Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

Pharmacophore
an International Journal
ISSN 2229-5402

ADİPOKİNES AND INSULİN RESİSTANCE; ROLE OF INTERLEUKİN-6, TUMOR NECROSİS FACTOR-A AND PROTEİN-4

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ARTICLE INFO

Received:
03th Jun 2017
Accepted:
29th Nov 2017
Available online:
14th Dec 2017

Keywords: *Adipose tissue; Adipokines; Insulin Resistance*

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 interleukin (IL)-6, tumor necrosis factor (TNF)-α and retinol binding protein (RBP)-4. The adipokines have broad activities on metabolical pathways, endothelial function and inflammation and are implicated in the pathogenesis of several disorders, particularly insulin resistance. The aim of this review is to explain of basic mechanisms that are used by mentioned adipokines (including IL-6, TNF-α and RBP-4] to influence on insulin resistance.

To Cite This Article: Hosien Shahdadi, Reza Mohammadpourhodki, Amir Mahdi Iranshahi, Esmat Bandadni, (2017), "adipokines and ınsulin resistance; role of ınterleukin-6, tumor necrosis factor-α and protein-4", ***Pharmacophore, 8(6S),*** *e-1173046*

Introduction

Insulin signaling is initiated through its binding with and mediation of protein kinase activity in the beta subunit of the insulin receptor (IR) [1]. This stimulation permits phosphorylation of the insulin receptor substrate (IRS) to promote the activation of the phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) pathway. PI3K/Akt is a major metabolic pathway of insulin [2]. Insulin resistance exists whenever normal concentrations of insulin produce less than normal biological responses with respect to:

1. Glucose uptake
2. Suppression of hepatic glucose production
3. Decreased lipolysis
4. Increased lipogenesis
5. Prevention of proteolysis [3].

Insulin resistance increases the risk for various diseases, including type 2 diabetes mellitus (T2DM) and several other metabolic diseases [4,5], cerebrovascular and coronary artery diseases [6,7] and cancer [8,9].

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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” [10]. 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, metabolic syndrome (MetS) and atherosclerosis [11,12].

The aim of this review is to explain of basic mechanisms that are used by mentioned adipokines [including IL-6, TNF-α and RBP-4] to influence on insulin resistance.

Adipokines and Insulin Resistance

2.1. Interleukin-6

IL-6 is a single polypeptide chain of 185 amino acids that forms a bundle of four α-helices [13]. The molecular weight of this adipokine ranges between 21 and 28 kDa, depending on the state of glycosylation and phosphorylation [14,15]. IL-6 is produced by several cells such as fibroblasts, endothelial cells, monocytes and AT, which is increased in obesity [16,17]. In healthy humans, approximately 10-35% of circulating IL-6 plasma levels is from AT, in resting [18]. Inflammatory meditors, including TNF-α and IL-6 itself, also promote IL-6 production in vitro [19]. 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 [20,21]. IL-6 produced by intra-abdominal AT could directly contribute to visceral obesity-related hypertriglyceridaemia by stimulating hepatic secretion of triglycerides especially in the form of very low-density lipoprotein (VLDL) [22]. Furthermore, Several studies suggest lipolytic properties of IL-6 [23-25]. AT and adipocytes cultured with IL-6 showed increased lipolysis [25,26]. IL-6 infusion in humans increased free fatty acids (FFAs) concentrations and whole body fat oxidation [24,27]. Recent studies suggest that IL-6 could be implicated in insulin resistance and its complications [28-30]. The crosstalk of IL-6 and insulin-dependent metabolism has been addressed by several investigators over the last years and was discussed in detail recently [31,32]. IL-6 has adverse effects on insulin action in liver and AT as demonstrated in animals and in cell culture studies, even though not all reports on IL-6 action on insulin-dependent metabolism did support this [33-35]. IL-6 reduced insulin-dependent hepatic glycogen synthesis [36,37] and glucose uptake in adipocytes [38] by suppression of insulin signal transduction via suppressor of cytokine signaling (SOCS)-3 [39] and by down-regulating transcription of IRS-1 and glucose transporter (GLUT)-4 [38]. In contrast, IL-6 could sensitize myotubes for the effects of insulin which was shown as enhanced insulin-dependent glycogen synthesis and glucose uptake [33,40,41]. IL-6 has been shown to directly interfere with insulin signal transduction by serine phosphorylation of IRS-1. This appears to be a tissue-specific regulation, which includes other insulin signaling molecules as protein kinase B/Akt (PKB/Akt) or SOCS-3 and could provide a possible explanation for the initially controversial results on IL-6 and insulin action in the different peripheral organs liver, AT and skeletal muscle [42]. The regulation of hepatic glucose production by IL-6 is still a matter of debate. While IL-6 infusion during exercise has been shown to increase endogenous glucose production [43] and a single dose of IL-6 increased fasting blood glucose levels in resting subjects [44], other studies failed to show enhanced glucose output from the liver [33,45]. Recently, the crosstalk of IL-6 and insulin in the regulation of hepatic gluconeogenesis received a novel fascinating aspect, as at least in rodents central effects of insulin leading to suppression of glucose production are mediated by IL-6 synthesis in hepatic non-parenchymal cells [46]. Although the hope to possess a new drug which could be applied for treatment of insulin resistance was premature, studies on the metabolic functions of IL-6 will elucidate further therapeutic options. Therefore, IL-6 is an independent predictor of T2DM and cardiovascular disease and is correlated with insulin resistance.

