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Minireview

Role of adiponectin system in insulin resistance

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ABSTRACT

The knowledge of the pathogenesis of obesity and its metabolic sequelae has significantly advanced over the last few decades and adipose tissue is now considered a link between obesity and insulin resistance. Adiponectin, one of the major adipocyte-secreted proteins, has attracted scientific interest in recent years and has been extensively studied both in human and animal models. Adiponectin exerts insulin-sensitizing effects through binding to its receptors, leading to activation of AMPK, PPAR-α, and potentially other unknown molecular pathways. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated, leading to activation of signaling pathways involved in metabolism regulation. Up-regulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may be an interesting therapeutic strategy for obesity-linked insulin resistance. In this review we will focus on the recent research related to the relationship between the adiponectin system and insulin resistance. The potential use of adiponectin or its receptor for therapeutic intervention will be also discussed.

Contents

1. Obesity and insulin resistance

In Western countries, obesity is reaching epidemic proportions and is associated with a high prevalence of type 2 diabetes mellitus (T2DM) characterized by insulin resistance of peripheral tissues such as liver, muscle, and fat [1]. In 80% of cases the presence of T2DM was related to obesity [2]. Our understanding of the pathogenesis of obesity and its metabolic sequelae has significantly advanced over the past few decades, and adipose tissue is now considered a link between obesity and insulin resistance [3,4].

Adipose tissue is now regarded as not just a storage depot for excess energy, but rather as an endocrine organ, secreting a large number of bioactive molecules called adipokines [5]. This family of cytokines includes molecules with high biological activity, such as adiponectin, resistin, leptin, and PAI-1 (plasminogen activator inhibitor-1). These adipose-tissue-derived factors show paracrine activity, sustaining the inflammatory condition of adipose tissue, as well as endocrine activity, having effects on metabolism and inflammation [6–8].

Adiponectin is an abundantly expressed adipokine that exerts a potent insulin-sensitizing effect through binding to its receptors. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated, leading to activation of signaling pathways involved in metabolism regulation [9–12]. Upregulation of

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adiponectin/adiponectin receptors or enhancing adiponectin receptor function may be an interesting therapeutic strategy for obesity-linked insulin resistance.

2. Adiponectin

Adiponectin is a major adipocyte-secreted protein and is downregulated in obesity and its related pathology [9,11]. In contrast to the other adipokines, adiponectin exerts antidiabetic, anti-atherogenic and anti-inflammatory activities [12–18]. Due to these positive actions, adiponectin has attracted tremendous scientific interest in recent years, and has been extensively studied both in human and animal models. The structure, biosynthesis, and signaling of adiponectin in muscle and liver are illustrated in Fig. 1.

2.1. Structure and biosynthesis

The gene encoding human adiponectin, also called Acrp30, AdipoQ, apM1 or GBP28, is located on chromosome 3q27 [19], a locus linked with susceptibility to diabetes and cardiovascular disease [20]. The full-length protein consists of 247 amino acids, including the N-terminal hypervariable region, a conserved collagenous domain comprising 22 Gly-Xaa-Yaa repeats and a C-terminal C1q-like globular domain [21]. Adiponectin is present in peripheral circulation as three oligomeric complexes. The trimeric adiponectin represents the basic unit and is called low-molecular-weight (LMW) adiponectin. Two subunits of the trimer are linked by the collagen-like domain to form a hexamer, also termed middle-molecular-weight (MMW) adiponectin. Hexamer subunits are linked in a bouquet-like high-molecular-weight (HMW) adiponectin [22–24]. Moreover, cleavage of the full-length form generates the 17 kDa globular fragment of adiponectin, called globular adiponectin, which is found at lower levels (about 1% of total adiponectin) in the circulation [25].

Multimeric complex formation of adiponectin is recognized as an important mechanism modulating its biological functions [24]. Both *in vitro* and *in vivo* studies have suggested that HMW is the biologically active form and that HMW, rather than total adiponectin, may exert anti-atherogenic, anti-diabetic and anti-inflammatory actions that could prevent the development of metabolic and cardiovascular disease [26].

