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Hypoglycemia as a Pathological Result in Medical Praxis

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1. Introduction

Maintenance of blood glucose homeostasis is fundamentally important for health. The maintain of stable levels of glucose in the blood is one of the most finely regulated of all homeostatic mechanisms and one in which the liver, the extrahepatic tissues, and several hormones play a part. Even mild disruptions of glucose homeostasis can have adverse consequences.

The physiological post absorptive serum glucose concentration in healthy humans range is 4, 4-5,8 mmol/L (80 to 105 mg/dL). The stability of the plasma glucose level is a reflection of the balance between the rates of whole body glucose production and glucose utilization.

Generally, hypoglycemia is defined as a serum glucose level below 3. 8 mmol/L (70 mg/dL).As a relatively rare disorder, hypoglycemia most often affects those humans at the extremes of age, such as infants and the elderly, but may happen at any age.

As a medical problem, hypoglycemia is diagnosed by the presence of three key features (known as Whipple's triad). Whipple's triad is:

1. symptoms consistent with hypoglycemia,
2. a low plasma glucose concentration, and
3. relief of symptoms after the plasma glucose level is raised.

The etiology of hypoglycemia is numerous:

1. Inborn error of metabolism (more common in the pediatric patient than in adults). Disturbance in carbohydrates metabolism: Malabsorption of glucose/galactose, alactasia, asucrasia, galactosemia, fructose intolerance. Glycogen storage disease, Type I ,or von Gierke Disease, glycogen storage disease, Type III, a deficiency of glycogen disbranching enzyme activity (limit dextrinosis), Type VI glycogen storage disease, a deficiency of liver phosphorylase)
2. **Hormonal disturbance** .The hormone insulin plays a central role in the regulation of the blood glucose concentration. It is produced by the β cells of islets of Langerhance in the pancreas. Insulin exerts hypoglycemic effect. Glucagon is the hormone produced by the α

cells of Langerhance islets in the pancreas. Its secretion is stimulated by hypoglycemia. The hormone glucagon, epinephrine, norepinephrine, growth hormone, and cortisol exert the opposite effects to insulin and they belong in the counter-regulatory hormones

3. The disorders of some organs (Liver and Kidney Disorders especially). Any abnormality in the functioning of the liver can disturb the process of blood-sugar regulation, resulting in hypoglycemia. On the other hand, kidney disorder can be one of the major causes of low blood sugar.

4. Infection-related hypoglycemia (in older adults)

5. The adverse medication reactions

6. Hypoglycemia as the complication of treatment of diabetes mellitus.

The central nervous system requires glucose as its primary fuel. The brain uses more than 30% of blood glucose. The brain does not produce the glucose required for its functioning and it is completely dependent on the rest of the body for its supply. So, fluctuations in blood sugar levels can prove to be harmful for the brain; a continual supply of glucose is necessary as a source of energy for the nervous system and some other organs like erythrocytes, testes and kidney medulla .Gluconeogenesis, the biosynthesis of new glucose, (i.e. not glucose from glycogen) from other metabolites (lactic acid, amino acids and glycerol) is necessary for use as a fuel, since glucose is the sole energy source for these organs.

The symptoms caused by low blood sugar come from two sources and may resemble other medical conditions. The first symptoms are caused by the release of epinephrine from the nervous system. These include sweating, pale skin color, shakiness, trembling, rapid heart rate, a feeling of anxiety, nervousness, weakness, hunger, nausea and vomiting. Lowering of the brain's glucose causes: headache, difficulty in thinking, changes in vision, lethargy, restlessness, inability to concentrate or pay attention, mental confusion, sleepiness, stupor, and personality changes.

To treat low blood sugar immediately the patients should eat or drink something that has sugar in it, such as orange juice, milk, or a hard candy. It is need to find out the causes of hypoglycemia.

Laboratory diagnosis of hypoglycemia is very important in medical praxis especially in pediatric, internal medicine (hepatology, renal failure, and cardiology) neuropsychiatry disorders and so on.

Glucose is the name of the simple sugar found in plant and animal tissues. It is made within plants as a product of photosynthesis. Although glucose can be produced within the human body, most of it is supplied to people by dietary carbohydrate intake principally as starch. Once consumed and digested, glucose will either be used immediately or stored as glycogen for future use, (Caraway & Watts,1986; Mayer,1975).

Glucose is the major energy source for human body and is derived primarily from dietary carbohydrates (grains, starchy vegetables, and legumes), from body stores of carbohydrates (glycogen) and from the synthesis of glucose from protein and glycerol moiety of triglycerides (gluconeogenesis) (King, 2011).

The glucose level in blood is kept within narrow range through a variety of influences. While there is some variation in blood glucose as circumstance changes (feeding, prolonged fasting), levels above or below the normal range usually indicate disease.

High blood glucose due to diabetes mellitus is the most commonly encountered disorder of carbohydrate metabolism. Low blood glucose is an uncommon cause of serious diseases. There are numerous rare conditions that cause hypoglycemia in neonatal period and early

childhood. In adults, low blood glucose in the fasting state is almost always due to a serious underlying condition (Caraway & Watts,1986; King, 2011; Mayer, 1975; Service,1992).

2. Digestion and absorption of carbohydrates

Carbohydrates are important components of the diet. The carbohydrates that we ingest range from simple monosaccharides (glucose, fructose and galactose) to disaccharides (lactose, sucrose) and complex polysaccharides, starch and glycogen. Most carbohydrates are digested by salivary and pancreatic amylases, and are further broken down into monosaccharides by enzymes in the brush border membrane (BBM) of enterocytes. Maltase, lactase and sucrase-isomaltase are disaccharidases involved in the hydrolysis of nutritionally important disaccharides, maltose, lactose, saccharose. Once monosaccharides are presented to the BBM, mature enterocytes, expressing nutrient transporters, transport the sugars into the enterocytes, (Drozdowski & Thomson, 2006).

The resultant glucose and other simple carbohydrates, galactose (from lactose) and fructose (from succrose) are transported across the intestinal wall to the hepatic portal vein and then to liver parenchymal cells. Both fructose and galactose are readily converted to glucose by hepatocytes Absorption of glucose and galactose occurs by an active carrier-mediated transfer process. Fructose is absorbed by facilitated diffusion (Harper,1975; King, 2011; www.deo.ucsf.edu/type1/understanding-diabetes).

Fructose and galactose are phosphorylated by specific enzymes, fructokinase and galactokinase, presented only in the liver, and converted to glucose. Glucose is transported from the liver via the bloodstream to be used by all the body cells as the most important source of energy. Glucose, as unique sugar in systemic blood circulation, leaves the blood, enters cells through specific transport proteins and has one principal fate: it is phosphorylated by ATP to form glucose-6-phosphate by hexokinase in all human body cells or by the action of glucokinase in hepatocytes. This step is notable because glucose-6-phosphate cannot diffuse through the membrane out of the cells (Haris, 1997; Harper,1979; King,2011; Tietz,1986; Voet & Voet, 2004a).

3. Glycemia - Physiological regulation

Maintenance of blood glucose homeostasis is fundamentally important for health. The plasma glucose level is tightly controlled throughout life in the normal individual, in spite of intermittent food ingestion and periods of fasting, as the net balance between the rates of glucose production and utilization. The stability of the plasma glucose level is a reflection of the balance between the rates of whole body glucose production and glucose utilization.

The amount of plasma glucose level in healthy humans is usually maintained within a range of 4.4 to 5.8 mmol/L , 80 to 110 mg/dL), (Carraway & Watts,1986; King, 2011; Mayes,1975; Service, 1992; Voet & Voet, 2004a).

4. Intermediary metabolism of carbohydrates

4.1 Glycogen synthesis
Glycogen is the storage form of glucose and serves as a tissue reserve for the body's glucose needs. Glycogen synthesis occurs in virtually all animal tissues, but it is especially prominent in the liver and skeletal muscles. In the liver, glycogen serves as a reservoir of

glucose, readily converted into blood glucose for distribution to other tissues, whereas in muscles glycogen is broken down via glycolysis to provide energy for muscle contraction. In human body, glycogen is synthesized and stored when glucose levels are high and is broken down during starvation or periods of high glucose demand.

Glycogen is a highly branched polymeric structure containing glucose as the basic monomer (Mayes, 1975; Voet & Voet, 2004b). It is composed of polymers of α-1-4 linked glucose, interrupted by α 1-6 linked branch point every 4-10 residues (Fig 1).
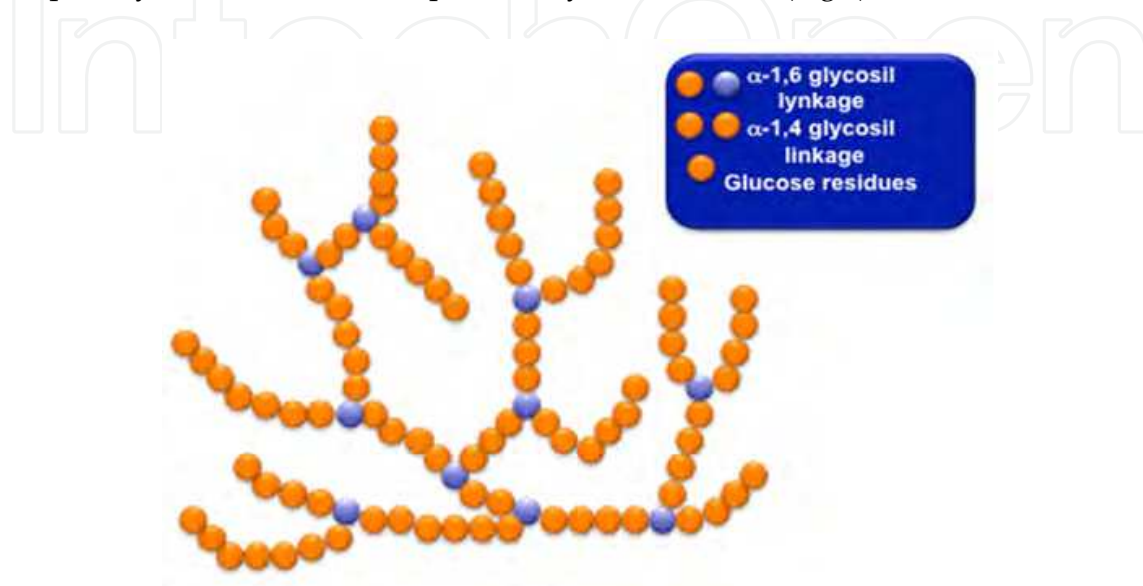

Fig. 1. Glycogen structure

Uridine diphosphate glucose (UDP-glucose) is the immediate precursor for glycogen synthesis. Glycogen synthase will only add glucose units from UDP-glucose onto a preexisting glycogen chain that has at least four glucose residues. Linkage of the first few glucose units to form the minimal "primer" needed for glycogen synthase recognition is catalyzed by a protein called glycogenin, which attaches to the first glucose and catalyzes linkage of the first eight glucoses by alpha(1,4) bonds. The enzyme, glycogenin, initiates glycogenynthesis (oregonstate.edu/…/summer09/lecture/glycogennotes.html; Voet & Voet, 2004b).

The enzyme glycogen synthase then catalyzes elongation of glycogen chains initiated by glycogenin to a chane of 9 – 11 glucose molecule. Glycogen synthase catalyzes transfer of the glucose moiety of UDP-glucose to the hydroxyl at C_4 of the terminal residue of a glycogen chain to form an   α(1-4)-glycosidic linkage (Fig 2) (Mayes,1975; King, 2011; Voet & Voet, 2004b; www.uic.edu/…/glycogen%20metab/Glycogen%20biochemistry.htm).

