

Insulin hormone: Mechanism and effects on the body and relationship with central nervous system

İnsülin hormonu: Vücuttaki mekanizması ve etkileri ve merkezi sinir sistemi ile ilişkisi

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ABSTRACT

Diabetes mellitus (DM) is one of the most common and chronic disease all over the world. It is characterized with either insulin deficiency or insulin resistance. Insulin is a hormone which is secreted by beta cells in the Langerhans Islets of pancreas and playing a role in carbohydrate metabolism regulation in association with glucagon. Regarding the insulin's effects on carbohydrates, almost in all tissues (except brain) insulin increases the facilitated diffusion of glucose into cells and shows an effect to reduce the blood glucose levels. In other words, it has a regulator role on blood sugar level; insulin secretion is known to be associated with an increase in the amount of energy. Insulin secretion is related with increasing glucose level. It has been shown that it is closely related with intracellular enzymes and has a stimulating effect on transcription of glucokinase, pyruvate kinase, phosphofructo kinase and fructose-2,6 biphosphatase that are glycolytic and an inhibitory effect on transcription of phosphoenolpyruvate carboxykinase that is gluconeogenic. Besides being the primary regulator of carbohydrate metabolism, insulin also has an important effect on lipid and protein metabolisms that are interrelated with carbohydrate metabolism. For the basis of diabetes effects on Central Nervous system (CNS) two mechanisms are emphasized; first is the oxidative stress developed due to metabolic changes and the second is damages of calcium ion metabolism. In this review, it was intended to reach detailed information by reviewing insulin's basic effect mechanism, its reflection on cellular level and its relationship with central nervous system.

Key words: Central nervous system, insulin, diabetes mellitus, carbohydrate metabolism

ÖZET

Diabetes Mellitus (DM) dünyadaki en yaygın kronik hastalıklardan biridir. Ya yetersiz insülin salgınması ya da insüline karşı oluşan direnç ile karakterizedir. İnsülin pankreasın Langerhans adacıklarındaki beta hücrelerinden salgılan ve vücuttaki karbonhidrat metabolizmasının düzenlenmesinde glukagon ile birlikte rol alan bir hormondur. İnsülinin, karbonhidratlar üzerindeki etkileri bağlamında, insülin hemen hemen tüm dokularda (beyin hariç), glikozun hücrelere kolaylaştırılmış difüzyonunu hızlandırmakta ve kan glikoz düzeyini azaltmaya yönelik bir etki oluşturmaktadır. Bir başka ifadeyle insülin kan şekeri düzeyinin düzenlenmesinde görev alır. İnsülin sekresyonunun enerji miktarındaki artışla alakalı olduğu bilinmektedir. Hücre içi enzimlerle yakından ilişkili olup, insülinin, glikolitik özelliğe sahip; glukokinaz, pirüvat kinaz, fosfofrukto kinaz ve fruktoz 2,6 bifosfataz üzerinde transkripsiyonu stimüle edici etkisi olduğu, glukoneogenik özellikli fosfoenolpiruvat karboksik kinaz üzerinde transkripsiyonu inhibe edici etkiye sahip olduğu gösterilmiştir. İnsülinin, karbonhidrat metabolizmasının birincil dengeleyicisi olmasının yanında, karbonhidrat metabolizması ile ilişki içinde bulunan yağ ve protein metabolizmaları üzerinde de önemli etkileri vardır. Diyabetin Merkezi Sinir Sistemi (MSS) üzerindeki etkilerinin temelinde ise iki mekanizmanın önemi üzerinde durulmakta, bunlardan ilkinin metabolik değişiklikler sonucu ortaya çıkan oksidatif stres olduğu, diğerinin ise kalsiyum iyonu metabolizmasında meydana gelen bozuluklardan kaynaklandığı iddia edilmektedir. Bu derlemede insülinin temel etki mekanizmaları, hücresel düzeydeki yansımaları ve MSS ile olan ilişkisi üzerinde durularak detaylı bilgiye ulaşılmaya amaçlanmıştır.