The biosynthesis and secretion of adiponectin in adipocytes are regulated in the endoplasmic reticulum [27–29]. Post-translational modifications are required for intracellular assembly of the HMW oligomeric complex in adipocytes, for its secretion, and also for maintaining its stability in the circulation [30]. The development of ELISA methods contributed to a more widespread measure of the adiponectin levels in peripheral circulation, thus increasing the experimental data needed to confirm its role in different patho-physiological conditions, especially in cardiovascular disease [31].

2.2. Gene transcription

The adiponectin gene promoter contains multiple transcription factor binding sites through which a large number of diverse factors have been shown to modulate its activity [32,33]. Adiponectin gene expression is upregulated by transcription factors such as peroxisome proliferator activator receptor-γ (PPAR-γ) [34], C/EBPa, and Forkhead transcription factor FoxO1 [35,36]. Adiponectin gene expression is downregulated in the adverse environment associated with obesity, such as chronic low-grade inflammation and oxidative stress [33]. It is regulated through the Akt and JAK/STAT signaling pathways [37] by oxidative stress, through protein kinase C [38] and through the JNK signaling pathway by TNFa [39], and through p44/42 MAPK by IL-6 [40]. Moreover, under conditions of endoplasmic reticulum stress, adiponectin mRNA expression is downregulated [41,42]. Other transcription factors known to downregulate adiponectin include CREB, which activates ATF3, NFAT, and protein kinase A, which is stimulated by beta-adrenergic signaling [32,33].

2.3. Adiponectin receptors

The two main adiponectin receptors, AdipoR1 and AdipoR2, are structurally and functionally distinct from classic G-protein-coupled receptors. They contain seven transmembrane domains, have an inverted membrane topology with a cytoplasmic N-terminus and a short extracellular C-terminus of approximately 25 amino acids [43,44]. AdipoR1 is expressed ubiquitously, whereas AdipoR2 is expressed most abundantly in the liver [44].

Recently, molecules that couple the AdipoRs to their downstream signaling cascades have been identified, including the adaptor protein containing a PH (pleckstrin homology) domain (APPL1), receptor for activated protein kinase C1 (RACK1) [45–47], protein kinase CK2β, and endoplasmic reticulum protein of 46 kDa (ERp46) [48–51]. However, detailed molecular events remain elusive.

In addition to AdipoRs, T-cadherin has also been suggested as a potential receptor for adiponectin [52]. T-cadherin is different from classical cadherin molecules due to the lack of a cytoplasmatic domain (so T-cadherin is designated as truncated cadherin), and the presence of a highly conserved amino acid motif throughout evolution in vertebrates [53,54]. T-cadherin is highly expressed in the heart, smooth muscle and endothelium, representing the main targets of adiponectin. It is abundantly expressed in injured vascular endothelial and smooth muscle cells in atherosclerotic regions [55,56] and it has been shown to protect against cardiac stress [57]. However, the molecular mechanisms of transmission of the adiponectin signal and the functional relevance of this binding remain unclear and require more detailed studies.

Finally, similar to other members of the collectin family, adiponectin binds to calreticulin on the cell surface of macrophages, facilitating the uptake of dead cells [58,59]. These data suggest that adiponectin can protect the organism from systemic inflammation at least in part through its ability to function as a collectin protein [59].

2.4. Adiponectin and insulin resistance

AdipoRs are mainly involved in AMP-activated protein kinase (AMPK) and peroxisome-proliferator-activated receptor α (PPAR-α) ligand activities [44]. Adiponectin exerts effects on glucose uptake and ß-oxidation via AMPK [60]. In skeletal muscle, activation of AMPK is stimulated by globular and full-length adiponectin, while in the liver only by the full-length form [60,61]. The glucose-lowering effects of adiponectin may account for the phosphorylation of acetyl coenzyme-A carboxylase (ACC), increased fatty-acid combustion, glucose uptake and lactate production in myocytes. These activities stimulated by adiponectin limit gluconeogenesis in the liver. Via PPAR-α, adiponectin increases fatty-acid and energy consumption, leading to reduced triglyceride content and increased insulin sensitivity in the liver and skeletal muscle [62].

