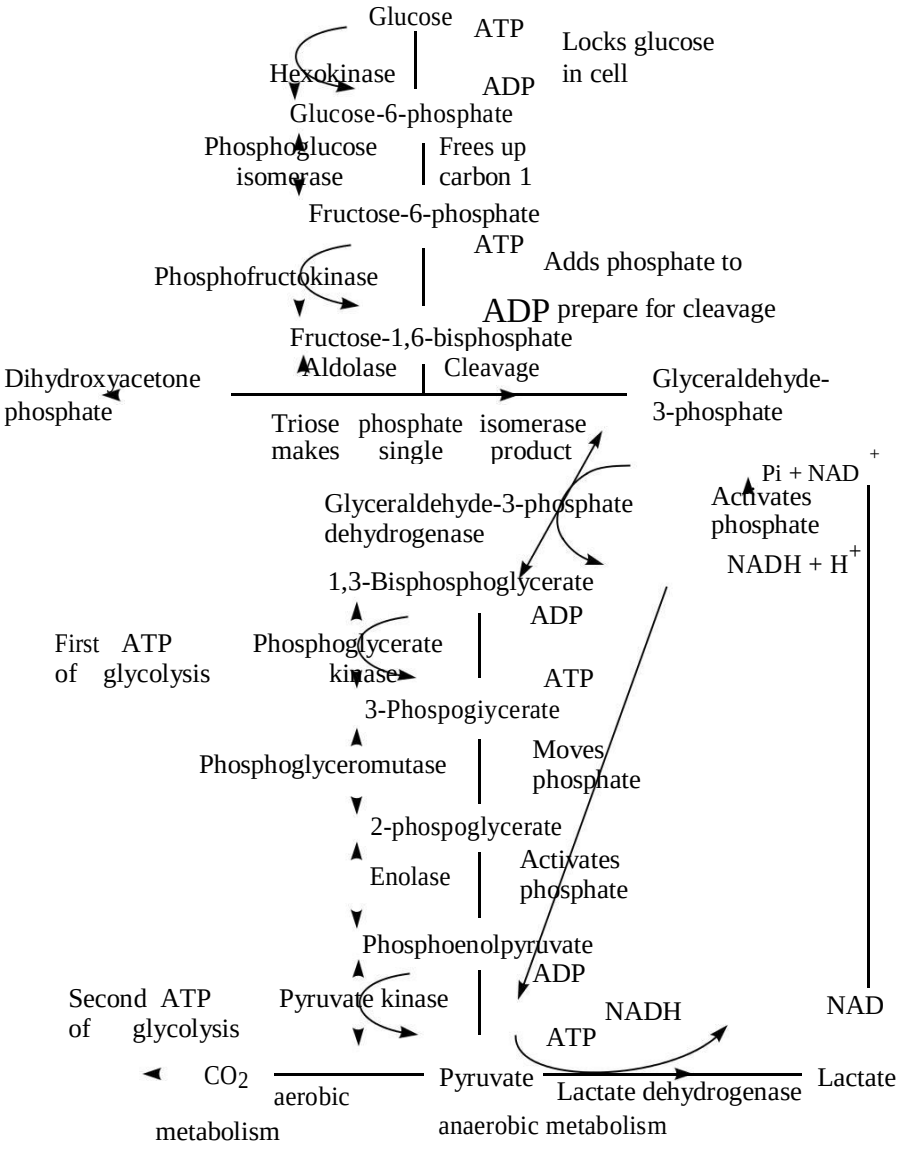
I. Aerobic conditions

II. Number of ATPs gained per glucose molecule is 8 ATPs

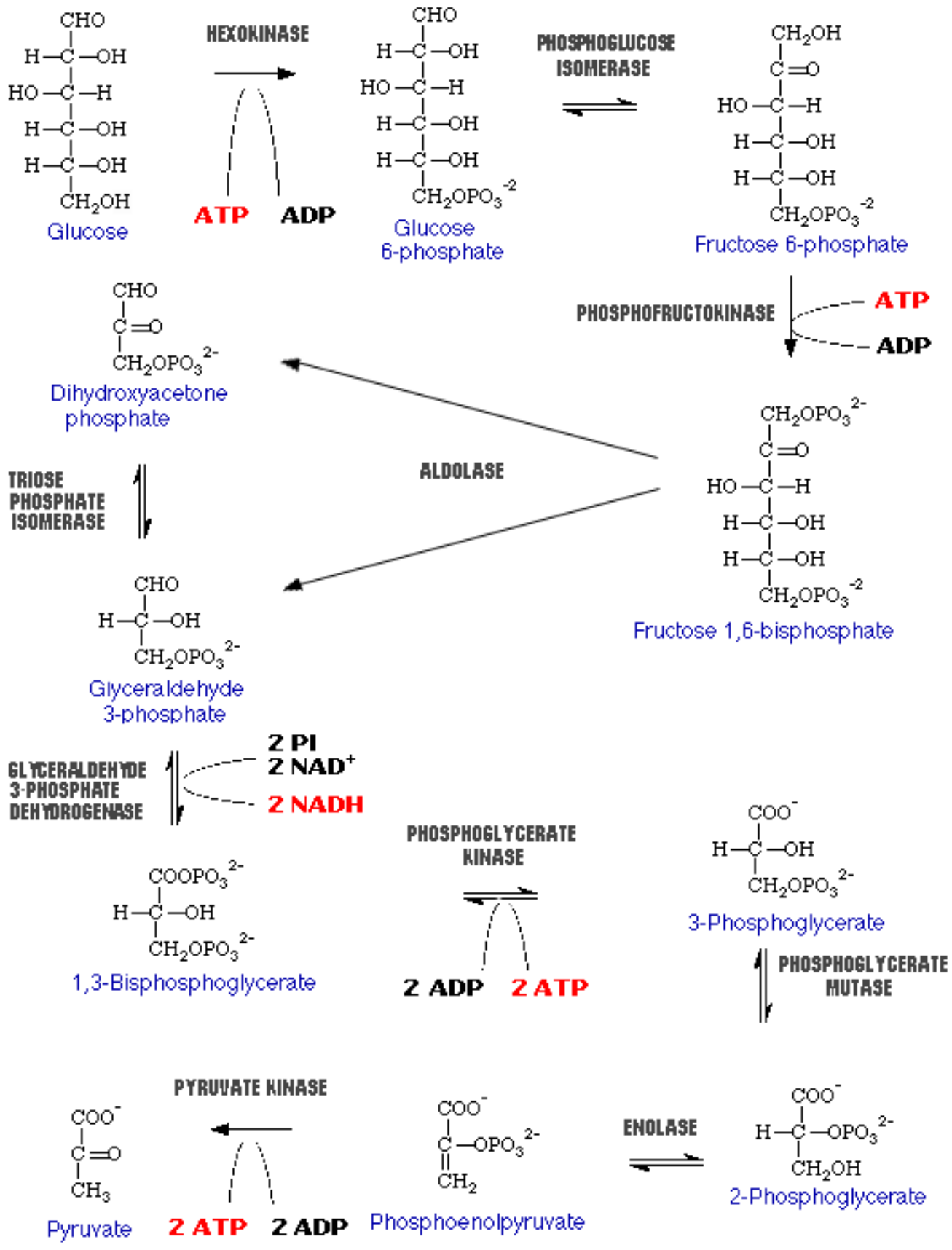
III. Anaerobic conditions

IV. Number of ATPs gained per glucose molecule is 2 ATPs

FLOW CHART EXPRESSING GLYCOLYSIS PATHWAY



GLYCOLYSIS PATHWAY



1.2. CITRIC ACID CYCLE: (KREB'S CYCLE)

Under aerobic conditions the end product of glycolysis is pyruvic acid. The next step is the formation of acetyl coenzyme A (acetyl CoA) - this step is technically not a part of the citric acid cycle, but is shown on the diagram on the top left.