2.2. Tumor Necrosis Factor-α

TNF-α is a 26 kDa transmembrane protein (mTNF), which plays a complex role in the response to injury, infection, angiogenesis, apoptosis and other physiological processes [47,48]. This pro-inflammatory cytokine has also been implicated in the pathology of endotoxin lethality [49], rheumatoid arthritis [50], Crohn’s disease [51], tumor-induced cachexia [52] and insulin resistance [53,54]. TNF-α is primarily secreted by macrophages and also by a broad variety of other cells including adipocytes [55,56]. Recent studies suggested that TNF-α treatment leads to a reduction of insulin-stimulated IR autophosphorylation and subsequent inhibition of IRS-1 phosphorylation without effecting the number of receptors or their insulin binding capacity in a variety of cell types such as fibroblasts, hepatoma cells, myeloid 32D cells, mouse adipocytes and human adipocytes [57-61]. A similar TNF-α-mediated inhibition of the insulin-induced tyrosine phosphorylations are also observed in the muscle and fat tissues of the obese and insulin resistant fa/fa rats [62]. The actual defect induced by TNF-α is likely to be at or near the IR itself. Partially purified receptors isolated from TNF-α treated adipocytes show reduced autophosphorylation and phosphorylation of exogenously added substrate [58]. This suggests that the IR itself is modified or TNF-α promotes the production of an inhibitor of the receptor that is associated with these preparations. Recent studies have shown that TNF-α induces serine phosphorylation of IRS-1 in cultured adipocytes and hepatoma cells. This modified IRS-1 inhibits both IR autokinase and exokinase activity [measured using IRS-1 as a substrate] in vitro. This effect is dependent upon IRS-1 serine phosphorylation, since enzymatic dephosphorylation of IRS-1 reduces its ability to inhibit the IR tyrosine kinase activity. Myeloid 32D cells, which lack endogenous IRS-1, are resistant to the effect of TNF-α on IR tyrosine phosphorylation. When IRS-1 is expressed ectopically in these cells, insulin-stimulated IR autophosphorylation becomes very sensitive to TNF-α, demonstrating that the presence of IRS-1 is necessary for the inhibition of the IR signaling by TNF-α in intact cells. In

addition to the cultured cells, an inhibitory form of IRS-1 is also observed in muscle and fat tissues of obese fa/fa rats [60,63]. This inhibition is also reduced after enzymatic dephosphorylation of IRS-1. Although the exact mechanism by which TNF-α induces IRS-1 phosphorylation is not clear, recent studies have suggested protein kinase c (PKC) isoforms as potential candidates [64,65]. In hepatoma cells, alterations in the interaction of IRS-1 and IR have been demonstrated upon TNF treatment, providing further insight into both TNF-mediated blockade of insulin signaling and also the potential role of IRS-1 in this process [66]. The role of IRS-2 is more complicated. In contrast to IRS-1, IRS-2 appears not to play any role in the inhibition of IR signaling by TNF-α in cultured white adipocytes [67] but plays an important role in other cell types such as cultured hepatoma cells and brown adipocytes [66,68]. Furthermore, TNF-α inhibits lipoprotein lipase (LPL) and stimulates lipolysis in adipocytes [62]. The resulting increase in circulating non-sterified fatty acids would be expected to contribute to insulin resistance [69]. Therefore, TNF-α over-production by AT may be involved in the aetiology and pathogenesis of the insulin resistance.

