Adiponectin and insulin: molecular mechanisms of metabolic disorders

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ABSTRACT

Adiponectin, the most common plasma adipocytokine, plays a crucial metabolic and anti-inflammatory role. With insulin resistance associated with obesity, an increase of adiponectin concentration, which leads to the activation of signaling pathways involved in the regulation of metabolism, occurs. Currently, adiponectin is being investigated as a potential therapeutic target for metabolic syndrome, although more research is required to understand the underlying mechanisms controlling its levels. In this review, we will examine the main mechanisms that control adiponectin levels in blood serum and its role in insulin-sensitizing effect, as well as evaluate the potential use of adiponectin and its receptors as a potential therapeutic target.

Keywords: adiponectin, insulin, adipocytes, obesity.

Адипонектин и инсулин: молекулярные механизмы реализации метаболических нарушений

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РЕЗЮМЕ

Адипонектин – самый распространенный адипоцитокин в плазме крови, который играет критическую метаболическую и противовоспалительную роль. При инсулинорезистентности, связанной с ожирением, происходит увеличение концентрации адипонектина, что приводит к активации сигнальных путей, участвующих в регуляции метаболизма. В настоящее время адипонектин исследуется в качестве потенциальной терапевтической мишени для метаболического синдрома, хотя необходимы дополнительные исследования, чтобы понять основные механизмы, контролирующие уровень адипонектина в крови. В этом обзоре мы представим основные механизмы, контролирующие уровень адипонектина в сыворотке крови, и его роль в

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инсулин-сенсибилизирующем действии, а также оценим потенциальное использование адипонектина и его рецепторов в качестве потенциальной терапевтической мишени.

INTRODUCTION

Adiponectin is one of the most studied adipocytokines. Since the discovery of adiponectin in adipose tissue, it has been shown that it can be secreted in skeletal muscle, osteoblasts, and lymphocytes [1, 2]. Nevertheless, adipose tissue remains the main source of adiponectin in the serum, and its concentration in the serum varies from 2 to 26 μg/ml, making up > 0.01% of serum protein [3, 4, 5].

In the last few years, the relationship between adiponectin and insulin has been widely studied since the sensitizing effect of adiponectin on insulin by binding to its receptors leads to the activation of adenosine monophosphate-activated protein kinases (AMPK), receptors activated by peroxisome proliferators (PPAR-α) and, possibly, other molecular ways which have not been studied; therefore, it is necessary to research it further. With insulin resistance (IR) associated with obesity, the content of adiponectin decreases, which leads to the activation of signaling pathways that regulate metabolism [3, 4]. At the same time, there is insufficient data on the effect of insulin on the synthesis and secretion of adiponectin. This review summarizes the latest findings on the effects of insulin on serum adiponectin levels and discusses the relationship between the adiponectin system and IR. In addition, the possible use of adiponectin or its receptors as a therapeutic target in cardiovascular diseases (CVD) was considered.

THE PRIMARY STRUCTURE OF ADIPONECTIN

Adiponectin is a glycoprotein [6] encoded by a single gene transcript and consisting of 247 amino acids. It has an N-terminal signal peptide (~28–32 amino acids) followed by a hypervariable region (12 amino acids) containing conservative amino acids necessary for oligomerization and a collagen region containing 22 Gly-X-Y repeats where X and Y are most often proline, isoleucine, or hydroxylisine (66 amino acids) and the C-terminal globular domain, which makes up 55% (136–137 amino acids) of the total number of amino acids [7]. Interestingly, the globular domain of adiponectin is a structural homolog to TNFα. However, despite the structural homology, there are not so many homologous sequences, with the exception of the four conservative residues responsible for maintaining structural folds. The collagen domain of adiponectin has a common homology with the complement protein C1q [7]. Thus, adiponectin belongs to the paralogous protein family known as C1Q/TNF-linked proteins or CTRPs [7].