Acetyl CoA, whether from glycolysis or the fatty acid spiral, is the initiator of the citric acid cycle. In carbohydrate metabolism, acetyl CoA is the link between glycolysis and the citric acid cycle. The initiating step of the citric acid cycle occurs when a four carbon compound (oxaloacetic acid) condenses with acetyl CoA (2 carbons) to form citric acid (6 carbons).

The whole purpose of a "turn" of the citric acid cycle is to produce two carbon dioxide molecules. This general oxidation reaction is accompanied by the loss of hydrogen and electrons at four specific places. These oxidations are connected to the electron transport chain where many ATP are produced.

Step 1

The acetic acid subunit of acetyl CoA is combined with oxaloacetate to form a molecule of *citrate*. The acetyl coenzyme A acts only as a transporter of acetic acid from one enzyme to another. After Step 1, the coenzyme is released by hydrolysis so that it may combine with another acetic acid molecule to begin the Krebs cycle again.

Step 2

The citric acid molecule undergoes an isomerization. A hydroxyl group and a hydrogen molecule are removed from the citrate structure in the form of water. The two carbons form a double bond until the water molecule is added back. Only now, the hydroxyl group and hydrogen molecule are reversed with respect to the original structure of the citrate molecule. Thus, *isocitrate* is formed.

Step 3

In this step, the isocitrate molecule is oxidized by a NAD molecule. The NAD molecule is reduced by the hydrogen atom and the hydroxyl group. The NAD binds with a hydrogen atom and carries off the other hydrogen atom leaving a carbonyl group. This structure is very unstable, so a molecule of CO_2 is released creating *alpha-ketoglutarate*.

Step 4

In this step, coenzyme A, returns to oxidize the alpha-ketoglutarate molecule. A molecule of NAD is reduced again to form NADH and leaves with another hydrogen. This instability causes a carbonyl group to be released as carbon dioxide and a thioester bond is formed in its place between the former alpha-ketoglutarate and coenzyme A to create a molecule of *succinyl-coenzyme A* complex.

Step 5

A water molecule sheds its hydrogen atoms to coenzyme A. Then, a free-floating phosphate group displaces coenzyme A and forms a bond with the succinyl complex. The

phosphate is then transferred to a molecule of GDP to produce an energy molecule of GTP. It leaves behind a molecule of *succinate*.

Step 6

In this step, succinate is oxidized by a molecule of FAD (Flavin adenine dinucleotide). The FAD removes two hydrogen atoms from the succinate and forces a double bond to form between the two carbon atoms, thus creating *fumarate*.

Step 7

An enzyme adds water to the fumarate molecule to form *malate.* The malate is created by adding one hydrogen atom to a carbon atom and then adding a hydroxyl group to a carbon next to a terminal carbonyl group.

Step 8

In this final step, the malate molecule is oxidized by a NAD molecule. The carbon that carried the hydroxyl group is now converted into a carbonyl group. The end product is *oxaloacetate* which can then combines with acetyl-coenzyme A and begin the Krebs cycle all over again.

Summary of Krebs cycle

In summary, three major events occur during the Krebs cycle. One GTP (guanosine triphosphate) is produced which eventually donates a phosphate group to ADP to form one ATP; three molecules of NAD are reduced; and one molecule of FAD is reduced. Although one molecule of GTP leads to the production of one ATP, the production of the reduced NAD and FAD are far more significant in the cell's energy-generating process. This is because NADH and $FADH_2$ donate their electrons to an electron transport system that generates large amounts of energy by forming many molecules of ATP.

