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Association of Neuregulin-1β with Physiological Cardiac Hypertrophy Following Acute and Chronic Exercise in Athlete and Non-Athlete Women

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Abstract—Neuregulin-1β (NRG-1β) is associated with cardiomyocyte proliferation and cardioprotection. Therefore, in the present study, the effect of acute and chronic exercise on plasma levels of NRG-1β and its association with cardiac hypertrophy in athlete and non-athlete women was investigated. Eighteen sedentary and 18 athlete women performed the Bruce test on a treadmill (acute) and 12 thrice-weekly sessions of water aerobic exercise (chronic). Plasma levels of NRG-1β were measured in all participants before and immediately after acute exercise, as well as, 24h and 72h after chronic exercise using ELISA kit. Moreover, echocardiographic parameters were analyzed before and after the exercise. The athletes had higher man levels of left ventricular end-diastolic diameter index (LVEDDI) and left ventricular mass index (LVMI) compared to the non-athletes before exercise. Moreover, 12-week exercise could significantly increase LVEDDI levels only in the non-athlete group. Plasma levels of NRG-1β were significantly higher in athletes than non-athletes. We found that chronic but not acute exercise could significantly increase levels of NRG-1β in both groups. The levels of NRG-1β were significantly lower three days after chronic exercise in comparison with 24h post-exercise in the non-athlete group. Plasma levels of NRG-1β had positive correlations with LVEDDI and LVMI in both groups. In conclusion, this study showed that chronic exercise could increase plasma levels of NRG-1β. Furthermore, the positive correlation between NRG-1β levels and cardiac hypertrophy indices suggests a role for NRG-1 in exercise-induced hypertrophy.

Keywords: Exercise, cardiac hypertrophy, physical activity, Neuregulin

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Physiological cardiac hypertrophy is associated with normal or even improved function of the heart that may occur in conditions such as postnatal growth, exercise, and pregnancy. In contrast, volume overload or long-term pressure in response to cardiac injury can result in pathological hypertrophy [1]. Although both types of hypertrophy accompany increased heart size, only the pathological hypertrophy is associated with cardiac dysfunction [2]. Due to the role of physiological hypertrophy in lowering the risk of pathological heart growth, increasing knowledge regarding exercise-induced hypertrophy may be of great importance.

Neuregulins (NRG) belongs to the epidermal growth factors (EGF) family and its isoforms are encoded by four genes (NRG-1 to -4). The expression of NRG-1 has been reported in various tissues, including the nervous and cardiovascular system, intestine, kidney, mammary glands, and skeletal muscles [3, 4]. However, the NRG-1 is dominantly expressed in the heart and it has been reported that the NRG-1 in the blood is mostly secreted from the cardiac tissue [5–7]. Although the expression of NRG-1 has been observed in skeletal muscles [8], its secretion to the blood from this tissue has not been addressed yet. Moreover, it has been indicated that progressive resistance training could not increase the expression of NRG-1 in skeletal muscles [9]. In the adult human heart, the expression of NRG-1 isoforms has been detected in the cardiac endothelial cells, while no expression has been observed in the myocytes [10, 11]. However, the expression of NRG-1 has been reported

in cardiomyocytes of rats [12]. The inter-species variations may explain the apparent discrepancy. The cardiac endothelial cells express NRG-1 that interacts with its receptors (ErbB3 and ErbB4) on cardiomyocytes and triggers the downstream signaling [13–15]. The role of NRG-1/ErbB signaling has been demonstrated in various cardiac functions, including cardiac development [16], angiogenic support or adaptation to stress, and cardioprotection [14]. Furthermore, NRG-1 may affect response to cardiac regeneration as a cardiomyocyte mitogen in the adult heart [16]. One essential role for NRG-1 is in mediating remodeling and myocardial hypertrophy following pressure overload [17, 18]. NRG-1 has two isoforms α and β, which type β has the most biological activity [19]. It has also been shown that administration of NRG-1β in rats with myocardial infarction could induce the growth and proliferation of cardiac cells [20]. NRG-1β can also prevent apoptosis of cardiac cells and induce angiogenesis after a heart attack [21, 22]. Given the role of NRG-1 in cardiac development, it can be postulated that this factor is involved in physiological hypertrophy. In this regard, it has been demonstrated that exercise-induced NRG-1 improved cardiomyocyte growth [23]. Moreover, in an animal study, it has been reported that high-intensity exercise induced NRG-1 expression in cardiomyocytes of rats [12].

