

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, phosphofructokinase 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 salınması ya da insüline karşı oluşan direnç ile karakterizedir. İnsülin pankreasın Langerhans adacıklarındaki beta hücrelerinden salınan 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 fosfoenolpirüvat 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.

REFERENCES

1. Best CH, Scott DA. The Preparation of Insulin. *J BiolChem* 1923;57(6):709-23.
2. Mather KJ, Lteif A, Steinberg HO, Baron AD. Interactions between endothelin and nitric oxide in the regulation of vascular tone in obesity and diabetes. *Diabetes* 2004;53(8):2060-6.

3. Rodrigues MA, Gomes DA, Andrade VA, Leite MF, Nathanson MH. Insulin induces calcium signals in the nucleus of rat hepatocytes. *Hepatology* 2008;48(5):1621-31.
4. Sanderson TH, Kumar R, Sullivan JM, Krause GS. Insulin blocks cytochrome c release in the reperfused brain through PI3-K signaling and by promoting Bax/Bcl-XL binding. *J Neurochem* 2008;106(3):1248-58.
5. Ishiki M, Klip A. Minireview: recent developments in the regulation of glucose transporter-4 traffic: new signals, locations, and partners. *Endocrinology* 2005;146(12):5071-78.
6. Grillo CA, Piroli GG, Hendry RM, Reagan LP. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. *Brain Res* 2009;1296(3):35-45.
7. Watson RT, Pessin JE. Intracellular organization of insulin signaling and GLUT4 translocation. *Recent ProgHorm Res* 2001;56:175-93.
8. Torlińska T, Maćkowiak P, Nogowski L, et al. Age dependent changes of insulin receptors in rat tissues. *J PhysiolPharmacol* 2000;51(4 Pt 2):871-81.
9. Thulasi R, Dias P, Houghton PJ, Houghton JA. Alpha 2-interferon-induced differentiation of human alveolar rhabdomyosarcoma cells: correlation with down-regulation of the insulin-like growth factor type I receptor. *Cell Growth Differ* 1996;7(4):531-41.
10. Zhao M, Wan ZL, Whittaker L, et al. Design of an insulin analog with enhanced receptor-binding selectivity. Rationale, structure, and therapeutic implications. *J BiolChem* 2010;285:11755-59.
11. Park S, Hong SM, Ahn IS. Exendin-4 and exercise improve hepatic glucose homeostasis by promoting insulin signaling in diabetic rats. *Metabolism* 2010;59(1):123-33.
12. Varea O, Arevalo MA, Garrido JJ, Garcia-Segura LM, Wandosell F, Mendez P. Interaction of estrogen receptors with insulin-like growth factor-I and Wnt signaling in the nervous system. *Steroids* 2010;75(8-9):565-9.
13. Hansotia T, Drucker DJ. GIP and GLP-1 as incretin hormones: lessons from single and double incretin receptor knockout mice: A review. *Regul Pept* 2005;128(2):125-34.
14. Havel PJ. Peripheral signals conveying metabolic information to the brain: short-term and long-term regulation of food intake and energy homeostasis: A review. *Exp Biol Med* (Maywood) 2001;226(11):963-77.
15. Simonson GD, Kendall DM. Diagnosis of insulin resistance and associated syndromes: the spectrum from the metabolic syndrome to type 2 diabetes mellitus: A review. *Coron Artery Dis* 2005;16(8):465-472.
16. Krupanidhi S, Sedimbi SK, Vaishnav G, Madhukar SS, Sanjeevi CB. Diabetes-Role of epigenetics, genetics, and physiological factors. *Zhong Nan Da XueBao Yi Xue Ban* 2009;34(9):837-45.