A branching enzyme forms the branching points in glycogen. The branches arise from α-(1-6) linkages which occur every 8 to 12 residues. Glycogen branches are formed by amylo-(1,4-1,6)-transglycosylase, also known as branching enzyme. The branching enzyme transfers a segment from the end of a glycogen chain to the C6 hydroxyl of a glucose residue of glycogen to yield a branch with an α-(1-6) linkage. In the presence of glycogenin, glycogen synthase, branching enzyme and UDP glucose (active glucose) form glycogen as a highly branched polymeric structure, containing glucose as the basic monomer (Figure 2).

Glycogen is synthesized and stored mainly in the liver and the muscles as well as in the cytoplasm of all human body cells as granules named "residual bodies", (Voet & Voet, 2004b).
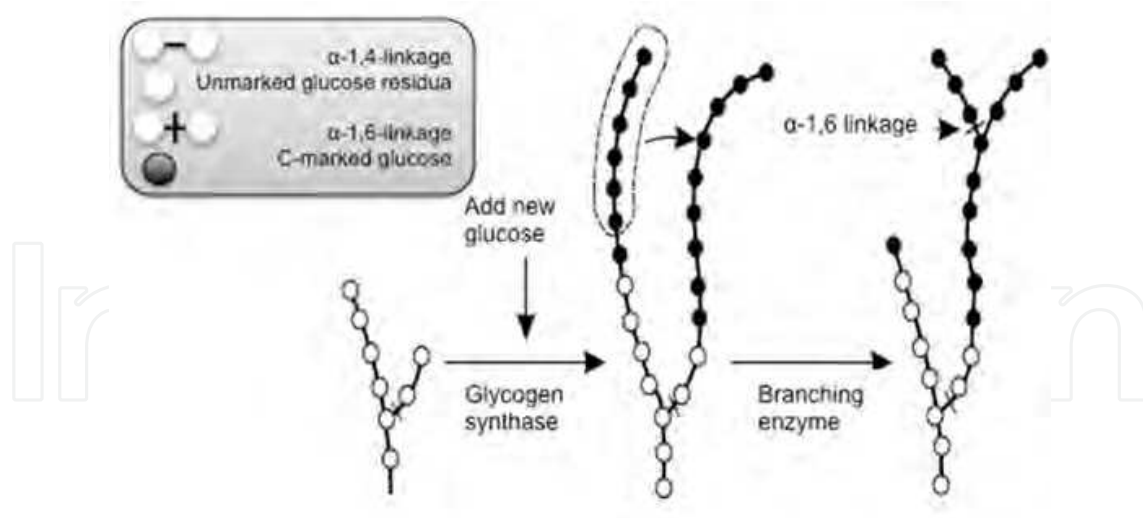
Fig. 2. Glycogenesis

4.2 Glycogen breakdown (glycogenolysis)

In the proceses of glycogen catabolism or glycogenolysis, glycogen, stored in the liver and muscles, is converted first to glucose-1-phosphate and then into glucose-6-phosphate. (Mayes,1975; Voet &;Voet, 2004b). Three enzymes participate in glycogenolysis: glycogen phosphorylase, oligo-1,4-1,4–glucan transferase or trisaccharide transferase, and α(1-6) glucosidase or γ- amylase. Glycogen phosphorylase catalyzes phosphorolytic cleavage of the α-1,4 glycosidic linkages of glycogen (using inorganic phosphate), releasing glucose-1-phosphate as reaction product and limit dextrin. After extensive phosphorylase action on glycogen, the molecule contains four glucose residues in α-1,4-glucosidic bond attached by a(1,6)-link to the glycogen molecule.

These structures can be further degraded by the action of a debranching enzyme, which carries out two distinct reactions. The first of these, known as oligo-a1,4-a-1,4) glucan transferase activity or trisaccharide transferase, removes a trisaccharide unit from limit branch and transfers this group to the end of another nearby glycogen chain, with resynthesis of the α-1,4 bond. This leaves a single glucose residue in a-(1,6) linkage to the main chain. The α-1,6-glucosidase or γ-amylase activity of the debranching enzyme then catalyzes hydrolysis of the α(1,6) linkage, leaving a polysaccharide chain with one branch fewer and yielding free glucose. This is a minor fraction of free glucose released from glycogen (Fig 3), since that the major product of glycogen breakdown by phosphorylase activity is glucose-1-phosphate. Phosphoglucomutase catalyzes the reaction: glucose-1-phosphate → glucose-6-phosphate.

Glucose-6-phosphate is the first step of the glycolysis pathway if glycogen is the carbohydrate source of further energy needed. If energy is not immediately needed, the glucose-6-phosphate is converted to glucose, by the action of the enzyme glucose-6-phosphatase (mainly in liver), for distribution to various cells by blood, such as brain, erythrocytes, adipocytes, etc.

The reactions involved in tissue glycogen synthesis and degradation are carefully controlled and regulated by hormones. The primary hormone responsible for conversion of glucose to glycogen is insulin. Opposite effects to glycogen metabolism have its antagonists: glucagon, adrenaline, cortisol, growth hormone which facilitate glycogenolysis in liver and muscles.

The principal enzymes of glycogen metabolism are glycogen synthase and glycogen phosphorylase, reciprocally regulated by allosteric effectors and covalent modification (through phosphorylation or dephosphorylation). Glycogen synthase is active when high blood glucose leads to intracellular glucose-6-P increase. Glycogen phosphorylase is active in the presence of high level of cyclic adenosine monophosphate (cAMP) which suggests that the cells need chemical energy in the form of ATP.
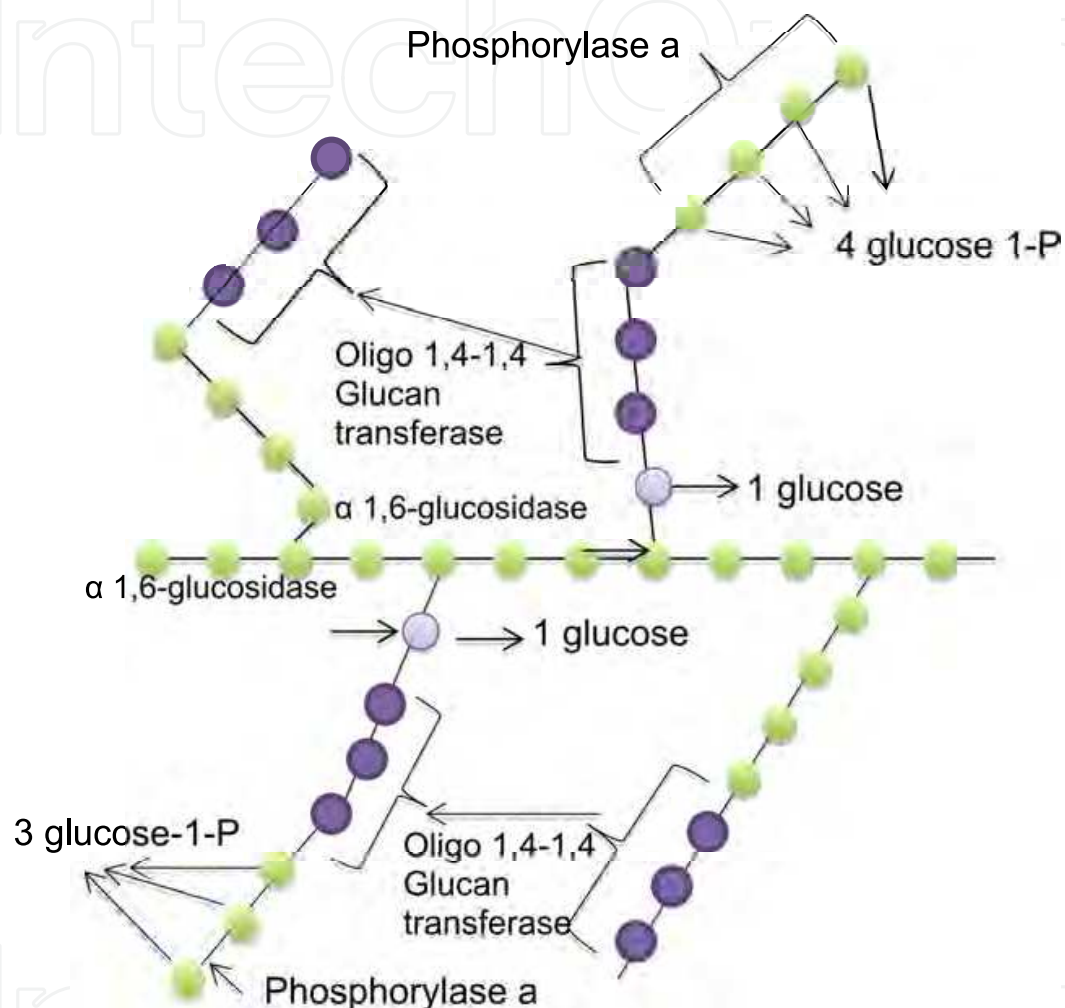

Fig. 3. Glycogenolysis

Glucagon, synthesized by pancreatic α-cells, and epinephrine (adrenaline), synthesized by adrenal medulla, regulate glycogen metabolism by covalent modification (phosphorylation and dephosphorylation) through cAMP cascades. Both hormones are produced in response to low blood glucose level. Glucagon activates cAMP formation in liver, while adrenaline activates its formation in muscle. Phosphorylation of the enzyme, via cAMP cascade, induced by adrenaline, results in further activation of glycogen phosphorylase. These regulatory processes ensure release of phosphorylated glucose from glycogen, for entry into glycolysis to provide ATP needed for muscle contraction.

Insulin, produced in response to high blood glucose, antagonizes effects of the cAMP cascade induced by glucagon and adrenaline. It is the only hormone inducing cAMP decrease (Mayes, 1975; Voet & Voet, 2004b).

4.3 Glycolysis

ATP depletion in cells, or low blood glucose level, lead to the activation of glycogenolysis and the enhancement of glucose degradation through glycolysis. Glycolysis is a central metabolic pathway of glucose metabolism, starting with glucose-6-phosphate, produced by glycogenolysis or gluconeogenesis. Glucose-6-phosphate could also be synthesized directly from blood-derived glucose by the action of hexokinase in all human body cells or by the action of glucokinase in hepatocytes.

