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Response of Protein Disulfide Isomerase A1 Expression of Cardiac Myocytes to High- and Moderate-Intensity Exercise Training and Alpha-Lipoic Acid in Hypertensive Rats

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ABSTRACT

Background and objectives: Hypertension is associated with vascular remodeling, which is supported by the protein disulfide isomerase A1 (PDIA1). Exercise training has beneficial effects on vascular function in subjects with hypertension. Alpha lipoic acid (ALA) is a powerful biological antioxidant. However, the role of exercise training and ALA on PDIA1 are not well understood. The aim of the present study was to investigate effects of training with different intensities and ALA supplementation on PDIA1 expression in cardiomyocytes of hypertensive rats.

Methods: In this experimental study, 35 male Wistar rats (age: eight weeks, weight: 190-220 g) were randomly divided into seven groups: control, hypertensive, hypertensive+ALA, hypertensive+high intensity interval training (HIIT), hypertensive+moderate-intensity training (MIT), hypertensive+HIIT+ALA, and hypertensive+MIT+ALA. Hypertension was induced by three weeks of L-NAME administration (40 mg/kg/day). The HIIT and MIT protocols was performed five days a week for six weeks. The HIIT protocol consisted of 10 bouts of four minute-running at 80–85% of Vmax, and the MIT protocol consisted of 13 bouts of four minute-running at 55–60% of Vmax. In the supplementation groups, 20 mg/kg of ALA was administered orally once a day. Immunohistochemistry staining was used to study protein expression.

Results: Induction of hypertension significantly decreased PDIA1 expression compared to the control group (p=0.001). Moreover, PDIA1 expression increased significantly in the hypertensive+ALA (p=0.023), HIIT (p=0.001), MIT (p=0.007), MIT+ hypertensive+ALA (p=0.0001) and HIIT+ hypertensive+ALA (p=0.0001) group compared to the control group.

Conclusion: Hypertension is associated with decreased cardiac PDIA1 level, and both HIIT and MIT along with ALA supplementation are effective in increasing cardiac PDIA1 expression in hypertension.

Keywords: Exercise, alpha-lipoic acid, hypertension.

INTRODUCTION

Hypertension is associated with oxidative stress, endothelial dysfunction, and increased vascular resistance, representing probably both a cause and a consequence of elevated levels of reactive oxygen species (ROS) and nitrogen species. In metabolic perturbation, increased ROS generation might trigger endothelial cells (ECs) dysfunction, possibly contributing to the development of hypertension (1). Mitochondrial dysfunction, preceding endothelial dysfunction, might favor the development of hypertension. Endothelial mitochondria serve as a pivotal sensor of the local environment and transduce damage signals, which leads to mitochondria damage, endothelial dysfunction, vascular remodeling, and vascular diseases (2). Vascular remodeling is a crucial mechanism of vascular caliber regulation in physiological and pathological conditions. Recently, Laurindo et al. (2018) showed that expansive vascular remodeling is supported by the extracellular pool of protein disulfide isomerase A1 (PDIA1) (3). This enzyme was the first PDI family member to be discovered and is a 57 kDa oxidoreductase and molecular chaperone that localizes in the lumen of the endoplasmic reticulum (ER) and accounts for roughly 0.8% of total cellular protein (4). The dysregulation of PDIA1 activity has been implicated in various diseases, including cancer, cardiovascular disease, and neurodegenerative disease. Extracellular PDIA1 is involved in many biological processes, such as platelet activation, thrombus formation, and viral infection (5).

Regular exercise is a well-established intervention for the prevention and treatment of several chronic diseases, including hypertension (6). Continuous moderate-intensity exercise training (MIT) that can be sustained for 30 minutes or more has been traditionally recommended for hypertension prevention and treatment (7). Recently, high intensity interval training (HIIT) has attracted considerable attention in the clinical context as an alternative to MIT. This type of training exerts a greater impact on various aspects of health, reducing the risk of cardiovascular diseases. Emerging research has indicated that HIIT is capable of stimulating changes in many physiological and health markers to a similar or even higher extent to MIT (8). The decrease in sympathetic nervous system activity, effects on baroreflex control, and improvement in nitric oxide production and action (endothelial function) are probably involved in the anti-hypertensive effects of HIIT. Moreover, effects on arterial remodeling, angiogenesis, and arterial distensibility might be related to the blood pressure decline after aerobic exercise training (9).

