Chapter 2

Glucose Homeostasis

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http://dx.doi.org/10.5772/67222

Abstract

Glucose is the main and preferred source of energy for mammalian cells. Mammalian cells need glucose constantly. Long-lasting disturbances in blood glucose concentrations can cause diseases and death. Therefore, blood glucose concentrations must be within narrow limits. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis.

Keywords: glucose homeostasis, glucose metabolism, pancreas, liver, kidney, hypothalamic-pituitary axis

1. Introduction

Carbohydrates play several roles in the metabolic processes and as structural elements of living organisms. An essential substrate for all mammalian cells is monosaccharide, glucose. In human glucose is obtained directly from the diet or by synthesis in the liver and kidney. Monosaccharides are transported across the intestinal wall to the portal vein and then to liver cells and other tissues. Monosaccharides play a role as a precursor of fatty acids, amino acids, and glycogen. They are also oxidized by the various catabolic pathways of cells, play an important role in the synthesis of pentose sugars for DNA and RNA, as well as generate NADPH + H^+ for the synthesis of lipids.

2. Transport of monosaccharides into cells

In the first step of carbohydrate metabolism, monosaccharides are transported across the plasma membranes. Due to hydrophilic nature of glucose and other monosaccharides, the lipid bilayer of plasma membrane is impermeable for these substances. Therefore,

monosaccharide transport across the plasma membrane is mediated *via* membrane transport proteins called glucose transporters.

In human, there are three classes of glucose transporters: the facilitative glucose transporters, the sodium-glucose cotransporters, and SWEETs. However, these transporters are named "glucose transporters"; they transport not only glucose but also other substances such as fructose, fucose, xylose, vitamins, ions, etc. GLUT1 was also suggested to be receptor for human T-lymphotropic virus (HTLV) and plays an essential role in CD4 T-cell activation

2.1. The GLUT family

GLUT proteins are encoded by the *SLC2* genes. These proteins are members of the major facilitator superfamily (MFS) of membrane transporters. These transporters are uniporters. They facilitate the diffusion of substrates across cellular membranes along a concentration gradient [1, 2]. The GLUT family comprises 14 isoforms GLUT1–GLUT12, GLUT14, and HMIT (GLUT13). HMIT is the proton-driven myoinositol transporter.

The human GLUT proteins are comprised of about 500 amino acid residues. They are predicted to possess 12 transmembrane-spanning α-helices and a single N-linked oligosaccharide [4]. The cytoplasmic domain contains a short N-terminal segment, a large intracellular loop between transmembrane domains 6 and 7, and a large C-terminal segment. The sequences among members of family are 14–63% identical and 30–79% conservative [5]. Sequence alignments of all members reveal several highly conserved structures [5]. The fact that the transmembrane domain primary structure is largely conserved suggests that the glucose channel is basically identical in structure among the members of this family [6]. One or more GLUT proteins are expressed in every cell type of the human body. It is highly likely that the major substrates for several GLUT proteins have not yet been identified [3].

2.2. The Na^+/glucose cotransporters

Sodium-glucose transporters, also known as Na^+/glucose cotransporters or symporters, are encoded by *SLC5* genes. These transporters are members of a larger gene family of sodium/substrate symporter family (SSSF) that contain a common SSF motif in the fifth transmembrane region [7]. There are 12 human genes in the *SLC5* family that are expressed in different tissues. These cotransporters transport substrates *via* a secondary active transport mechanism. SGLTs do not directly utilize ATP to transport glucose against its concentration gradient; rather, they must rely on the sodium concentration gradient generated by the sodium-potassium ATPase as a source of chemical potential [8]. The Na^+-electrochemical gradient provided by the Na^+-K^+ ATPase pump is utilized to transport substrate into cells against its concentration gradient. Except for SGLT3 which is glucose sensor, all are sodium cotransporters [9]. The function of ten are tightly coupled plasma membrane Na^+/substrate cotransporters for different solutes, one is a Na^+/Cl^-/Choline cotransporter and one is a glucose-activated ion channel [7].