17. Seneviratne HR, Lankeshwara D, Wijeratne S, Somasunderam N, Athukorale D. Serum insulin patterns and the relationship between insulin sensitivity and glycaemic profile in women with polycystic ovary syndrome. *BJOG* 2009;116(13):1722-8.
18. Wang Z, Iwasaki Y, Zhao LF, Nishiyama M, Taguchi T, Tsugita M, Kambayashi M, Hashimoto K, Terada Y. Hormonal regulation of glycolytic enzyme gene and pyruvate dehydrogenase kinase/phosphatase gene transcription. *Endocr J* 2009;56(8):1019-30.
19. Liu LF, Purushotham A, Wendel AA, Belury MA. Combined effects of rosiglitazone and conjugated linoleic acid on adiposity, insulin sensitivity, and hepatic steatosis in high-fat-fed mice. *Am J Physiol Gastrointest Liver Physiol* 2007;292(6):1671-82.
20. Rossi AS, Lombardo YB, Chicco AG. Lipogenic enzyme activities and glucose uptake in fat tissue of dyslipemic, insulin-resistant rats: Effects of fish oil. *Nutrition* 2010;26(2):209-17.
21. Dulloo AG. A role for suppressed skeletal muscle thermogenesis in pathways from weight fluctuations to the insulin resistance syndrome: A Review. *ActaPhysiolScand* 2005;184(4):295-307.
22. Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. *ClinBiochem* 2009;42(13-14):1331-46.
23. Griffin MJ, Sul HS. Insulin regulation of fatty acid synthase gene transcription: Roles of USF and SREBP-1c: A Review. *IUBMB Life* 2004;56(10):595-600.
24. Després JP. The endocannabinoid system: a new target for the regulation of energy balance and metabolism: A review. *Crit Pathw Cardiol* 2007;6(2):46-50.
25. Goldstein BJ, Müller-Wieland D. Type 2 Diabetes (Pathogenesis of Type 2 Diabetes) 2nd edition, 2008, Informa Healthcare USA, 2008;13-26.
26. Leibowitz MD, Biswas e. Brady EJ et al. A novel insulin secretagogue is a phosphodiesterase inhibitor. *Diabetes* 1995;44:67-70.
27. Taylor SI. Lilly Lecture: Molecular mechanisms of insulin resistance: lessons from patients with mutations in the insulin receptor gene. *Diabetes* 1992;41:1473-90.
28. Pedersen O, Bak JF, Andersen PH. Evidence against altered expression of GLUT 1 or GLUT 4 in skeletal muscle of patients with obesity or NIDDM. *Diabetes* 1990;39:865-70.
29. Nelson DL, Michael M. Cox MM. Lehninger Principles of Biochemistry. W. H. Freeman (Fourth Edition) 2004.
30. Fox SI. Human Physiology. McGraw-Hill Science / Engineering (Eighth Edition) 2003.
31. Das UN. GLUT-4, tumor necrosis factor, essential fatty acids and daf-genes and their role in insulin resistance and non-insulin dependent diabetes mellitus: A review. *Prostaglandins LeukotEssent Fatty Acids* 1999;60(1):13-20.
32. Mues C, Zhou J, Manolopoulos KN, et al. Regulation of glucose-6-phosphatase gene expression by insulin and metformin. *HormMetab Res* 2009;41(10):730-35.
33. Rajpathak SN, Gunter MJ, Wylie-Rosett J, et al. The role of insulin-like growth factor-I and its binding proteins in glucose homeostasis and type 2 diabetes. *Diabetes Metab Res Rev* 2009;25(1):3-12.
34. Woodcroft KJ, Hafner MS, Novak RF. Insulin signaling in the transcriptional and posttranscriptional regulation of CYP2E1 expression. *Hepatology* 2002;35(2):263-73.