Yield of ATP

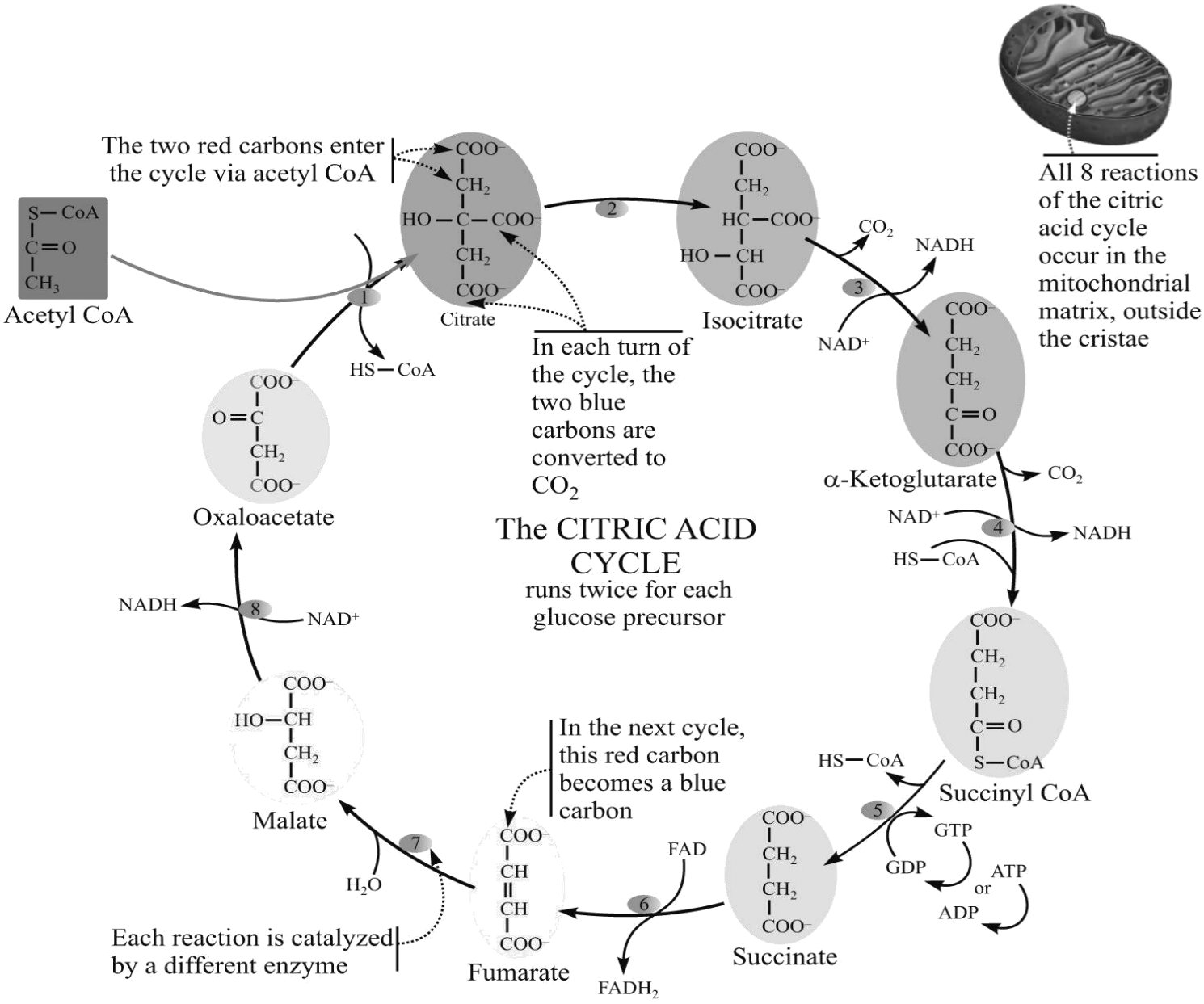
At this point the yield of ATP is 4 moles per mole of Glucose as it passes through the Krebs cycle.

- This is not much more than the 2 moles which would have been produced from glycolysis.
- However, NADH and FADH2 are energy rich molecules
- Their oxidation is highly exergonic and is coupled with the production of ATP from ADP
- Oxidation of 1 mole NADH produces 3 moles ATP
- Oxidation of 1 mole FADH2 produces 2 moles ATP
- Thus total ATP yield = (10 × 3) + (2 × 2) + 4 = 38 moles ATP per mole Glucose

<u>Biosynthesis of Glycogen</u>

The goal of glycolysis, glycogenolysis, and the citric acid cycle is to conserve energy as ATP from the catabolism of carbohydrates. If the cells have sufficient supplies of ATP, then

these pathways and cycles are inhibited. Under these conditions of excess ATP, the liver will attempt to convert a variety of excess molecules into glucose and/or glycogen.