Anahtar kelimeler: Merkezi sinir sistemi, insülin, diabetes mellitus, karbonhidrat metabolizması

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INTRODUCTION

The basic mechanism of insulin

The discovery of insulin; Medical researcher Frederick Banting and research assistant Charles Best studied the islets of Langerhans in the pancreas of dogs. In 1921, they isolated insulin and successfully tested in on diabetic dogs, lowering the dogs' blood sugar level.¹ Insulin has polypeptide structure, which is synthesized in pancreatic B-cells, have many important function in the mammalian body.²⁻⁴ It can bind to receptors in surface of cells.⁵⁻⁷ The receptors located cell membranes binding each other with disulphide bond and consist of four subunits. Two of these subunits, located in the cell surface membrane, named beta, other two of these subunits located out of cell surface named alpha.⁸⁻¹⁰ Insulin binds the first alpha subunits and leads to autophosphorylation of beta subunits which extending cytoplasm by having bonds of two subunits, and induces converting active protein kinase.^{10,11} Therefore, insulin triggers many enzymes phosphorylation and shows its intracellular effects. In brief, insulin is necessary for glucose carrying in tissues, so the tissues are more permeable to glucose.^{12,13} Except for endocytosis of insulin, the cells are more permeable for K⁺ and PO⁻⁴. Intracellular enzymes activation level with phosphorylation changing in approximately in 10-15 seconds, low effect of insulin appears in hours (or even days).¹²⁻¹⁵ These effects occur to produce new proteins or arranging DNA transcription and translation rates decelerating synchronously in ribosome.¹²⁻¹⁵ The effect of insulin on carbohydrate metabolism: insulin accelerates the facilitated diffusion to cells in almost all tissues (except for brain) and decreases the blood glucose level.^{14,15} In other words, insulin helps in decreasing the level of blood glucose.¹⁴⁻¹⁷ The effect of insulin on lipid metabolism: insulin prevents to lipolysis in the liver and adipose tissues as well as stimulates the lipogenesis.¹⁸⁻²⁰ Also the effect of insulin on protein and nucleic acid metabolism: it shows effects such as stimulation of the protein synthesis (anabolic effect) or in other word inhibition of the protein destruction.²¹⁻²⁴ Above we tried to explain basic function of the insulin in the body, now we try to explain "which mechanism is contributed or mediated the insulin action, and when the insulin functions is performed?" Insulin mediated signal releasing mechanism is started by target cell receptors

like other grown factors.²⁵ When internalization of insulin-receptor complex in the cell by endocytosis is realized, there are lysosome enzymes which separate the insulin-receptor complex from each other, then receptors are transferred the surface of cell by exocytosis to be used again and also the rest of insulin in the cell, to provide activation of tyrosine kinase in the cytoplasm. The phosphatidylinositol 3,4,5 triphosphate effectors phosphatidylinositol 3,4,5 triphosphate receptors were existed in the insulin pathway. The insulin pathway shows difference from classic protein tyrosine kinase receptors in that it is always dimerised, nonetheless only activated when insulin (its agonist) is bound. Also, in place of employing phosphatidylinositol 3-kinase directly, the insulin receptor first of all employ insulin receptor substrates including src homology 2 domains. IRS-1 in particular is phosphorylated on several tyrosine residues by the insulin receptor's intracellular catalytic part and these phosphorylated tyrosine residues in turn employ other proteins with src homology 2 domains, one of which is phosphatidylinositol 3-kinase. Phosphatidylinositol 3-kinase then catalysis the alteration of phosphatidylinositol 4,5 bisphosphate to phosphatidylinositol 3,4,5 triphosphate, which activates phospholipid dependent kinase 1. Activated tyrosine kinase leads to increase quantity of c-AMP in the cell, then protein named IRS-1, which is responsible for function of insulin in the cell, tyrosine, serine, and threonine residuals are phosphorylated by this IRS-1 protein.²⁵ At the same time IRS-1 also activates the number of proteins. In insulin depended tissues, glucose transportation from membrane may be performed via IRS-1 and IP-3-kinase with an increase of phosphatidylinositol 3,4,5- triphosphate. Insulin mediates cytoplasmic replacement of GLUT translocation and provides to be functional.^{25,26} In this review, it was intended to reach detailed information by reviewing insulin's basic effect mechanism, its reflection on cellular level and its relationship with central nervous system.

