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ADİPOKİNES AND INSULİN RESİSTANCE; THE İMPORTANT ROLE OF LEPTİN, ADİPONECTİN AND INTERLEUKİN-6

Reza Mohammadpourhodki[1], Arezou Salari[2], Hossein Balesh Abadi[3], Sanaz Noura[4], Zahra Ashrafi[5], Amir Mahdi Iranshahi*[6], Nasim SHirmohammadi[7]

1,5,7. MSc, School of Nursing and Midwifery, Shahroud University of Medical sciences, Shahroud, Iran

2,3,4,6. Students Research Committee, Faculty of health Zabol University of Medical Sciences, Zabol, Iran

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ABSTRACT

Adipose tissue (AT) was believed to be just an energy-storage organ, but it is now recognized to be an active organ, which secretes a variety of products known as "adipokines" such as leptin and adiponectin, as well as cytokines and chemokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. The adipokines have broad activities on metabolical pathways, endothelial function and inflammation and are implicated in the pathogenesis of several disorders, particularly insulin resistance.

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Introduction

Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response. Classically, this refers to impaired sensitivity to insulin-mediated glucose disposal [1,2].

Insulin resistance is a major component of metabolic syndrome (MetS), i.e. a group of risk factors that generally occur together and increase the risk of various diseases, including type 2 diabetes mellitus (T2DM) and several other metabolic diseases, cerebrovascular and coronary artery diseases and cancer [3-7].

AT is now regarded as not just a purely inert body compartment for excess energy storage, but rather as an active endocrine and paracrine organ, secreting a large number of hormones, cytokines and growth factors, collectively called "adipokines". The adipokines have broad activities on carbohydrate and lipid metabolism, endothelial function, inflammatory response and cytokine signaling and are implicated in the pathogenesis of insulin resistance, diabetes, MetS and atherosclerosis [8-10].

The aim of this review is to explain of basic mechanisms that are used by mentioned adipokines (including leptin, adiponectin and IL-6) to influence on insulin resistance.

Adipokines and Insulin Resistance:

Corresponding Author : Amir Mahdi Iranshahi

Leptin

Leptin is a 16 kDa protein hormone, which is secreted by adipocytes. Plasma leptin concentration increases in proportion to body fat mass and regulate food intake and energy expenditure to maintain body fat stores [11-16]. A number of mechanisms have been proposed to explain leptin and insulin resistance. These include alteration of leptin and insulin transport across the blood-brain barrier (BBB), alteration of their intracellular signal transduction (e.g. suppressor of cytokine signaling (SOCS)-3, protein tyrosine phosphatase (PTP)-1B and endoplasmic reticulum (ER) stress) and other such abnormalities [17-24]. In this part, we will focus on the mechanisms-mediated disruption of leptin and insulin signal transduction. ER stress is one of the mechanisms involved in defective action of leptin and insulin signaling. Accumulation of unfolded or misfolded proteins in the ER disrupts ER homeostasis, which in turn causes ER stress. In reaction to this ER stress, cells trigger an adaptive response termed "unfolded protein response" (UPR). To restore normalcy in ER function, UPR serves to down-regulate protein translation, up-regulate several chaperone proteins and activate degradation pathways to clear the unfolded or misfolded protein from the ER [25-28]. ER stress induces insulin resistance by impairing insulin receptor (IR) signaling [29]. Furthermore, ER stress is known to induce beta cell death, consequently, compromising insulin release [30]. PTP-1B is another mediator implicated in the attenuation of leptin and insulin signaling. PTP-1B inhibits leptin and insulin activities via dephosphorylation of janus kinase (JAK)-2 and the activated IR [22,31], respectively. Therefore, development of potent and specific inhibitors for PTP-1B has become interest in the treatment of insulin resistance and T2DM [32]. Besides PTP-1B, SOCS-3 is another regulator of leptin and insulin signaling. SOCS-3 inhibits leptin and insulin induced signal transduction [21,33,34]. Deletion of SOCS-3 in hypothalamic neurons enhances leptin sensitivity, reduces appetite and protects from diet-induced obesity [35]. while over-expression of SOCS-3 in proopiomelanocortin (POMC) neurons leads to hyperphagia and obesity [36,37]. Therefore, molecules that intervene SOCS-3 actions would represent a potential therapeutic target in the treatment of insulin resistance.