MULTIMERIC FORMS OF ADIPONECTIN (OLIGOMERIZATION)

Serum adiponectin exists in several oligomeric complexes: trimer (LMW or low molecular weight form), hexamer (MMW or medium molecular weight form), and a 12- or 18-measure form (HMW or high molecular weight form) [7, 8]. In addition to these forms of adiponectin, there is a small form called gAd (globular adiponectin). The gAd mainly consists of 3 C-terminal globular domains held together by the strong hydrophobicity of the inner trimmer core [8]. It has been suggested that the HMW-adiponectin can also serve as a form of gAd storage that can be obtained from HMW [9].

The existence of multiple oligomeric structures contributes to the multifaceted activity of adiponectin, so that different oligomers act on different target tissues with diverse biological effects. The HMW adiponectin acts on liver and reduces the level of glucose in the blood serum, while the LMW or MMW adiponectin does not have similar effects [10]. The HMW

oligomer is necessary for the sensitizing effect of adiponectin on insulin by inhibiting gluconeogenesis in the liver [7]. On the other hand, gAd enhances fatty acid oxidation and insulin sensitization in skeletal muscles [11, 12]. In cultured myotubes, C2C12 HMW and MMW adiponectin activate NF-κB; while the trimer form activates AMPKα [13, 14]. On the contrary, Hada et al. showed that HMW adiponectin binds well to the membrane fraction of C2C12 muscle tubes [15]. In the central nervous system, HMW oligomers (large sizes) do not cross the blood-brain barrier. Thus, the main actions of adiponectin are mediated only by trimer and hexamer oligomers.

It is noteworthy that exogenous oligomers of adiponectin do not undergo conversion in blood serum to other oligomeric forms [16]. It has been proven that the intracellular production of oligomers is crucial to maintaining their serum ratio. Moreover, the affinity of binding of various adiponectin oligomers to its receptors, as well as the tissue-specific distribution of receptors, apparently contribute to the differentiated action of adiponectin [17].

RECEPTORS OF ADIPONECTIN

AdipoR1 (Adiponectin Receptor 1) and AdipoR2 (Adiponectin Receptor 2) belong to the PAQR family (family of progestin and adipoQ (adiponectin, C1Q and collagen domain containing) receptors)), consisting of 7 transmembrane domains similar to G-protein coupled receptors (GPCR). However, unlike GPCR, adipoR is not associated with the G-protein and has

an extracellular C-terminus and an intracellular N-terminus [18]. Skeletal muscles are the main tissue expressing AdipoR1, and liver cells express primarily AdipoR2. In addition, AdipoR1 and AdipoR2 bind to oligomeric forms of adiponectin with different affinities, for example, gAd mainly binds to AdipoR1, while full-sized adiponectin mainly binds to AdipoR2 [18]. Then, activation of intracellular signaling pathways occurs after binding to the receptor, which leads to the appearance of various physiological effects.

PROTEINS INTERACTING WITH ADIPONECTIN RECEPTORS

It is known that AdipoR1 and AdipoR2 do not have their own kinase/phosphorylating activity. Mutagenesis of intracellular tyrosine residues, which usually act as initiator signaling residues in other receptors, does not block adiponectin signaling [19]. So far, APPL1 (an adapter protein containing the homologous domain of plextrin), ERp46 (endoplasmic reticulum protein 46), Rack1 (receptor for activation of C-kinase 1) and CK2β (casein kinase 2β) have been identified for direct interaction with AdipoRs (Fig. 1).