In addition to exercise interventions, the use of nutritional interventions is effective in controlling hypertension. As an antioxidant, alpha lipoic acid (ALA) is able to scavenge ROS, chelate transition metals (iron and copper), or regenerate reduced forms of some antioxidants (vitamin E, vitamin C, and glutathione), thereby preserving the endogenous reduced state and neutralizing oxidative stress (10). Previous studies have shown that ALA prevents development of hypertension, increased heart mitochondrial superoxide anion production, and hypotensive effects of insulin resistance in chronically glucose-fed rats (11). Moreover, ALA supplementation has a hypotensive effect in addition to its antioxidant effect (12).

Although exercise plays a pivotal role in the primary prevention, treatment, and control of hypertension, the optimal frequency, intensity, time, and type of exercise to modulate its signaling pathways are still unclear. In the present study, the effects of ALA consumption, HIIT and MIT, and their interactive effects on the expression of PDIA1, as special pathways in maintaining vascular remodeling and mitochondrial dynamics were examined in hypertensive rats. To the best of our knowledge, this study is the first to evaluate effects of the mentioned variables on PDIA1 expression in cardiac tissue of hypertensive rats.

MATERIALS AND METHODS

This experimental study was approved by the animal care and use committee at the Islamic Azad University of Sari, Iran. All animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals". Thirty-five male Wistar rats were purchased from the Pasteur Institute of Iran (Tehran, Iran). At first, five rats were separated as healthy control group (CON). To induce hypertension, the animals received L-Nitro-Arginine Methyl Ester (L-NAME) (40

mg/kg/day, orally) for three weeks. Blood pressure was measured by the tail-cuff method in all groups using the LE5001 non-invasive blood pressure meter (PANLAB, Spain). The animals were placed in a restrainer and allowed to rest for 10–15 minutes prior to blood pressure measurement. The tail was placed inside the cuff, which was automatically inflated and released, and systolic blood pressure values were obtained from the mean of three measurements (13). The rats in the L-NAME-treated group were fed with a standard diet (10% fat, 70% carbohydrate, 20% protein) and L-NAME in their drinking water, whereas rats in the control group were fed with a standard diet and distilled water (14). Rats in the L-NAME-treated group were randomly assigned into six subgroups: hypertensive (H), hypertensive+ALA (S), hypertensive HIIT, hypertensive MIT, hypertensive HIIT+ALA (HIIT+S), hypertensive MIT +ALA (MIT+S).

Prior to training, the rats become familiar with running on treadmill (at a speed of 10 m/min, and 0 inclination for 5 min/day). The HIIT and MIT protocols were performed five days a week for six weeks. For the HIIT protocol, the rats performed exercise sessions in 10 bouts of four-minute high intensity running on treadmill (80–85% of Vmax), alternating with two minutes of active recovery (running at 40–50% of Vmax). The MIT exercise protocol consisted of 13 bouts of four-minute moderate intensity running on treadmill (55–60% of Vmax), alternating with two minutes of active recovery (running at 40–50% of Vmax). No electric shock was used during the trainings. In the immobile condition on the treadmill, low tail pressure stimulated rats to run (14).

Within six weeks of the main experiment, the rats from the ALA, HIIT+ALA, and MIT+ALA groups were treated with 20 mg/kg of ALA (Neurolipon-MIP 600, MIP-Pharma Polska, Poland,) suspended in methylcellulose by oral gavage, once a day and one hour after exercise (15). After 24 hours of rest and six to eight hours of fasting to prevent the acute effects of exercise, the rats were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg) (15). Heart tissues were removed immediately after sacrifice, after which excessive blood content of heart tissues were eliminated using cold saline solution. The obtained heart tissues were then pulverized into a powder under liquid nitrogen, and stored at -80 °C for future use. For immunohistochemical measurements, the heart tissues were fixed in 10% neutral-buffered formalin and embedded in paraffin wax. The paraffin-embedded tissue sections (4 µm each) were deparaffinized, rehydrated, and subjected to hematoxylin and eosin staining. Immunohistochemistry was performed on formalin fixed, paraffin-embedded heart tissues. The sections were then incubated with primary antibodies (dilution 1:100, Santa Cruz Biotechnology) overnight at 4 °C, followed by incubation with secondary antibodies at room temperature for two hours. The immunoreactivity was visualized with diaminobenzidine staining (Vector Laboratories, Burlingame, CA, USA), and then counterstained with Mayer's hematoxylin (Vector Laboratories). The histopathological findings were observed using light microscopy (X400; Olympus IX51, Tokyo, Japan).

Data were expressed as mean value ± standard deviation (SD). The Shapiro–Wilk test was used to test for the normality of data. One-way analysis of variance (ANOVA) with the Tukey's post hoc test were used to analyze data. Statistical significance level was set to 0.05.