Adiponectin

Adiponectin is a 30 kDa plasma protein, which was identified in the mid-1990s and was named Adipo Q, adipose most abundant gene transcript (apM)-1, gelatin-binding protein (GBP)-28 or adipocyte complement-related protein (Acrp)-30 [38-41]. Adiponectin improves insulin sensitivity and has anti-atherogenic and anti-inflammatory properties [42,43]. This adipokine increases energy expenditure, lipid catabolism and fatty acid oxidation [44]. Plasma adiponectin levels are inversely correlated with T2DM, insulin resistance and obesity [45]. Adiponectin is believed to improve insulin sensitivity through a number of different mechanisms. In skeletal muscle, adiponectin increases the expression of molecules involved in fatty acid transport such as CD-36, acyl-coenzyme A oxidase involved in combustion of fatty acids and uncoupling protein-2 required during energy dissipation. These changes led to decreased triglyceride content in skeletal muscle [46]. Decreased tissue triglyceride content in muscle may contribute to improved insulin signal transduction by facilitating of insulin-stimulated phosphatidylinositol 3 kinase (PI3k) activation, subsequent glucose transporter (GLUT)-4 translocation and glucose uptake. Adiponectin also increases fatty acid combustion and energy consumption via peroxisome proliferator-activator receptor (PPAR)-α activation, which led to decreased triglyceride content in the liver and skeletal muscle and thus increased insulin sensitivity. Furthermore, adiponectin may stimulate β-oxidation and glucose uptake via adenosine monophosphate-activated protein kinase (AMPK). Adiponectin stimulates phosphorylation and activation of AMPK in skeletal muscle. In parallel with its activation of AMPK, adiponectin stimulates phosphorylation of acetyl-coenzyme A carboxylase (ACC), increases fatty acid combustion, glucose uptake and lactate production in myocytes. This reduces gluconeogenesis in the liver, which can account for the acute glucose-lowering effects of adiponectin [47,48].

Interleukin-6

IL-6 is a 185 amino acids polypeptide, which is produced by several cells such as fibroblasts, endothelial cells, monocytes and AT and is increased in obesity [49-51]. Most of IL-6 comes from the stromal vascular fraction (non-adipocyte fraction), composed of endothelial cells and monocytes/macrophages [52,53]. IL-6 targets several tissues and cell types. One of its major actions is control of the hepatic production of inflammatory proteins such as C reactive protein (CRP). There is a positive relationship between IL-6 levels in AT and circulating CRP levels, which is an important cardiovascular risk factor [54,55]. Recent studies suggest that IL-6 could be implicated in insulin resistance and its complications [56-58]. IL-6 reduced insulin-dependent hepatic glycogen synthesis and glucose uptake in adipocytes by suppression of insulin signal transduction via SOCS-3 and by down-regulating transcription of insulin receptor substrate (IRS)-1 and GLUT-4 [59-61]. IL-6 also has been shown to directly interfere with insulin signal transduction by serine phosphorylation of IRS-1 [62].

Conclusion:

AT is the key regulator of lipid-storage and release as well as a large active organ. Adipokines, which are directly produced by adipocytes or non-adipocyte fraction of AT, have numerous roles on metabolism, endothelial function and inflammation and are implicated in the pathogenesis of insulin resistance, diabetes, MetS and atherosclerosis. In this review, we focused on basic mechanisms that are used by some adipokines (including leptin, adiponectin and IL-6) to influence on insulin resistance. We found out that the mentioned mechanisms are varied from genetic mutations to cellular and molecular mechanisms. In conclusion, leptin and adiponectin increase insulin sensitivity and can considered as preventer factors of insulin resistance. In contrast, IL-6 decreases insulin sensitivity and have a potent role in creation and progression of insulin resistance. Based on

the above evidences, it is necessary to determine the other precise mechanisms that are used by these adipokines to influence on insulin resistance and it may provide novel therapeutic approaches to prevent or treat insulin resistance.

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