APPL1 protein was identified as an adapter protein that binds to AdipoR, acting on both AdipoR1 and AdipoR2 to facilitate intracellular signaling. Binding of the ligand to AdipoR1 enhances the relationship of AdipoR1-APPL1 [20]. Overexpression of APPL1 in C2C12 muscle tubes increases the basal and adiponectin-induced phosphorylation of AMPK, p38 and ACC (acetyl-CoA carboxylase), which mediates the meta-
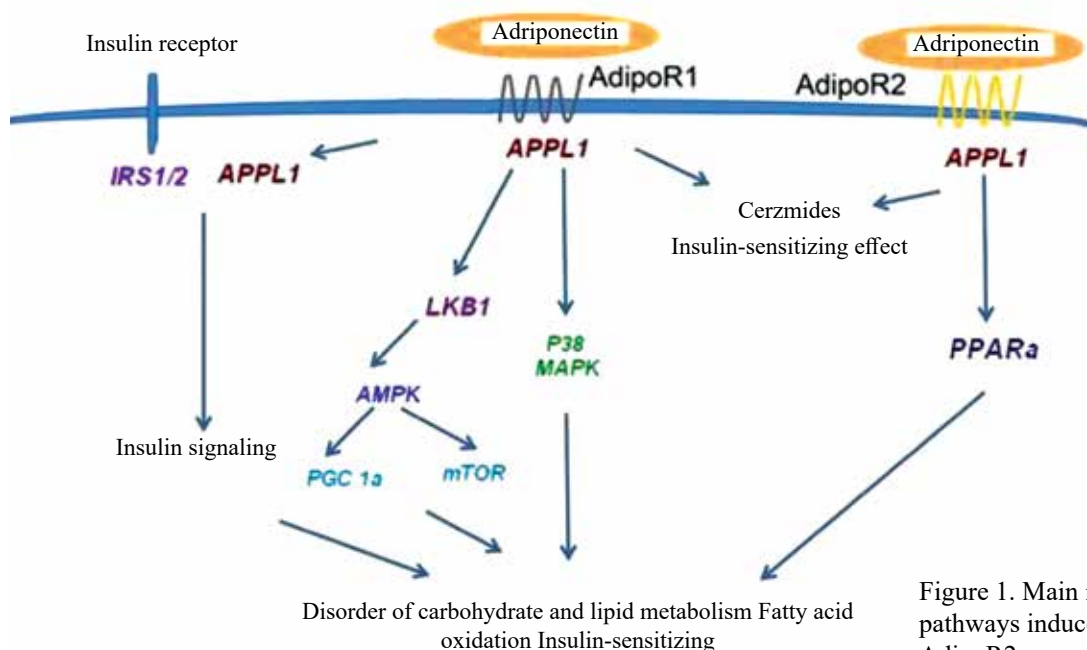

Figure 1. Main intracellular signaling pathways induced by AdipoR1 and AdipoR2

bolic functions of adiponectin. Accordingly, APPL1 knockout has been shown to inhibit AdipoR1-mediated signaling [21].

APPL2 is an isoform of APPL1 with 54% sequence similarity and similar domain organization. It acts as an inhibitor of APPL1 activity [22]. In addition, it is able to communicate with AdipoR through its BAR (Bin/Amphiphysin/Rvs) domain. Transgenic expression of APPL2 prevents the binding of AP-PL1-AdipoR1, which occurs either by competition of APPL1 for binding to AdipoR1, or by the formation of a heterodimer with APPL1, thereby inhibiting the interaction of APPL1-AdipoR1. Suppression of APPL2 expression improves adiponectin-induced fatty acid oxidation and glucose uptake [19]. APPL1 also enhances eNOS activation and NO production in endothelial cells by blocking by direct competition the compound Akt (a signal intermediate in the signaling pathway of insulin with its endogenous inhibitor 3 (TRB3)). In adipocytes and muscle cells, APPL1 forms a complex with Akt2, which dissociates when stimulated by insulin to regulate insulin-stimulated translocation of the GLUT4 membrane. APPL1 also facilitates the binding of IRS1/2 to the insulin receptor.

INTERMEDIATE SIGNAL MOLECULES

LKB1 (liver b1-kinase): after activation by ligand-bound AdipoR1 in the cytoplasm, APPL1 interacts and activates PP2A (phosphatase 2A protein). Activated PP2A deactivates PKC (protein kinase C) through dephosphorylation (threonine 410). PKC is a serine/threonine kinase that phosphorylates LKB1 to serine (307) and promotes its nuclear translocation. Deactivation of PKC leads to the accumulation of LKB1 in the cytoplasm, and also increases its interaction with APPL1. In the cytoplasm, APPL1 binds LKB1 and phosphorylates AMPK [22].