Insulin Deficiency or resistance

Nowadays diabetes mellitus has two broad categories designated as type1 (T1DM) and type2 (T2DM). Both types problems are the same, people suffer from diabetes mellitus needing to use external insulin usage for their life, T1DM divided two subunits. The first one is immunologic type T1DM,

it is characterized pathologically by pancreatic beta cells destruction, and the second one is named idiopathic T1DM, is characterized with insulin deficiency, and in this type pancreatic beta cell destruction does not occur.²⁷ Both types of diabetes mellitus complications are classified as acute and chronic complications. Acute metabolic complications; diabetic ketoacidosis, ketoacidosis coma, hyperosmolar non-ketosis coma, lactic acidosis coma and hyperglycemia coma as a result of treatment complication. Diabetic effect of different tissues and organs are classified as chronic diabetic complication (neuropathy, nephropathy, and retinopathy) and macrovascular complications (atherosclerosis, paresis, myocardial infarction and gangrene).²⁷

The intracellular effects of insulin

In this section, we tried to explain that which gene expression is effected in case of releasing and synthesis of insulin, which proteins are produced as a result of this expression, what is the function of these proteins in the cells. The first stage of insulin synthesis, the mRNA transcription was realized from coding insulin genes in the cell's nucleus, then occurred mRNA was translated in the rough endoplasmic reticulum (REG) and polypeptide synthesis is started with occurring signal polypeptide. This polypeptide penetrates into endoplasmic reticulum membrane and preproinsulin were produced in its lumen, which the storage form of insulin is called proinsulin. Preproinsulin is converted into proinsulin with leaving N-terminal signal polypeptide.²⁸⁻³¹ Proinsulin is then moved into a golgi body, here c-peptide synthesis is stopped by the effect of proteases and converted into insulin. Producing insulin is secreted by partial exocytosis.²⁸⁻³¹ Insulin secretion mediates the glucose, amino acids (especially arginine), glucagon, gastrointestinal hormones (secretin, gastrin, vasoactive intestinal peptide, and cholecystokinin), growth hormones, glucocorticoids, prolactin, placental lactogen, sex hormones, and parasympathomimetic agents. Except for above, also hyperthyroid makes B cells sensitive to glucose, parathyroid hormone stimulates B cells at low levels, and high-levels parathyroid hormone inhibits the B cells. In previous studies showed that somatostatin and epinephrine inhibits the insulin secretion.²⁸⁻³¹ Which genes are arranged by insulin effect? Insulin stimulates glucose-6-phosphate,³² insulin like growth factor binding protein,³³ CYP2E1,³⁴

surfactant protein-A,³⁵ lipid acid sentetase,³⁶ plasminogen activator inhibitor-1,³⁷ SHARP2,³⁸ hexokinase-2³⁹ genes by phosphatidylinositol-3 kinase signal pathway.⁴⁰ Also insulin inhibits microsomal triglyceride⁴¹ and stimulates Apo A1, c-fos, fos related antigen-1⁴² by map kinase signal pathway. In addition, insulin effects the intracellular enzymes, integral proteins, hormones, secretory proteins, proto-oncogenes and transcription factors.^{43,44} The effect of insulin on intracellular enzymes are transcript stimulation effect on glucokinase, pyruvate kinase and transcript inhibition effect on fructose 2,6 biphosphatase, which has glycolytic effect and phosphoenolpyruvate-carboxykinase, which has glycogenic effect.⁴³ Other effects of insulin on integral proteins are transcription stimulation factor on GLUT-1 stimulation of GLUT-1 gene transcription and tryptophan (Trp), and transcription inhibition factor on GLUT-4 gene transcription.⁴⁴ The effects of insulin on secretory proteins are transcript stimulation factor of amylase, prolactin, and glucagon, and transcript inhibition factor of Apo Clir, IGFBP-1 and NPY.⁴⁴ Also insulin shows transcript stimulation effect on c-src, c-jun, c-fos, p21, Ras, and SREBP1c.^{43,44}

Insulin effects and selected samples

We try to explain the relationship between glucose metabolism and insulin for better understanding the effect of the insulin hormone on metabolism. Glycogen is the principal carbohydrate reserve; it is a branched polymer of -D-glucose. Partial or complete failure of insulin secretion leading to glycogen production by glycogenesis of amino acids and fats.^{45,46} In this case (i.e. the lack of insulin), glucose uptake reduces in the insulin-dependent tissues, such as fat and muscle tissue.^{45,46} When fatty acid concentration is increased, this results in a raise of the intra-mitochondrial acetyl CoA/CoA and NADH/NAD⁺ ratios, with following inactivation of pyruvate dehydrogenase. This causes increase of citrate concentrations, which leading to inhibition of phosphofruktokinase. These subsequent events catalysis increases in intracellular glucose-6-phosphate concentration, which may inhibits hexokinase II activity and result in an increase in intracellular glucose concentration and a decrease in tissue glucose uptake.⁴⁷ In this way, hyperglycemia occurs in the intercellular area due to failure in the cellular glucose uptake.^{45,46} An increase in osmolality by in-