Studies in animal models have confirmed the importance of AdipoRs in mediating physiologically metabolic regulation by adiponectin, and have highlighted their functional differences [63–65], also reporting conflicting data. The adiponectin-induced activation of AMPK is blocked in mice by an AdipoR1-targeted deletion; disruption of AdipoR2 decreased adiponectin-stimulated PPAR-α signaling; and simultaneous ablation of both AdipoR1 and AdipoR2 blocked the binding and actions of adiponectin, leading to insulin resistance and glucose intolerance [63]. AdipoR1-null mice showed increased adiposity and glucose intolerance, whereas AdipoR2-null mice were lean and resistant to diet-induced glucose intolerance, indicating that AdipoR1 and AdipoR2 might have opposing effects [64]. By contrast, deletion of AdipoR2 reduced diet-induced insulin resistance, but increased their susceptibility to T2DM [65].

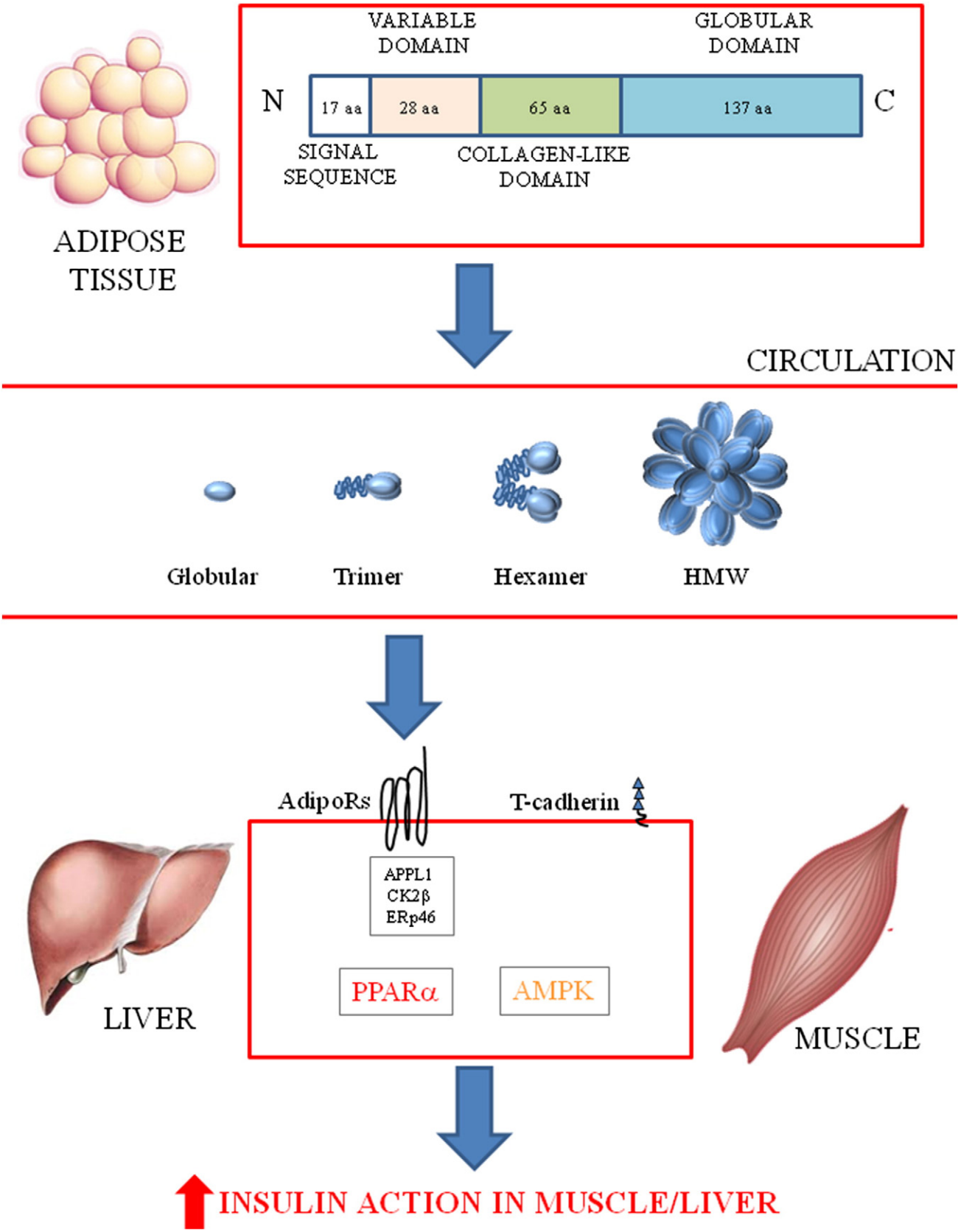

Fig. 1. Adiponectin biosynthesis from adipose tissue, its release into bloodstream, and its mechanisms of action on target tissues, such as muscle and liver. Adiponectin molecules are produced by adipocytes and, after post-translational modifications, globular, trimer, hexamer and HMW isoforms of adiponectin are secreted in peripheral circulation. After their binding to AdipoRs on target tissues, adiponectin exerts effects on glucose uptake and ß-oxidation via AMPK and it increases fatty-acid and energy via PPAR-α. Collectively, these actions lead to improving insulin action in liver and muscle.

Besides the insulin-sensitizing effect of adiponectin by linking to AMPK and PPAR-α, adiponectin decreases tissue triglyceride levels and increases insulin signaling. In skeletal muscle, adiponectin increases fatty-acid transport, stimulating the expression of proteins such as CD36, acyl-coenzyme A oxidase [66]. On the contrary, high tissue triglyceride levels could interfere with glucose uptake through activation of insulin-stimulated phosphatidylinositol (PI) 3-kinase as well as translocation of glucose transporter-4 (GLUT-4), thus leading to the development of insulin resistance.