CaMKK (calcium/calmodulin dependent kinase kinase) has significant sequence and structural homology with LKB1 [23]. There are two CaMKK isoforms: CaMKKα and CaMKKβ. They are encoded by two different genes and have 70% amino acid sequence homology. Adiponectin has been shown to enhance the production of cytoplasmic Ca^{2+} either by releasing Ca^{2+} from the sarcoplasmic reticulum, or by an extracellular influx of Ca^{2+} [24]. Unlike LKB1, CaMKK-mediated phosphorylation of AMPK depends only on Ca^{2+} [25]. In addition, in an experimental study performed on mice knocked out by AdipoR1, Iwabu et al. demonstrated that binding of AdipoR1 to

the ligand induces Ca^{2+} influx and activates CaMKKβ, which leads to AMPK phosphorylation [26].

AMPK is a serine/threonine protein kinase, also called a metabolic cell sensor. Functional AMPK protein is a heterotrimer consisting of α, β and γ subunits. The catalytic α subunit also has a threonine phosphorylation site (172), while β- and γ- subunits act as regulators. The α subunit has two options: α1 (is exclusively cytoplasmic) and α2 (localized in the nucleus). In addition to the kinases listed above (LKB1 and CaMKKβ), AMPK is also activated by allosteric binding of AMP, the cellular level of which increases in a state of energy depletion [27].

Adiponectin induces AMPK activation in major peripheral target tissues. AdipoR1-mediated phosphorylation of AMPK was shown to inhibit skeletal muscle glycogen synthesis [28]. It is likely that the inhibition is due to phosphorylation of glycogen synthase to serine (7) only with AMPK α2 [29]. AMPK can also phosphorylate and activate PGC1α, receptors activated by peroxisome proliferators γ-coactivated 1α [30]. There are also data on an alternative pathway for PGC1α activation by adiponectin, including deacetylation of PGC1α through activation of sirtuin 1 (SIRT1). Subsequently, sirtuin 1-mediated activation of PGC1α activates gluconeogenic genes and hepatic glucose level, as well as PGC1α-mediated inhibition of glycolysis [31]. Activated CaMKKβ can also activate PGC1α independently of AMPK [31]. In addition, activated PGC1α enhances mitochondrial biogenesis and mitochondrial respiration, which consequently enhances muscle fatty acid oxidation [31].

Activated AMPK also induces the translocation of the insulin-dependent glucose transporter GLUT4 (type 4 glucose transporter) to the cell surface of various cell types, including skeletal muscles, adipocytes and cardiomyocytes, thereby increasing glucose uptake, which is one of the insulin-sensitizing effects of adiponectin. S.L. Torn et al. proposed a GLUT4 translocation model in which AMPK was activated directly or via mTOR the AS160 inactivation pathway (substrate for Akt protein kinase 160 kDa), similar to the one transmitting insulin signals [32], thereby initiating GLUT4 translocation to the cell surface [33]. Moreover, through AMPK-mediated Rheb phosphorylation (Ras homolog), adiponectin inhibits the p70 S6 kinase, which is unable to phosphorylate serine (302) and activate IRS1 (insulin receptor substrate 1). Finally, this contributes to the insulin-sensitizing effect of adiponectin [34].

The addition of various oligomeric forms of adiponectin (HMW or LMW) to the culture medium containing hepatocytes leads to a decrease in glucose production in the medium due to transcriptional suppression of G6P (glucose 6 phosphate) and PEPCK (phosphoenolpyruvate carboxylase), which is responsible for gluconeogenesis and glycogenolysis, respectively, via the AMPK dependent mechanism [35]. In addition, data appeared on the independent inhibition of LKB1-AMPK gluconeogenesis [35].