RESULTS

The level of PDIA1 in the hypertensive group was significantly reduced compared to the control group (p=0.0001). In other words, induction of hypertension with L-NAME altered the level of PDIA1 expression in hypertensive rats.

The levels PDIA1 in the ALA group were significantly higher than in the hypertensive group (p=0.023). Compared with the hypertensive group, the levels of PDIA1 was significantly higher in the HIIT (p=0.001), MIT (p=0.007), HIIT+S (p=0.001), and MIT+S (p=0.001) groups. Moreover, PDIA1 expression in the HIIT+S and MIT+S groups were significantly higher than in the HIIT (p=0.029, p=0.044, respectively) and MIT (p=0.008, p=0.001, respectively) group, indicating the synergistic effect of exercise training and ALA supplementation (Figure 1).

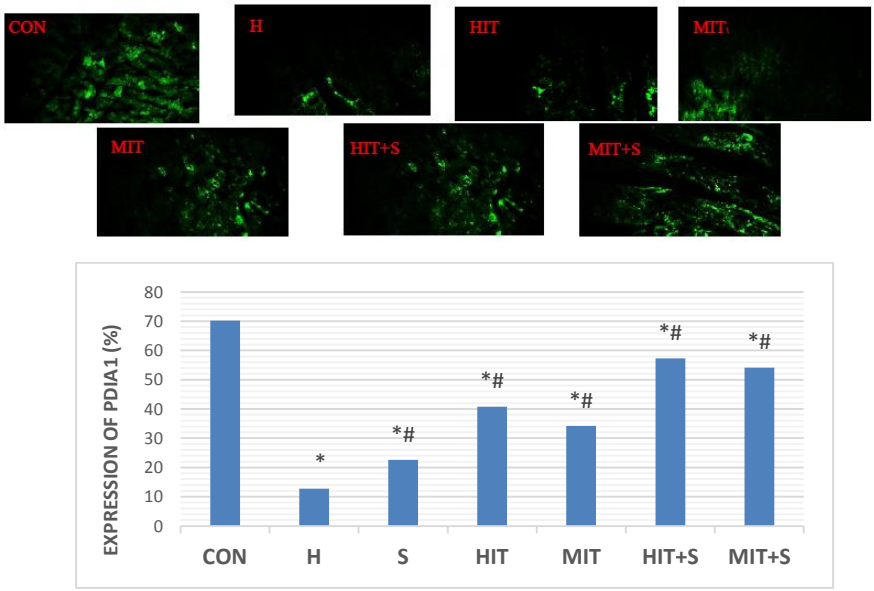

Figure 1- Expression of PDIA1 in the cardiac tissues of rats in different study groups. (A) Immunohistochemistry analysis of PDIA1 expression in the cardiac tissue of control and hypertension rats, where representative photomicrographs are shown and sections were counter-stained with haematoxylin (images were taken under X400 magnification and scale bar represents 50 µm). Green areas represent PDIA1 expression. (B) Level of PDIA1 expression in the cardiac tissue of rats in the study groups. Data are presented as mean ± standard error of the mean. CON: control, H: hypertensive, S: hypertensive+supplement, HIT: hypertensive+ high intensity training, MIT: hypertensive+ moderate intensity training, HIT+S: hypertensive+supplement+ high intensity training, MIT+S: hypertensive+supplement+ moderate intensity training. *indicates significant difference compared to the CON group. # indicates significant difference compared to the H group.

DISCUSSION

Given the important role of PDIA1 in the vascular remodeling pathway and development of hypertension, this study primarily examined the interactive effects of HIIT and MIT along with ALA supplementation on the expression of cardiac PDIA1. We believe that the results of this study can ultimately help establish a new approach for the treatment of hypertension.

Based on the findings, hypertension resulted in a significant decrease in cardiac PDIA1 level. An approach reveals that endogenous PDIA1 redox activity is required to protect against EC senescence. Because PDIs are known to facilitate the proper folding of nascent proteins in the ER (16), it is generally assumed that PDIs prevent ER stress in various diseases, such as neurodegenerative disease. Consistent with our result, Kim et al. (2018) found that PDIA1 depletion promotes EC dysfunction, including EC senescence or impaired endothelium-dependent vasodilation or angiogenesis without inducing ER stress (17).

