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Regulation of Adiponectin and its Receptors by Endogenous and Exogenous Factors

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Review Article

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Abstract

Adiponectin is a hormone-derived adipose tissue. There is two form of adiponectin as low molecular weight (LMW) and high molecular weight (HMW). It has important role in energy homeostasis and is related to disease such as insulin resistant and obesity. In fact, the fluctuant in its serum level is affective in abnormality of energy homeostasis. Here, we reviewed the effect of both endogenous and exogenous factors on regulation of adiponectin. Based on our review, adiponectin and its receptors can consider as special therapeutic targets to treat diabetes, obesity and cardiovascular disease.

Keywords: Adiponectin; Adipose tissue; Insulin resistant; Obesity

Abbreviations: LMW: Low Molecular Weight; HMW: High Molecular Weight; AMPK: Adenosine Monophosphate Protein Kinase; ACC: Acetyl Coenzyme a Carboxylase; PPAR: Peroxisome Proliferators Activated Receptor; SREBP1c: Sterol Regulatory Element-Binding Protein 1c.

Introduction

Adiponectin has been identified as an adipocyte complement-related protein that obtained from murine 3T3-L1 adipocytes during 1990s [1]. In fact, this achievement leads to expansion of our perception from physiological activities of adipose tissue so that it is either energy storage or hormone secreting organ [2]. The chromosome 3q27 with three exons and two introns is locus related to adiponectin gene and ultimately a protein of 247 amino acids obtained from it [1,3]. The Cys39 is a main region for adiponectin oligomerization so that results in production of its two forms, including low molecular weight (LMW) as two trimers and high molecular weight (HMW) as four to six trimmers [4]. The concentration of adiponectin circulation is about 2-20 mg/ml and as comprised 0.05% of total serum protein can considers as a protein with high concentration in serum [5]. When its serum level is within normal range, any fluctuant in homeostasis of glucose, triglycerides, and free fatty acids has been not observed, while followed by its reduction occurs many problem related to energy homeostasis such as type 2diabetes, metabolic syndrome,

obesity, and atherosclerosis [5-8]. Because, it has been reported molecules derived by adipose tissue have a pivotal role in pathophysiology of insulin resistance, obesity, and atherosclerosis [5]. Inflammation is considers as relating factor between obesity and adiponectin reduction, also the expansion of inflammation leads to insulin resistance and cardiovascular disease [9]. In addition, the prevention of type two diabetes and cardiovascular disease through proceeding related to increase level of circulating adiponectin such as low-calorie, high-unsaturated fat diet and/or exercise confirm important role of adiponectin in energy homeostasis [10]. Thus, to stable adiponectin serum level adiponectin through pharmacotherapy interventions is a solution for treatment of many disease so that achievement using PPAR-δ agonists and statins have been obtained [11,12]. The physiological action of adiponectin occurs through its binding to AdipoR1 and AdipoR2. These receptors stimulate phosphorylation of adenosine monophosphate protein kinase (AMPK), acetyl coenzyme A carboxylase (ACC) and peroxisome proliferators activated receptor (PPAR) signaling pathways in skeletal muscle (AdipoR1) and liver (AdipoR2) [13-16]. It have been reported that these receptors have different affinity for adiponectin so that the affinity of AdipoR1 is higher than AdipoR2 [17,18]. Given that their actions in energy homeostasis by increase of glucose uptake and fatty acid oxidation in skeletal muscle and glucose output reduction in liver, thus they are pivotal treatment goals to improve diabetes, obesity and cardiovascular disease [19,20]. For example, diabetes induction leads to increase of adiponectin receptor 1 expression in heart and skeletal muscle and reduction of adiponectin level in serum. In addition, insulin administration is requiring or preserving adiponectin receptor 1 in normal range. Surprisingly, diabetes induction was not affective on gene expression of adiponectin receptor 2 in liver [21,22]. In study on non-diabetic subject (with or without family history of Type 2 diabetes) has been determined that gene expression of both adiponectin receptors reduce in non-diabetic with family history of T2D. This study indicates that they can be good predicators for diabetes diagnosis [23]. The expression of adiponectin receptors has a positive correlation with PPAR-δ expression. Moreover, donors' fasting plasma triglycerides has a negative association with AdipoR1 expression in myocyte [24].