AMPK signaling also activates autophagy by phosphorylation of Ulk1 (Unc-51-like kinase 1 or a kinase that initiates mammalian autophagy) under conditions of nutrient deficiency, i.e. serine (317) and serine (777). Moreover, AMPK phosphorylates and thereby deactivates mTOR (mammalian rapamycin target), which is a known inhibitor of autophagy. In nutrient-rich environments, mTOR inhibits the induction of autophagy by phosphorylating serine (757) Ulk1, thereby preventing AMPK binding and subsequent activation of Ulk1 [36]. Adiponectin was shown to induce autophagy in an AMPK-dependent manner in various cell types, including cardiomyocytes and skeletal muscle [37]. It also induces the differentiation of vascular smooth muscle cells through AMPK-mediated inhibition of the mTOR complex [38]. It is noteworthy that autophagy is an important mechanism for the differentiation of cells of various types [38].

p38 MAPK: APPL1 acts as an anchor for adiponectin-mediated activation of the p38 MAPK pathway. In experimental studies, it was shown that p38-MAPK and signal components of the cascade were combined using APPL1. Under basal conditions, TAK1 (transforming growth factor β-activated kinase) is found with APPL1, while MKK3 (MAP kinase-3) and p38 MAPK remain weakly bound to APPL1 [38]. Adiponectin-activated APPL1 further activates TAK1, and subsequently a complex consisting of MAPK AdipoR1, APPL1, TAK1, MKK3 and p38 is formed. Activated TAK1 then phosphorylates MKK3, which in turn phosphorylates p38 MAPK. After phosphorylation, MKK3 and TAK1 dissociate from APPL1, and TAK1 activity rapidly decreases. TAK1 can also directly phosphorylate AMPK. It was also shown that activated p38 MAPK has an antilipogenic effect on muscles [40].

PPAR activates ACO (acetyl CoA oxidase) and UCPs (uncoupling proteins), which ultimately promotes the fatty acid oxidation and increased energy expenditure in skeletal muscles [41]. PPARα signaling increases the sensitivity of hepatic insulin and

therefore improves glucose uptake in the liver [41]. PPAR-mediated signaling also activates catalase and SOD1 (type 1 superoxide dismutase) in hepatocytes, which additionally contributes to the insulin-sensitizing effect of adiponectin in the liver by reducing oxidative stress [41]. On the other hand, PPARγ, which induces adiponectin expression in adipose tissue, is also activated by adiponectin [41].

INSULIN-SENSITIZING EFFECT OF ADIPONECTIN

Adiponectin has a sensitizing effect on insulin and other beneficial metabolic effects, inhibiting hepatic gluconeogenesis and enhancing fatty acid oxidation by activating AMP-activated protein kinase (AMPK) and proliferator-activated peroxisome α receptor (PPARα) [42, 43], as well as inhibition of acetyl-coenzyme A-carboxylase (ACC) in the liver and muscles [44]. Moreover, its anti-inflammatory effect is due to a decrease in the migration of macrophages and foam cells through the vascular wall and the polarization of macrophages [44]. A study by Fu et al. showed that overexpression of adiponectin in adipocytes increases insulin sensitivity by modulating proliferation, differentiation, and lipid accumulation [45].

With obesity, there is an active growth in adipose tissue: hyperplasia and hypertrophy. In response to energy balance, adipocytes produce and secrete various peptides. Studies have shown that adiponectin is a potential key mediator of glucose homeostasis in obesity and IR [46]. However, the autocrine actions and functions of adiponectin for adipocyte insulin signaling and glucose transport are not fully understood. In an experimental study, Chang et.al added insulin to a culture medium containing adipocytes, which induced a decrease in adiponectin mRNA expression [47]. In turn, adiponectin deficiency in the culture medium led to a decrease in insulin-stimulated glucose uptake and a decrease in the activation of AMPK in insulin-sensitive adipocytes.