Glycolysis is the anaerobic catabolism of glucose. It occurs in cytosol of virtually all cells. The glycolytic pathway converts a molecule of glucose into 2 molecules of pyruvic acid and captures 2 molecules of ATP. If glycolysis proceeds in aerobic conditions 2 molecules of pyruvic acid enter mitochondria, transforms into acetyl-CoA which is oxidized by the citric acid cycle. One cycle provides 12 mol ATP per one molecule of pyruvate. Aerobic conditions provide a mechanism for converting NADH back to NAD^+ which is essential for glycolysis to operate (Fig 4).
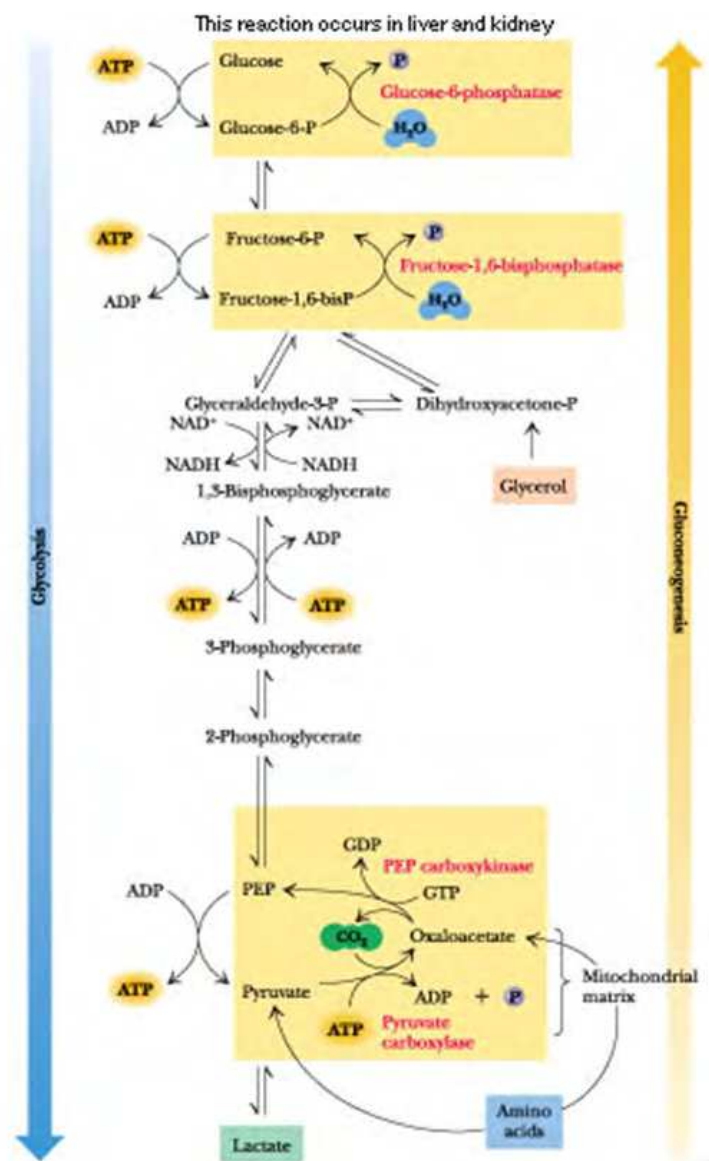

Fig. 4. Glycolysis and Gluconeogenesis

Under anaerobic conditions 2 molecules of pyruvate, under the action of lactate dehydrogenaze, and by using $NADH_2$, convert to 2 molecules of lactate. The reaction is freely reversible (Haris, 1997; Mayes, 1975; Voet & Voet, 2004b; users.rcn.com/.../I/ IntermediaryMetabolism.html).

4.4 Gluconeogenesis

If glucose is not obtained in the diet, during fasting , the body must produce new glucose from noncarbohydrate precursors by the proces of gluconeogenesis. The term gluconeogenesis means the generation (*genesis*) of new (*neo*) glucose.

The production of glucose from other metabolites is necessary to maintain the glucose level in the blood as a fuel source by the brain, erythrocytes, kidney medulla and testes, since glucose is the sole energy source for these organs. During starvation, however, the brain can derive energy from ketone bodies which are converted to acetyl-CoA. The adipose tissue needs glucose which is also necessary for the synthesis of triacylglycerls and glycerophospholipids. The main precursors for gluconeogenesis are lactate and alanine from muscle, glycerol from adipose tissue, and glucogenic amino acids from the proteolysis in peripheral tissues and proteins from the diet. The most of the amino acids, as well as their α-keto acids, are TCA cycle intermediates. In addition, the gluconeogenetic processes are used to clear the intermediary products of metabolism of other tissues from the blood, e.g. lactate, produced by muscles and erythrocytes, and glycerol, which is continuously produced by adipose tissue.The principal organs responsible for gluconeogenesis are the liver and kidneys, which account for about 90% and 10% of the body's gluconeogenic activity, respectively. Interestingly, the mammalian organs that consume the most glucose, namely, brain and muscle, carry out very little glucose synthesis (Gerich et al, 2001; King, 2011; Mayes,1975; Voet & Voet, 2004b; Woerle & Stumvoll, 2001).

Gluconeogenesis is similar but not the exact reverse of glycolysis; some of the steps are the identical in reverse direction and three of them are new ones (Fig 4). In glycolysis energy barriers obstruct a simple reversal of glycolysis: reactions catalyzed by pyruvate kinase, phospho-fructokinase and hexokinase. These barriers are circumvented by new, special enzymes of gluconeogenesis: pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructoso-1,6-diphosphatase and glucose-6-phosphatase. The conversion of lactate to glucose begins with the oxidation of lactate, by the action of lactate dehydrogenase, to pyruvate. In the presence of ATP, pyruvate carboxylase and CO_2 convert pyruvat to oxaloacetate. The enzyme, phosphoenolpyruvate carboxykinase (PEPCK) transfers oxaloacetate to phosphoenolpyruvate in the presence of GTP and by elimination of CO_2. Thus, with the help of these two enzymes, and lactate dehydrogenase, lactate can be converted to oxaloacetate. The pyruvate and oxaloacetate are the intermediary products of catabolic pathway of many glycolytic amino acids. The next steps of reversal glycolysis continue just to formation of fructose-1,6-diphosphate, the substrate for fructose-1, 6-diphosphatase. Fructose-6-phosphate, formed by elimination of inorganic phosphate, converts to glucose-6-phosphate (G6P). The energy required for the hepatic synthesis of glucose from lactate is derived from the oxidation of fatty acids. In the liver and kidney, G6P can be dephosphorylated to glucose by the enzyme glucose 6-phosphatase. This is the final step in the gluconeogenesis pathway.

4.4.1 Cory cycle

Lactate, formed by the oxidation of glucose in skeletal muscles and by erythrocytes through the proceses of anaerobic glycolysis, is transported to the liver and kidney, where it re-forms glucose, which again become available via the circulation for oxidation in the tissues. This process is known as the Cory cycle or lactic acid cycle (Fig 5).

4.4.2 Glucose-alanine cycle

It has been noted that of the amino acids transported from muscles to the liver during starvation or under the action of cortisol, alanine predominate. Glucose-alanine cycle represents a cycling glucose from the liver to the muscles and alanine from muscles to liver, effecting a net transfer of amino nitrogen from muscle to liver and free energy from liver to muscle. At the level of muscles, pyruvate, formed by glycolysis, transforms to alanine by the action of alanine transaminase (ALT) or glutamate pyruvat transaminase (GPT). The reaction is freely reversible; at the level of hepatocytes alanine transfers to pyruvate by the action of the same anzyme (Fig 5).

Glycerol, necessary for the synthesis of triacylglicerols and glycerophosholipids is derived, initially, from the blood glucose since free glycerol cannot be utilised readily for the synthesis of these lipids in tissues. Instead of free glycerol, adipose tissue uses α-glycero phosphate or "active glycerol" produced during degradation of glucose by glycolysis.
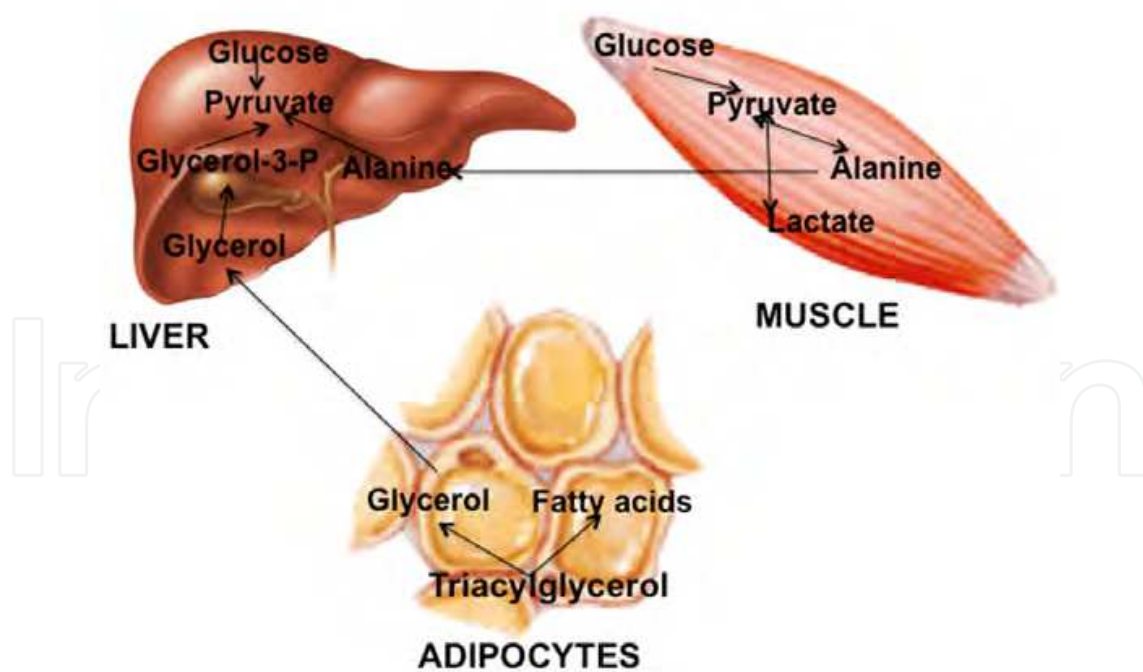

Fig. 5. Cory cycle , glucose-alanine cycle and glycerol-glucose cycle

4.4.3 Glycerol - Glucose cycle

Glycerol, a product of the continual lipolysis, diffuses out of the tissue into the blood. It is converted back to glucose by gluconeogenic mechanisms in the liver and kidney. Thus, a continous cycle exists in which glucose is transported from the liver to adipose tissue and, hence, glycerol is returned to be synthesized into glucose by the liver. Glycerokinase, which requires ATP, catalyzes the conversion of glycerol to α-glycero phosphate. Glycerokinase is present in liver and kidney. The enzyme α -glycero phosphate dehydrogenase oxidizes α-glycero phosphate to the dihydroxacetone phosphate, the component of glycolysis, which enters the glycolytic pathway as a substrate for triose phosphate isomerase (Fig 4). Thus, liver is able to convert glycerol to blood glucose by making use of above enzymes - some of the enzyme of glycolysis and specific enzymes of gluconeogenic pathway, fructose-1,6-diphosphatase and glucose-6-phosphatase(Harris & Crabb, 1997; King, 2011; Mayes,1975).

Glucose produced by gluconeogenesis in the liver and kidney is released into the blood and is subsequently absorbed by all human body cells especially brain, heart, muscle, and red blood cells to meet their metabolic needs. In turn, pyruvate, lactate and glycerol produced in these tissues are returned to liver and kidney to be used as gluconeogenic substrates.

5. The physiological regulation of carbohydrate metabolism

5.1 Glucose homeostasis

The maintaining of stable levels of blood glucose is one of the most finely regulated of all homeostatic mechanisms and one in which the liver, extrahepatic tissues and several hormones play a part. Even mild disruptions of glucose homeostasis can have adverse consequences. The physiological post absorptive serum glucose concentration in healthy humans range is 4. 4-5.8 mmol/L (80 to 110 mg/dL).

Glycemia is controlled by several physiological processes. It tends to fluctuate to higher levels after meals, due to intestinal absorption of carbohydrates of low molecular weight present in the diet or broken down polysaccharides, such as starch or glycogen. On the other hand, glucose tends to decrease to lower levels induced by cell metabolism, particularly after stress, temperature regulation and physical exercise. Glucose can also be supplied via breakdown of cellular reserves of glycogen. Another input to glycemia levels is gluconeogenesis, whereby glycogen stored in the liver and skeletal muscles are depleted.

The stability of the glycemia is a reflection of the balance between the rates of whole body glucose production and glucose utilization. The glucose homeostasis is tightly regulated by the levels of hormones and substrates in blood and by the physiologic functions of body tissues and organs (Carraway & Watts, 1986; Haris, 1997; King,2011).