35. Miakotina OL, Goss KL, Snyder JM. Insulin utilizes the PI 3-kinase pathway to inhibit SP-A gene expression in lung epithelial cells. *Respir Res* 2002;3(1):27.
36. Murdolo G, Smith U. The dysregulated adipose tissue: a connecting link between insulin resistance, type 2 diabetes mellitus and atherosclerosis: Review. *NutrMetabCardiovasc Dis* 2006;16(1):35-38.
37. Morange PE, Aubert J, Peiretti F, et al. Glucocorticoids and insulin promote plasminogen activator inhibitor 1 production by human adipose tissue. *Diabetes* 1999;48(4):890-5.
38. Yamada K, Kawata H, Shou Z, Mizutani T, Noguchi T, Miyamoto K. Insulin induces the expression of the SHARP-2/ Stra13/DEC1 gene via a phosphoinositide 3-kinase pathway. *J BiolChem* 2003;278(33):30719-24.
39. Pendergrass M, Koval J, Vogt C, et al. Insulin-induced hexokinase II expression is reduced in obesity and NIDDM. *Diabetes* 1998;47(3):387-94.
40. Kok K, Geering B, Vanhaesebroeck B. Regulation of phosphoinositide 3-kinase expression in health and disease: A review. *Trends BiochemSci* 2009;34(3):115-27.
41. Au WS, Kung HF, Lin MC. Regulation of microsomal triglyceride transfer protein gene by insulin in HepG2 cells: roles of MAPKerk and MAPKp38. *Diabetes* 2003;52(5):1073-80.
42. Kim SJ, Kahn CR. Insulin stimulates phosphorylation of c-Jun, c-Fos, and Fos-related proteins in cultured adipocytes. *J BiolChem* 1994;269(16):11887-92.
43. O'Brien RM, Granner DK. Regulation of gene expression by insulin: A Review. *Biochem J* 1991;278(Pt3):609-19.
44. Maciel RM, Moses AC, Villone G, Tramontano D, Ingbar SH. Demonstration of the production and physiological role of insulin-like growth factor II in rat thyroid follicular cells in culture. *J Clin Invest* 1988;82(5):1546-53.
45. Goldstein BJ, Müller-Wieland D. Type 2 Diabetes (Insulin Therapy in Type 2 Diabetes) 2nd edition, Informa Healthcare USA, 2008;181-206.
46. Kahn CR, Weir GC, King GI, Jacobson AM, Moses AC, Smith RJ (ed.). *Joslin's Diabetes mellitus 2005*; chapter 19:336-7.
47. Randle PJ, Newsholme EA, Garland PB. Regulation of glucose uptake by muscle. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan, diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. *Biochem J* 1964;93:652-65.
48. Rosenthal MD, Glewm RH. *Medical biochemistry: Human metabolism in health and disease*. A John Wiley & Sons, Inc., Publication, USA, 2009;112-40.
49. Morgensen CE, Christensen CK. Blood pressure changes and renal function in incipient and overt diabetic nephropathy. *Hypertension* 1985; 7: II64-II73.
50. Delibaş N, Kılınç İ. İnsülin ve gliklazid tedavisinin streptozotosin diabetik rat hipokampuslarında lipid peroksidasyonuna etkisi. *Türk Klinik Biyokimya Derg* 2003;1:33-9.
51. Biessels GJ, Kamal A, Urban IJ, Spruijt BM, Erkelens DW, Gispen WH. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. *Brain Res* 1998;800(1):125-35.
52. Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus, A Review. *Trends Neurosci* 2000;23(11):542-9.
53. Friedman EA. Renal syndromes in diabetes. *Endocrinol Metab Clin North Am* 1996;25(2):293-324.
54. Makar TK, Rimpel-Lamhaouar K, Abraham DG, Gokhale VS, Cooper AJ. Antioxidant defense systems in the brains of type II diabetic mice. *J Neurochem* 1995;65(1):287-91.
55. Kum W, Zhu SQ, Ho SK, Young JD, Cockram CS. Effect of insulin on glucose and glycogen metabolism and leucine incorporation into protein in cultured mouse astrocytes. *Glia* 1992;6:264-8.
56. Zhu SQ, Kum W, Ho SK, Young JD, Cockram SS. Structure-function relationships of insulin receptor interactions in cultured mouse astrocytes. *Brain Res* 1990;529:329-32.
57. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol* 2001;12(Suppl. 17):15-9.
58. Knudsen GM, Jakobsen J, Barry DI, Compton AM, Tomlinson DR. Myo-inositol normalizes decreased sodium permeability of the blood-brain barrier in streptozotocin diabetes. *Neuroscience* 1989;29(3):773-7.
59. Altınova A, Aktürk M, Törüner FB, Arslan M. Tip 1 Diabetes mellitus ve insülin direnci (Type 1 diabetes mellitus and insulin resistance: Review). *Türkiye Klinikleri J Med Sci* 2007;27(1):220-23.