At present, it is known that IRS proteins are of the greatest importance for insulin signal transmission; IRS-1 and IRS-2 are expressed in almost all types of cells and tissues [43]. IRS-1 mediates the regulatory effects of insulin on peripheral metabolic and growth processes, while IRS-2 is more responsible for the central effects of insulin, including control of differentiation and growth of neuronal cells, central regulation of eating behavior, glucose homeostasis and endocrine functions. It has been proven that a decrease in the content of IRS-1 is associated with IR and T2DM

[48]. In addition, Yamauchi et al. found that administration of globular adiponectin to lipotropic mice improved insulin sensitivity by enhancing the insulin-stimulated tyrosine phosphorylation of IRS-1 [43]. In C2C12 myotubes, adiponectin treatment reduces the IRS-1 phosphorylation to serine (636/639), which inhibits the subsequent insulin-stimulated IRS-1 tyrosine phosphorylation using the insulin receptor. It was proved that the presence of IR leads to a change in the expression of GLUT4 in the plasma membrane and intracellular compartments of adipocytes with a deletion of the adiponectin gene [49].

AKT (protein kinase B), the next target for insulin signaling in the cell, also causes various metabolic effects mediated by insulin, and AKT activity has been shown to decrease markedly in T2DM [50]. In their study, Chang et al. showed that the addition of insulin to a culture medium containing adipocytes is accompanied by activation of AKT. However, the adiponectin deletion did not lead to further AKT activation compared to control cells transfected with siRNAs (a double-stranded RNA class, 20–25 nucleotides long) [47].

These results suggest that AKT signaling is not involved in adiponectin-induced reduction in insulin-stimulated glucose transport. GLUT 4 plays a key role in this process, which is involved in the clearance of glucose, and GLUT1 plays a secondary role, mainly for glucose uptake during non-insulin stimulation [50]. In IR conditions, including obesity and T2DM (type 2 diabetes mellitus), the expression of GLUT4 in adipocytes decreases [50]. Overexpression of GLUT4 in adipose tissue leads to an increase in glucose tolerance [50].

It should be noted that the expression of AdipoR1/R2 in insulin target tissues appears to be inversely correlated with plasma insulin levels, since insulin negatively regulates adiponectin receptor expression levels via the PI3 kinase/Foxo1 pathway. Thus, it is both AdipoR1/R2 agonism and strategies to increase AdipoR1/R2 that can be logical approaches to provide a new method for the treatment of IR and T2DM, as we have shown that in patients with visceral obesity in the late post-infarction period manifestation of T2DM [52].

It is also known that adiponectin indirectly regulates insulin sensitivity by modulating immune responses. It is noteworthy that adiponectin has an anti-apoptotic effect on cardiomyocytes and β-cells of the pancreas and reduces oxidative stress in endothelial cells [43]. Despite these well-known endocrine effects of adiponectin, its autocrine/paracrine effects are still to be further researched. For example, adiponectin reduces ceramide in the liver by enhancing their catabolism and the production of the antiapoptotic metabolite sphingosine-1-phosphate (S1P), thereby improving insulin sensitivity, inhibiting inflammation. However, the role of adiponectin in controlling fatty ceramides is unclear. Overexpression of adiponectin in the adipose tissue of ob/ob mice reduces the thickness of AT and systemic inflammation and promotes the accumulation of fat in subcutaneous fatty deposits, including smaller adipocytes, which leads to improved sensitivity to systemic insulin and pancreatic β-cell survival [43]. However, the physiological effect of endogenous adiponectin derived from adipocytes on AT is not known.

When studying the molecular mechanisms underlying the insulin-sensitizing effect of adiponectin, there is growing evidence that adiponectin activates intracellular signaling pathways by activating AMPK and p38MAPK in skeletal muscle cells [53]. Stimulation of glucose utilization and fatty acid oxidation by adiponectin is mediated by AMPK and p38MAPK [44]. An increased expression of AMPK in C2C12 myotubes reduces the insulin-sensitizing effect of adiponectin [44]. In addition, blocking of the AMPK pathway inhibits adiponectin-induced insulin-sensitizing effects [54]. Thus, at present, the insulin-sensitizing effects of adiponectin have been studied only on peripheral tissues such as muscles and liver. It has been proven that a deletion of the adiponectin gene impairs insulin signaling simultaneously with a decrease in AMPK activation in insulin-sensitive, but not insulin-resistant, adipocytes. However, the autocrine effects of adiponectin on glucose uptake by adipocytes and insulin signaling have not been fully elucidated.