2.3. Retinol Binding Protein-4

RBP-4 is a protein of 201 amino acids and has a molecular mass of approximately 21 kDa [70,71]. It is encoded by the RBP-4 gene, localized in the chromosome 10q23-q24 [72]. Liver has the highest expression level of RBP-4; however, AT has the second highest rate of expression, i.e. 20-40% of that found in the liver [73]. Many studies also show that serum RBP-4 levels correlate with other components of the MetS in humans, including hypertension [74,75], dyslipidemia [74,76], waist/hip ratio [74,77], cardiovascular disease [78] and intra-abdominal fat mass [77,79,80]. Although many studies show strong correlations of serum RBP-4 levels with obesity and the severity of insulin resistance [79,81-83]. RBP-4 is a transport protein for retinol [vitamin A] in the circulation. It transports retinol from the liver to the peripheral tissues [84]. Plasma RBP-4 levels positively correlate with retinol levels. Therefore, subject's retinol status can influence circulating RBP-4 levels. In clinical studies, RBP-4-to-retinol ratio is used to correct for retinol status of the investigated subject [85]. Of importance, RBP-4 does not interact only with retinol. Formation of a complex with transthyretin -a carrier of thyroid hormone and retinol- prevents glomerular filtration of RBP-4 and its subsequent excretion through the kidney [86]. It is debatable whether increased transthyretin levels and/or enhanced RBP-4 to transthyretin interaction can result in decreased renal clearance of RBP-4 and consequently its increased circulating levels [87,88]. Circulating RBP-4 levels are also influenced by iron and ferritin status. Indeed, there is an interaction between iron and vitamin A status, of which RBP-4 is a surrogate. For instance, vitamin A deficiency may impair iron metabolism and aggravate anemia, iron deficiency anemia and vitamin A deficiency often coexist or increased iron intake and raised iron stores have been recognized as significant contributes to insulin resistance in parallel with increased RBP-4. Iron supplementation significantly increased plasma retinol and RBP [89]. Several mechanisms link RBP-4 to insulin resistance:

1. Genetic mutations have a potential role in creation of insulin resistance; Various studies showed that single nucleotide polymorphisms (SNPs) rs3758539, rs34571439 and rs116736522 in the RBP-4 gene increased the risk of insulin resistance and T2DM [72,90-94]. Furthermore, a study in approximately 6500 aging adults showed that a gain-of-function SNP in the RBP-4 promoter is associated with a 2-fold-increased risk of insulin resistance and T2DM [93]. This SNP increases RBP-4 promoter activity and is positively associated with RBP-4 expression in AT and with body mass index (BMI) [95]. Recently, a identified RBP-4 cell surface receptor, stimulated by retinoic acid gene homolog (STRA)-6, seems to be of special importance [96]. SNPs in this transmembrane protein, which has high affinity for RBP-4 and is a major mediator of intracellular retinol uptake, have been identified that are linked to insulin resistance and T2DM [97].

2. RBP-4 impair insulin signaling via cellular and molecular mechanisms; Recently, a study suggest that RBP-4 inhibited insulin signaling in the skeletal muscle at the level of IRS-1 and PI3K. In addition, RBP-4 treatment increases phosphoenolpyruvate carboxykinase (PEPCK) expression and glucose production in hepatoma cells. PEPCK expression is elevated in the livers of RBP-4-injected mice [98]. Incubation of isolated adipocytes with RBP-4 reduces the sensitivity to insulin-stimulated extracellular signal-regulated kinase (ERK) phosphorylation [99]. At the cellular level, a recent study showed that RBP-4 stimulates cytokine secretion from mouse macrophages [100]. Another study showed that the RBP-4/retinol complex stimulates janus kinase 2/signal transducer and activator of transcription 5 (JAK2/STAT5) signaling and expression of SOCS-3 [101], which has been implicated in insulin resistance [102,103]. Our data indicate that serum RBP-4 is related to decreased insulin sensitivity and it might be involved in the pathogenesis of insulin resistance.

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 IL-6, TNF-α and RBP-4) to influence on insulin resistance. We found out that the mentioned mechanisms are varied from genetic mutations to cellular and molecular mechanisms. In conclusion, IL-6, TNF-α and RBP-4 decrease 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.

AcknowledgmentsThis article is part of the thesis research project in Zabol University of Medical Sciences which is implemented with the financial support of the university, so we appreciate of this support.
source of Funding: Zabol University of Medical Science

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