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Evaluation of CITED4 Gene Expression in the Cardiac Muscle of Male Rats as a Result of Resistance Exercise and Spirulina Supplement

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Abstract

***Background and Objective*:** Effects of resistance training and herbal supplements on cardiac signaling pathways are sparsely reported in the literature. This study aimed to evaluate the CITED4 gene expression in the cardiac muscle of male rats as a result of resistance exercise and spirulina supplementation.

Material and Methods: Thirty-two rats (male - Sprague Dally) were grouped into 4 groups (1. resistance training: RE, 2. spirulina + resistance training: SP +RE, 3. spirulina platensis: SP, 4. control: Co, n = 8). The training program was performed for healthy training groups 5 sessions per week for 8 weeks. Supplementation included 200 mg/kg/ day of Spirulina for the supplement groups. Real-time PCR was used to measure gene expression. We used of Two-way ANOVA in SPSS ($p<0.05$).

Results: In comparison with the control group, we observed a significant increase in CITED4 gene expression in RE (P= 0.001) and RE+SP (P= 0.001) groups. Also, there was a significant difference in CEBP gene expression between CO with RE (P= 0.001), SP (P= 0.034), RE+SP (P= 0.001) groups.

Conclusion: Spirulina supplementation alone has no effect on the signaling pathway of cardiac hypertrophy. However, if used concomitantly with resistance training, it can affect the signal pathway of cardiac hypertrophy.

Keywords: CITED4[MeSH], hypertrophy[MeSH], Resistance Training [MeSH], Spirulina [MeSH]

Highlights

- Exercise increases CITED4 levels in the heart and is sufficient to cause physiological hypertrophy.
- Spirulina supplementation alone has no effect on the signaling pathway of cardiac hypertrophy.
- If used concomitantly with resistance training, it can affect the signal pathway of cardiac hypertrophy

Introduction

For many years, exercise has been mentioned as an essential element for maintaining cardiovascular health (1, 2) and it has been found that exercise has the primary and secondary prevention effect of cardiovascular disease (2). So that continuous exercise protects the occurrence and progression of cardiovascular diseases and by improving heart function (3) reduces the risk of mortality and also reduces the incidence of cardiovascular disease (1). Exercise causes significant changes in the cardiovascular system by altering the metabolism, vascular, and skeletal muscles (4) and also coordinates the responses of various organs such as the heart, lungs, skeletal muscle, and vascular (5). Various adaptations such as improved cardiovascular function increased metabolism, and cardiac growth (physiological hypertrophy) develop in response to exercise (6).

Changes in the heart caused by mechanical stress or various stimuli can increase the growth of the heart and eventually cause hypertrophy (7). Exercise can increase left ventricular mass by 20% or more (8). Exercise has been shown to stimulate the growth of the heart by producing new cardiomyocytes (9). Preliminary laboratory studies have shown that CITED4 causes hypertrophy and hyperplasia in cardiomyocytes (4). Exercise increases CITED4 levels in the heart and is sufficient to cause physiological hypertrophy and by regulating mTOR activity, it protects the heart against pathological hypertrophy (10). CITED4 is one of the regulators of mTOR signaling that is effective in causing physiological hypertrophy (11). The C/EBPB-CITED4 signaling pathway is one of the mediated signaling pathways that causes cardiac hypertrophy due to exercise (12). Decreased C/EBPβ can be mentioned as a central signal involved in hypertrophy and physiological proliferation (4). high-intensity exercise increased CITED4 more than in the low-intensity exercise (13).

Spirulina Platonists is a blue-green alga (14) which has been considered for its potential sources of protein and vitamin (15). 60 to 70 percent of spirulina weight is a protein (15). Spirulina has been reported to increase muscle strength as well as rate of muscle protein synthesis (16). The result of the study showed that the combination of exercise and spirulina significantly increases muscle strength compared to exercise or spirulina alone (17). Sandho et al. (2009) in a study during 8 weeks of spirulina use found that spirulina supplementation with exercise resulted in a significant increase in isometric strength and endurance compared to spirulina use or exercise alone (18). In the searches we did, no article was found that examined the effect of exercise and spirulina supplementation on the CITED4 in the heart muscle. The present research aimed to investigate the effect of 8-week resistance exercise and spirulina supplementation on CITED4 gene expression in the cardiac muscle.