All members of the *SLC5* family code for 60 to 80 kDa proteins contain 580–718 amino acids [10]. The genes *SLC5* contain 14–15 exons; however, *SLC5A7* gene contains 8 exons, and

SLC5A3 gene contains 1 exon [7]. SGLTs contain 14 transmembrane α-helices (TMH) with both NH_2 terminus and the COOH terminus facing the extracellular (luminal) side of the cell [11, 12]. The human sodium cotransporters share an amino acid identity of 21–70%. The transporter contains a single glycosylation site [11]. Of note, glycosylation is not required for functioning of the protein. Phosphorylation sites are suggested between transmembrane helices 5 and 6 [13] and between transmembrane helices 8 and 9 [14].

2.3. The SWEET proteins

Sugar efflux transporters are essential for the maintenance of human blood glucose levels. In mammals, glucose efflux from the liver is crucial for the maintenance of blood glucose levels. Chen et al. [15] identified a new class of sugar transporters, named SWEETs. The SWEETs are ubiquitously expressed in plant. SWEET belongs to a novel transporter family with 17 members in *Arabidopsis* and 21 in rice [15]. Homologs of SWEETs have also been identified in humans (SWEET1) [15]. Although human and animal genomes typically contain only a single SWEET gene, a major exception is *Caenorhabditis elegans*, which contains seven SWEET paralogs [16]. SWEET is a glucose uniporter.

The human SWEET1 is expressed in the oviduct, epididymis, intestine, and β-cell lines [15]. It is a candidate for the vesicular efflux from enterocytes, hepatocytes, and β cells [15]. The SWEET class of transporters is predicted to have seven transmembrane helices. Eukaryotic SWEETs have a predicted topology comprising a repeat of three membrane-spanning domains that are connected by an inversion linker helix with extracellular N-terminus and intracellular C-terminus [15–17]. Cytosolic C-terminus of the SWEETs is very long and may serve as a docking platform for protein interactions [18]. C-termini show much less conservation and are characterized by extensive length variability [19].

3. General information on glucose metabolism

3.1. Glucose as a source of cellular energy

When energy is needed, glucose is rapidly metabolized to produce adenosine triphosphate (ATP), a high-energy product. Glucose is oxidized through a long series of reactions that extract the great amount of possible energy from it.

3.1.1. Glycolysis

The first which begins the complete oxidation of glucose is called glycolysis (or Embden-Meyerhof-Parnas pathway). It is an anaerobic process. During glycolysis, each glucose molecule is split and converted to two three-carbon units. The next result of glycolysis is the production of two pyruvate molecules, two ATP, and two NADH + H^+. During glycolysis, the cell receives about 5% of the total energy available. In the presence of oxygen, aerobic organisms oxidize pyruvate to CO_2 and H_2O. In the absence of oxygen, pyruvate can be converted to several types of reduced molecules, such as ethanol (e.g., yeast) or lactate (e.g., muscle cells, red blood cells). This anaerobic process is referred to as fermentation.

3.1.2. Oxidative decarboxylation

During aerobic metabolism of glucose, pyruvate is transported inside mitochondria, where is oxidized. Oxidation of pyruvate to acetyl coenzyme A (Acetyl-CoA) produces two molecules of CO_2 and NADH + H^+.

3.1.3. Krebs cycle

Further series of reactions is collectively called "Krebs cycle," also known as the "citric acid cycle" or the "tricarboxylic acid cycle (TAC)." Through a series of reactions in mitochondria, acetyl-CoA is oxidized to CO_2. Fuel for the Krebs cycle comes also from lipids (fats) and proteins (amino acids), which produce the molecule acetyl-CoA. If carbohydrates are the fuel for Krebs cycle, this cycle occurs twice since each glucose produces two pyruvates and then in the process of oxidative decarboxylation two molecules of acetyl-CoA.

3.1.4. Electron transport chain

The oxidative phosphorylation, which occurs in mitochondria, is a series of reactions that utilize the energy from NADH + H^+ and $FADH_2$. The electrons are successively passed down the chain of cytochromes, each time releasing some of their energy, which is then used to pump protons actively across the membrane into the matrix down this chemiosmotic gradient but can only do so through the ATP synthase. The result of the electron transport chain is three molecules of ATP, if a donor of protons and electrons is NADH + H^+ and one molecule of H_2O. In the case of $FADH_2$, the result of this process is two molecules of ATP and one molecule of H_2O.