5.2 Hormonal regulation of glycemia

The hormones involved in glycemia regulation include insulin (which lowers the blood sugar level) and other hormons which raise blood sugar, namely antagonists of insulin such as glucagon, epinephrine, cortisol, growth hormone, thyreoid hormones (T3 and T4) and many others. The proper functions of these hormones is precise control of glucose concentration in the blood. Insulin and glucagon are two major hormones involved in regulation of blood glucose level. They are both secreted in response to blood sugar levels, but in opposite fashion. At the same time, enhanced insulin secretion induced increased glucagon secretion.

Insulin has a hypoglycemic effect. Secretion of insulin is a response to increased glucose level in the blood. In addition to the direct effects of hyperglycemia in enhancing the uptake of glucose into both the liver and peripheral tissues, the hormon insulin plays a central role in the regulation of the blood glucose concentration. Similarly, as blood glucose falls, the amount of insulin secreted by the pancreatic islets goes down.

Glucagon, as a direct antagonist of insulin, has a hyperglycemic effect. Secretion of glucagon is a response to decreased glucose level in the blood (Chattoraj & Watts,1986; Ginsberg, 1990 a, 1990b; Mayes,1975; King, 2011).

5.2.1 Insulin

Insulin is a small protein consisting of an alpha chain of 21 amino acids linked by two disulfide (S−S) bridges to a beta chain of 30 amino acids. The precursor of insulin is a proinsulin, which contains C peptide (conective peptide). The conversion of proinsulin to insulin requires biologic proteolysis (Ginsberg,1990; Bowen, 2010; Harper, 1975; Chattoraj & Watts,1986).

The stimulus for insulin secretion is a high blood glucose. Insulin is produced by β cells of Langerhans islets in pancreas and is secreted into the blood as a direct response to hyperglycemuia. Beta cells have channels in their plasma membrane that serve as glucose detectors. When blood glucose levels rise (after a meal), insulin is secreted from the pancreas into the pancreatic vein, which empties into the portal vein system, so that insulin traverses the liver before it enters the systemic blood supply. Insulin acts to rapidly lower blood glucose concentration in several ways. It stimulates the active transport of glucose across plasma membranes through glucose transporter (GLUT 4) of muscle and adipose tissue. The liver, brain and red blood cells do not require insulin for glucose uptake. Insulin is an anabolic hormone. It promotes anabolic processes in these cells, such as increasing the rate of glycogenesis, lipidogenesis and proteins synthesis. The cellular uptake of glucose from the blood have the net effect of lowering the high blood glucose levels into the normal range. Insulin stimulates cells in most tissues of the body to preferentially use glucose as their metabolic fuel. It increases cellular glucose utilization by inducing the synthesis of several important glycolytic enzymes, namely, hexokinase, glucokinase, phosphofructokinase, and pyruvate kinase. In addition, insulin inhibit gluconeogenesis in liver. All of these physiological effects of insulin serve to lower blood glucose levels. In each case, insulin triggers these effects by binding to the insulin receptor - a transmembrane protein embedded in the plasma membrane of the responding cells. When the the glucose concentration in the blood falls, pancreas stops releasing insulin (Ginsberg, 1990 a, 1990b; Bowen, 2007; King, 2011).

5.2.2 Amylin

Pancreatic beta cells secrete amylin, a peptide of 37 amino acids. All of its actions (inhibition of glucagon secretion, slowing down the stomach emptying, sending a satiety signal to the brain) tend to supplement those of insulin, reducing the level of glucose in the blood (King, 2011; Silvestre et al, 2001; Young, 2005; users.rcn.com/.../I/IntermediaryMetabolism.html).

5.2.3 Glucagon

Glucagon is another 29 amino acid peptide hormone produced by pancreas. It is a hyperglycemic hormone (Bowen, 2007). Glucagon is produced by alpha (α) cells of

Langerhans islets as proglucagon and proteolytically processed to yield glucagon within alpha cells of the pancreatic islets. Proglucagon is also expressed within the intestinal tract, where it is processed not into glucagon, but to a family of glucagon-like peptides (GLP) (Ginsberg,1990b; Bowen, 2007). Glucagon is secreted in response to hypoglycemia. It is active in liver and adipose tissue, but not in other tissues. This peptide hormone travels through the blood to specific receptors on hepatocytes and adipocytes. When the concentration of glucose in blood decreases, α cells of the pancreas begin to release glucagon. Glucagon stimulates hepatocytes to glycogenolysis and gluconeogenesis, resulting in hyperglycemia. It increases the amount of cAMP and stimulates lipolysis, contributing to reduction of the cellular glucose utilization, the increasing of lipolysis in adipose tissue, providing glycerol and free fatty acids which enter β oxidation cycle, producing the chemical energy (ATP) to most cells. Glycerol leaves the adipose tissue, and through the blood enters the hepatocytes where it may serve as the substrate in the process of gluconeogenesis (Fig 5).

5.2.4 Epinephrine (adrenaline)

Epinephrine is a hormone of adrenal medulla, which consists of masses of neurons that are the part of the sympathetic branch of the autonomic nervous system. Instead of releasing their neurotransmitters at a synapse, these neurons release them into the blood. Thus, although part of the nervous system, the adrenal medulla functions as an endocrine gland. It releases catecholamines: adrenaline (epinephrine) and noradrenalin (also called norepinephrine).

Synthesis of both catecholamines begins with the amino acid tyrosine, which is taken up by chromaffin cells. Called the "fight or flight" hormone, adrenaline prepares the organism for mobilization of large amounts of energy and dealing with stress. Together with cortisol and growth hormone   they are named "stress hormones". Following release into blood, these hormones bind adrenergic receptors on target cells, where they induce essentially the same effects as direct sympathetic nervous stimulation. Adrenaline acts on liver and muscles. Mechanisms of the actions of adrenaline are the same as the mechanisms of glucagon. Through augmentation of cAMP in the cells, adrenaline initiates the enzyme cascade which leads to the activation of glycogen phosphorylase, leading to rapid breakdown of glycogen, inhibition of glycogen synthesis, stimulation of glycolysis and production of energy. In fat cell, it stimulates lipolysis, providing fatty acids as energy source in many tissues. Stimulation of lipolysis contributes to the reduction of the cellular glucose utilization and aids in conservation of dwindling reserves of blood glucose. The stimulation of hepatocytes to glycogenolysis and gluconeogenesis results in regulation of glycemia (Ginsberg,1990a; Chattoraj, & Watts, 1986; www.ncbi.nlm.nih.gov/books/NBK22429/).

5.2.5 Glucocorticoids

The glucocorticoids (cortisol as the principal one) get their name from their effect of raising the level of blood glucose. Glucocorticoids are a class of steroid hormones, synthesized and secreted from zone fasciculate of adrenal cortex, that exert distinct effects on liver, skeletal muscles, and adipose tissue (Bjelakovic et al,2008,2009). The effects of cortisol are best described as catabolic, because it promotes protein breakdown and decreases protein synthesis in skeletal muscles. However, in the liver, it stimulates gluconeogenesis, inducing increased gene expression of several enzymes of the gluconeogenic pathway. Cortisol-

induced gluconeogenesis results, primarily, in increased conversion of glycogenic amino acids (from protein breakdown in peripheral tissues) and glycerol (from fat) into glucose (Ginsberg, 1992c; Chattoraj & Watts, 1986; Gil, 1992; Litwak & Schmidt, 1997a; users.rcn.com/…/I/IntermediaryMetabolism.html.)

5.2.6 Growth hormone (GH)
Human growth hormone (GH; also called somatotropin), the protein of 191 amino acids, secreted by somatotrophs of the anterior part of pytuatary gland, regulates overall body and cell growth, carbohydrate, protein and lipid metabolism, and water-electrolyte balance. The GH-secreting cells are stimulated by growth hormone releasing hormone (GHRH) from hypothalamus and inhibited by somatostatin. The release of GH might be regulated not only by hypothalamic GHRH, but also by ghrelin derived from the stomach (Kojima et al., 2005). GH promotes body growth by binding to receptors on the surface of liver cells and stimulates them to release insulin-like growth factor-1 (IGF-1, also known as somatomedin). GH exerts the hyperglycemic effect, stimulating glycogenolysis and lypolysis in peripheral tissues. In liver, GH also stimulates glycogenolysis and glyconeogenesis (Barry, 1992c; Frohman,1992; Litwak.& Schmidt, 1997b).

5.2.7 Thyroid hormones
Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are: triiodothyronin (T3) and thyroxin (T4). Thyroid hormones receptors are intracellular DNA-binding proteins that function as hormone-responsive transcription factors. The effect of the hormone-receptor complex binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes. It is likely that all cells in the body are targets for thyroid hormones. Thyroid hormones affect oxidative metabolism, especially the metabolism of carbohydrates. Thyroid hormones enhance glucose absorption and the utilization of carbohydrates. They stimulate both the synthesis and disposal of glucose Hypothyroidism or thyroid hormone deficiency leads to decrease in basal metabolic rate and hypoglycemia (Bowen, 2010; Harper, 1975; Zmire et al, 1999).

6. Physiological functions of liver, kidneys and brain in carbohydrate metabolism

Beside hormones, some organs have the important roles in glycemia regulation. Among them, the most important are liver, kidneys and brain.

6.1 The role of liver in carbohydrate metabolism
The metabolic activities of the liver are essential for providing fuel to the brain, muscle, and other peripheral organs. The liver removes two-thirds of the glucose from the blood and all of the remaining monosaccharides (Lehninger,1977; Cherrington,1999). The absorbed glucose is converted into glucose 6-phosphate by hexokinase and the liver-specific glucokinase, whose K_m (Michaelis constant) for glucose is sufficiently higher than the normal circulating concentration of glucose (5mM). The liver plays a unique role in controlling carbohydrate metabolism by maintaining glucose concentrations in a normal range. It possesses the key enzymes for glucose intake (hexokinase and glucokinase) and for

releasing of glucose from hepatocytes (glucose-6-phosphatase). The liver has a great capability for synthesis and storing of glycogen (glycogenesis), and, in opposite direction, for glycogen breakdown (glycogenolysis). Also, the liver is the place for gluconeogenesis. (King.2011, Nordlie et al, 1999; Radziuk & Pye, 2001).

Glucose-6-phosphatase liberates free glucose molecules from hepatocytes into blood, catalyzing the following reaction: glucose-6-phosphate + H2O → glucose + Pi.The substrate for this enzyme is glucose-6-phosphate, the product of glycogenolysis or the end product of gluconeogenesis (Berg, 2002; Radziuk & Pye, 2001; Raddatz & Ramadori, 2007; Yamashita et al, 2001; Berg, 2002) .

6.2 The role of kidney in carbohydrate metabolism

Kidney may play a significant role in carbohydrate metabolism under both physiological and pathological conditions due to renal gluconeogenesis (King, 2011; Gerich et al., 2001). Although the liver is the major site of glucose homeostasis, the kidney plays a vital role in the overall process of regulating the level of blood glucose. Glucose is continually filtered by the glomeruli but is ordinarily returned completely to the blood by the enzymatic reabsorptive system of the renal tubules. The reabsorption of glucose is a process which is similar to that responsible for the absorption of this sugar from the intestine. The capacity of tubular system to reabsorb glucose is limited by the capacity of enzymatically systems of the tubule cells to a rate of about 350 mg/ minute, representing as tubular maximum for glucose (Tmg). Due to that capacity of the kidney, the definitive urine doesn't contain glucose. When the blood levels of glucose are elevated, the glomerular filtrate may contain more glucose then can be reabsorbed; the excess passes into urine to produce glycosuria. In normal individuals, glucosuria occures when the venous blood sugar excesss 9.5-10 mmol/L (170-180 mg/100 ml). This level of the venous blood sugar is termed the renal threshold for glucose (Mayes,1975; Woerle & Stumvoll, 2001).