Materials and Methods

- **Experimental Animals**

We used of Thirty-two rats (male; Sprague–Dawley). All rats had free access to standard food (company of Pars feed) and healthy water. Then, all rats were randomly grouped into 4 groups (1. resistance training: RE, 2. spirulina + resistance training: SP +RE, 3. spirulina platensis: SP,4. control: Co, n = 8).

- **Training Protocol**

One week was used for an adaptation period. The training protocol included climbing a ladder for resistance training for eight weeks. Before the start of each training session, the rats performed a weightless climb up the ladder to warm up three times. The training program was for 8 weeks (30–100% of body weight per week) and 5 sessions per week (each training session: 3 sets per day with 2 minutes' rest between each set and each set includes 5 repetitions with one minute of rest between each repetition) (19).The present study has a code of ethics in research from the ethics committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1398.011).

- **Spirulina Supplementation**

Each day, spirulina (200 mg/kg/ day) was added to the drinking water of rats in the SP group and SP + RE group (20).

- **Sampling**

Twenty-four hours after the last training session, all rats were decapitated (19). The rat was anesthetized for about 5 minutes by injecting ketamine 10% (50 mg/kg body weight) and Xylazine 2% (10 mg/kg body weight) to measure the parameters. Then the heart of the animal was removed from the chest (Heart weight was calculated by the German KERN digital scale with an accuracy of 0.001 g) and the left ventricle was also removed. The left ventricular tissue will be placed immediately in the nitrogen tanks and will be transferred to an 80-degree freezer for extraction of RNA (Ribonucleic Acid). RT-PCR was used for evaluate C/EBPß and CITED4 gene expression.

- **RNA Isolation And Real-Time PCR Analysis**

Total RNA was isolated from the tissues using RNA extraction kit (Cinnagen Inc., Iran). The purity, integrity, and concentration of RNA were determined by measuring the optical density 260/280 and agarose gel (1%) electrophoresis. Complementary DNA (cDNA) was synthesized from 1 µg of RNA using Revert Aid ™ first strand cDNA synthesis kit (Fermentas Inc.). Real-time PCR was performed according to the protocol of Real Q Plus 2x Master Mix Green (Ampliqon Inc.) in applied Bio Systems Step One ™ Instrument (ABI, Step One, USA).

Real-time PCR for expression analysis of the primer pairs for C/EBPß, CITED4 and □2M were designed, as shown in Table 1. The β2M housekeeping gene was also used as the internal control of real-time PCR reactions. The real-time PCR conditions were set for 10 minutes at 94°C followed by 40 cycles of 15 seconds at 94°C, 60 seconds at 60°C and extension steps. After each real-time PCR run, gel electrophoresis and melting curve analysis were carried out to confirm specific amplification of targets. The amplification signals of different samples were normalized to β2M Ct (cycle threshold), and then delta-delta CT (2- ΔΔ CT) method was applied for comparing mRNA levels of test versus control which represented as fold change in data analysis.

Table 1. Real-time PCR (qPCR) Primer Pairs Used in the Study

Genes	Primer Sequences	Sizes (bp)
C/EBPß	Forward: 5’- GCGGAACTTGTTCAAGCAGC-3’	264
	Reverse: 5’- CCACGTTTGATCCGGATTGC-3’	
CITED4	Forward: 5’- CGAGGCGTGTACTGACTGAC-3’	198
	Reverse: 5’- AAAGAGCCGTATGCCAAGGT-3’	
β2M	Forward: 5’- CGTGCTTGCCATTCAGAAA -3’	244
	Reverse: 5’- ATATACATCGGTCTCGGTGG -3’	

- **Statistical Analysis**

For comparing the effect of resistance training and spirulina and also the combination of resistance training + spirulina we used of Two-way ANOVA in SPSS ($p<0.05$). We also used Graph Pad Prism 6 to draw the graphs.