ADIPONECTIN AND ITS RECEPTORS AS A THERAPEUTIC TARGET IN CVD AND T2DM

Several strategies are considered to enhance the beneficial effects of adiponectin, including increasing both its plasma level and its activity. The levels of circulating adiponectin can be increased either by directly using exogenous adiponectin, for example, by injection, or by increasing endogenous adiponectin through treatment. Due to a high level of circulating blood and multimeric conformations of adiponectin, the direct use of exogenous adiponectin is difficult. Thus, increasing the level of endogenous adiponectin through the use of pharmacological agents, nutraceutical compounds and lifestyle modifications remains

the best option. Pharmaceutical products effective to increase circulating adiponectin include PPAR-α thiazolinedione (TZD) agonists, renin-angiotensin inhibitors such as angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) [55, 56].

In addition, the effect of statins is being actively discussed, and so recently we have shown that early use of statins in patients with MI leads to a significant increase in adiponectin levels and the adiponectin/leptin ratio, which is considered as a favorable effect of atorvastatin, which helps to reduce adipokine imbalance, normalize lipid exchange and reduce IR [57].

Among nutraceutical compounds, fish oil, linoleic acid, green tea extract, polyphenol resveratrol and osmotin, a representative of plant defense proteins, have recently been identified as potential adiponectin receptor agonists that can increase the concentration of adiponectin [58]. In addition, weight loss or physical activity can increase adiponectin levels, especially among people with obesity or diabetes [58].

An alternative approach to enhancing the beneficial effects of adiponectin is to enhance its transmission through compounds that may affect AdipoR. Treatment with PPARγ agonists, such as pioglitazone and rosiglitazone, increases plasma adiponectin levels and also increases insulin sensitivity in patients with IR and diabetes [58]. In addition, treatment with pioglitazone increases plasma adiponectin levels. Lin et al. showed that administration of rosiglitazone increases adiponectin mRNA levels in differentiated 3T3-L1 adipocytes for 1 day [59].

It has also been shown that insulin negatively regulates the HMW adiponectin complex. Accordingly, thiazolidinedione (TZD) mediated improvement in insulin sensitivity correlated with HMW concentration of adiponectin [59]. Although TZD is a widely used class of antidiabetic drugs, most patients do not show an improvement in insulin sensitivity [49]. The mechanism by which TZD stimulates an increase in adiponectin levels is unknown, but the secretory pathway of adipocytes appears to be the main site of action.

Pharmacological activation of AMPK by metformin has therapeutic potential for eliminating metabolic disorders, such as T2DM and non-alcoholic fatty liver disease. AMPK directly phosphorylates enzymes and transcription factors involved in the absorption of glucose and fatty acids and their mitochondrial metabolism by switching catabolic pathways [60]. It also disables the synthesis of glucose, glycogen and lipids

in the liver through anabolic pathways and promotes the absorption of glucose in the muscles. It is also reported that metformin improves insulin sensitivity by activating AMPK, thereby inhibiting the synthesis of fatty acids and triglycerides and promoting fat oxidation [61].

CONCLUSION

Over the last few years, adiponectin has been of greatest clinical interest due to its positive regulatory effect in certain conditions, including IR. Some of the problems associated with the molecular and cellular mechanisms underlying the functioning of the insulin-adiponectin system can be taken into account as potentially useful in the development of new pharmacological approaches. Further study of the effect of insulin on adipokines is needed to fully elucidate the molecular mechanisms of biosynthesis, secretion and signal transduction and their potential therapeutic value.

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