6.3 The role of brain in carbohydrate metabolism

Glucose is the major energy source for maintenance of brain metabolism and function, except during prolonged starvation. However, the brain has limited glucose reserves and needs a continuous supply of glucose. Endogenous glucose provides more than 90% of energy needed for brain function (Cryer, 1997; Gerich et al, 2001; Halmos & Suba,2011; King, 2011). Since the brain cannot synthesize glucose or store more than a few minutes' supply as glycogen, it is critically dependent on a continuous supply of glucose from the circulation. Fatty acids do not serve as fuel for the brain, because they are bound to albumins in plasma and so do not traverse the blood-brain barrier. In prolonged starvation, ketone bodies, generated by the liver, partly replace glucose as fuel for the brain, (Cahill, 2006).

Glucose is transported into brain cells by the glucose transporter GLUT3. This transporter has a low KM for glucose (1.6 mM). Thus, the brain is usually provided with a constant supply of glucose. At normal (or elevated) arterial glucose concentrations, the rate of blood-to-brain glucose transport exceeds the rate of brain glucose metabolism. However, as arterial glucose levels fall below the physiological range, blood-to-brain glucose transport becomes limiting to brain glucose metabolism, and ultimately survival.

Nowadays it is hypothesised that the brain, in particular the hypothalamus, has a great role in carbohydrate metabolism and glucose homeostasis. The brain is an insulin-sensitive organ. Brain-insulin action is required for intact glucose homeostasis. Receptors for insulin

are concentrated in hypothalamic area. Hypothalamus is the site of afferent and efferent stimuli between special nuclei and β- cells and α cells of pancreas, and it regulates induction/inhibition of glucose output from the liver. Insulin gets across the blood-brain barrier, links to special hypothalamic receptors, regulating peripheral glucose (the hypothalamus-pancreas) (Halmos & Suba, 2011). In addition, the hypothalamus can affect metabolic functions by neuroendocrine connections: the hypothalamus-pancreas axis (the control of insulin and glucagone release), the hypothalamus-adrenal axis (the control of the release of adrenaline and noradrenaline) and the hypothalamus-pituitary axis (release of glucocorticoids and thyroid hormones through adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH) control, respectively, which modulate glucose metabolism.

Recently, evidence is accumulating demonstrating that gastrointestinal hormones (peptides) are involved in regulating glucose metabolism through humoral gut–brain axis. Some of them are: ghrelin, neuropeptide Y (NPY), cholecystokinin - CCK, gastric inhibitory polypeptide - GIP, glucagon-like peptide (GLP) etc. (Kojima & Kangawa, 2005; King, 2011; Korner & Leibel, 2003; Neary et al, 2004 ; Young, 2005).

7. Neuro-endocrine defence to hypoglycemia

Generally, hypoglycemia is defined as a serum glucose level below (3.8 mmol/L or, 70 mg/dL). Hypoglycemia is a rare disorder, considered as pathophysiological state rather than a disease. Just as pain and fever require identification of the underlying condition, hypoglycemia warrants diagnosis of the primary disorder causing the low plasma glucose concentration.

The symptoms of hypoglycemia are not specific. For this reason it is necessary to demonstrate a low plasma glucose concentration concomitant with symptoms and subsequent relief of symptoms by correction of the hypoglycemia, i.e., Whipple's tirade. This triade can be considered to be the basis for a patient's symptoms, regardless of the cause of hypoglycemia (Service,1992). Whipple's triad considers: 1) symptoms consistent with hypoglycemia, 2) a low plasma glucose concentration, and 3) relief of symptoms after the plasma glucose level is raised. Hypoglycemia most often affects those at the extremes of age, such as infants and the elderly, but may happen at any age. Given the survival value of maintenance of the plasma glucose concentration, it is not surprising that very effective physiological mechanisms prevent or rapidly correct hypoglycemia have evolved.

Hypoglycemic symptoms are related to the brain and the sympathetic nervous system. The central nervous system requires glucose as the preferred energy substrate. Though the brain accounts for only about 10% of body weight, it uses more than 30% of blood glucose. Hypoglycemic symptoms are mediated through both central and peripheral nervous systems. Once plasma glucose concentration fall belows 3.8 mmol/L or 70 mg/dL, a sequence of events begins to maintain glucose delivery to the brain and prevent hypoglycemia.

The first of all events is the stimulation of the autonomic nervous system and, after that, release of neuroendocrine hormones (counter-regulatory or anti-insulin hormones). Peripheral autonomic symptoms (adrenergic), including sweating, irritability, tremulousness, anxiety, tachycardia, and hunger, serve as an early warning system and

preceed the central neuroglycopenic symptoms due to cerebral glucose deprivation (e.g., confusion, paralysis, seizures, and coma) (Zammitt & Frier, 2005).

A hierarchical hormonal response exists in response to decreasing blood glucose levels. As blood glucose drops, pancreatic β-cell reduce insulin secretion. If blood glucose drops further, the pancreatic α-cell secrete glucagon and the adrenal medulla release adrenaline. Both, glucagon and adrenaline, act rapidly to increase glucose availability and therefore are the two major counter-regulatory hormones. Cortisol and growth hormone are also released, but they are unable to prevent prolonged hypoglycemia withouth the preliminary actions of glucagone and adrenaline. In sensing hypoglycemia, the nutritionally deprived brain also stimulates the sympathetic nervous system, leading to neurogenic symptoms.Decreased levels of glucose lead to deficient cerebral glucose availability i.e., neuroglycopenia, that can manifest as confusion, headache, difficulty with concentration. If the symptoms are overlooked, there can be irreversible brain damage. Eventually, the patient may go into coma and death. The adrenergic symptoms often precede the neuroglycopenic symptoms and, thus, provide an early warning system for the patient, (Cryer,1997; Heijboer et., 2006).

8. Hypoglycemia as a result of inherited or acquired disorder of carbohydrates metabolism

8.1 Hypoglicemia and inborn errors of carbohydrate metabolism

Hypoglycemia is not a disease by itself, but its presence is an indication of a problematic health condition. As a relatively frequent common event in the pediatric newborn period (childhood), hypoglicemia may be a consequence of some inborn errors of carbohydrate metabolism (Service,1992; Sinclair,1979; Caraway & Watts, 1986).

8.1.1 Defects in digestion & absorption of carbohydrates

8.1.1.1 Inherited lactase deficiency (alactasia)

Enzyme lactase is necessary to digest lactose to glucose and galactose in the small intestine. Lactase deficiency is a rare congenital disorder in which infants are born without lactase. If lactase is deficient,undigested lactose enters the large intestine, where it is fermented by colonic bacteria, producing lactic acid and gases (hydrogen, methane, carbon dioxide).The gas produced creates the uncomfortable feeling of gut distention and the annoying problem of flatulence. The lactic acid produced by the microorganisms is osmotically active and draws water into the intestine, as does any undigested lactose, resulting in diarrhea. As children are weaned and milk becomes less prominent in their diets, lactase activity normally declines to about 5 to 10% of the level at birth (Gary,1978; Sinclair,1979; Tietz et al,1986). The simplest treatment is to avoid the consumption of products containing much lactose. Alternatively, the enzyme lactase can be ingested with milk products.

8.1.1.2 Lactose intolerance

Lactose intolerance is an inability to digest significant amounts of lactose due to an absence of the enzyme lactase in adult intestines. The symptoms of this disorder, which include diarrhea and general discomfort, can be relieved by eliminating milk from the diet (Maxton et al, 1990; Tietz et al,1986).

8.1.1.3 Sucrase deficiency

Enzyme sucrase decomposes disaccharide sacharose to glucose and fructose molecules. There is a number of reports of an inherited deficiency of the disaccharidases, sucrase and isomalatase, occurring within the mucosa of the small intestine. Symptoms occur in early childhood following ingestion of sucrose. The symptoms are the same as those described in lactase deficiency except that they are evoked by the ingestion of table sugar (Gary,1978 ; Sinclair,1979; Tietz et al,1986)

8.1.1.4 Glucose galactose malabsorption

Glucose Galactose Malabsorption (GGM) is a genetic disorder caused by a defect in glucose and galactose transport across the intestinal brush border membrane. Normally, lactose in milk is broken down into glucose and galactose by lactase, an ectoenzyme on the brush border, and the hexoses, having nearly identical chemical structure, are transported into the cell by the Na^+-glucose cotransporter SGLT1 (Fig 6). The mutations causing the defect in sugar transport have been identified (Gary, 1978; Wright, 1998; Wright et al, 2002; Wright et al, 2004; Wright, 2003).
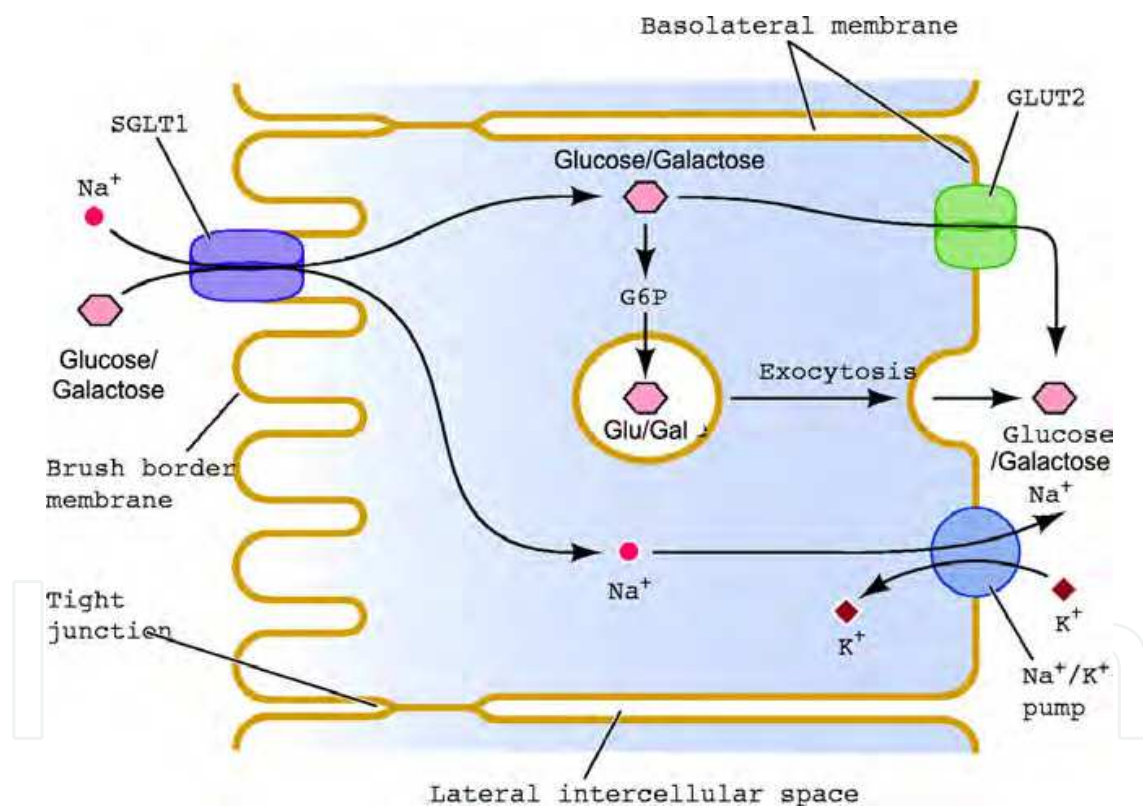

Fig. 6. Sugar transport across intestinal apithelium (Wright et al., 2004, modified)

Glucose-galactose malabsorption is an autosomal recessive disorder in which affected individuals inherit two defective copies of the SGLT1 gene, located on chromosome 22. This disease presents in newborn infants as a life-threatening diarrhea. The diarrhea ceases within 1 h of removing oral intake of lactose, glucose and galactose, but promptly returns with the introduction of one or more of the offending sugars into the diet. We conclude that mutations in the SGLT1 gene are the cause of glucose-galactose malabsorption, and sugar transport is impaired mainly because the mutant proteins are either truncated or are not

targeted properly to the cell membrane. The glucose and galactose, if left untransported, draw water out of the body into the intestinal lumen, resulting in diarrhea.