3.2. Glycogenesis

Glycogenesis is the process of glycogen synthesis from glucose. Glycogen is the storage form of glucose. Glycogenesis occurs after a meal, when blood glucose levels are high. All cells contain glycogen, but most is stored in liver cells (about 90 g in a 70-kg man) and muscle cells (about 350 g in a 70-kg man). In this process, glucose molecules are added to chains of glycogen for storage in mentioned organs.

Glucose-6-phosphate is converted to glucose-1-phosphate by phosphomutase. Sugar-nucleotide synthesis is a reaction preceding sugar polymerization processes. Uridine diphosphate glucose (UDP-glucose) is more reactive than glucose. By itself, this is a readily reversible reaction; however, the subsequent hydrolysis of pyrophosphate to two inorganic phosphates (PPi) will readily occur, and this will drive the reaction over the product side.

For the synthesis of glycogen, the starting point is the protein glycogenin. If the chain contains more than ten molecules of glucose residues, it acts as a primer for proglycogen synthase which elongates primer. The elongation is due to the addition of new glucose molecules to the existing chain.

3.3. Glycogenolysis

When the blood sugar levels fall, glycogen stored in the muscle and liver may be broken down. This process is called glycogenolysis. The liver can consume glucose-6-phosphate in glycolysis and can also remove the phosphate group using the enzyme glucose-6-phosphatase and release the free glucose into the bloodstream. Since muscle cells lack glucose-6-phosphatase, they cannot convert glucose-6-phosphate into glucose and therefore use the glucose-6-phosphate to generate energy for muscle contraction.

3.4. Gluconeogenesis

Gluconeogenesis generates glucose from noncarbohydrate precursors such as lactate, glycerol, pyruvate, and glucogenic amino acids. It occurs primarily in the liver. Under certain conditions, such as metabolic acidosis or starvation, the kidney can make small amounts of new glucose. When liver glycogen is depleted, the gluconeogenesis pathway provides the body with adequate glucose. The major substrates for gluconeogenesis are lactate (formed in muscle and red blood cells), amino acids (derived from the muscle), and glycerol (produced from the degradation of triacylglycerols). During anaerobic glycolysis, pyruvate is reduced to lactate. Lactate is released to the bloodstream and transported into the liver. In the liver lactate is converted to glucose, and then glucose is returned to the blood for use by the muscle as an energy source. This cycle is termed the Cori cycle. The gluconeogenesis of the cycle is a net consumer energy, costing the body four molecules of ATP more than are produced during glycolysis. The reaction sequence in gluconeogenesis is largely the reverse of glycolysis.

Of all the amino acids that can be converted to glycolytic intermediates, alanine is perhaps the most important. When the muscle produces large quantities of pyruvate, for example, during exercise, some of these molecules are converted to alanine. Alanine is transported to the liver, reconverted to pyruvate and then to glucose. This cycle is termed the glucose-alanine cycle. The glucose-alanine cycle plays a role in recycling α-keto acids between the muscle and liver as well as is a mechanism for transporting amino nitrogen to the liver (the muscle cannot synthesize urea from amino nitrogen).

3.5. The pentose phosphate pathway

The pentose phosphate pathway is primarily a cytoplasmic anabolic pathway which converts the six carbons of glucose to five carbon sugars and reducing equivalents. Its principal products are NADPH + H^+, for reductive biosynthesis reactions within cells, and ribose-5-phosphate, for synthesis of the nucleotides and nucleic acids.

The pentose phosphate pathway occurs in the cytoplasm and is an alternative to glycolysis. There are two distinct phases in the pathway. The first is the oxidative phase. In this phase, two molecules of $NADP^+$ are reduced to NADPH + H^+, utilizing the energy from the conversion of glucose-6-phosphate into ribose-5-phosphate. The nonoxidative phase of the pathway primarily generates ribose-5-phosphate. This pathway also converts five carbon sugars into

both six (fructose-6-phosphate) and three (glyceraldehyde-3-phosphate) carbon sugars which can then be utilized by the pathway of glycolysis.

