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Endocrine interaction between skeletal muscles and adipose tissue in the regulation of tissue insulin sensitivity

Endokrynologiczna interakcja pomiędzy mięśniami szkieletowymi a tkanką tłuszczową w regulacji tkankowej wrażliwości na działanie insuliny

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Summary

Obesity is a worldwide problem which carries significant health risks and reduces a quality of life. Excessive accumulation of adipose tissue leads to increased secretion of hormones, inflammatory mediators and immune system effectors that are involved in the pathogenesis of inflammation and insulin resistance. Nowadays, it is believed that regular moderate physical activity may be associated with beneficial health effects including a reduction of adipose tissue mass, improvement of adipokines secretion profiles, and, as a consequence, reduced insulin resistance. It should be emphasized that the beneficial health effect of exercise can be associated with endocrine activity of muscles. Muscles release many humoral factors, called myokines, that affect other organs including adipose tissue, liver, brain and cardiovascular system. It is suggested that myokines can neutralize the negative effects of many adipokines. In this review we would like to summarize the current knowledge of endocrine interaction between adipose tissue and skeletal muscles in the regulation of tissue insulin sensitivity.

Streszczenie

Otyłość, jako problem ogólnoświatowy, stanowi poważne zagrożenie dla zdrowia ludzi oraz obniża jakość ich życia. Nadmierne nagromadzenie tkanki tłuszczowej prowadzi do zwiększonego wydzielania licznych hormonów, mediatorów zapalnych i innych efektorów systemu immunologicznego, które są zaangażowane w patogenezę stanu zapalnego i insulinooporności. Obecnie uważa się, że regularna aktywność fizyczna o umiarkowanym natężeniu może wywierać korzystny wpływ na zdrowie człowieka, który przejawia się redukcją masy tkanki tłuszczowej, poprawą profilu wydzielanych adipokin i w konsekwencji zmniejszeniem oporności na działanie insuliny. Należy podkreślić, że korzystny wpływ aktywności fizycznej może być związany z czynnością wydzielniczą mięśni. Mięśnie wydzielają wiele czynników humoralnych, zwanych miokinami, które mogą oddziaływać na inne narządy, takie jak tkanka tłuszczowa, wątroba, mózg oraz układ sercowo-naczyniowy. Sugeruje się, że miokiny mogą łagodzić negatywne skutki działania wielu adipokin. Obecna praca poglądowa ma na celu przedstawienie aktualnej wiedzy na temat oddziaływań endokrynnych występujących pomiędzy tkanką tłuszczową i tkanką mięśniową w odniesieniu do regulacji tkankowej wrażliwości na działanie insuliny.

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INTRODUCTION

Insulin is a pleiotropic hormone, which under normal conditions determines intensity of the metabolism of carbohydrates, proteins and lipids. Insulin regulates many processes. It stimulates glucose transport, protein synthesis and glycogen synthesis as well as it inhibits lipolysis and regulates cell survival (1). The insulin action on the target cells is dependent on a specific membrane receptor IR (insulin receptor). The highest number of IRs is observed on the surface of adipocytes, hepatocytes and miocytes. Activated receptor initiates a cascade of protein kinase phosphorylation. Insulin activates two main signaling pathways. The first one is the phosphatidylinositol 3-kinase (PI3-K) pathway, which stimulates cell growth, survival, differentiation and homeostasis of the metabolism. The second one is the Ras-mitogen activating protein kinase (Ras-MAPK) pathway, which regulates gene expression and determines the cell proliferation (2).

Impairment of the insulin signaling leads to disturbed glucose homeostasis and results in decreased tissues insulin sensitivity. The state described above is known as an insulin resistance. Insulin resistance affects many tissues and organs, especially the skeletal muscles, liver, adipocytes and brain. Up to date, three types of disturbances have been described, all of which result in the development of insulin resistance:

1. The pre-receptor insulin resistance being related to the genetically incorrect structure of the insulin molecule.
2. Insulin resistance may result also from receptor abnormalities. Mutations in the gene encoding the insulin receptor were found in patients with inherited insulin resistance (3). These mutations result in a lack of ability of the insulin receptor to transmit insulin signaling to the target cell.
3. The post-receptor level abnormalities, including abnormal course of metabolic pathways, disturbed structure and function of regulatory proteins, and impaired glucose transport, can also induce insulin resistance. In addition to the genetic factors also environmental factors such as obesity, physical inactivity and sedentary lifestyle contribute to the decreased insulin sensitivity. In this review we would like to summarize the current knowledge of endocrine crosstalk between skeletal muscles and adipose tissue, and their effect on insulin action.