Although no cure exists for GGM, patients can control their symptoms (diarrhea) by removing lactose, sucrose and glucose from their diets. Infants showing a prenatal diagnosis of GGM will thrive on a fructose-based replacement formula and will later continue their "normal" physical development on a fructose-based solid diet. Older children and adults with severe GGM can also manage their symptoms on a fructose-based diet and may show improved glucose tolerance and even clinical remission as they age (Wright et al., 2001; Wright,1998; Gary, 1978).

8.1.2 Galactosemia

Galactose is found in the disaccharide lactose, the principal milk sugar, made from galactose and glucose. It will be recalled that galactose is required in the body, not only in the formation of milk lactose during lactogenesis in lactating mammary glands, but also as a constituent of the glucosphyngolipids (cerebrosides, globosides, gangliosides) and for the synthesis of mucopolysaccharides (MPS) or glucosaminoglycanes (GAG). Glucosaminoglycanes are linked to core proteins forming proteoglycanes. Proteoglycanes and glucosphyngolipids perform numerous vital functions within the body, some of which still remain to be studied (King, 2011; Segal, 1989).

The disruption of galactose metabolism is referred to as galactosemia. Galactosemia can result from deficiencies of three different enzymes: galactose-1-phosphate uridyl transferase (GALT), galactokinase (GALK) and uridine diphosphate galactose 4-epimerase (GALE).

8.1.2.1 Galactokinase deficiency

Galactokinase is the first enzyme in the pathway of galactose metabolism, converting galactose to galactose-1-P. The only consequence of galactokinase deficiency is the development of cataract.

8.1.2.2 Deficiency of galactose-1-phosphate uridyl transferase (GALT)

The most common and severe form of galactosemia, called classic galactosemia or Galactosemia Type 1, is an inherited deficiency of GALT, the enzyme that converts galactose-1-phosphate (galactose-1-P) to uridine diphosphate galactose (UDPgalactose). Absence or deficiency of GALT prevents the conversion of galactose into glucose in liver. People with absent or deficient GALT have intolerance to galactose.

When an infant or neonate is given milk the blood galactose level is markedly elevated (galactosemia), and galactose is found in urine (galactosuria). These can cause severe damage to eyes, kidneys, liver and brain. Afflicted infants fail to thrive. They vomit or have diarrhea after consuming milk and enlargement of liver and jaundice are common, sometimes progressing to cirrhosis. Cataracts will form, and lethargy and retarded mental development are also common. A cataract, the clouding of the normally clear lens of the eye, is a consequence of the accumulation of galactose in the lens of the eye; in the presence of high galactose amount and of aldose reductase, galactose is reduced to galactitol. The absence of the transferase in red blood cells is a definitive diagnostic criterion (Mayatepek et al, 2010).

These problems can be prevented by removing galactose and lactose from the diet. In classic galactosemia conversion of UDP-galactose to UDP-glucose is blocked. The epimerase reaction is, however, present in adequate amounts, so that the galactosemic individual can

still form UDP-galactose from glucose. This explains the normal growth and development of affected children in spite of the galactose-free diets which are used to control the symptoms of the disease (Harper, 1975).

In adults, the toxicity of dietary galactose appears to be less severe, due, in part, to the metabolism by alternative metabolic pathway of galactose-1-P by UDP-glucose pyrophosphorylase, which apparently can accept galactose-1-P in place of glucose-1-P. The levels of this enzyme may increase in the liver of galactosemic individuals, in order to accommodate the metabolism of galactose, later, after 10 years.

8.1.2.3 Uridine diphosphate galactose 4-epimerase deficiency

Uridine diphosphate galactose-4-epimerase (UDP-galactose-4-epimerase, GALE) converts UDP-galactose to UDP-glucose. Reaction is freely reversible (Fig 7). In this manner, glucose, as a unique monosaccharide in systemic blood circulation in healthy subects , can be converted to galactose in many different tissues of human body if UDP-galactose-4-epimerase is present.

Galactosemia due to epimerase deficiency is the rarest and most poorly understood form. In most patients with GALE (or epimerase) deficiency, the defect presenting with clinical features is similar to classic galactosemia. The treatment for children with generalised GALE deficiency, as with GALT deficiency is the restriction of dietary galactose.

Since galactose is an essential component of galactoproteins and galactolipids, theoretically, in generalised GALE deficiency, no endogenous production of galactose is possible, with a resulting deficiency in galactolipids and galacto-proteoglycanes production.

The most common treatment is to remove galactose (and lactose) from the diet. The enigma of galactosemia is that, although elimination of galactose from the diet prevents liver disease and cataract development, the majority of patients still suffer from central nervous system malfunction, most commonly a delayed acquisition of language skills. Females will also display ovarian failure (Sarkar et al, 2010; Segal, 1989; Walter et al, 1999).

8.1.3 The inherited abnormalities in fructose metabolism

Fructose is monosacharide found in honey and in numerous vegetables and fruits. Disacharide sucrose consists of one molecule fructose attached to a molecule of glucose. It should be mentioned that fructose constitutes the main sugar of seminal fluid. Three inherited abnormalities in fructose metabolism have been identified: essential fructosuria, hereditary fructose intolerance and hereditary fructose-1,6-bisphosphatase deficiency (Baerlocher et al,1978; Gitzelmann et al., 1989; Froesch, 1978).

After absorption by the proces of facilitated diffusion, fructose enters hepatocytes , by the portal blood. A specific kinase, fructokinase, in liver and kidney catalyzes the phosphorylation of fructose to fructose 1-phosphate. Fructose 1-phosphate is cleaved to D-glyceraldehyde and dihydroxyacetone phosphate by aldolase B, an enzyme found in the liver. D-glyceraldehyde enters glycolysis via phosphorylation to glyceraldehyde 3-phosphate catalyzed by triokinase. The two triose phosphates, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, may either be degraded by glycolysis or may be substrates for aldolase A , the enzyme which forms fructose1,6-diphosphate and hence gluconeogenesis, which is the fate of much of the fructose metabolized in the liver.

$$\text{Fructose} + \text{ATP} \; fructokinase \rightarrow \text{Fructose} - 1 - \text{P} + \text{ADP}$$
$$\text{Fructose} - 1 - \text{P} \; aldolaseB \rightarrow \text{dihydroxyacetone} - \text{P} + \text{glyceraldehyde}$$
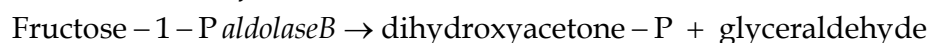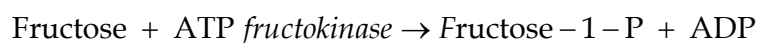
8.1.3.1 Essential fructosuria

Essential fructosuria is a benign metabolic disorder caused by the lack of fructokinase, which is normally present in liver and kidney cortex. The disorder is asymptomatic and it may go undiagnosed.

8.1.3.2 Hereditary fructose intolerance (aldolase B deficiency)

Hereditary fructose intolerance is a potentially lethal disorder resulting from a lack of aldolase B which decomposes fructose-1-phosphate to dihydroxyaceton-phosphate plus glycerine aldehyde. The disorder is characterized by severe hypoglycemia and vomiting following fructose or sacharose intake. Prolonged intake of fructose by infants with this defect leads to vomiting, poor feeding, jaundice, hepatomegaly, hemorrhage and eventually death. The hypoglycemia that results, following fructose uptake, is caused by fructose-1-phosphate inhibition of glycogenolysis, by interfering with the phosphorylase reaction and inhibition of gluconeogenesis at the deficient aldolase step. Patients remain symptom free on a diet devoid of fructose and sucrose(Baerlocher et al, 1978; Gitzelman at al, 1989; Odièvre et al, 1978).

8.1.3.3 Hereditary fructose-1,6-bisphosphatase deficiency

This disordered is characterized by hypoglycemia, ketosis and lactic acidosis and oftern lethal course in newborn infants. Due to enzyme defect gluconeogenesis is severely impaired. Gluconeogenis precursors, such as amino acids, lactate and ketones, accumulate as soon as liver glycogen stores are depleted (Asberg et al, 2010; Baerlocher et al, 2010; Froesch, 1978; Mortensen, 2006; Song, 2010; Zaidi, 2009).

8.1.4 The glycogen storage diseases (GSDs)

Glycogen is the storage form of glucose and is present in virtually all living cells, although the liver is primary organ for storage and subsequent release of glucose into the circulation. Glycogen biosynthesis from glucose (glycogenesis), along with the release of glucose from glycogen by the process of glycogenolysis, is highly regulated process that aids in the maintaing of normal blood glucose concentration during fasting.

During the last century, patients who have deficient activity in virtually every enzyme important in the normal synthesis, degradation or regulation of glycogen have been identified. Most of them are inherited in an autosomal recessive manner. Several inborn errors of glycogen metabolism have been described, and they result from mutations in genes that code for proteins involved in various steps of glycogen synthesis, degradation, or regulation. Glycogen storage diseases are characterized by an abnormal tissue concentration (>70 mg per gram of liver or 15 mg per gram of muscle tissue of normal or abnormal structure of glycogen). Hypoglycemia is the main biochemical consequence of GSD type I and some of the other GSDs. The basis of dietary therapy is nutritional manipulation to prevent hypoglycemia and improve metabolic dysfunction (Heller et al, 2008; Mayatepek et al, 2010).

All glycogenosis may divide in two groups: hepatic and muscular forms of glycogenosis. The various hepatic enzyme deficiencies are expressed primarily as hypoglycemia and hepatomegaly. In glycogenosis type I, III and VI there is limitation in the output of glucose from hepatic tissue, and hypoglycemia is an prominent laboratory sing. (Goldberg & Slonim, 1993; Heller et al, 2008; Howell, 1978; Wolfsdorf.& Weinstein, 2003).

8.1.4.1 Glycogen storage disease type I

Glycogen storage disease type I (glucose-6-phosphatase deficiency; von Gierke disease; Hepato-renal glycogenoses). GSD type I (or von Gierke disease) is an autosomal recessive disorder that is caused by deficient G6Pase activity. Glucose-6-phosphatase (G6Pase), an enzyme found mainly in the liver and kidneys, plays a critical role in blood glucose homoeostasis, providing glucose during starvation. One of the important functions of the liver and, to a lesser extent, of the kidney cortex is to provide glucose during conditions of starvation. Glucose is formed from gluconeogenic precursors in both tissues, and in the liver also from glycogen. Both glycogenolysis and gluconeogenesis result in the formation of glucose 6-phosphate, which has to be hydrolysed by G6Pase before being liberated as glucose into the circulation.

Glucose-6-phosphatase is the enzyme that catalyzes the last step of glycogenolysis and gluconeogenesis in liver and kidneys, i.e. the hydrolysis of glucose 6-phosphate to free glucose and inorganic phosphate. Its genetic deficiency is characterized by the association of hepatomegaly and nephromegaly due to the accumulation of large amounts of glycogen in these organs, with hypoglycaemia and lactic acidosis.