4. Role of the pancreas in the glucose homeostasis

The pancreas plays a key role in the glucose homeostasis. The endocrine and exocrine pancreas has a complex anatomical and functional interaction [20]. Glucose metabolism is highly dependent on hormones secreted by the islets of Langerhans [21]. To avoid postprandial hyperglycemia and fasting hypoglycemia, the body can adjust glucose levels by secreting two hormones: insulin and glucagon. These hormones work in opposition to each other [22]. There are four major cell types in the pancreatic islets of Langerhans: the β-cells that secrete insulin and amylin, α-cells secrete glucagon, δ-cells secrete somatostatin, and PP cells secrete pancreatic polypeptide (PPY) [22, 23].

4.1. Insulin

Insulin secretion depends on the circulating glucose concentrations. It is secreted if the blood glucose concentration is ≥ 3 mmol/L [24]. Increased circulating glucose levels > 5 mmol/L results in increase of output of insulin and C peptide by the β-cells. Postprandially, the secretion of insulin occurs in two phases [26]. Long-term release of insulin occurs if glucose concentrations remain high [25]. Insulin secretion needs at least two signaling pathways, the K_{ATP} channel dependent and K_{ATP} channel independent, respectively [27, 28]. Glucose enters β-cells *via* GLUT2, which is believed to play a role in glucose-stimulated insulin secretion.

Insulin regulates glucose homeostasis at many sites, as for example, reducing hepatic glucose output (*via* decreased glucogenesis and glycogenolysis), inducing a process of glycogenesis (liver, muscle), and increasing the rate of glucose uptake, primarily into striated muscle and adipocytes. In most nonhepatic tissues, insulin increases glucose uptake by increasing the number of plasma membrane GLUT1 and GLUT4.

4.2. Glucagon

Glucagon is a hormone which is secreted by α-cells in response to hypoglycemia. It acts as the counter-regulatory hormone to insulin. Pancreatic α-cells contain a special set of channels that generate action potentials of Na^+ and Ca^{2+} in the absence or at low levels of glucose [29].

Glucagon activates glucose formation and release from the liver to stabilize blood glucose [30]. Glucagon stimulates gluconeogenesis and glycogenolysis and decreases glycogenesis and glycolysis. It also stimulates gluconeogenesis by stimulation of uptake of amino acids in the liver and increases the release of glycerol from adipose tissue which can further be used in the liver during gluconeogenesis [31]. An elevated glucagon-to-insulin ratio accelerates gluconeogenesis as well as fatty acid β-oxidation and ketone bodies formation [30, 32].

4.3. Somatostatin

Somatostatin is secreted by many tissues, including pancreatic δ-cells, intestinal tract, and central nervous system. It is released in response to glucose at lower concentrations than β-cells [33]. Somatostatin is a potent local inhibitor adjacent β- and α-cells [34]. Somatostatin release is increased in response to glucose stimulation [35, 36] and is Ca^{2+} dependent [36]. Acute administration of somatostatin to animals reduces food intake [37, 38]. Somatostatin has been reported to have no direct effect on basal glucose production (gluconeogenesis or glycogenesis) in isolated hepatocytes [39], and in vivo it does not alter the basal glucose production rate when the levels of insulin and glucagon are maintained [39, 40]. The portal vein insulin and glucagon levels were significantly decreased by somatostatin infusion [40].

4.4. Amylin

Amylin is produced by β-cells and stored in their secretory granules. It is co-secreted with insulin from pancreatic β-cells in response to glucose as same as insulin [41], in a roughly about 1:10 amylin/insulin ratio [42]. Plasma amylin levels are low during fasting and increase during meals and following glucose administration, and the levels are directly proportional to body fat [42]. Amylin participates in glucose homeostasis by two mechanisms: retarding gastric emptying in dose-response manner [43] and suppressing postprandial glucagon secretion [43, 44]. There is also evidence that amylin functions as an adiposity signal in addition to a satiety signal.

