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Effect of High-Intensity Interval Training and High-Fat Diet on Nrg-1 And Pgc-1α in Aging Rats' Heart Tissue

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A B S T R A C T

Objective: Neuregulin is activated by exercise and has been implicated as a mediator of the beneficial effects of exercise training on metabolism. The aim of this study was to effect of high-intensity interval training and high-fat diet on NRG-1 and PGC-1α in aging rats' heart tissue.

Materials and Methods: 20 male Wistar rats aged 48 to 52 weeks were purchased and kept inside standard cages at a temperature of 22±2 degrees Celsius. After one week of acclimatization to the laboratory environment, the animals were divided into four groups (normal diet, normal diet+training, high-fat diet, and high-fat diet+ training). According to the research design, the training group underwent 8 weeks of training. This was followed by high-intensity interval training at an intensity of 85% to 90% of VO2max. Two-way ANOVA (DIET×HIIT) were used to examine (P<0.05).

Results: The findings indicated a High-fat diet had a significant and decreasing effect on NRG-1 (p=0.004, F=11.17). Exercise did not have a significant effect (p=0.039, F=5.04) on NRG-1, although it increased NRG-1 levels. The interactive effect of diet and exercise on NRG-1 was not statistically significant (p=0.93, F=0.008). The findings indicate that diet reduced and exercise increased NRG-1 levels. In fact, the effect of exercise in the high-fat diet group reduced the differences and led to non-significant results statistically.

Conclusion: Eight weeks of HIIT training, along with a normal diet, led to an increase in the expression of neuregulin in the heart tissue of aged mice. The expression of PGC-1α also increased following the HIIT. This increase can be attributed to the increased neuregulin expression, leading to improved mitochondrial biogenesis.

Keywords: *Neuregulin-1, PGC-1α, high intensity interval training, fat diet, heart tissue.*

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1. Introduction

Neuregulin (NRG) growth factor is from a group of proteins structurally related to the epidermal growth factor (EGF) (1). The expression of its isoforms happens in cells of endothelial, mesenchymal, and neuronal origin being critical for survival of cardiomyocytes and differentiation of embryonic steam cell (2, 3).

In the heart, endothelial cells and binds release NRG1 to ErbB3 or ErbB4 on the adjacent cardiomyocytes' surface [36]. Based on previous research, the mice which have disruption in the expression of NRG1, ErbB2, or ErbB4 die in the uterus failing in the development their cardiac (4). NRG-1β differentiates embryonic cardiomyocytes into the cardiac conduction system's cells (2). In addition, NRG is responsible for regulating the expression of mitochondrial gene (1). They suggest that weakened NRG-ErbB signaling in cardiomyocytes is one of the factors causing mitochondrial dysfunction and loss of apoptotic cardiomyocyte in aging myocardium as well as failing myocardium (5). The transcriptional coactivator PGC-1a is the major regulator of mitochondrial biogenesis; NRG-1 causes the stimulation of the phosphorylation of PGC-1a of peroxisome proliferator-activated receptor (PPAR) as well as the GA-binding protein, which contributes to the PGC-1a's recruitment to the GA-binding protein complex (6-8). As additional evidence for promotion of mitochondrial biogenesis by PGC-1 is the fact that cardiac-specific overexpression of PGC-1 in transgenic mice led to mitochondria high proliferation (8-10). Hearts without PGC-1α enjoy normal volume density of their mitochondria but reduced mitochondrial gene expression, oxidative capacity, and fatty acid oxidation (8, 11). Exercise is believed to have protect against a variety of cardiovascular diseases. This may be due to its ability to reduce cardiovascular risk factors, increase physiological growth in the heart, enhance antioxidant capacity, and promote mitochondrial function.

Exercise Training appears to also promote CM growth in a healthy heart by increasing the expression of NRG1 and PGC-1α. The results of a study by Cai et al. (2016) pointed to beneficial effects for only four weeks of endurance training on health regeneration. However, it remains unclear whether the increased NRG1 levels are the result of cumulative effects from long endurance training, or a serious response to a single exercise session (12).

It has been hypothesized that nutrition is an influential factor in NRG1 signaling. For Example, treatment using palmitate causes impaired activation of AKT by NRG1in isolated rat cardiac myocytes; nevertheless, the mono-unsaturated fatty acid oleate has a counteractive effect (13). In addition, caloric restriction leads to restoration of cardiac NRG1 signaling in aging rats by upregulating the ErbB receptors(5). Physical activity may also play a role in regulation of NRG1 signaling as enhanced intracellular calcium concentration during skeletal muscle contraction causes cleavage and release of NRG1 (14).

High-intensity interval training (HIT) involving alternating periods of vigorous exercise with rest periods, may be a promising approach to incorporate higher-intensity physical activity. The intermittent nature of HIT makes it a favorable option compared to continuous, steady-state exercise (15).

Research findings point to higher effectiveness of HIT compared to moderate-intensity continuous training for promoting aerobic power and dealing with the metabolic syndrome risk factors (16). HIT leads to improved aerobic capacity concurrently changing the mitochondrial associated mRNA, protein levels and mitochondrial enzyme activity, showing an increase in the oxidative potential (17). The mechanisms underlying the benefits of cumulative exercise sessions are well supported by the related studies (18); it leads to enhanced expression of the PGC-1α gene, which is upregulated in the skeletal muscle of human as the result of acute endurance exercise (19, 20) as well as low-volume HIT (21).