GSD type Ia is the most frequent form of glycogenosis, accounting for about 80% of the cases. It is caused by a lack of G6Pase activity, which is easily demonstrated by measuring the activity of this enzyme in a liver biopsy specimen. The deficiency of G6Pase activity is caused by mutations in the gene encoding this enzyme.
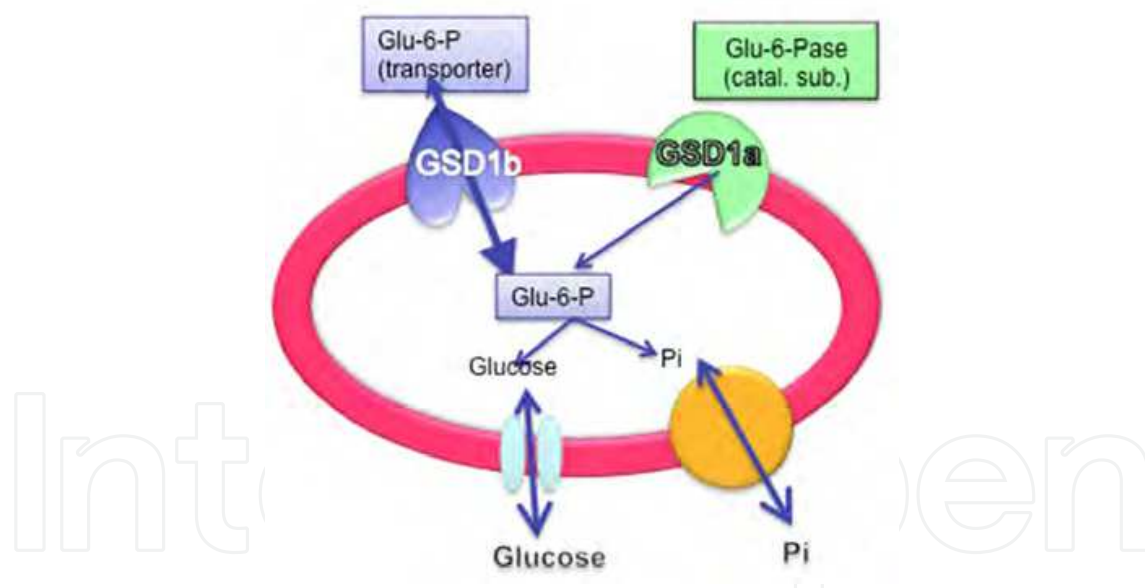

Fig. 7. The glucose-6-phosphatase system

On the basis of the imunological studies, by using the antibodies against to several of five components of glucose-6-phosphatase, GSD type I has been subcategorised into types a, b, and c, with type a as the most common, but all types have similar clinical manifestation as hypoglycemia and hepatomegaly due to the deposition of glycogen with normal structure. Fasting-induced hypoglycemia may be extreme, and with combination with lactic acidosis. Although severely affected patients may suffer brain damage in early infancy, this is not usually the case, and the most patients have normal intelligence. During starvation, however, the brain can derive energy from ketone bodies which are converted to acetyl-

CoA. It is likely that the nervous system is able to metabolise such substance as ketones and lactic acid.

Glucose-6-phosphatase consists of a hydrolase, whose catalytic site faces the lumen of the organelle and of translocases required for the transport of glucose 6-phosphate, Pi and glucose (Figure 7). Glucose 6-phosphate is transported into the lumen of the endoplasmic reticulum by a specific transporter before being hydrolysed by glucose-6-phosphatase, a transmembrane protein with its catalytic site oriented towards the lumen of the endoplasmic reticulum. Glycogen storage disease type Ia (GSD Ia) is due to a defect in glucose-6-phosphatase catalytic site and glycogen storage disease type Ib, to a defect in the glucose 6-phosphate transporter (Schaftingen and Gerin, 2002).

8.1.4.2 Debranching enzyme deficiency (type III glycogen storage disease; limit dextrinosis; Cori's disease)

Type III glycogen storage disease (amylo-1, 6-glucosidase (debrancher) deficiency) most often affects only liver, but may affect muscles as well. In this form of glycogen storage disease, a glycogen accumulates which has a structure resembling the limit dextrin produced by degradation of of glycogen by phosphorylase a , which is free of debrancher (amylo-1, 6-glucosidase) activity. Early in life, hepatomegaly and growth retardation may be striking. In contrast to patients with Type I glycogenosis, moderate enlargement of the spleen is sometime seen. Glycogen of abnormal structure frequently accumulates in muscle and heart, as well as in the liver. In the older patients it may cause a chronic progressive myopathy and cardiomegaly. With muscle involvement, the serum creatine phosphokinase (CPK) activity is elevated, and patients are usually classified as having type III b diseases. There is no renal enlargement in this disease. Generally, the clinical course of this disease is milder than that of Type I glycogenoses.

8.1.4.3 Type VI glycogenosis (hepatic phosphorylase deficiency; Hers' disease)

Large group of patients with hepatic forms of the glycogen storage diseases have increased hepatic glycogen (with normal structure) and a reduction to about 25 percent normal of hepatic phosphorylase activity. Patients with increased liver glycogen and profound reduction in liver phosphorylase activity (and normal activating system) continued to be observed. Hypoglycemia is present (Wolfsdorf & Weinstein, 2003; Heller et al, 2008).

8.1.4.4 Glycogen synthase deficiency (type 0 glycogen storage disease; GSD0)

Type 0 glycogen storage disease (GSD0) is caused by deficiency of the hepatic isoform of glycogen synthase (Weinstein et al, 2006). Although GSD0 has been classified as a glycogen storage disease, this is a misnomer. In contrast to all other types of glycogenoses, which are characterized by increased glycogen storage, deficiency of glycogen synthase causes a marked decrease in liver glycogen content. GSD0 is the only GSD not associated with hepatomegaly and hypoglycemia typically is milder than in the other types of GSD (Wolfsdorf & Weinstein, 2003; Weinstein, 2006).

Patients with GSD0 have fasting ketotic hypoglycemia. Most children are cognitively and developmentally normal. Until recently, the definitive diagnosis of GSD0 depended on the demonstration of decreased hepatic glycogen on a liver biopsy. The need for an invasive procedure may be one reason that this condition has been infrequently diagnosed. Mutation analysis of the GYS2 gene (12p12.2) is a non-invasive method for making this diagnosis in patients suspected to have this disorder.

8.1.5 Disorders of gluconeogenesis

A key role of gluconeogenesis is in the maintenance of blood sugar. Deficiency of any enzyme participating in gluconeogenesis can lead to hypoglycemia with lactic acidosis. Inborn deficiencies are known of each of the four enzymes of the glycolytic-gluconeogenic pathway that ensure a unidirectional flux from pyruvate to glucose: pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase (van den Berghe, 1996).

8.1.5.1 Pyruvate carboxylase deficiency (PCD)

Pyruvate carboxylase, a member of the biotin-dependent enzyme family, catalyses the ATP-dependent carboxylation of pyruvate to oxaloacetate. Pyruvate carboxylase is an important enzyme in gluconeogenesis. Deficiency of pyruvate carboxylase can lead to hypoglycemia with lactic acidosis. Pyruvate carboxylase deficiency is a rare disorder that can cause developmental delay and failure to thrive starting in the neonatal or early infantile period. PCD results in malfunction of the citric acid cycle and gluconeogenesis, thereby depriving the body of energy. Based on the severity of the clinical presentation and the biochemical disturbances, two clinical forms have been described. The milder form A presents in infancy with delayed neurological development, chronic lactic acidemia and a normal lactate to pyruvate ratio. Longer survival, but with severe clinical sequelae, is common in the mild form A. The complex form B presents neonatally or in early infancy with severe metabolic acidosis, lactic acidosis, ketosis, and hepatomegaly (Jitrapakdee &. Wallace, 1999; Ahmad et al., 1999).

8.1.5.2 Phosphoenolpyruvate carboxykinase deficiency

Phosphoenolpyruvate carboxykinase is an important enzyme in gluconeogenesis. It is found in both cytosol and mitochondria of the liver cells. Deficiency of the enzyme, a rare inherited disorder, can cause severe, persistent neonatal hypoglycaemia and liver impairment (Hommes et al, 1976; Vidnes & Sovik, 1976).

8.1.5.3 Fructose-1,6-diphosphatase (FDPase) deficiency

Fructose-1,6-diphosphatase (F1,6DPase) catalyzes the conversion of fructose-1,6-diphosphate (F1,6DP) to fructose-6-phosphate. The F1,6BPase reaction is a major point of control of gluconeogenesis. Fructose-1,6-diphosphatase (FDPase) deficiency is an autosomal recessive disorder caused by a mutation of the FDP1 gene and results in impaired gluconeogenesis (Froesch, 1978; Gitzelmann et al, 1989; Hellerud, 2010).
Patients with FDPase deficiency typically present in the newborn period with symptoms or signs related to hypoglycemia and metabolic acidosis following ingestion of fructose. Patients lacking FDPase accumulate intrahepatocellular fructose-1,6-bisphosphate (FDP) which inhibits gluconeogenesis and, if intracellular phosphate stores are depleted, inhibits glycogenolysis. The inability to convert lactic acid or glycerol into glucose leads to hypoglycemia and lactic acidosis (Asberg et al, 2010; Hellerud, 2010; Song, 2011; Zaidi, 2009; Mortensen, 2006). The accumulation of fructose 1,6-diphosphate (FDP) inhibits phosphorylase a in liver, the first enzyme of glycogenoslysis.

8.1.5.4 Glycero kinase deficiency

Glycerol kinase (GK) catalyzes the phosphorylation of glycerol to glycerol 3-phosphate (G3P) which is important in the formation of triacylglycerol (TAG) and fat storage. GK is at the interface of fat and carbohydrate metabolism. GK deficiency (GKD) is an X-linked

inborn error of metabolism that is characterized biochemically by hyperglycerolemia and glyceroluria and is due to mutations within or deletions of the GK gene on Xp21 (Rahib et al, 2007). Isolated GKD can occur in patients with or without symptoms, mainly due to disturbed energy homeostasis associated with hyperketotic hypoglycemia (Sjarif et al, 2004). The greater importance of glycerol as a gluconeogenetic substrate in children than in adults may explain the episodes in young patients with GKD, often elicited by catabolic stress (Hellerud et al, 2004).

8.1.6 Leucine-sensitive hypoglycemia

This type of hypoglycemia was reported in 1956 by Cochrane who described children who became hypoglycemic on a casein-rich diet and whose symptoms worsened on feeding on high protein and low carbohydrate diet. The one-third of all infants with unexplained hypoglycemia may be sensitive to leucin. Presentation is most often in the first year of life.A common symptom is the development of convulsion after milk-feeding, (MacMullen et al., 2001) .

Leucine produces hypoglycemia by causing the release of insulin from the pancreas islet cells. The hypoglycemia found in maple syrup urine diseases is probably caused by high circulating levels of leucin. Two-thirds of the infants who have had leucine-sensitive hypoglycemia have subsequently mental retardation and neurological disorders (Roe &, Kogut, 1982; Sinclair, 1979).

8.1.7 Hyperinsulinism/hyperammonemia (HI/HA) syndrome

Hyperinsulinism is the most common cause of hypoglycemia in early infancy. Congenital hyperinsulinism, is usually caused by genetic defects in beta-cell regulation, including a syndrome of hyperinsulinism plus hyperammonemia (Kelly et al., 2001; Kogut, 1982; Stanley, 1997).

The hyperinsulinism/hyperammonemia (HI/HA) syndrome is a form of congenital hyperinsulinism in which affected children have recurrent symptomatic hypoglycemia together with asymptomatic, persistent elevations of plasma ammonium levels. The disorder is caused by dominant mutations of the mitochondrial enzyme, glutamate dehydrogenase (GDH), that impair sensitivity to the allosteric inhibitor, GTP. These data confirm the importance of allosteric regulation of GDH, as a control site for amino acid-stimulated insulin secretion and indicate that the GTP-binding site is essential for the regulation of GDH activity by both GTP and ATP (MacMullen et al, 2001; Kogut,1982).

