BRIEF COMMUNICATION
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Improved ovarian adiponectin system expression in polycystic ovary syndrome treated with exenatide

Asma Vatankhah[1], Mohabbat Jamhiri[2], Sima Vatankhah[3], Keivan Lorian[4], Mohammad Ebrahim Rezvani[1], Mahin Izadi[4]

[1]Department of Physiology, School of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd; [2]Department of Physiology, Medical School, Shahid Beheshti University of Medical Sciences, Tehran; [3]Schools of Medicine, Kashan University of Medical Sciences, Kashan; [4]Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder that can cause infertility. This experimental study was conducted to elucidate the role of adiponectin signaling in rats with PCOS treated with exenatide. Twenty-eight adult female Wistar rats were divided into four groups of seven. The normal group did not receive any drug. The PCOS+vehicle (Veh) group received estradiol valerate to induce PCOS, then was divided into PCOS +E50 and PCOS+E100 groups and treated with 50 or 100 mg/kg doses of exenatide, respectively. The mRNA expression of adiponectin and adiponectin receptor 1 (Adipo-R1) was evaluated using a semi-quantitative real-time polymerase chain reaction. The results indicated that the level of adiponectin diminished in the PCOS rats while exenatide increased adiponectin expression at both doses. Adiponectin receptor mRNA levels were higher in the PCOS rats than in the normal rats (p<0.05). In addition, exenatide decreased the levels of Adipo-R1 expression. Taken together, our results showed that exenatide may improve PCOS characteristics in rats through the molecular regulation of adiponectin and its receptor.

Keywords: Adiponectin; Exenatide; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common multifaceted and intricate endocrine disorder that affects 5% to 10% of women of reproductive age and likely leads to infertility, hirsutism, menstrual irregularities, hyperandrogenism, and insulin resistance [1]. A previous study reported low levels of serum adiponectin in women with PCOS [2]. Adiponectin is a peptide secreted by fat cells, which regulates glucose levels, lipid metabolism, and insulin sensitivity through its anti-fibrotic and antioxidant effects [3]. There are two types of membrane receptors for adiponectin, including adiponectin receptor 1 (Adipo-R1) and adiponectin receptor 2 (Adipo-R2), which improve the metabolism of glucose [4]. The mRNA expression of Adipo-R1 is positively related to insulin, triglyceride, cholesterol [5], and testosterone [6] levels. It has been found that tissues treated with testosterone and estradiol increase the expression of these receptors [7]. An increase in adiponectin receptors has also been reported in PCOS [8]. To alleviate the metabolic complications of PCOS, an effective and accurate intervention should be considered. Exenatide is a synthetic glucagon-like peptide 1 (GLP-1) agonist [9]. Various GLP-1 analogs improve the menstrual cycle in women with PCOS [10]. The specific mechanism by which exenatide improves the complications of PCOS has yet to be determined. Therefore, this study investigated the impact of exenatide on the expression of mRNA levels in the ovarian adiponectin system in the rat model of PCOS.

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Corresponding author: **Mahin Izadi**
Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Tel: +98-9177521021 Fax: +98-89137-84891 E-mail: Mizadi890112@gmail.com

Co-corresponding author: **Mohammad Ebrahim Rezvani**
Department of Physiology, School of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran
Tel: +98-38203414 Fax: +98-38203414 E-mail: merezvani@gmail.com