4.5. Pancreatic polypeptide (PPY)

The pancreatic polypeptide (PP) is produced predominantly by F cells (PP cells). Circulating PP concentrations increase following nutrient ingestion in a biphasic manner in proportion to the caloric load [45]. The secretion of PP during meals requires an intact vagus nerve. Pancreatic polypeptide affects metabolic functions including glycogenolysis and decreases fatty acid levels [46]. It also inhibits pancreatic secretion.

5. Role of the liver in the glucose homeostasis

The liver plays a major role in blood glucose homeostasis by maintaining a balance between the uptake and storage of glucose *via* glycogenolysis and gluconeogenesis. The liver is the primary organ for glucose metabolism. About 90% of all circulating glucose not derived directly from the diet comes from the liver. Hepatocytes take up glucose by GLUT2 in the presence of high concentrations of glucose. In hepatocytes, glucose is phosphorylated by glucokinase to glucose-6-phosphate. From glucose-6-phosphate, the glucose is directed into glycogenesis, the pentose phosphate pathway, or glycolysis.

In response to ingestion of glucose and the resulting hyperinsulinemia and hyperglycemia, the fasting liver shifts from net output to net uptake of glucose. Healthy human adults ingesting 75 g glucose exhibited peak plasma glucose and insulin concentrations of 7.8 mmol/L and 325 pmol/L, respectively [47]. Key enzymes in opposing metabolic pathways, glycolysis, and

glycogenesis must be regulated for net flux in the appropriate direction to be achieved. The net glucose release is the result of two simultaneously ongoing pathways that are tightly regulated. Two enzymes specific for gluconeogenesis are opposed to the glycolytic enzymes. These enzymes regulate substrate cycles between gluconeogenesis and glycolysis. Glycogenolysis occurs within 2–6 hours after a meal in humans, and gluconeogenesis has a greater importance with prolonged fasting [48].

The rate of gluconeogenesis is controlled principally by the activation of gluconeogenic enzyme genes that are controlled by glucagon, glucocorticoids, and the interleukin-6 family of cytokines [48]. Insulin decreases gluconeogenesis by suppressing the expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, and glucagon and glucocorticoids stimulate glucose production by inducing these genes [49]. Glucagon is a regulator of hepatic glucose production during fasting, exercise, and hypoglycemia. It also plays a role in limiting hepatic glucose uptake. In response to a physiological rise in glucagon, hepatic glucose production is rapidly stimulated. This increase in hepatic glucose production is due to an enhancement of glycogenolysis, with little, or no, acute effect on gluconeogenesis [50]. The liver can release of glucose into the circulation. The skeletal muscle releases lactate, from where it can shuttle back to the liver (the Cori cycle).

The newborn mammals are in a transitional state of glucose homeostasis [51]. The diet of neonate is a low-carbohydrate, high-fat milk diet. The neonate must oxidize the stored liver glycogen, which is synthesized in the final days of gestation [51]. The initiation of hepatic glycogenolysis and gluconeogenesis in the first postnatal hours is critical for the maintenance of glucose homeostasis at this time [52]. Fetal life is characterized by chronic hyperinsulinemia. At birth hyperinsulinemia continues briefly and is one of the factors involved in the natural delay in hepatic glycogenolysis [53]. Counter-regulatory hormone actions are vital for the reversal of the postnatal hypoglycemia and for establishing glucose homeostasis at this time. Glucagon released in response to the postnatal hypoglycemia is responsible for initiation glycogenolysis and switching on hepatic gluconeogenesis [52].