duced more dense solution (i.e. the excess of glucose) in the intercellular area causes dehydration within the cell.^{45,46} As a result, because the absence or lack of insulin prevents the use of glucose in the peripheral tissues, alternative ways occur to provide the energy needs in the tissues. At this point, the produced amino acids from protein demolition are used in the gluconeogenesis. Lipids are directly broken down in order to supply requirement of energy. If fatty acid is not completely broken down, ketone bodies accumulate in the blood. An increase in free fatty acids simulates the lipolysis in near tissues via heavy insulin deficiency. The free fatty acids are resource of ketogenesis, which is producing ketone bodies as a result of fatty acid breakdown (beta-hydroxybutyrate, acetoacetate, and acetone) in liver and. It is accelerated by insulin deficiency and glucagon excess. The excess ketone bodies cause acidosis and electrolyte loss in body.^{46,48} An increase in free fatty acids, glycerol and ketogenic amino acids in the blood break down of running catabolism toward Krebs cycle in the liver and it cause accumulation of the hydrogen-ion donor acid bodies (ketone bodies) in the blood. So, bicarbonate and pH decreases in the blood and tissue. Carbon dioxide result of from bicarbonate consumption moves out of body by respiratory expiration. Because, the ketones are excreted by the urine, excess carbonate and liquid-electrolyte loss occurs. The progressive dehydration, asides, hyperosmolitate and decreased cerebral oxygen consumption can cause patient to go into coma.^{46,47,49}

The effect of insulin on the central nervous system

Insulin resistance and deficiency are a serious metabolic and functional problem on central nervous system.⁵⁰ These problems can lead to cerebral atrophy, subcortical, brain stem damages, and cognitive dysfunctions.^{50,51} Related studies showed that there are two possible effects of diabetic mechanism; the first one is characterized the dynamics of metabolic change during oxidative stress, the second one is abnormalities in calcium mechanism.⁵² The hyperglycemic effect of circulation system; in brain tissue rest of glucose convert into sorbitol and fructose via polyol, increasing level of sorbitol and fructose upset the relationship between the reactive oxygen species production and elimination. Therefore, it leads to toxic effect on related tissues.⁵³ The previ-

ous studies prove above results, increasing of lipid peroxidation in induced-diabetic rat brain,⁵² antioxidant protection system members decreased activity of super oxide dismutase and Catalase prove the above results.^{52,54} Although, in the brain glucose transportation is realized without insulin, this glucose intake stage is controlled by insulin.^{52,54} Insulin receptors are expressed by astrocytes and neurons in the brain, like growing factors. Insulin enhances glucose uptake into astrocytes⁵⁵ but not in neurons. Neuronal insulin receptors are intensive at synapses. In addition, peripheral sensory and autonomic ganglia have insulin receptors.^{55,56} In anaerobic condition, the brains metabolizes the glucose or are forced to metabolize glucose as glycogen, it leads to lactate formation. Hence, increased level of lactate is indicative of tissue hypoxia and possible damage. Lactic acidosis is related with lactate levels >5 mmol/L and serum pH <7.35.⁵⁷ Lactic acidosis inhibits the glycolytic enzymes, especially phosphofructokinase; anaerobic glycolysis rate needs metabolic increases to provide the cell energy consumption by ATP production. Nevertheless, glycogen level is not enough, so glycogen is exhausted soon, intracellular pH decrease and causes brain cell damage.^{58,59} In brief, in cases of insulin deficiency and resistance some structural and functional damages may lead to central nervous system abnormalities.

In conclusion, this review emphasized the relatively novel concept that effects of insulin on the body and especially brain function. Insulin receptors are expressed in many body regions. Recent studies show that the influence of insulin on the molecular and cellular mechanisms of neurodegeneration is important in contemporary neuroendocrinology the body. Many diseases with dysfunction of insulin are progressively growing day by day such as senile dementia, diabetes. Therefore, this conceptual review will hopefully lead to scientists designing their experiments aimed at a full understanding of the neural mechanisms involved in neuroendocrine system insulin mechanism in the body.

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