2.5. Adiponectin as therapeutic target

Several strategies have been suggested for increasing the favorable effects of adiponectin, including enhancing both its plasma level and activities (Fig. 2).

Adiponectin circulating levels could be elevated either by directly using exogenous adiponectin, e.g., through an injection, or by increasing the endogenous adiponectin through treatments. Because of the high circulating levels and multimeric conformations of adiponectin, the direct use of exogenous adiponectin is difficult. Thus, the best option remains increasing endogenous adiponectin through the use of pharmacological drugs, nutraceutical compounds and lifestyle modification. Pharmaceutical products effective in elevating adiponectin circulating levels include the PPAR-α agonists thiazolinediones (TZDs) [67–71], inhibitors of the renin–angiotensin system such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) [72,73], and statins, although their role is still debated. Among nutraceutical compounds, fish oil, linoleic acid, seed extract, green tea extract, and polyphenol resveratrol are able to elevate adiponectin concentration [74]. Moreover, weight loss or physical activity is able to increase adiponectin levels, especially among obese or diabetic subjects [75].

An alternative approach for increasing favorable adiponectin effects is enhancing its signaling through compounds that can act on AdipoR. Agonists of PPAR-α, PPAR-γ and ARBs are able to up-regulate expression of AdipoR [76]. Moreover, a member of the plant defense proteins, osmotin, has been recently identified as a potential adiponectin receptor agonist [77]. Very recently, an orally active synthetic small-molecule AdipoR agonist (AdipoRon) was identified. In animal models, AdipoRon was able to ameliorate obesity-related diseases such as insulin resistance, glucose intolerance, and T2DM, and to prolong lifespan [78]. Due to the presence of AdipoR1 dimers in various cell lines as well as the regulation of this dimerization by adiponectin, the