RELATIONSHIP BETWEEN OBESITY AND INSULIN RESISTANCE

According to data presented by the World Health Organization (WHO) obesity has reached epidemic proportions. In the European countries, the problem of overweight and obesity concerns 30-80% of adults. It was also found that almost 20% of children and adolescents is overweight, and one in three is obese (4). Obesity is a major factor of morbidity and mortality, associated with increased risk of development of several diseases such as hypertension, coronary heart disease, atherosclerosis, dyslipidemia, type 2 diabetes and certain types of cancer. Moreover, the last epidemiological studies indicated that obesity also predisposes to the development of neuroinflammation and neurodegenerative diseases.

It is now believed that adipose tissue (AT) is not only a storage depot of the energy, but also it is considered to be the largest endocrine organ that produces and secretes several factors called adipokines. Adipokines through autocrine, paracrine and endocrine action are involved in the regulation of many processes, such as food intake, insulin secretion, insulin sensitivity, energy expenditure, inflammation and the function of the cardiovascular system (5). AT is composed of preadipocytes, adipocytes, endothelial cells, mesenchymal stem cells and immune cells (monocytes and macrophages), which have a secretory activity (6). The large group of bioactive adipocyte-derived protein molecules includes: leptin, adiponectin, resistin, visfatin, chemerin, tumor necrosis factor (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1) (7) and others. Excessive accumulation of adipose tissue mass leads to dysregulation of the expression of adipokines and, in consequence, to development of many pathological conditions. Moreover, obesity is associated with increased macrophage infiltration, endothelial cell activation and fibrosis (8). In the recent years, special attention has been paid to the relationship between adiposity, inflammation and the development of insulin resistance. Actually, several potential mechanisms have been suggested to be as involved in the development of obesity-associated insulin resistance.

1. The metabolic hypothesis assumes that enhanced plasma free fatty acid (FFA) concentration results in an increase in intracellular longchain Acyl-CoA, diacylglycerol (DAG) and ceramides concentrations. Consequently these factors cause an activation of protein kinases, such as protein kinase C (PKC) isoforms (9), the inhibitor of nuclear factor-κB kinase-β (IKKβ), and Jun kinase (JNK) (10). Then, activated kinases can impair insulin signaling by increasing the inhibitory serine phosphorylation of insulin receptor substrates 1 (IRS-1), which in turns lead to decreased IRS-1 tyrosine phosphorylation (11).
2. In the last decade, numerous studies indicated the involvement of selected adipokines in the development of insulin resistance. It should be noticed that concentration of adipokines correlates with adipose tissue mass. In obese subjects there was observed a significant increase in the expression of pro-inflammatory cytokines (TNF-α, IL-6), and adipokines (leptin, resistin) that contribute to the development of insulin resistance (12). The overexpression of cytokines and adipokines leads to activation of pro-inflammatory signaling pathways, such as JNK and IKKβ pathways, resulting in impaired insulin action in insulin sensitive tissues. In 2015, Xie et al. (13) have proposed a new mechanism by which chemerin may induce development of insulin resistance in skeletal muscles. These authors demonstrated that chemerin, through a protein kinase B – forkhead box O3α (AKT-FoxO3α)-dependent signaling pathway, impaired mitochondrial function, which in turn may be involved in development of insulin resistance. It should be emphasized that in obesity decreased expression and release of anti-inflammatory adipokines, such as adiponectin and omentin has been observed.
3. Increased tissue inflammation results in recruiting macrophages to the area of inflammation. The most important chemokine involved in this process is MCP-1. Data from studies on transgenic mice overexpressing MCP-1 in the adipose tissue and MCP-1-deficient mice (MCP-$1^{-/-}$ mice)

showed that MCP-1 plays a role in the recruitment of macrophages in adipose tissue (14). An increase in MCP-1 expression in an adipose tissue contributes to the macrophage infiltration into this tissue and causes insulin resistance. Tissue macrophages are phenotypically a heterogeneous population of cells, which are classified according to activation state (polarization). There are two well-known subtypes: classically (phenotype M1) and alternatively (phenotype M2) activated macrophages. M1 macrophages express CD11c surface marker, increase the activity of inducible NO synthase (iNOS) and secrete pro-inflammatory cytokines, such as TNF-α and IL-6 (15). These cytokines suppress secretion of adiponectin and increase insulin resistance. Moreover, diet-induced obesity causes a phenotype switch from M2-polarized state to M1 pro-inflammatory state (16). Interestingly, in lean subjects there is a larger amount of alternatively activated macrophages, which are characterized by expression of chitinase-like protein Ym1, arginase and secretion of the anti-inflammatory cytokines, such as IL-10 and IL-1Ra (15). It is believed that M2 macrophages in lean subjects may be involved in maintenance of homeostasis in the adipose tissue by mute of an inflammatory response, which in turn leads to increased insulin sensitivity.