6. Role of the kidneys in the glucose homeostasis

The human kidney is involved in the regulation of glucose homeostasis *via* three mechanisms: release of glucose into the circulation *via* gluconeogenesis, uptake of glucose from the circulation, and reabsorption of glucose from glomerular filtrate to conserve glucose carbon [54]. The kidney is unable to release glucose through glycogenolysis [55]. Glucose utilization occurs predominantly in the renal medulla. These enzymes can take up, phosphorylate, glycolyse, and accumulate, but cannot release, free glucose into the circulation. Glucose release is confined to the renal cortex [56]. Cells in the renal cortex possess gluconeogenic enzymes, and they can release glucose into circulation [57, 58]. The main precursor for renal glucogenesis is lactate [57]. Obtained results revealed that lactate is the most important renal gluconeogenic substrate followed by glutamine and glycerol [59]. Renal conversion to glucose of these precursors accounted for ~ 50, 70, and 35%, respectively, of their overall systemic gluconeogenesis [57]. After an overnight fast, 20–25% of glucose released into the circulation derives from the kidneys [54].

Renal glucogenesis is chiefly regulated by insulin and adrenaline. Insulin reduces renal gluconeogenesis and reduces the availability of gluconeogenic substrates, thus reducing glucose release into circulation [60]. On the other hand, insulin stimulates renal glucose uptake [61]. Adrenaline stimulates renal glucogenesis and glucose release and reduces renal glucose uptake [60]. It was shown in animal studies that glucagon increases renal glucose release into circulation.

With a daily glomerular filtration rate of 180 L, approximately 162 g of glucose must be reabsorbed each day to maintain a normal fasting plasma glucose concentration of 5.6 mmol/L [62]. Reabsorption of glucose in the proximal tubule is mediated by glucose transporter proteins that are present in cell membranes. SGLTs mediate active transport of glucose. SGLT2, which is in the convoluted section on the proximal tubule (S1), is considered most important. It is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. SGLT1, which is found in the straight section of the proximal tubule (S3), contributes to the other 10% of glucose reabsorbed in the proximal tubule [63]. GLUT proteins are expressed at the basolateral membrane of the epithelial cells. These transporters release into circulation the glucose reabsorbed by SGLTs in the tubular cells. Glucose reabsorbed by SGLT2 is then released into the circulation *via* GLUT2 and reabsorbed by SGLT1 [64]. In the postabsorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body. After meal ingestion, their glucose utilization increases in absolute sense [54].

7. Role of the hypothalamic-pituitary axis in the glucose homeostasis

The role of the brain to control glucose homeostasis was introduced in 1964 [65, 66]. Energy homeostasis is maintained by adapting meal size to current energy requirements. This control is achieved by communication between the digestive system and central nervous system. Two systems regulate the quantity of food intake: short term, which prevents overeating, and long term, involved in the energy stores as a fat [67]. Several regions of the brain are involved in regulation of food intake and energy homeostasis [68–72]. The hypothalamus is the most important locus involved in the neural control peripheral metabolism through the modulation of autonomic nervous system activity. The autonomic nervous system modulates hormone secretion (insulin and glucagon) and metabolic activity of the liver, adipose tissue, and muscle. The hypothalamus is in turn informed of the energy status of the organism. This is due to the metabolic and hormonal signals. There are two ways for the hypothalamus to signal to the peripheral organs: by stimulating the autonomic nerves and by releasing hormones from the pituitary gland. The hypothalamus consists of three areas: lateral, an important region regulating the cessation of feeding [73]; medial; and paraventricular, which is involved in the initiation of feeding [74]. In addition to direct neural connections, the hypothalamus can affect metabolic functions by neuroendocrine connections.

In the hypothalamus-pancreas axis, autonomic nerves release glucagon and insulin, which directly enter the liver and affect liver metabolism. In the hypothalamus-adrenal axis, autonomic nerves release catecholamines from adrenal medulla, which also affect liver metabolism. The hypothalamus-pituitary axis, which consists of neuroendocrine pathways from the

hypothalamus, can also regulate liver functions. The hypothalamus sends signals to the pituitary gland, which release different hormones. Among them, three are thought to be intensely involved in the regulation of liver glucose metabolism [75].