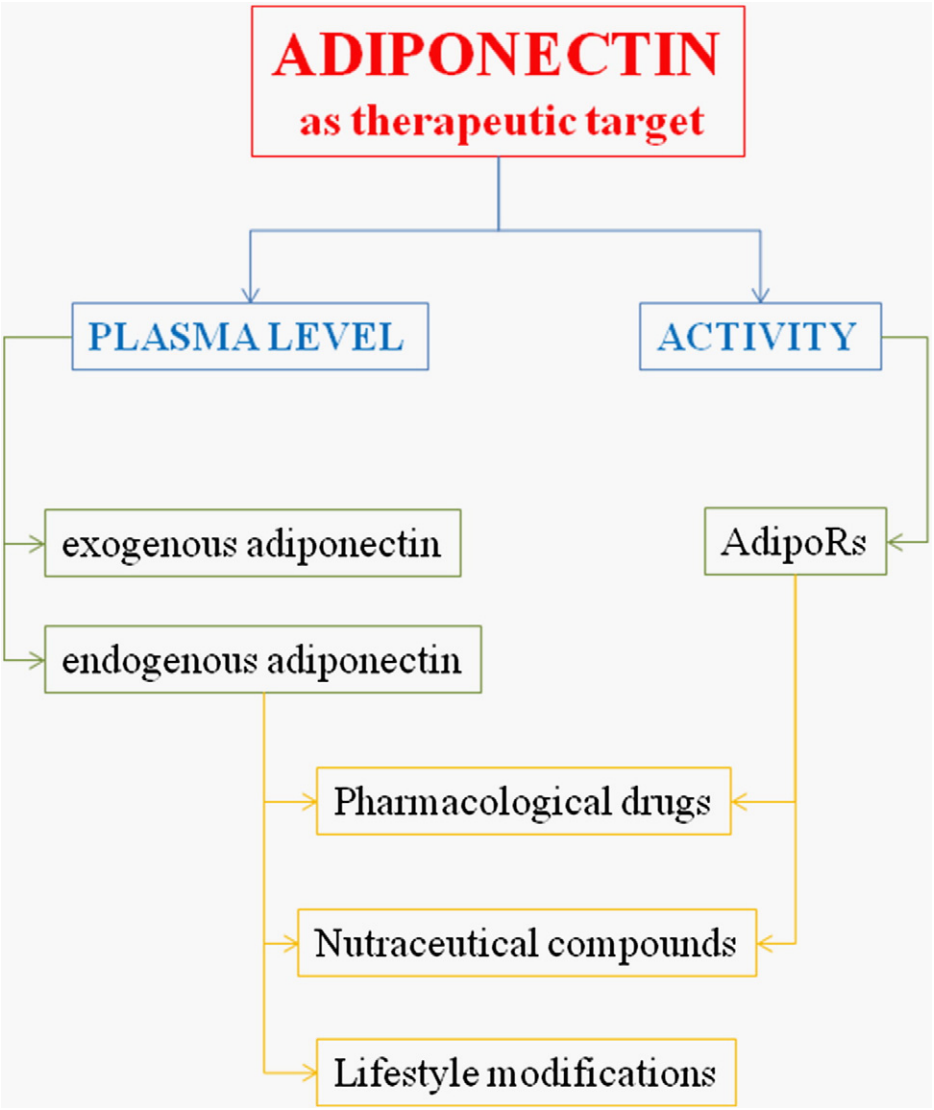

Fig. 2. Summary of the potential strategies that could be used to increase adiponectin effects. The positive effects of adiponectin could be obtained either rising directly the adiponectin circulating levels (supplementing with exogenous adiponectin as well as by increasing the release of endogenous adiponectin), or increasing indirectly its activity at target tissue level. Pharmacological drugs, nutraceutical compounds, and lifestyle modification could represent reliable options able to therapeutically target adiponectin system.

oligomerizion of AdipoRs could be considered a potential pharmacological target in obesity-associated disorders [79,80].

3. Conclusion

In recent years, due to its positive regulatory action in several conditions including insulin resistance, the adiponectin system has become critical for designing new drugs. Several issues linked to the molecular and cellular mechanisms underlying the adiponectin system could be taken into account as potentially useful targets in new pharmacological approaches. These include the biosynthetic pathway of adiponectin; the multimerization process, in order to increase the HMW adiponectin, considered the biologically active form; the modulation of adiponectin levels and/or activity at gene level; adiponectin signaling, including both AdipoRs and downstream post-receptor mechanisms; and the protective activities of adiponectin at the intracellular level, in order to develop adiponectin-based therapeutics with cell-specific delivery approaches.

In conclusion, further work is needed to completely elucidate the molecular mechanisms of biosynthesis, secretion and signaling of adiponectin and their potential therapeutic value. Moreover, biologically active adiponectin forms or chemical entities that can activate adiponectin receptors should be additionally investigated and applied in human trials to test their potential benefit in clinical settings.

4. Conflict of interest

The author declares that she has no conflict of interest.

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