Results

The results of Two-way ANOVA test on rat Heart weight in the last week showed a significant difference between the study groups (F= 65.11, P= 0.001). Comparison of rat heart weight in groups showed that there was a significant difference between the CO group with the RE group (0.933 ± 0.091 vs. 1.421± 0.024, p = 0.001), the CO group with SP (0.933 ± 0.091 vs. 1.119 ± 0.056, p = 0.001), the CO group with the RE+SP group (0.933 ± 0.091 vs. 1.198 ± 0.077, p = 0.001).

The results of Two-way ANOVA test on CITED4 in the last week showed a significant difference between the study groups (F= 40.19, P= 0.001). Comparison of CITED4 in groups showed a significant difference between the CO group with the RE group (P= 0.001) and the CO group with the RE+SP group (P= 0.001) but there was not significant between CO group with SP (P= 0.997) (Table 2, Fig2).

The results of Two-way ANOVA test on CEBP in the last week showed a significant difference between the study groups (F= 50.65, P= 0.001). Comparison of CEBP in groups showed a significant difference between the CO group with the RE group (P= 0.001), the CO group with SP (P= 0.034), the CO group with the RE+SP group (P= 0.001) (Table 2, Fig1).

Table 2. Changes in CEBP and CITED4 after eight weeks of resistance training and Consumption of spirulina in research groups

Parameter	Group			
	CO	SP	RE	SP + RE
CEBP	1 ± 0.067	0.86 ± 0.092*	0.56 ± 0.13*	0.53 ± 0.054*
CITED4	0.99 ± 0.27	1.21 ± 0.411	7.19 ± 2.97*	10.73 ± 2.99*

CO; Control, SP; Spirulina, RE; Resistance Exercise, SP +RE; Spirulina + Resistance Exercise. Data are presented as the mean ± standard error of the mean. *p value less than 0.05 considered as significant in compare with CO group.

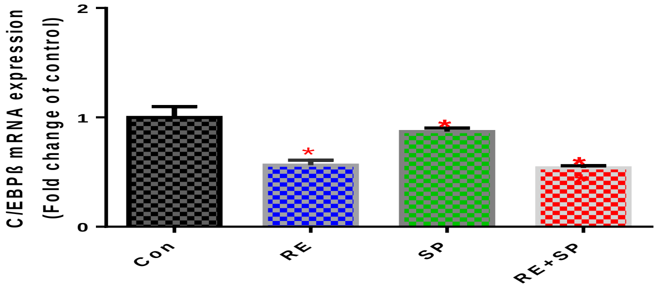

Figure 1. Changes in C/EBPß in cardiac muscle after eight weeks of resistance training and Consumption of spirulina. CO; Control, SP; Spirulina, RE; Resistance Exercise, SP +RE; Spirulina + Resistance Exercise. Data are presented as the mean ± standard error of the mean. *p value less than 0.05 considered as significant.

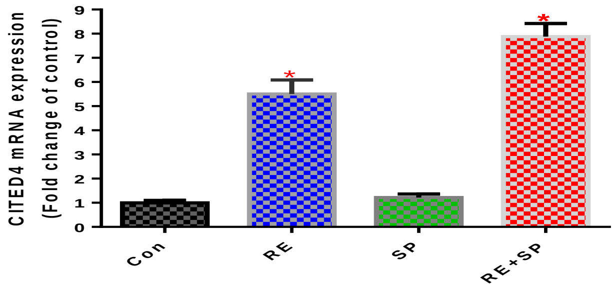

Figure. 2. Changes in CITED 4 in cardiac muscle after eight weeks of resistance training and Consumption of spirulina. CO; Control, SP; Spirulina, RE; Resistance Exercise, SP +RE; Spirulina + Resistance Exercise. Data are presented as the mean ± standard error of the mean. *p value less than 0.05 considered as significant