Review Method

In this study, we reviewed the effect of endogenous and exogenous factors on adiponectin regulation and its receptors using to search databases such as PubMed, science direct, and web of Science from 2000 to now.

Endogenous Factors

Insulin resistant along with increase of TNF- α and IL-6 are the factors that can be affective in adiponectin level reduction because in a study was determined that adiponectin serum level reduced in obese diabetic patients. In addition, this study was showed that insulin leads to adiponectin releasing from adipose tissue only in lean individuals; therefore increase of TNF- α and IL-6 from adipose tissue during obesity prevents adiponectin secretion in normal range from adipose tissue [25]. Probably, the major portion of serum adiponectin is related to omental cells because it has been determined that treatment with insulin or rosiglitazone as alone or combinatorial results in adiponectin secretion increase from omental cells compared to subcutaneous adipocytes. Moreover, there is a direct or indirect relationship in adiponectin secretion from omental cells or subcutaneous adipocytes to body mass index, respectively [26]. Nevertheless, in a study was confirmed that insulin infusion equally leads to suppression of adiponectin secretion both lean and obese people and also treatment with BQ123 as a endothelin receptor antagonism was indicated that endothelin has not any effect on adiponectin serum level during insulin infusion [27]. Increase of adiponectin plasma level and mRNA in adipose tissue related to lean people and inversion relationship between adiponectin and cytokines-divided adipose tissue (IL-6, IL-8, and TNF-α) indicate role of these cytokines in reduction of adiponectin level in obese people [28]. In addition, down-regulation of adiponectin after treatment with TNF-α in C57BL/6J mouse has been showed [29] and also adiponectin resistance in skeletal muscle result from during continuing inflammatory condition by treatment with TNF-α [30]. Adipocyte determination and differentiation-dependent factor 1 (ADD1)/sterol regulatory element-binding protein 1c (SREBP1c) transcription factor (ADD1/SREBP1c) is a regulatory factor of adiponectin gene expression so that it leads to increase of adiponectin mRNA [31]. Although increase of adiponectin serum level is associated with higher levels of testosterone and lower level of estradiol in serum but other probably, factors lead to difference in serum level of adiponectin in both genders [32]. Id3 as a helix–loop–helix factor binds to E47 as E-proteins so that results in inhibition of its binding to DNA. In addition, it can be a negative regulator of adiponectin gene expression, because its increase leads to reduction of adiponectin gene expression by interaction with E47 as SREBP-1c–mediated adiponectin promoter activation [33]. In a study was found that hypoxia inducible factor-1 (HIF-1) induces adiponectin gene expression in heart and specially white adipose tissue so that its production in

heart can improves ischemia/reperfusion injury during diabetes along with obesity [34]. It has also been reported that the protein family CTRPs (C1q/TNF-related proteins)as type of adipokines are effective on improvement of endothelial dysfunction through biding to adiponectin receptor-1. Therefore, adiponectin receptor-1 can consider as a therapeutic strategy [35]. Based on our study in relation to effect of thyroid hormones on adiponectin gene expression at adipose tissue determined that induction of hyperthyroidism by levothyroxine results in significantly increase of adiponectin mRNA in adipose tissue [36]. In addition, thyroid hormones increase AdipoR1 and AdipoR2mRNA levels according to our obtained results [37].