Given the stimulatory effect of exercise on NRG-1 expression in the cardiomyocytes of animal models [12] and also the association of NRG-1 with cardiac development, we aimed to evaluate the effects of acute and chronic exercise on plasma levels of NRG-1β and its association with cardiac hypertrophy in athlete and non-athlete women.

METHODS

Subjects and study design. Eighteen sedentary and 18 athlete women with a mean age of respectively 34 ± 6 and 36 ± 7 years were recruited to the study. It should be mentioned that the samples of 10 non-athlete and 8 athlete women were obtained from our previous published study [24]. The written informed consent was obtained from all participants prior to the research and the study process was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and all the procedure was approved by the Ethical Committee of Urmia University.

Sedentary women had no specific physical activity and individuals in the athlete group were professional runners regularly exercise at least five two-hour sessions per week. Moreover, all participants were of reproductive age with no history of smoking, diabetes, cardiovascular, liver, thyroid, and kidney diseases.

Exercise protocol. To predict VO2 max, the graded exercise test, Bruce protocol on a treadmill, was used. In brief, the test consists of several 3-min stages, where the speed (starting at 2.7 km/h and gradually continuing as follows: 4, 5.5, 6.8, 8, and 8.9) and grade (start from 10% and gradually increase as follows: 12, 14, 16, 18, and 20%) are increased progressively and the heart rate is measured each minute. The VO2 max can be calculated as follow: where the "T" is the total time completed (expressed in minutes and fractions of a minute) VO2 max (mL/kg/min) = 14.76 – (1.379 × T) + (0.451 × T2) – (0.012 × T3). The venous blood samples before and after the test were taken from participants and stored at –80°C until analysis. For the chronic exercise (B), both groups underwent a total of 12 thrice-weekly sessions of water aerobic exercise. It initiated with 60% of participants' maximum heart rate (MHR) during a 30-min exercise session, then the duration of sessions increased up to 60 min until reaching the intensity of 70–80% MHR. To minimize the effect of acute exercise, blood sampling was done on the following day of the last session and also 72 hours after that for evaluating long term effects.

Echocardiographic parameters. Echocardiographic parameters were analyzed before and after entering the training program. Standard transthoracic echocardiography using the ultrasound equipment Contron Sigma Iris (Contron Medical, Pans France Instrument) with a 2.5-MHz probe was performed. The following parameters were evaluated in the present study: heartbeat, posterior wall thickness (PWT), relative wall thickness (RWT), septal thickness, left ventricular end-diastolic diameter index (LVEDDI), left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF), and end-systolic stress (ESS). RWT = (2 × PWT)/LVIDD formula was used for calculation of RWT in which LVIDD is the left ventricular internal diastolic dimension [25]. The M-mode was used for measurement of left and right ventricular dimension in diastole and thickness of posterior wall. Moreover, LVMI, LVEF, and ESS were calculated according to previously published methods of Devereux, Simpson, and Reichek, respectively [26–28].

Hormonal analysis. A commercially available enzyme-linked immunosorbent assay (ELISA) kit (EHNRG1, Thermo Fisher Scientific, MA, USA) was used to measure human NRG-1β levels in plasma according to the manufacturer's protocol. The detection range of the kit for NRG-1β was 82.3–20000 pg/mL with a sensitivity of 50 pg/mL. The intra- and inter-assay precision were <10 and <12%, respectively.