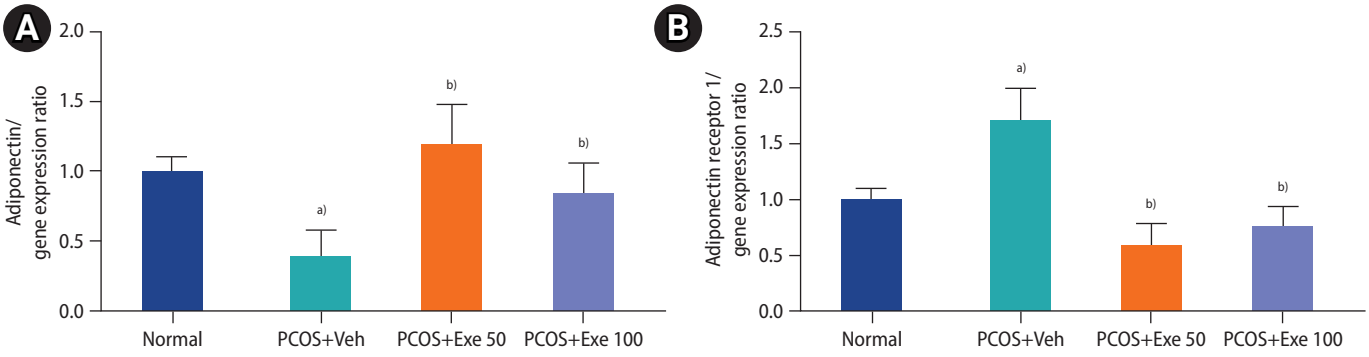

Figure 1. The effect of exenatide (Exe) on the mRNA levels of (A) adiponectin and (B) adiponectin receptor 1. Normal: no intervention; polycystic ovary syndrome (PCOS)+vehicle (Veh): PCOS rats; PCOS+Exe 50: PCOS rats received Exe at dose of 50 μg/kg; PCOS+Exe 100: PCOS rats received Exe at dose of 100 μg/kg. [a)]$p<0.05$: when compared to the normal group; [b)]$p<0.05$: when compared to PCOS group.

Methods

1. Animals

Twenty-eight Wistar female rats weighing 175 to 200 g were distributed into four groups. Seven rats per cage were maintained in the animal house at a temperature of 20±2 ℃, with 12/12 hours of light/dark conditions and free access to water and food. Ethical approval was received from the Animal Ethics Committee of the Yazd University of Medical Sciences (IR.SSU.medicine.REC.1394. 240).

According to accepted protocols, normal estrous cycles were identified and included in this study [11]. Estradiol valerate (4 mg/kg) (Aburaihan Pharmaceutical Co.) was injected intramuscularly in each rat [12]. Abnormal estrous cyclicity and disturbances in the cycle indicated the development of PCOS in the rats, as described in the study by Asadi et al. [13]. The rats in the normal group remained without intervention (control). Rats in the second group became polycystic and received the vehicle (PCOS+Veh). The groups 3 (PCOS+Exe 50) and 4 (PCOS+Exe 100) rats with PCOS received an intraperitoneal injection of exenatide at doses of 50 or 100 μg/kg, respectively, for 30 days.

Under anesthesia, the bilateral ovaries were removed and freshly frozen at −70 ℃ for molecular assays. Total RNA was extracted for the molecular assays (RNX-plus solution; CinnaGen). Next, cDNA was synthesized (Thermo Fisher Scientific Inc.) and the cDNA underwent real-time polymerase chain reaction using SYBR Green MasterMix (Takara Holdings Inc.). The ribosomal protein L13a gene was used as the reference. The relative comparison of gene expression was done with the $2^{-\Delta\Delta Ct}$ method. The obtained data were analyzed using one-way analysis of variance and Tukey's multiple comparison *post hoc* test. Statistical significance was set at $p<0.05$.

Results

1. Effects of exenatide on the mRNAs of adiponectin and Adipo-R1

Our results indicated that, in the PCOS+Veh group, the mRNA levels of adiponectin decreased significantly when compared with the normal group ($p<0.05$). In both exenatide-treated groups, the mRNA level of adiponectin was significantly higher than the PCOS+Veh group ($p<0.05$). The expression level of Adipo-R1 was also higher in the PCOS+Veh group than in the normal group ($p<0.05$). The expression level of Adipo-R1 decreased in the PCOS+E50 and PCOS+E100 groups when compared to the PCOS+Veh groups (Figure 1).

Discussion

In this study, the effects of different doses of exenatide on ovarian adiponectin system expression in a rat model of PCOS were investigated. Our study showed that both 50 and 100 μg/kg doses of exenatide significantly increased the mRNA expression of adiponectin and reduced the expression of Adipo-R1 in ovarian tissue. In line with our results, other studies revealed that exenatide can decrease the complications of PCOS [14,15]. However, the exact mechanism of exenatide on PCOS improvement is still not fully understood. According to the present study, exenatide probably exerts its protective effects by increasing adiponectin levels. In conclusion, this study revealed that adiponectin may play a partial but important role in the effect of exenatide on improving PCOS.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Asma Vatankhah https://orcid.org/0000-0002-3383-0049
Mohammad Ebrahim Rezvani https://orcid.org/0000-0001-6146-806X
Mahin Izadi https://orcid.org/0000-0002-7907-6168

Author contributions

Conceptualization: MER, MI. Methodology: AV, MER, MI. Formal analysis: MER. Data curation: MER. Funding acquisition: AV. Project administration: MER, MI. Visualization: MER, MI. Software: MER, MI. Validation: MER, MI. Investigation: AV. Writing-original draft: AV, MJ. Writing-review & editing: MER, MI. Approval of final manuscript: AV, MJ, SV, KL, MER, MI.

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