Exogenous Factors

Treatment with exogenous growth hormone (rAAV2/1-CMV-GH1) increases gene expression of adipoR2 in liver, HMW adiponectin in liver and serum, respectively but there was not any change in adipoR1 expression after injection of rAAV2/1-CMV-GH1 in skeletal muscle [38]. Administration of CL316, 243 as a β_3-adrenergic agonist markedly increases both serum level and adiponectin mRNA in white adipose tissue [39]. It has also been reported that both CL-316,243 and BRL37344 as β-adrenoceptor agonists upregulate adiponectin receptor 2 (not receptor 1) in white adipose tissues related to epididymal and subcutaneous [40]. Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (thiazolidinediones) are important factors for adiponectin level increase. Indeed, they increase interaction between PPAR-responsive element to retinoid X receptor or liver receptor homolog-1 in adipose tissue [41]. On the other hand, rosiglitazone as a peroxisome proliferators activated receptor γ (PPARγ) agonist leads to increase expression of adiponectin and its receptors (AdipoR1 and AdipoR2) in adult rat, thus PPARγ is a main regulator for adiponectin [42]. In addition, increase of adiponectin level results from troglitazone administration in diabetic and non-diabetic individuals' weather lean or obese [43]. Given that *Citrus aurantium* L (particularly its isolated compound such as naringenin and hesperetin) is used to treat cardiovascular, in a study the effect of naringenin and hesperetin on adiponectin expression was performed. The results were showed that these flavonoids have antiatherogenic property through adiponectin expression up-regulation [44]. The other type of flavonoids have also are adiponectin regulator for example kaempferol glycosides CO-1 and CO-2 isolated from *C. osmophloeum* leaves induce adiponectin secretion in differentiated mouse 3T3-L1 adipocytes [45]. Tongqiaohuoxue decoction (THD) is a water extract prepared from eight herb species that numerous utilizing in traditional medicine particularly induction of adiponectin secretion from adipose tissue [46]. In a study, the effect of methanolic leaf extract of *Gymnema sylvestre* on expression of adiponectin in 3T3 L1 murine adipocyte cell line was evaluated. The result was showed that it markedly leads to increase of adiponectin gene expression and can considers as an adiponectin regulator [47]. In addition, chlorogenic acid has anti-diabetic effect due to increase of adiponectin level in adipose tissue and improvement of signaling pathways of its receptor [48]. The using of natural product as adiponectin regulator can be a good strategy to treat adiponectin-related disease so that has been confirmed that oleic acid and hydroxytyrosol prevent TNF-α-induced suppression of total adiponectin secretion through abrogation of TNF-α-stimulated JNK phosphorylation [49]. Dietary saturated fatty acids specially palmitic acid up-regulate mRNA and protein levels of hepatic AdipoR2 through increase level of FoxO1 protein, inhibition of its hyperacetylation and enhancement of its association with the AdipoR2 promoter in the livers [50]. In a study, we confirmed that treatment with ginsenoside Rb1 results in activation of adiponectin signaling in C2C12 myocytes so that it increased noticeably gene expression of AdipoR1 and AdipoR2 [51] (Table 1).

Endogenous regulators	Exogenous regulators
TNF- α↓	Exogenous growth hormone ↑
IL-6 ↓	CL316, 243 (a β_3-adrenergic agonist) ↑
IL-8 ↓	BRL37344 (a β_3-adrenergic agonist) ↑
Insulin ↑or ↓*	Thiazolidinediones ↑
ADD1/SREBP1c ↑	Rosiglitazone ↑
Testosterone ↑	Troglitazone ↑
Estradiol↓	Antioxidants(Naringenin)↑
Id3 (a helix–loop–helix factor) ↓	Hesperetin ↑

HIF-1 ↑	Kaempferol glycosides CO-1 and CO-2 ↑
C1q/TNF-related proteins ↑	Tongqiaohuoxue decoction
Thyroid hormone	Methanolic leaf extract of *Gymnema sylvestre*
	Chlorogenic acid
	Oleic acid ↑
	Hydroxytyrosol ↑
	Palmitic acid ↑
	Ginsenoside Rb1 ↑

Table1: The endogenous and exogenous factors affective on adiponectin level.
TNF- α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; IL-8: Interleukin-8; ADD1/SREBP1c: Adipocyte determination and differentiation-dependent factor 1 (ADD1)/sterol regulatory element-binding protein 1c (SREBP1c) transcription factor; HIF-1: Hypoxia inducible factor-1. *In relation to insulin have been reported both additive and decreasing effects.

Conclusions

Here, we reviewed several endogenous and exogenous adiponectin regulators. This study can be useful to understand pivotal role of adiponectin and its receptors in disease related to energy homeostasis such as insulin resistant and obesity. Given that our review, adiponectin and its receptors can be important treatment goals and regulated through drugs or active compounds derived herbs. Therefore, we suggest that specifically attend to adiponectin and its receptors in further studies for disease treatment.

Declarations

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Conflict of interest statement

The authors declare that there is no conflict of interest regarding this study.

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Contribution of Authors

This work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article was borne by the authors named in this article.

Ethical approval

This research does not contain any studies with human participants or animals and was performed by the authors alone.

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