Statistical analysis. The SPSS V.25 software was used for analyzing data. After confirmation of the data normal distribution by Kolmogorov-Smirnov test, Independent-samples *t*-test was used to compare the values between two groups. Levene's test confirmed homoscedasticity of variances and two-way ANOVA was used to evaluate the interaction between groups and sampling times points. We used the Pearson test for evaluating the correlation between cardiac hyper-

Table 1. Echocardiogram Parameters before and after a 12-week Aerobic Exercise in Non-Athlete and Athlete Women

	Non-athlete ($n = 18$)		Athlete ($n = 18$)	
	before	after	before	after
Septal thickness, mm	7.9 ± 1.5	8.1 ± 1.0	8.2 ± 1.3	8.3 ± 0.8
Posterior wall thickness, mm	8.3 ± 1.0	8.2 ± 1.2	8.9 ± 1.1	9.1 ± 1.3
RWT, %	38.2 ± 6.9	39.1 ± 7.7	40.0 ± 8.2	40.9 ± 7.4
LVEDDI, mm/m^2	23.6 ± 3.4	26.6 ± 4.7†	27.8 ± 4.3*	28.0 ± 4.5
LVMI, g/m^2	73.4 ± 7.1	75.8 ± 7.9	83.9 ± 8.3*	84.2 ± 9.1*
ESS, kdyne/cm^2	66.0 ± 8.0	67.0 ± 5.0	69.0 ± 8.0	71.0 ± 9.0
LVEF, %	60.2 ± 11.0	63.1 ± 10.7	64.6 ± 9.1	66.0 ± 12.1

RWT: Relative wall thickness; LVEDDI: left ventricular end-diastolic diameter index; LVMI: left ventricular mass index; ESS: end-systolic stress; LVEF: left ventricular ejection fraction. Data are shown as Mean ± SD. *—Significant difference ($p < 0.05$) between the Non-athlete and athlete groups. †—Significant difference ($p < 0.05$) between before and after exercise at the same group.

Table 2. Correlation between Plasma Levels of Neuregulin-1β and Echocardiogram Parameters in Non-Athlete and Athlete Women

		Septal thickness	Posterior wall thickness	RWT	LVEDDI	LVMI	ESS	LVEF
Neuregulin-1β	Non-athletes ($n = 12$)	$r = 0.09$ $p = 0.701$	$r = 0.19$ $p = 0.430$	$r = -0.22$ $p = 0.603$	**$r = 0.58$ $p = 0.031$**	**$r = 0.41$ $p = 0.047$**	$r = -0.28$ $p = 0.704$	$r = 0.28$ $p = 0.175$
	Athletes ($n = 12$)	$r = 0.11$ $p = 0.642$	$r = 0.22$ $p = 0.174$	$r = -0.09$ $p = 0.769$	**$r = 0.62$ $p = 0.018$**	**$r = 0.52$ $p = 0.029$**	$r = -0.15$ $p = 0.522$	**$r = 0.48$ $p = 0.043$**

r: Pearson-Rho; RWT: Relative wall thickness; LVEDDI: left ventricular end-diastolic diameter index; LVMI: left ventricular mass index; ESS: end-systolic stress; LVEF: left ventricular ejection fraction. The number in bold indicates the presence of a significant correlation.

trophy indices and NRG-1 levels. A *p*-value lower than 0.05 was considered significant.

RESULTS

There was no significant difference between the non-athlete and athlete groups in body mass index (26.1 ± 4.6 vs. 23.8 ± 4.9 kg/m^2) and body surface area (1.82 ± 0.40 vs. 1.68 ± 0.62 m^2). Furthermore, the fitness level as assessed by maximal oxygen uptake (VO2 max) was 53 ± 1.2 mL/kg/min in the athlete group vs. 31 ± 4.2 in the non-athlete group. We found that athletes had higher mean levels of LVEDDI and LVMI compared to the non-athletes before exercise. Moreover, our results demonstrated that 12-week exercise could significantly increase LVEDDI levels only in the non-athlete group (Table 1).

Mean plasma levels of NRG-1β were 1149.1 ± 192.9 and 2850.8 ± 566.4 pg/mL in non-athlete and athlete groups, respectively; showing a significant difference between the groups. We found that chronic but not acute exercise could significantly increase levels of plasma NRG-1β in both athletes and non-athletes ($p < 0.05$). Interestingly, the positive effect of chronic exercise on NRG-1β remained after three days as we observed significantly higher levels of NRG-1β three days after the exercise compared to the baseline levels in both groups ($p < 0.05$). However, the plasma levels of NRG-1β were significantly lower three days after chronic exercise in comparison with 24h post-exercise in the non-athlete group ($p < 0.05$, Fig. 1).