Discussion

This study aimed to evaluation of CITED4 gene expression in the cardiac muscle of male rats as a result of resistance exercise and spirulina supplement. In Compared with the control group, we observed a significant increase in CITED4 gene expression in RE and RE+SP groups. Also, there was a significant difference in CEBP gene expression Between CO with RE, SP and RE+SP group. In the cardiovascular system, the C / EBPβ -CITED4 signal pathway is recognized as a mediator of exercise-induced cardiovascular growth. After recognizing its role in cardiac activity, which was first reported in 2010, further evidence supports it (21, 22). Various studies suggest that exercise may stimulate cardiomyocyte proliferation (4, 23-25).Consistent with the findings of the present study, Naderi et al. (2019) stated that high-intensity interval training (running on a treadmill with 10 4-minute intervals at 70-65% VO2max) on myocardial infarction rats, C / EBPβ and CITED4 levels Significantly decreased and increased (13), respectively. Bahramian et al. (2018) also stated that 6 weeks of high-intensity interval training in rats exposed to left coronary artery occlusion, C / EBPβ levels decreased significantly and CITED4 levels also increased significantly in the high-intensity interval training group. It seems that high-intensity exercise is an effective factor in enhancing the expression of C / EBPβ and CITED4, and higher intensity exercise is an effective factor in increasing cardiac function and regenerative capacity in myocardial infarction. Thus, exercise activity has emerged as an important variable in clinical research (26).

In the case of exercise and C/EBPβ, various studies show that exercise reduces C / EBPβ (4, 21). About sports and gene studies show that exercise reduces the gene. for example, it has been reported that the C / EBPβ reduced after swimming exercises (21) or the results of another study showed that endurance training reduces C / EBPβ (4). An important point in the treatment of heart disease is to understand the molecular mechanisms involved in the heart physiological hypertrophy (27). In cardiac hypertrophy due to exercise, the C / EBPβ is reduced, which can lead to the growth of heart muscle (4).

Spirulina is recognized as a dietary supplement with antioxidant, anti-inflammatory, cardioprotective and immune modulating properties (28). Spirulina supplementation has beneficial effects in protecting the heart against heart damage (29) and improves heart function (30). Spirulina supplementation provides cardiac protection by reducing kinases in the heart muscle and promoting anti-inflammatory mechanisms, thereby reducing heart damage and improving ventricular contraction (31). Spirulina can have a protective effect on the heart against oxidative stress by maintaining the activity of SOD and GPx and reducing the activity of nicotinamide adenine dinucleotide phosphate oxidase. (32). Studies show that spirulina is a preventative factor for the heart and cardiovascular system (33).

The present study showed a decrease in C / EBPβ expression in trained rat compared to the control group. Research shows that several signal mechanisms and pathways regulate myocardial regeneration, which is a complex behavior (34). In this case, Bei et al. Reported that C / EBPβ decreased in mice that practiced swimming for 4 weeks, while CITED4 levels in the heart muscle increased (21). C / EBPβ appears to produce signaling that is important in the cardiac response to exercise and to protect the heart against adverse adaptation (4, 35). Negative regulation of C / EBPβ releases the serum reaction factor (SRF) to bind to target gene promoters. It can also stimulate the heart by activating a set of exercise genes (GATA-4, Tbx5, Nkx2.5 and Mef2c). According to the results of various studies, negative regulation of C / EBPβ is an important factor for improving heart function and regulation of markers of cardiac hypertrophy (4). Research shows that increased expression of CITED4 is able to activate cyclin D1, thereby causing cardiomyocytes to proliferate (36). C / EBPβ has also been shown to exert its anti-proliferative effect by inhibiting CITED4 (4). However, little is known about the extent to which cardiac cell proliferation, including the formation of new cardiomyocytes, can contribute to the effect of exercise on heart protection (21).

Conclusion

In summary, these data suggest that our resistance exercise has resulted in physiological hypertrophy of the heart. Spirulina supplementation alone has no effect on the signaling pathway of cardiac hypertrophy. However, if used concomitantly with resistance training, it can affect the signal pathway of cardiac hypertrophy. On the other hand, resistance training alone can have a positive effect on the signal pathway of cardiac hypertrophy.

The present study is the first to investigate the simultaneous effect of resistance training and spirulina on gene expression changes in the heart. However, the present study has limitations that can be considered not to study different doses of spirulina supplement and not to use other methods of measuring genes.

Authors' Contribution

All authors had an equal role in study design, work, statistical analysis and manuscript writing.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Ethical Approval

The code of ethics was IR.JUMS.REC.1398. 011. Written informed consent was obtained.

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