Evidence suggests that ALA increases intracellular GSH levels by the ability to continuously supply cysteine for its formation (22). In the present study, ALA supplementation also affected the activity of antioxidant enzymes. Decreased superoxide dismutase (SOD) levels have generally been observed in hypertension, possibly due to inactivation by ROS (23). Therefore, it is likely that ALA was able to restore SOD activity through its direct ROS scavenging function. Similar effect of ALA has been reported in kidney of salt-induced hypertensive rats (24). In addition, ALA also reduced the increased renal GPx activity in hypertensive rats at 16 weeks and 28 weeks when compared to age-matched non-ALA supplemented rats. This reduction could be due to decrease of H_2O_2 levels and probably a normalization of antioxidant enzymes that were elevated earlier, as a compensatory mechanism to overcome metabolic changes in hypertension.

The results of this study indicated that HIIT and MIT can significantly increase PDIA1 expression in cardiac tissue. Exercise training impedes and delays the development of

mitochondrial dysfunction by improving mitochondrial metabolism, biogenesis, mitophagy, mitochondrial dynamics, anti-apoptotic signaling, and mitochondrial quality control (25). Kim et al. (2018) provided evidence that PDIA1 functions as a thiol reductase for DRP1 in ECs, thereby maintaining normal mitochondrial dynamics and endothelial function. Unexpectedly, loss of PDIA1 in ECs induces mitochondrial fragmentation and mtROS elevation without ER stress by increasing DRP1 activity, which drives EC senescence and impairs endothelium-dependent vasorelaxation and angiogenesis (17). Recently, a study showed that exercise training improved the imbalance between mitochondrial fission and fusion in obesity through an overexpression of mitofusin and optic atrophy 1 in order to enhance the mitochondrial fusion process and to reduce or maintain the levels of mitochondrial fission proteins (26). It has been also shown that exercise inhibits the reduction of the MFN2/DRP1 ratio in the heart tissue of mice and reduces cytochrome C leakage (27). Ebadi and Damirchi (2018) reported that the levels of MFN2 and peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α proteins increased and DRP1 decreased significantly after MIIT compared to sedentary subjects with myocardial infarction. It was concluded that MIIT improved the mitochondrial fission and fusion in rats with myocardial infarction. The mentioned study also reported that HIIT could induce a slight increase in MFN2 and PGC-1 and a decrease in DRP1 (28).

It is known that exercise training increases the expression of potentially atheroprotective vascular proteins, such as endothelial nitric oxide synthase, extracellular SOD (SOD3), Co/Zn-SOD (SOD1), and angiotensin receptor type II (29), and downregulates potentially atherogenic vascular proteins such as subunits of endothelial and vascular smooth muscle nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and angiotensin receptor type I (30,31). Mechanical forces activate many intracellular pathways including mitogen-activated protein kinase kinase (MAPK) and induce sequential phosphorylation of activating transcription factors and gene expression. Such mechanotransduction mechanisms are mediated by integrins (32), which are known to mediate cell adhesion and cell migration by binding to extracellular matrix proteins (33,34). Integrins are among the best-characterized PDIA1 targets (16). It is known that PDIA1, as well as Erp57 (PDIA3) and Erp5 (PDIA6), all reported in platelets, EC, and the vessel wall, can exert thiol reductase effects, which contributes to integrin transition from the extended moderate affinity to the extended high-affinity conformation, subsequently enhancing thrombus formation (16).

Furlan-Freguia et al. (2011) reported that PDIA1 sustains integrin-1 expression and thiol reduction during post-injury arterial repair (35).

Transduction of signals mediated by shear stress-induced activation of integrins include phosphorylation of kinases, such as focal adhesion kinase, c-Src, Akt kinase, phosphatidylinositol 3-kinase, myosin light chain kinase, and MAPKs such as extracellular signal-regulated kinase. These molecular mechanisms result in shear stress-induced upregulation of genes mediating anti-atherogenic effects by promoting anti-apoptotic and anti-proliferative signals, and increasing vascular nitric oxide bioavailability (35).

The lack of calorie control the study groups, different responses to L-NAME in rats, and the lack of ROS measurement and arterial stiffness are some limitations of the present study.

CONCLUSION

Overall, the results indicated the negative effects of hypertension on down-regulated PDIA1 expression. It seems that interval exercise with different intensities, particularly MIT, along with ALA supplementation results in the improvement and regeneration of mitochondrial function by increasing PDIA1 expression in hypertensive rats.

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DECLARATIONS

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Ethics approvals and consent to participate

This study was approved by the Ethics Committee of the Medical Sciences Faculty of Sari Islamic Azad University, Iran (ethical code: IR.IAU.SARI.REC.1399.124).

Conflict of interest

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

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