Plasma levels of NRG-1β had positive correlations with LVEDDI and LVMI in non-athlete and athlete groups. Moreover, LVEF was significantly correlated with plasma levels of NRG-1β in athletes (Table 2).

DISCUSSION

NRG-1/ErbB signaling is involved in various cardiac functions, including hypertrophic growth, cardiomyocyte proliferation, and cardioprotection [14]. There is growing evidence in support of the inducing effects of NRG-1 on cardiomyocyte proliferation [29, 30]. However, the association of NRG-1β with exercise-induced cardiac hypertrophy is not clearly understood. Therefore, in the present study, we evaluated the effects of acute and chronic exercise on plasma NRG-1β (the most active isoform of NRG-1) levels in athletes and sedentary women. Besides, the possible association of this peptide with cardiac hypertrophy indices was investigated.

Our results showed that baseline levels of plasma NRG-1β were higher in the athletes compared to the controls, showing that regular exercise may increase

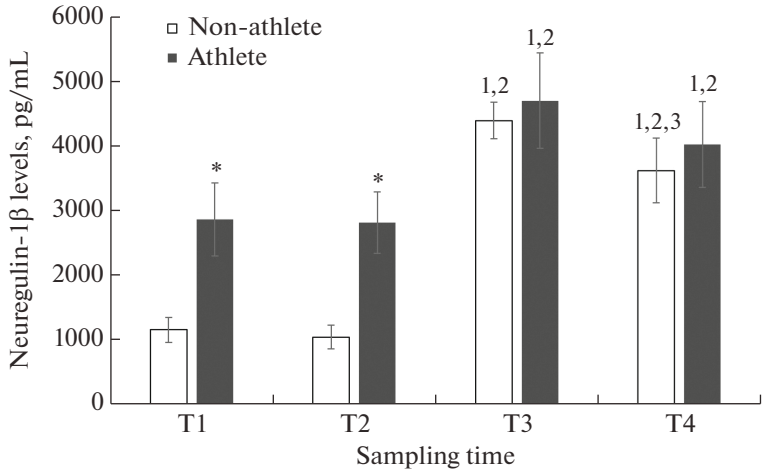

Fig. 1. Plasma levels of Neuregulin-1β following acute and chronic exercises in non-athlete ($n = 18$) and athlete ($n = 18$) women. Data are shown as Mean ± SD; Levene's test confirmed homoscedasticity of variances and two-way ANOVA was used to evaluate the interaction between groups and sampling time points; Significant difference ($p < 0.05$) in comparison with [1] T1 (Before exercise), [2] T2 (Immediately after acute exercise), and [3] T3 (24 h after a 12-weeks chronic exercise) in the same group. T4: Three days after a 12-weeks chronic exercise. *—Significant difference in comparison with the non-athlete group on the same time course.

NRG-1β synthesis and secretion to support cardiac function. In supporting this hypothesis, we also found that the levels of NRG-1β significantly increased after the 12-weeks exercise in both athletes and non-athletes. Interestingly, we could not observe a statistically significant difference in plasma levels of NRG-1β between two groups after the chronic exercise. This finding may suggest one of the possible mechanisms through which exercise supports cardiac function and development even during almost short term (12 weeks) is NRG-1β/ErbB signaling pathway; however, further in vivo and in vitro studies about the effect of NRG-1β on cardiac cells and functions are required to confirm this hypothesis. In accordance with the present study, animal studies have demonstrated that exercise training could up-regulate the expression of NRG-1 in the heart tissue [12, 30]. Moreover, it has been shown that one week of high-intensity exercise increased NRG-1 in rat cardiomyocytes [12]. The positive effect of chronic resistance training on the expression of NRG-1 in cardiac muscles has also been observed in rats [31]. Cai et al. [30] have also reported that four weeks of moderate-intensity exercise could induce the expression of NRG-1 protein in the cardiac tissue of rats with myocardial infarction. In contrast, Lebrasseur et al. [9] found no significant change in NRG-1 expression following 8 weeks of progressive resistance training in human skeletal muscles [9]. This controversy could be attributed to the differences in the duration and intensity of the chronic exercise and also the differences in the evaluated tissues. It can be hypothesized that chronic exercise may induce NRG-1 production more quickly and potently in heart muscles rather than skeletal muscles. However, further studies are required to clarify the underlying reason. Since the levels of NRG-1β decreased three days after the chronic exercise in non-athletes, although were still higher than baseline, it can be postulated that the stimulatory effect of exercise on NRG-1 production is not long-lasting. This finding suggests the importance of regular physical activity during daily lives for improving cardiac function.

