NATURE AND MECHANISMS OF INSULIN RESISTANCE – ROLE OF ADIPOKINES IN ETIOLOGY AND PATHOGENESIS

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ABSTRACT
Insulin resistance is the main link between obesity and a number of metabolic and cardiovascular disorders. Still mechanisms, by which white adipose tissue impairs insulin sensitivity, are not well understood. White adipose tissue produces hormones, such as leptin, resistin and adiponectin, and a great number of protein signals known as adipokines. These include proteins, playing role in energy balance, lipid and glucose metabolism, angiogenesis and blood pressure regulation. Visceral obesity is associated with a state of low grade inflammation, which has a direct impact on development of diabetes type 2 and atherosclerosis. Intraabdominal adipose depots produce a number of cytokines (TNF-α, IL-1, IL-6, IL-8), which together with some adipokines (leptin, resistin, adiponectin) take part in pathogenesis of inflammation and acute phase response. The aim of the present overview is to summarize the existing scientific data, concerning the role of white adipose tissue secretory products in etiology and pathogenesis of obesity - associated insulin resistance.

Key words: leptin, adiponectin, resistin, tumor necrosis factor- α, interleukin-6

INTRODUCTION
Insulin resistance is an impaired biological response to the action of exogenous or endogenous insulin. It is characterized by inability of insulin to induce its biological effects in concentrations that are effective in healthy individuals. Insulin resistance is a state in which main target tissues – muscles, liver and adipose tissue, become less sensitive to insulin. Thus storage of glycogen in muscles and liver, clearance of glucose in blood, and use of glucose for production of energy and synthesis of fats in adipose tissue are being reduced (1). Insulin available in circulation can not suppress release by liver of endogenous glucose (2). These conditions force pancreas to secret more insulin to maintain glucose blood levels in the normal range. Insulin resistance is directly linked to a number of syndromes, diseases and metabolic disorders, including impaired glucose tolerance, hyperinsulinemia, dyslipidemia, hypertension, increased blood coagulation (3), polycystic ovary syndrome, metabolic syndrome (known also as syndrome X), cancer, acute and chronic infections, trauma and mostly obesity and diabetes mellitus type 2 (1). These and some other conditions and diseases (acanthosis nigricans, Cushing’s syndrome, acromegalia, osteoporosis, some autoimmune diseases), also being linked to insulin resistance, make it become a phenomenon of extreme interest. At this point a number of questions, concerning its etiology, arise for scientists to study. Far more are questions concerning pathogenesis of insulin resistance and its role in the development of so many various pathological processes. Defining the primary pathogenetic event is the base for understanding the origin and nature of insulin resistance and far more it is the essence of a successful radical therapy. Suspected reasons leading to development of insulin resistance are many. This supposes not well understood etiology and pathogenesis. Different concepts exist: influence of genetic factors (2, 4, 5); hormonal disorders – more exactly disorders in hormone-receptor interactions of growth hormone (GH), glucocorticoids, sex hormones, hormones of

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thyroid gland (6, 7, 8, 9, 10, 11); increased levels of non-esterified fatty acids (NEFA) in circulation (12, 13, 14, 15); liver parasympatic innervation disorders linked to secretion of hepatic insulin sensitizing substance (HISS) (16, 17, 18, 19). Acute and especially chronic infectious processes – viral and bacterial, post-traumatic inflammatory processes, fractures, autoimmune diseases having distinctive inflammatory symptoms – chronic juvenile arthritis, polymyalgia rheumatica and many others are accompanied by a continuous and sometimes chronic insulin resistance (20, 21, 22, 23, 24).

OBESITY AND INSULIN RESISTANCE

In people and animal models it has been proved that high correlation between obesity and development of insulin resistance exists. It has been determined that intraabdominal (visceral) adipose depots play more important role (25, 26, 27). In a number of studies in the recent years it was established that adipose tissue is not only a depot of triacylglycerols, but to great extent it possesses typical features of an endocrine organ secreting various hormones, cytokines and other biologically active substances: estrogens, factors of blood coagulation and fibrinolysis /PAI-1/, interleukin 6 /IL-6/, interleukin 1 /IL-1/, interleukin 8 /IL-8/, tumor necrosis factor α /TNF-α/, prostaglandin E2 /PG-E/, and of course leptin, adiponectin and resistin, which are specific for adipose tissue. Also highly positive correlation was found between amounts of adipose depots, insulin resistance and a number of disorders – hypertension, hyperlipemia, dyslipidemia, impaired glucose tolerance, diabetes type 2, endothelial dysfunction, increased blood coagulation, atherosclerotic lesions in blood vessels and others (26, 28, 29). Insulin resistance and pro-inflammatory cytokines (IL-1, IL-6, TNF-α) produced by adipose tissue play leading role in mechanism of these disorders. Increased levels of these cytokines in circulation during obesity, lead to a chronic, low-grade, systemic inflammatory process (30, 31, 32).