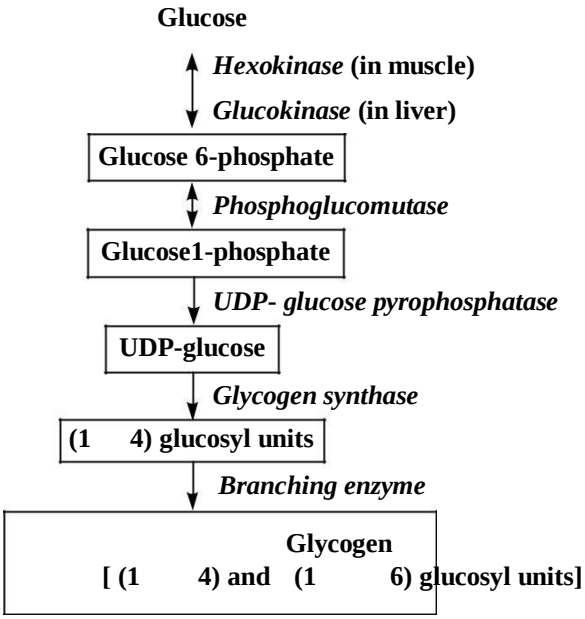


Glycogenesis and Glycogenolysis

1.3 Glycogenesis

Glycogenesis is the formation of glycogen from glucose. Glycogen is synthesized depending on the demand for glucose and ATP (energy). If both are present in relatively high amounts, then the excess of insulin promotes the glucose conversion into glycogen for storage in liver and muscle cells.

In the synthesis of glycogen, one ATP is required per glucose incorporated into the polymeric branched structure of glycogen. Actually, glucose-6-phosphate is the cross-roads compound. Glucose-6-phosphate is synthesized directly from glucose or as the end product of gluconeogenesis.



Steps of Glycogenesis

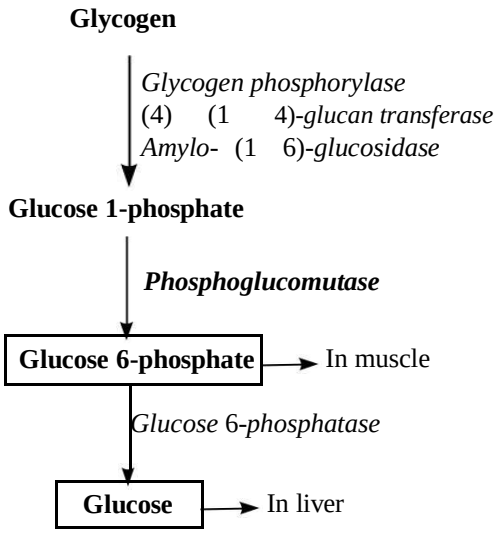
1.4 Glycogenolysis

In glycogenolysis, glycogen stored in the liver and muscles, is converted first to glucose-1- phosphate and then into glucose-6-phosphate. Two hormones which control glycogenolysis are a peptide, glucagon from the pancreas and epinephrine from the adrenal glands.

Glucagon is released from the pancreas in response to low blood glucose and epinephrine is released in response to a threat or stress. Both hormones act upon enzymes to stimulate glycogen phosphorylase to begin glycogenolysis and inhibit glycogen synthetase (to stop glycogenesis).

Glycogen is a highly branched polymeric structure containing glucose as the basic monomer. First individual glucose molecules are hydrolyzed from the chain, followed by the addition of a phosphate group at C-1. In the next step the phosphate is moved to the C-6 position to give glucose 6-phosphate, a cross road compound.

Glucose-6-phosphate is the first step of the glycolysis pathway if glycogen is the carbohydrate source and further energy is needed. If energy is not immediately needed, the glucose-6-phosphate is converted to glucose for distribution in the blood to various cells such as brain cells.