Our results showed that acute exercise could not significantly affect the levels of plasma NRG-1β in either athletes and non-athletes. This finding is consistent with those of Moondra et al. [32], who found no significant change in serum levels of NRG-1 following acute exercise in healthy men. In contrast, NRG-1 cleavage and activation of ErbB receptors in muscles after a single bout of acute exercise have been reported by other studies [9, 33]. Such a controversial effect of acute exercise on NRG-1 could be due to the difference in the samples that were evaluated since the acute exercise effect can be quickly observed in muscles than in blood [9, 33]. It may be assumed that NRG-1 which is activated by acute training in muscles needs more time for releasing into the circulation [32].

In the current study, we found higher LVEDDI and LVMI in athletes compared to the controls, demonstrating mild levels of cardiac hypertrophy in athletes. However, LVEDDI significantly increased after 12 weeks of chronic exercise in non-athlete women and there was no significant difference in LVEDDI levels between the groups at the end of the course. These results support the previous finding of the association between physical activity with left ventricular mass and cardiac hypertrophy [34]. Based on our results regarding the increased levels of NRG-1β following chronic exercise in non-athletes, it may be suggested that the increase in LVEDDI could be a conse-

quence of NRG-1 production; however, a direct effect of NRG-1β on cardiac functions, particularly LVEDDI, needs to be evaluated in future studies. The stimulatory effect of exercise on NRG-1 signaling may serve as an adaptive mechanism that accompanies cardiac differentiation, regeneration, proliferation, and inducing hypertrophic markers, such as Brain Natriuretic Peptide (BNP) [10, 16, 30]. Therefore, NRG-1 can be associated with cardiac parameters. In this regard, we found that NRG-1β was positively correlated with LVEDDI and LVMI. These findings are in agreement with the previously described role of NRG-1 in remodeling and myocardial hypertrophy [35]. Moreover, we found a positive correlation between LVEF and plasma levels of NRG-1β in athletes. Parry et al. [13] also reported that the administration of NRG-1 improved LVEF and some other functional and morphological parameters of the left ventricle in rats with myocardial infarction. In contrast, another group of researchers stated that NRG-1 does not induce cardiac hypertrophy [36]. Given the almost small sample size of our study and the impossibility of histological studies due to the human nature of the study, further human studies with larger sample size and also animal studies with histological analysis following different type of exercise are required to clarify the role of NRG-1 in exercise-mediated cardiac hyperthrophy.

CONCLUSIONS

In conclusion, the present study was determined the effect of acute and chronic exercise on plasma level of NRG-1β and its possible association with cardiac hypertrophy in athlete and non-athlete women. This study showed that chronic exercise could increase plasma levels of NRG-1β in both groups. Furthermore, the positive correlation between NRG-1β levels and cardiac hypertrophy indices suggests a possible role for NRG-1 in exercise-induced hypertrophy. However, further research regarding the role of NRG-1 in cardiovascular function during exercise would be worthwhile.

COMPLIANCE WITH ETHICAL STANDARDS

Before the initiation of the study, all participants received an explanation of the procedure and the risks that would later be faced in their participation and they provided informed consent to participate in this study. All procedures were in accordance with the Declaration of Helsinki.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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