INTERACTION BETWEEN SKELETAL MUSCLES AND ADIPOSE TISSUE

In non-obese subjects, skeletal muscles account approximately for 40-50% of the total body weight, therefore constitutes the largest organ in the human body. Krogh-Madsen et al. (17) observed that even a short periods of physical inactivity lead to metabolic changes including a reduction of insulin sensitivity, loss of muscle mass and accumulation of visceral adipose tissue (WAT). These metabolic changes increase the risk of development of many diseases. Today, it is known that regular moderate physical activity is associated with beneficial health effects: reduction of adipose tissue mass, improvement of adipokines secretion profiles, which can result in reduced insulin resistance.

The results of numerous studies conducted during the last decade have indicated that skeletal muscles in addition to regulation of the whole-body glucose and fatty acid metabolism, can also act as an endocrine active organ releasing humoral factors that affects other organs including adipose tissue, liver, brain and cardiovascular system. The cytokines or other peptides that are produced, expressed and released by muscle fibers and exerted endocrine effects has been classified as myokines (18). Several myokines have been identified so far. Interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-15 (IL-15) (19), brain-derived neurotrophic factor (BDNF) (20), leukemia inhibitory factor (LIF) (21), fibroblast growth factor 21 (FGF21), irisin and myonectin (CTRP15) (22) are amongst them.

IL-6 was described for the first time by Muraguchi et al. (23) as a B cells stimulatory factor 2 (BSF2). IL-6 is produced and released by many different type of cells. IL-6 is a pleiotropic cytokine, which presents dual role in a regulation of insulin sensitivity. It is known that IL-6 depending on the *in vivo* environment can act as an enhancer or inhibitor of insulin signaling. In obesity, an adipose tissue is a major source of circulating IL-6 that causes a development of insulin resistance. Paradoxically, skeletal muscle contraction during exercise leads to increase in IL-6 mRNA expression and subsequently it enhances circulating IL-6 concentration (24), which in turn improves the whole-body insulin sensitivity. It is known that the effect of IL-6 on insulin signaling is mediated by activation of AMP-activated protein kinase (AMPK). Exposure of the mouse soleus muscle to supraphysiological levels of IL-6 enhances fatty acid oxidation, glucose uptake and the translocation of glucose transporter 4 (GLUT4) to the plasma membrane, which is mediated by AMPK (25).

Moreover, it seems that muscle-derived IL-6 can play an important role in a regulation of a low-grade inflammation generated during obesity. It was observed that IL-6 induces an anti-inflammatory environment by promoting production of the two classic anti-inflammatory cytokine, interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10) (26, 27). Both of these cytokines could inhibit nuclear factor kappa B (NF-κB) activity. IL-6 is also involved in the regulation of TNF-α level. *In vitro* studies, both in cultured human monocyte and in the human monocyte cell line U937, indicated that administration of IL-6 inhibits production of lipopolysaccharide (LPS)-induced TNF-α (28).

In the recent years experimental data have demonstrated that other myokine, IL-15 can improve insulin resistance. IL-15 is a member of the common receptor γ-chain family of cytokines, which includes IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 (29). It was found that IL-15 is produced by many tissues, including liver, placenta, epithelial cells, activated macrophages and skeletal muscles, while little or no IL-15 mRNA is expressed in 3T3-L1 adipogenic cells (30). IL-15 signaling is transduced through a specific receptor for IL-15, interleukin-15 receptor (IL-15R) (31, 32). The IL-15R consists of three subunits: α-subunit, which is specific for IL-15 (IL-15Rα); β-subunit, which is also affected by IL-2 (IL-15/IL-2Rβ) and the γc subunit (33). It has been observed that IL-15 had an anabolic effect on the protein metabolism in skeletal muscles. Additionally, study on human myoblast cultures indicated that IL-15 in an insulin-growth factor (IGF) – independent manner stimulated the process of proliferation and differentiation of muscle cells and induced accumulation of the myosin heavy chain (MHC) in multinucleated myotubes (34). It has also been described that, besides its positive impact on skeletal muscle, IL-15 can play a very important role in a fat metabolism. A consecutive administration of IL-15 in rats for 7 days resulted in a decrease in white adipose tissue mass by reducing the rate of