The hypothalamic-pituitary-adrenal (HPA) axis referees to a complex set of homeostatic interactions between the hypothalamus, the pituitary gland, and the adrenal gland. The core of the HPA axis is the paraventricular nucleus (PVN) of the hypothalamus. The PVN contains neurocrine neurons, which synthesize and secrete vasopressin (AVP) and corticotrophin-releasing hormone (CRH). These two peptides can stimulate the secretion of the adrenocorticotropic hormone (ACTH) from anterior pituitary. In turn, ACTH enters peripheral circulation where it reaches the adrenal cortex to induce glucocorticoid hormone production (cortisol). Glucocorticoids exert a negative feedback on the paraventricular nucleus of the hypothalamus and pituitary to suppress CRH and ACTH production, respectively. Activation of glucocorticoids in vivo causes activation of glycogen synthase and inactivation of phosphorylase, resulting in glycogen synthesis [76]. Glucocorticoids lead to lipolysis in adipose tissue and proteolysis in the skeletal muscle by inhibiting glucose uptake by these tissues resulting in release of glycerol from adipose tissue and amino acids from the muscle [77, 78]. In turn, glycerol and amino acids are used as substrates to produce glucose in the liver. Glucocorticoids stimulate hepatic gluconeogenesis and antagonize actions of insulin in the liver and muscle, thus tending to increase glucose levels. The expression of GLUT4 is increased by glucocorticoids in the skeletal muscle and adipose tissue. Increased lipolysis may be important in glucocorticoid-induced insulin resistance. Glucocorticoids inhibit insulin secretion from pancreatic β-cells.

Maintenance of thyroid function is depended on a complex interplay between the hypothalamus, anterior pituitary, and thyroid gland (HPT). The thyroid gland is controlled by the activity of the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin-releasing hormone (TRH) which stimulates the biosynthesis, and release of thyrotropin (TSH) forms the anterior pituitary. TSH stimulates the thyroid gland which releases thyroxine (T4) and triiodothyronine (T3) into the circulation. Thyroid hormone action has been long recognized as a significant determinant of glucose homeostasis [79, 80]. Glucose homeostasis appears to be the result of the T3 and insulin synergistic regulation of gene transcription involved metabolic pathways of glucose and lipids [81]. T3 regulates a gene expression of glucose metabolism (the enzymes for oxidation of glucose and lipids, glucose storage, glycolysis, cholesterol synthesis, and glucose-lipid metabolism) [82]. T3 directly stimulates basal and insulin-mediated glucose uptake in the rat skeletal muscle. This induction was shown to be due primarily to an increase in Glut4 protein expression [83].

Human growth hormone (GH) is an essential regulator of carbohydrate and lipid metabolism. It increases indirectly the production of glucose in the liver. Glycerol released into the blood acts as a substrate for gluconeogenesis in the liver. GH antagonizes insulin action; increases fasting hepatic glucose output, by increasing hepatic gluconeogenesis and glycogenolysis; and decreases peripheral glucose utilization through the inhibition of glycogen synthesis and glucose oxidation [84].

The main regulatory factor of reproductive functions is gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus. GnRH is a primary stimulator of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men, LH stimulates testes to synthesis and secrete sex hormone, testosterone. In women, FSH acts on the ovary to stimulate and

release estrogens. Estrogens are considered in blood glucose homeostasis. Estrogens have an adverse effect on carbohydrate metabolism. Administration of estrogens increases the insulin content of the pancreas in rats. In β-cells estrogens increase biosynthesis of proinsulin. During pregnancy, estrogen receptor integrates information from estrogen, glucose and other nutrients in the blood to regulate insulin gene expression and, therefore, contributes to the maintenance of insulin and glucose homeostasis [85]. Estrogen increases expression of glucose transporters and glucose transport in blood-brain barrier endothelium. Androgens can influence body composition, which is associated with insulin sensitivity. Testosterone may affect insulin sensitivity. Patients treated with androgen deprivation therapy have elevated glucose and increased insulin resistance. Testosterone treatment in hypogonadal men reduces fasting insulin. Testosterone activates the glucose metabolism-related signaling pathway in the skeletal muscle. The addition of testosterone to the cultured skeletal muscle induces the elevation of GLUT4 protein expression and accelerates its translocation from cytosol to plasma membrane. In women, testosterone induces selective insulin resistance in cultured subcutaneous adipocytes.

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