Steps of glycogenolysis

1.5 Gluconeogenesis

Gluconeogenesis is a metabolic pathway that results in the production of glucose from non-carbohydrate carbon substrate like as pyruvate, lactate, glycerol and glucogenic amino acids.

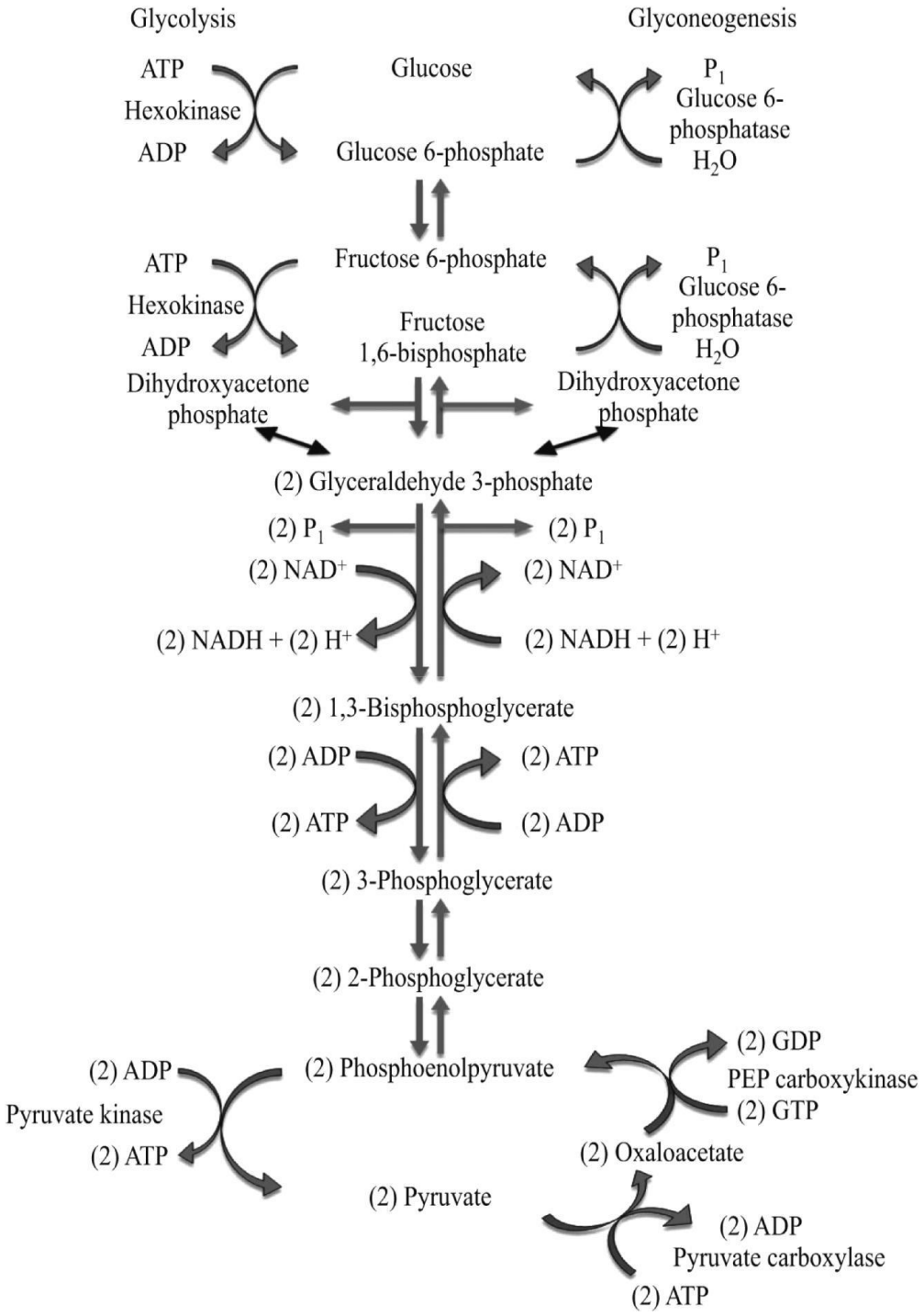
The vast majority of gluconeogenesis takes place in the liver and, to a smaller extent, in the cortex of kidneys. This process occurs during periods of fasting, starvation, or intense exercise and is highly endergonic. Gluconeogenesis is often associated with ketosis.