lipogenesis process and decreasing of the activity of lipoprotein lipase (LPL) (35). In other study, IL-15 administration inhibited lipid accumulation in differentiating 3T3-L1 preadipocytes, and increased secretion of the adiponectin (insulin-sensitizing, anti-inflammatory and antiobesigenic factor) by differentiated 3T3-L1 adipocytes (30). Moreover, overexpression of IL-15 in transgenic IL-15 Tg mice (transgenic mice that overexpressed IL-15 from a skeletal muscle specific promoter) resulted in a reduction of adipose tissue mass and resistance to diet induced obesity (DIO) (36). The authors also showed that overexpression of IL-15 reduced circulating leptin levels, altered skeletal muscle genes expression involved in the regulation of fatty acid metabolism, such as the mammalian sirtuin family members 1 and 4 (SIRT1, SIRT4) and uncoupling protein 2 (UCP2), which in turn could be responsible for DIO-resistance and whole-body insulin sensitivity. In the white adipose tissue, SIRT1 additionally to the impact on metabolic pathways may repress the inflammatory signaling and prevent from macrophage accumulation in adipose tissue caused by chronic high-fat feeding (37). It is highly probable that mechanism described above could be one of the IL-15-dependent molecular pathways that could reduce WAT inflammation and improve insulin resistance. Tamura and coworkers (38) studies confirmed the hypothesis that muscle-derived IL-15 could play a role as an important mediator of anti-adipogenic and insulin-sensitizing effects of endurance exercise. These studies indicated that IL-15 exerted not only autocrine and paracrine activity but also acted as a classical endocrine factor. Moreover, these findings suggested that muscle-derived IL-15 can be also classified as a cytokine that increases tissue sensitivity to insulin. However, the molecular pathways mediating the effect of IL-15 on adipose tissue and skeletal muscles have not been characterized in detail yet, and further investigations are needed to explain this problem.

In the recent years several novel muscle-derived proteins have been described. Its expressions are restricted to the skeletal muscles and they are classified as myokines. One of them is myonectin/CTRP15, which belongs to the C1q/TNF-related protein (CTRP) family of secreted proteins that mediates cross-talk between skeletal muscles and other tissues, especially adipose tissue and liver (22). It was observed that recombinant myonectin leaded to induce phosphorylation of AMPK, which in turns enhanced glucose uptake and stimulated fatty acid oxidation.

CONCLUSIONS

Regular physical activity may be an important strategy to prevent progression of insulin resistance associated with obesity. Moreover, regular physical activity contributes to reduction of visceral fat amount and improves tissue insulin sensitivity. It should be emphasized that the beneficial health effect of exercises can be associated with endocrine activity of muscles. Muscle-derived peptides, myokines, can neutralize the negative effects of many adipokines, which production is increased in a course of obesity. The better understanding of the molecular mechanisms of myokines actions will allow to develop new and more effective therapies of obesity-associated diseases.