ROLE OF INSULIN RECEPTOR DYSFUNCTION AND IMPAIRED POST-RECEPTOR SIGNALING PATHWAYS IN INSULIN RESISTANCE ORIGIN

Glucose enters the cell through facilitated diffusion, but in muscles, adipose tissue and some other tissues insulin contributes to utilizing of glucose by means of increasing the number of glucose transport proteins in cell membranes. Action of insulin on target tissues and realization of its biological effects is due to activation of specific insulin receptors on surface of cell membranes. First studies proving the existence of such receptors were conducted in 1971 (33, 34). Following studies in this sphere revealed direct link between disorders in synthesis, structure and affinity of insulin receptors and insulin resistance (35, 36, 37). Mutations of gene encoding the insulin receptor have been described to cause disorders in receptor synthesis and impaired structure and function of the receptor in patients with syndromes linked to insulin resistance (38). Caro et al. (39) found that insignificant decrease in the number of insulin receptors in tissues and cells in patients having diabetes type 2, leads to a reduced response to hyperinsulinemia. Normal structure and functional activity of insulin receptor and normal function of post-receptor signaling mechanisms and pathways are of decisive importance for an adequate cell response to insulin stimulation. Activation of insulin receptor tyrosine kinase results in autophosphorylation and phosphorylation of intracellular substrates, which plays a major role in the complicated and multi-component post-receptor signaling cascade mediating the complex of cell reactions (40, 41, 42). Autophosphorylation and substrate phosphorylation can be affected by the priority of phosphorylation of amino-acid residues of insulin receptor (IR) and substrates of insulin receptor (IRS) – tyrosine or serine. Decreased tyrosine phosphorylation of IR and IRS is the molecular basis for inhibition of insulin action (43, 44, 45) and impaired intracellular translocation of glucose transport systems, called glucose transporters (GT) (46). Variations in size of adipocytes, which are due to reduction or increase in the amount of fat accumulated, lead to modulation and changes in their endocrine and metabolic functions. Studies confirm that adipose tissue produces leptin (47, 48), adiponectin (49, 50), resistin and some similar molecules (51, 52), which are linked to insulin resistance and are being intensively investigated. It was also proved that adipose tissue cells in obese individuals (and especially cells of stromal vascular fraction) produce greater amounts of proinflammatory cytokines - IL-1, IL-6, TNF-α and others (53, 54), as compared to
individuals with normal body weight. Besides these proinflammatory cytokines, and especially TNF-α, take an active part in etiology and pathogenesis of insulin resistance and disorders linked to it.

**ADIPOGENES AND INSULIN RESISTANCE**

**Tumor necrosis factor-α**

TNF-α is secreted mainly by phagocytic cells of immune system, but it is produced also by adipose tissue, especially in visceral obesity. Production of small amounts of TNF-α has been found in skeletal muscles and heart. This cytokine is a factor having multiple effects on different tissues, taking part in immune and inflammatory reactions, and is one of the main mediators of insulin resistance (55, 56, 57). TNF-α regulates sensitivity of target cells to insulin by affecting signaling pathways and expression of genes encoding structure of glucose transporters. Spiegelman et al. (58) present data showing that exposing of adipocytes to action of TNF-α leads to increased phosphorylation of serine residues of IRS-1, resulting in inhibition of insulin induced phosphorylation of tyrosine residues. IRS-mediated inhibition of insulin receptor tyrosine kinase activity may be due both to a direct or indirect interaction between IR and IRS-1 (56, 59, 60). Experiments involving lines of genetically obese mice have studied four potential mechanisms by means of which TNF-α can provoke insulin resistance in this animal species. Four potential mechanisms include – regulation of levels of non-esterified fatty acids, production of leptin, number of glucose transporters and activity of insulin receptors (61, 62, 63).