9. Hypoglycemia as results of acquired disorders of carbohydrates metabolism

9.1 Liver and kidney disorders

Although hypoglycemia is usually linked with diabetes, there are various types of conditions, which are generally rare, that can cause it even in those who do not have diabetes. Any disorder or abnormality in the functioning of the liver can disturb the process of blood-sugar regulation, resulting in hypoglycemia. On the other hand, disorders in kidney can cause problems in excretion of certain medications. Hence, kidney disorders can be one of the major causes of low blood sugar.

9.1.1 Hypoglycemia in liver disorders

Symptomatic hypoglycemia is uncommon in liver diseases because glucose homeostasis can be maintained with as little as 20 per cent of healthy parenchymal cells, but biochemical hypoglycemia has been reported in a wide variety of aquired hepatic diseases. The hypoglycemia of Reye's syndrome and sepsis, as well as alcohol hypoglycemia, are considered to be the consequence of hepatic disturbance. Acute viral hepatitis results in serious impairment in hepatic glycogen synthesis and gluconeogenesis and frequently gives rise to fasting hypoglycemia (Felig et al., 1970). Glycogen stores rapidly disappear as liver disease (including cirrhosis due to alcoholism) progresses, causing recurrent hypoglycemia (Service, 1992).

Reye syndrome is a fatal disease, most commonly occuring following some virus infections (influenza A, influenza B, herpes, varicella zoster and several other common viral infections). Epidemiologic evidence suggests that aspirin plays a potentiating role in the pathogenesis of this syndrome. The hepatic dysfunction appears to be the primary error and the direct result of a mitochondrial disturbance that causes secondary metabolic derangement, (hyperamoniemia, hypoprotrombinemia without hyperbilirubinemia), including hypoglycemia.

Hypoglycaemia in patients with hepatocellular carcinoma usually occurs during the terminal stage of the illness, but there are patients with hepatocellular carcinoma who develop hypoglycaemia early in the course of their illness. Hypoglycemia occurs predominantly as a paraneoplastic manifestation of hepatocellular carcinoma, (Sorlini et al., 2010; Thipaporn et al., 2005; Young, 2007).

Ethanol is a potent hypoglycemic agent, causing decreased endogenous glucose production and glycogenolysis. The volume of alcohol intake is correlated with the degree of resulting hypoglycemia (Raghavan et al., 2007; Smeeks, 2008). Ethanol-induced hypoglycemia arises from inhibition of gluconeogenesis as a result of the increase in the NADH-NAD ratio, which suppresses the conversion of lactate to pyruvate, glycerophosphate to dihydroxyacetone phosphate, and glutamate to α-ketoglutarate and several tricarboxylic cycle reactions. Ethanol reduces rates of hepatic glucose production, supresses plasma insulin concentration, increases plasma lactate concentration, beta hydroxybutirate, glycerol and free fatty acids, and increases lactate-pyruvate and beta-hydroxybutirate-acetoacetate ratios. Hypoglycemia usually develops within 6 to 36 hours of the ingestion, of even moderate amounts of ethanol by persons chronically malnouriched or by healthy persons who have missed one of the meals. Healthy children are especially susceptible to ethanol hypoglycemia. Blood ethanol levels may not be elevated when the patient is hypoglycemic. Healthy children are especially susceptible to ethanol hypoglycemia. Blood ethanol levels may not be elevated when the patient is hypoglycemic(Arky, 1989; Badawy, 1977; Service, 1992).

9.1.2 Hypoglycemia in kidney disorders

Kidneys play a significant role in carbohydrate metabolism under both physiological and pathological conditions due to renal gluconeogenesis. Hypoglycemia in patients with renal failure may be due to inadequate gluconeogenic substrate availability. It seems that disturbances in renal gluconeogenesis together with lower degradation of insulin played the key role in creating hypoglycaemia in patients with renal diseases. Hypoglycemia should be suspected in any patient with renal failure who exhibits any change in mental or neurologic status (Arem, 1989; Rutsky,1978). Also, kidney disease is a frequent cause of adverse medication reactions due to the problems in excretion of certain medications and, therefore, causing hypoglycemia in older adults (Gerich, 2001).

9.2 Hormonal disturbances and hypoglycemia

Adrenocortical insufficiency or **Adrenocortical hypofunction** is defined as the deficient production of glucocorticoids or mineralocorticoids, or both. Hypoglycemia is common in adrenocortical insufficiency. Primary adrenocortical insufficiency (Addison's disease) is due to destruction of the adrenal cortex, whereas in secondary adrenocortical insufficiency impaired cortisol production is due to deficient ACTH production. Spontaneous hypoglycemia has been reported to be a frequent finding in isolated ACTH deficiency. The cause for primary adrenocortical insufficiency is autoimmune destruction or tuberculosis of the adrenal cortex.

Hypoglycemia in hypopituitarism is common in children under 6 years of age but less so beyond that age. Asymptomatic hypoglycemia has been observed in isolated growth hormone deficiency after prolonged fasting (Tyrrell, 1992).

Insulinoma. Insulin-producing tumors of pancreas can cause severe hypoglycemia; among these are islet cell adenoma and carcinoma (insulinoma). Insulinoma is uncommon in persons less than 20 years of age and is rare in those less than 5 years of age. Of the patients with insulinoma, approxymately 87 per cent have single benign tumors. These tumors are most common in women (60%), with median age of diagnosis 50 years (Service, 1992).

9.3 Reactive hypoglycemia

The post-prandial hypoglycemia occurs immediately following meals, with no known causes (idiopathic reactive hypoglycemia, RH) (Krinsley & Grover, 2007).

Alimentary hypoglycemia, another form of RH related to prior upper GI surgery (Guettier, 2006), results from rapid glucose absorption into the intestine and increased insulin secretion after every meal. The food stimulated hypoglycemia usually cause symptomes mediated by the autonomic nervous system - sweating, shakiness, anxiety, palpitations, and weakness, and rarely those of impairment of central nervous system function. The food deprived hypoglycemia, on the other hand, usually result in impariment of central nervous system functions - reduced intellectual capacity, confusion, irritability, abnormal behavior, convulsions and coma (Service,1992).

Infections. Hypoglycemia often occurs during or following acute infections in older adults. Infection-related hypoglycemia increases the risk of death and morbidity among persons over age 70 Secretion of glucagon, epinephrine, and growth hormone during hypoglycemia diminishes significantly after age 65, reducing autonomic warning symptoms in older adults.

Sepsis as a cause of hypoglycemia should be readily apparent. The mechanism for hypoglycemia with sepsis is not well defined. Depleted glycogen stores, impaired gluconeogenesis, and increased peripheral utilization of glucose may all be contributing factors. Laboratory testing can confirm the suspicion of hepatic dysfunction (Rattarasarn, 1997).

9.3.1 Hypoglycemia due to drug medications

Insulin treatment of Diabetes mellitus. Hypoglycaemia is a serious, frequent and recurrent complication of treatment of diabetes mellitus with insulin, which may become a direct danger to the patient's life. Hypoglycaemia represents the limiting factor to obtain good glycemic control. Dysregulation of counteracting mechanisms and autonomic nervous system neuropathy contribute to a strong increase in the incidence of hypoglycaemia in type 1 diabetic patients, but also in long lasting type 2 diabetic patients (Cryer, 2001, 2008).

Predictors of hypoglycemia in patients with type 2 diabetes include treatment with insulin and duration of insulin treatment, a history of previous hypoglycemia. Primary risk factors for hypoglycemia in decreasing importance have been reported as age over 64, current insulin treatment, sulfonylurea treatment, polypharmacy, renal impairment and previous hypoglycemic episodes (Miller et al., 2001).

Antibiotics. Pentamidine used in treating opportunistic infections associated with immunosuppression (e.g. Pneumocystis pneumonia) and protozoan parasites, causes severe hypoglycemia by increasing insulin secretion. Isoniazid causes hypoglycemia through cytotoxic hepatic damage (Service, 1992).

Sulfonamides and Fluorquinolones have been known to cause significant, life-threatening hypoglycemia by increasing insulin secretion.

Cardiac medications. Beta-blockers inhibit glycogenolysis and are most likely to be associated with hypoglycemia in older adults. Isolated reports indicate that angiotensin-converting enzyme inhibitors can cause hypoglycemia by increasing insulin sensitivity.

Salicylates. It has been determined more recently that salicylates, such as aspirin, decrease serum glucose by reversing or inhibiting the process of insulin resistance related to generalized inflammatory responses.

Psychotropic medications. It should be avoided haloperidol in older adults with a history of hypoglycemia, or sulfonylurea or insulin use, due to the risk of severe hypoglycemic interactions. Tricyclic antidepressants, chlorpromazine, MAO inhibitors, and lithium also have been reported to cause severe hypoglycemia.

Quinolines. Quinines, used as an anti-malarial and anti-arrhythmic agents, have strong hypoglycemic properties, increasing insulin secretion as the sulfonylureas do (Service, 1992).

10. Conclusion

Hypoglycemia is defined as a serum glucose level below (3.8 mmol/L or, 70 mg/dL). The plasma glucose level is tightly controlled throughout life in the normal individual. The stability of the plasma glucose level is a reflection of the balance between the rates of whole body glucose production and glucose utilization. The physiological post absorptive serum glucose concentration in healthy humans range is 4.4-5.8 mmol/L (80 to 110 mg/dL). Variation in blood glucose levels above or below the normal range usually indicate to serious diseases. Even mild disruptions of glucose homeostasis can have adverse consequences.

Hypoglycemia most often affects those at the extremes of age, such as infants and the elderly, but may happen at any age, in neonatal period and early childhood As a relatively frequent common event in the pediatric newborn period (childhood), hypoglicemia may be a consequence of some inborn errors of carbohydrate metabolism. In adults, hypoglycemia is a result of acquired disorders, primarily due to disturbance of physiological function of some organs (liver, kidney, CNS) or manifests disorders of some endocrine glands, involved in carbohydrate metabolism .

The symptoms of hypoglycemia are not specific and are related to disturbance of the brain and the sympathetic nervous system. The stimulation of the autonomic nervous system produces sweating, pale skin, irritability, anxiety, weakness, hunger, nausea, serving as an early warning system and preceding the neuroglycopenic symptoms due to cerebral glucose deprivation, e.g. headache, confusion, inability to concentrate or pay attention, mental confusion, difficulty in thinking, changes in vision, lethargy, sleepiness, stupor.

Biochemical hypoglycemia has been reported in a wide variety of acquired hepatic and renal diseases. Also, kidney disease is a frequent cause of adverse medication reactions due to the problems in excretion of certain medications and, therefore, causing hypoglycemia in older adults due to drug medications. Hypoglycaemia is a serious, frequent and recurrent complication of diabetes mellitus treatment with insulin, which may become a direct danger to the patient's life.

Laboratory diagnosis of hypoglycemia is very important in medical praxis, especially in pediatric praxis, suggesting some inborn errors of carbohydrate metabolism, or, in adults, suggesting hepatic disorders, renal failure, and cardiac disorders, neuropsychiatric disorders, etc.

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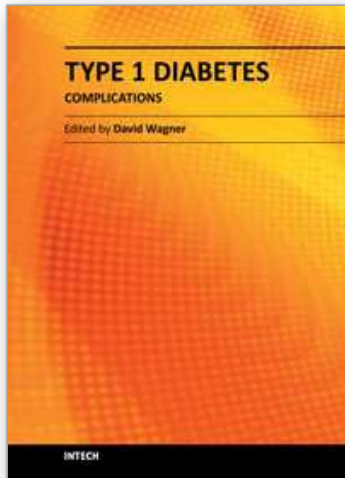
Type 1 Diabetes Complications

Edited by Prof. David Wagner

This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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