Entering the pathway

Several non-carbohydrate carbon substrates can enter the gluconeogenesis pathway. One common substrate is lactic acid, formed during anaerobic respiration in skeletal muscle. Lactate is transported back to the liver where it is converted into pyruvate by the **Cori cycle** using the enzyme lactate dehydrogenase. Pyruvate, the first designated substrate of the gluconeogenic pathway, can then be used to generate glucose. All citric acid cycle intermediates, through conversion to oxaloacetate, amino acids other than lysine or leucine, and glycerol can also function as substrates for gluconeogenesis. Amino acids must have their amino group removed by transamination or deamination before entering the cycle directly (as pyruvate or oxaloacetate), or indirectly via the citric acid cycle.

Fatty acids cannot be converted into glucose in animals, the exception being odd-chain fatty acids which yield propionyl CoA, a precursor forsuccinyl CoA. In plants, specifically in seedlings, the glyoxylate cycle can be used to convert fatty acids (acetate) into the primary carbon source of the organism. The glyoxylate cycle produces four-carbon dicarboxylic acids that can enter gluconeogenesis. Glycerol, which is a part of alltriacylglycerols, can also be used in gluconeogenesis. In organisms in which glycerol is derived from glucose (e.g., humans and other mammals), glycerol is sometimes not considered a true gluconeogenic substrate, as it cannot be used to generate new glucose.

Gluconeogenesis is a pathway consisting of eleven enzyme-catalyzed reactions. The pathway can begin in the mitochondria or cytoplasm, depending on the substrate being used. Many of the reactions are reversible steps found in glycolysis.



Glycolysis and Gluconeogenesis

Gluconeogenesis begins in the mitochondria with the formation of oxaloacetate through carboxylation of pyruvate at the expense of one molecule of ATP. This reaction is catalyzed by

pyruvate carboxylase, which is stimulated by high levels of acetyl-CoA(when fatty acid oxidation is high in the liver) and inhibited by high levels of ADP.

Oxaloacetate must then be reduced into malate using NADH in order to be transported out of the mitochondria.

In the cytoplasm, malate is oxidized to oxaloacetate using NAD+, where the remaining steps of gluconeogenesis occur. Oxaloacetate is then decarboxylated and phosphorylated to produce phosphoenolpyruvate by phosphoenolpyruvate carboxykinase. One molecule of GTP is hydrolyzed to GDP in the course of this reaction.

The next steps in the reaction are the same as reversed glycolysis. However, fructose-1,6-bisphosphatase converts fructose-1,6-bisphosphate to fructose-6-phosphate. The purpose of this reaction is to overcome the large negative G.

Glucose-6-phosphate is formed from fructose-6-phosphate by phospho gluco-isomerase. Glucose-6-phosphate can then be used for glucose generation or in other metabolic pathways. Free glucose is not generated automatically because glucose, unlike glucose-6-phosphate, tends to freely diffuse out of the cell.

The final reaction of gluconeogenesis, the formation of glucose, is carried out in the lumen of the endoplasmic reticulum. Glucose-6-phosphate is hydrolyzed by glucose-6-phosphatase to produce glucose. Glucose is then shuttled into the cytosol by glucose transporters located in the membrane of the endoplasmic reticulum

1.6 Insulin and Glucagon: Control of Blood Glucose

One of the most important responses in the human body is the concentration of blood glucose (blood sugar). Glucose is the major catabolic product of cellular metabolism. As such, it is required both as an energy source and as a source of carbon for making organic molecules.