BIBLIOGRAPHY

1. Cantley LC: The phosphoinositide 3-kinase pathway. Science 2002; 296: 1655-1657.
2. Taniguchi CM, Emanuelli B, Kahn CR: Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006; 7: 85-96.
3. Accili DD: Molecular defects of the insulin receptor gene. Diabetes Metab Rev 1995; 11: 47-62.
4. Branca F, Nikogosian H, Lobstein T: The challenge of obesity in the WHO European region and the strategies for response. WHO Europe, Denmark 2007.
5. Gulcelik NE, Usman A, Gürlek A: Role of adipocytokines in predicting the development of diabetes and its late complications. Endocrine 2009; 36: 397-403.
6. Poulos SP, Hausman DB, Hausman GJ: The development and endocrine functions of adipose tissue. Mol Cell Endocrinol 2010; 323: 20-34.
7. Trayhurn P, Wood IS: Adipokines: inflammation and pleiotropic role of white adipose tissue. Br J Nutr 2004; 92: 347-355.
8. Bourlier V, Zakaroff-Girard A, Miranville A et al.: Remodeling phenotype of human subcutaneous adipose tissue macrophages. Circulation 2008; 117: 806-815.
9. Boden G, Lebed B, Schatz M et al.: Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. Diabetes 2001; 50(7): 1612-1627.
10. Petersen KF, Shulman GI: Etiology of insulin resistance. Am J Med 2006; 119: S10-16.
11. Yu C, Chen Y, Cline GW et al.: Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. J Biol Chem 2002; 277: 50230-50236.
12. Trayhurn P, Wood IS: Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochem Soc Trans 2005; 33: 1078-1081.
13. Xie Q, Deng Y, Huang C et al.: Chemerin-induced mitochondrial dysfunction in skeletal muscle. J Cell Mol Med 2015; 19: 986-995.
14. Kanda H, Tateya S, Tamori Y et al.: MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity J Clin Inves 2006; 116: 1494-1505.
15. Gordon S: Macrophage heterogeneity and tissue lipids. J Clin Invest 2007; 117: 89-93.
16. Lumeng CN, DelProposto JB, Westcott DJ, Saltiel AR: Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. Diabetes 2008; 57: 3239-3246.
17. Krogh-Madsen R, Thyfault JP, Broholm C et al.: A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. J Appl Physiol (1985) 2010; 108: 1034-1040.
18. Pedersen BK, Steensberg A, Fischer C et al.: Searching for the exercise factor: is IL-6 a candidate? J Muscle Res Cell Motil 2003; 24: 113-119.
19. Pedersen BK, Edward F: Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. J App Physiol (1985) 2009; 107: 1006-1014.
20. Matthews VB, Aström MB, Chan MHS et al.: Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia 2009; 52: 1409-1418.
21. Broholm C, Laye MJ, Brandt C et al.: LIF is a contraction-induced myokine stimulating human myocyte proliferation. J Appl Physiol (1985) 2011; 111: 251-259.
22. Seldin MM, Peterson JM, Byerly MS et al.: Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. J Biol Chem 2012; 287: 11968-11980.

23. Muraguchi T, Hirano T, Tang B et al.: The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. J Exp Med 1988; 167: 332-344.
24. Febbraio MA, Hiscock N, Sacchetti M et al.: Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. Diabetes 2004; 53: 1643-1648.
25. Stuart RG, Ratkevicius A, Wackerhage H et al.: The effect of interleukin-6 and the interleukin-6 receptor on glucose transport in mouse skeletal muscle. Exp Physiol 2009; 94: 899-905.
26. Steensberg A, Fischer CP, Keller C et al.: IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol Endocrinol Metab 2003; 285: E433-437.
27. Ropelle ER, Flores MB, Cintra DE et al.: IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKKbeta and ER stress inhibition. PLoS Biol 2010; 8(8).
28. Schindler R, Mancilla J, Endres S et al.: Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. Blood 1990; 75: 40-47.
29. Santos SA: IL-15: a relevant cytokine for lymphoid homeostasis and autoimmune diseases. Biotecnol Apl 2006; 23: 79-86.
30. Quinn LS, Strait-Bodey L, Anderson BG et al.: Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat signaling pathway. Cell Biol Int 2005; 29: 449-457.
31. Diniz SN, Pendeloski KP, Morgana A et al.: Tissue-specific expression of IL-15Rα alternative splicing transcript and its regulation by DNA-methylation. Eur Cytokine Netw 2010; 21: 308-318.
32. Liu X, Zuo Y, Zhang W et al.: Expression of interleukin-15 and its receptor on the surface of stimulated human umbilical vein endothelial cells. J Huazhong Univ Sci Technolog Med Sci 2009; 29: 527-534.
33. Budagian V, Bulanova E, Paus R, Bulfone-Paus S: IL-15/IL-15 receptor biology: a guided tour through an expanding universe. Cytokine Growth Factor Rev 2006; 17: 259-280.
34. Furmanczyk PS, Quinn LS: Interleukin-15 increases myosin accretion in human skeletal myogenic cultures. Cell Biol Int 2003; 27: 845-851.
35. Barra NG, Reid S, MacKenzie R et al.: Interleukin-15 contributes to the regulation of murine adipose tissue and human adipocytes. Obesity (Silver Spring) 2010; 18: 1601-1607.
36. Quinn LS, Anderson BG, Conner JD et al.: Overexpression of interleukin-15 in mice promotes resistance to diet-induced obesity, increased insulin sensitivity, and markers of oxidative skeletal muscle metabolism. Int J Interferon Cytokine Mediator Res 2011; 3: 29-42.
37. Gillum MP, Kotas ME, Erion DM et al.: SirT1 regulates adipose tissue inflammation. Diabetes 2011; 60: 3235-3345.
38. Tamura Y, Watanabe K, Kantani T et al.: Upregulation of circulating IL-15 by treadmill running in healthy individuals: is IL-15 an endocrine mediator of the beneficial effects of endurance exercise? Endocr J 2011; 58: 211-215.

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