**Interleukin-6**

Together with TNF-α, adipose tissue produces another multifunctional cytokine – IL-6, having an important role for the development of insulin resistance (53). Investigations show that one third of circulating IL-6 descends from adipose tissue. Omental adipose tissue produces three times more IL-6 than does subcutaneous adipose tissue. Like other proinflammatory cytokines (TNF-α, IL-1, IFN-γ) local and circulating levels of IL-6 strongly correlative increase during cancer, cachexia, and most infections, which are almost always accompanied by insulin resistance. IL-6 is the one of proinflammatory cytokines to have highest correlation with insulin resistance and diabetes type 2 (64, 65, 66). Effects of IL-6 on regulation of glucose metabolism are mainly due to his action in the liver. IL-6 increases glucose blood levels by stimulating glucose production in hepatocytes (64). Increased levels of IL-6 are linked to inhibition of hepatic glycogen synthase, activation of glycogen phosphorylase and lipase and increased production of triglycerides (68, 67).

**Leptin**

Hormone leptin is one of the many products secreted by adipose tissue. In humans its structure is encoded in ob-gene and its molecular weight is 16 kDa. Leptin is the key regulator of energy expenditure and energy intake, so it regulates energy balance of organism. Leptin is secreted mainly by subcutaneous adipose tissue, and its production is proportional to amount of adipose depots. Data prove that leptin is increased in all experimental models of obesity. In obese humans leptin levels are four times higher as compared to normal levels. Effects of leptin are due to its influence on some structures of hypothalamus (arcuate nucleus), which are responsible for regulation of appetite and thermogenesis. Signaling pathways of leptin action are being intensively investigated. These include influence on melanocortin and inhibiting synthesis of neuropeptide Y – powerful stimulator of appetite (70, 71). Leptin reaches hypothalamus by means of specific transport systems that transfer it through blood-brain barrier and disorders in these transport systems lead to leptin resistance even during hyperleptinemia (72). Etiology of leptin resistance is still not well understood, but it is clear that both leptin resistance and leptin deficiency are linked to development of insulin resistance. This is probably due to the ability of leptin to stimulate oxidation of fatty acids and to prevent ectopic fat accumulation in tissues outside typical fat depots, by means of which it increases insulin sensitivity (73).

**Resistin**

Resistin is one of the lately found adipokines and has its name from its ability to induce insulin resistance (52). Resistin expression is increased both on mRNA (74) and protein level (75, 76) in intraabdominal adipose depots, which links visceral obesity to insulin resistance and its metabolic disorders. In mice plasma levels of resistin are high both in diet induced obesity and genetic forms of obesity (52). Application of recombinant resistin in
mice leads to a systemic insulin resistance and decrease in insulin stimulated glucose transport in adipose tissue. Infusion of resistin in rats leads to increased production and release in circulation of glucose by liver, as a result of hepatic insulin resistance (77, 74). On the contrary, data concerning humans are controversial and the significance of resistin in development of insulin resistance has not been proved statistically yet (78).

**Adiponectin**
Adiponectin is a collagen-like protein, whose encoding gene is highly expressed in adipocytes. Unlike most adipokines, expression of adiponectin and its overall concentration do not increase, but on the contrary decrease in many cases of insulin resistance and obesity (79), more over in experimental animal models this tendencies have been proved to have strong correlation (80). Multivariable analyses in humans have determined that hypoadiponectinemia is more closely linked to insulin resistance and hyperinsulinemia, than are degree of obesity and impaired glucose tolerance (81). Basic mechanisms of these interactions are unknown, but some data reveal that TNF-α reduces expression and secretion of adiponectin by adipocytes (82, 83, 84).

Pharmacological effects of adiponectin, together with reduction of insulin resistance, include decrease in plasma levels of fatty acids and decrease of triacylglycerols in muscles and liver in obese mice (85, 86). Data show that these effects of adiponectin are due to its ability to increase expression of genes concerning β-oxidation and energy expenditure. Adiponectin also increases insulin stimulated phosphorylation of IR and IRS-1 in skeletal muscles, phosphorylation of acetyl-CoA carboxylase and reduction of molecules taking part in gluconeogenesis in liver (87).

**CONCLUSION**
Adipokines produced by adipose tissue play central role in a number of physiological processes taking part in control of energy balance, regulation of lipid and carbohydrate metabolism, insulin secretion and action, blood pressure control and changes in cardiovascular system. Production of these proteins by adipose tissue and its stromal vascular fraction, which is rich in macrophages, is being increased in obesity, diabetes type 2 and some other disorders linked to insulin resistance. In spite of the intensive studies in this sphere in the recent years, role of adipokines for the development of insulin resistance is still not well understood. Future attempts for detailed clarifying of the role and place of each factor in etiology and pathogenesis of insulin resistance will be the key for a successful therapy of diseases linked to insulin resistance.

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