Blood glucose concentrations are regulated by negative feedback pathways that are modulated by two separate hormones: **Insulin** and **glucagon**. Both of these hormones are produced in **special cells** called **islet cells, or islets of Langerhans** – are found in clusters throughout the pancreas. Islet cells make up a very small percentage of the pancreas (about 1-2%); the remainder of the organ is an exocrine gland producing Digestive Enzymes and Bicarbonate ion. This tiny number of endocrine cells is exceedingly important. Each islet contains two kinds of cells: alpha cells, which produce glucagon, and beta cells, which produce insulin.

Metabolic disorders of carbohydrates:

1. Diabetes mellitus
2. Glysuria
3. Hypoglycemia

Diabetes mellitus:

Diabetes mellitus is a metabolic disease, characterized by hyperglycemia. It is divided into 2 groups IDDM & NIDDM.

Insulin dependent diabetes mellitus (IDDM)

- Type 1 Diabetes – Juvenile onset diabetes
- Occurs in childhood
- 10-20% on known diabetics
- Characterized by almost total deficiency of insulin-> due to destruction of Beta cells of Pancreas
- Symptoms appear after 80-90% of Beta cells have been destroyed.
- Pancreas fails to secrete insulin in response to insulin ingestion
- Therefore, patient require insulin therapy

Non-Insulin dependent diabetes mellitus (NIDDM)

- Type 2 diabetes- Adult onset diabetes
- Most common, 80-90% of diabetic population
- Occurs in adults
- Commonly occurs in obese individuals
- Decreasing insulin receptors on insulin responsive cells.
- Increased level of Tumor Necrosis Factor

Glycosuria

- Commonest cause of glucose excretion in urine.
- It is first line screening test for diabetes
- Normally, glucose does not appear in urine until plasma glucose concentration exceeds renal threshold (180mg/dL)

Renal glycosuria

- Benign condition due to reduced renal threshold for glucose
- Unrelated to diabetes
- Not accompanied by classical symptoms of diabetes

Hypoglycemia

Hypoglycemia, also known as **low blood sugar**, is when blood sugar decreases to below normal levels. This may result in a variety of symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures or death. A feeling of hunger, sweating, shakiness and weakness may also be present.[1] Symptoms typically come on quickly.

The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin and sulfonylureas. Risk is greater in diabetics who have eaten less than usual, exercised more than usual or have drunk alcohol. Other causes of hypoglycemia include kidney failure, certain tumors, such as insulinoma, liver disease, hypothyroidism, starvation, inborn error of metabolism, severe infections, reactive hypoglycemia and a number of drugs including alcohol. Low blood sugar may occur in otherwise healthy babies who have not eaten for a few hours

Hypoglycemic symptoms and manifestations can be divided into those produced by the counter regulatory hormones (Epinephrine/Adrenaline and Glucagon) triggered by the falling glucose, and the neuroglycopenic effects produced by the reduced brain sugar.

Symptoms of hypoglycemia:

- Shakiness, anxiety, nervousness
- Palpitations, tachycardia
- Sweating, feeling of warmth (sympathetic muscarinic rather than adrenergic)
- Pallor, coldness, clamminess
- Dilated pupils (mydriasis)
- Hunger, borborygmus
- Nausea, vomiting, abdominal discomfort
- Headache

Central nervous system

- Abnormal thinking, impaired judgment
- Nonspecific dysphoria, moodiness, depression, crying, exaggerated concerns
- Feeling of numbness, pins and needles (paresthesia)
- Negativism, irritability, belligerence, combativeness, rage
- Personality change, emotional lability
- Fatigue, weakness, apathy, lethargy, daydreaming, sleep
- Confusion, memory loss, lightheadedness or dizziness, delirium
- Staring, glassy look, blurred vision, double vision
- Flashes of light in the field of vision
- Automatic behavior, also known as automatism
- Difficulty speaking, slurred speech
- Ataxia, incoordination, sometimes mistaken for drunkenness
- Focal or general motor deficit, paralysis, hemiparesis
- Headache
- Stupor, coma, abnormal breathing
- Generalized or focal seizures

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