Waring et al. (2014) investigated the impact of low- and high-intensity exercise on Wistar rats' NRG1 (22). Based on their findings, the greatest changes in the NRG1 levels occurred as the result of the high-intensity exercise. The peak of this change was on the 7th day and even further increased until the 14th day to the baseline levels during the exercise process (22). According to Waring et al., NRG1 was involved in cardiac hypertrophy regulation as well as myocyte replacement after cardiac injuries. They concluded that vigorous exercise can lead to a significant increase in the myocyte count and mass pointing to the importance of this phenomenon as a component of the cardiac physiology and homoeostasis (22).

Accordingly, as a time-efficient strategy, HIT can improve the physiological function of the whole body preventing metabolic diseases. Despite that, only a small number of studies have examined the metabolic adaptations involved in which the improved exercise performances (23).

Although there are a large number of studies in this regard, few have dealt with the mechanisms involved in stimulation of the mitochondrial biogenesis by exercise.

On this basis, the present study seeks to examine the impact of diet and HIIT on NRG1 and PGC1α in the rats' cardiac muscle. We hypothesize that besides the significant role of NRG/erbB signaling in the development of the cardiac muscle, this system is also likely to be involved in acute and long-term proliferative and metabolic adaptative changes following exercise training playing a mediating role in this respect. The present study tries to examine and show the NRG/erbB system's native expression in cardiac muscle of rats., The dynamic regulation of NRG and PGC1α expression in response to a HIIT program is also tested in the present study.

2. Materials and Methods

2.1 Animals

In the present experimental study, 20 male Wistar rats aged 48 to 52 weeks were purchased and kept inside standard cages at a temperature of 22±2 degrees Celsius. The light-dark cycle (12 hours of light and 12 hours of darkness) was maintained. After one week of acclimatization to the laboratory environment, the animals were divided into four groups based on weight matching (mean and standard error of weight): normal diet, normal diet+training, high-fat diet, and high-fat diet+ training. This intervention continued until the end of the research protocol. The animals had free access to water and food and were fed either a high-fat diet (60% of kilocalories) or a standard diet. All care and ethical principles were fully observed based on the guidelines for using and caring for laboratory animals.

2.2 Familiarization Phase

For familiarity and adaptation to high-intensity training (HIT), the rats were trained on a treadmill for 2 weeks. At the beginning of the first week of adaptation to the training, the rats started exercising at a speed of 10 meters per minute and a 0% incline for 10 minutes. By the end of the second week, the exercise duration was increased to 30 minutes at the same speed of 10 meters per minute. The rats were divided into two main groups: the high-intensity training (HIT) group and the control group. According to the research design, the training group underwent 8 weeks of training.

2.3 Evaluation of Rats' Aerobic Capacity

An indirect protocol was used to assess the rats' aerobic capacity (24). The protocol began with a 5-minute warm-up on the treadmill at a speed of 6 meters per minute and 0% incline, followed by an increase in speed by 3 meters per minute every 3 minutes until the animals reached exhaustion and were no longer able to continue. The criterion for reaching VO_2max was the inability of the rats to continue the exercise protocol with the increase in speed. Therefore, the rats' VO_2max was determined based on the running speed. To comply with the overload principle in the training program of the present study, every week the test was performed to the point of exhaustion to determine the percentage of VO_2max.

2.4 The Exercise Procedure

After determining the average maximum speed to determine the maximum oxygen consumption in all the rats, an 8-week interval training program was planned. The interval training was as follows:

At the beginning of each session, the warm-up phase included running for 2 minutes at an intensity of 6 meters per minute, followed by 2 minutes at an intensity of 10 meters per minute. This was followed by high-intensity interval training at an intensity of 85% to 90% of VO2max, which corresponded to 7 1-minute attempts at a speed of 18 to 20 meters/minute, with 2 minutes of active recovery at a speed of 5 meters per minute between the attempts. This protocol was performed in the first and second weeks, and then the speed was incrementally increased by an average of 2 meters/minute every two weeks, reaching 7 1-minute attempts at a speed of 24 to 26 meters/minute in the seventh and eighth weeks (17).

Table 1. Training Protocol

Week	Session	Intensity (meters per second)	Set	Slope (degree)
1 and 2	1-6	18-20	7 1-minute attempts with two minutes of active recovery at 5 meters per minute	٠
3 and 4	7-12	20-22	7 1-minute attempts with two minutes of active recovery at 5 meters per minute	+5
5 and 6	13-18	22-24	7 1-minute attempts with two minutes of active recovery at 5 meters per minute	+10
7 and 8	19-24	24-26	7 1-minute attempts with two minutes of active recovery at 5 meters per minute	+15

2.5 The Experimental Methods

2.5.1 Tissue Sampling

Forty-eight hours after the last training session and after 12 hours of fasting, the rats were anesthetized with a combination of ketamine (50 mg/kg) and xylazine (5 mg/kg) injected intraperitoneally. The rats were then sacrificed by removing the heart, and the tissue samples were rapidly dissected and stored at -80°C until RNA extraction.

2.5.2 NRG-1 and PGC-1α expression analysis

To assess the expression of NRG-1 and PGC-1α genes, real-time PCR was used. All primers were designed using Allele IDv7.8 software, and β2m (β2 microgloboline) was used as the internal control gene. All primbers were designed as exon-exon junction primers. To ensure no genomic DNA amplification, 25 ng of cDNA and 25 ng of RNA were tested separately with PCR and 1.5% agarose gel electrophoresis. Amplification of cDNA and observation of the expected bond by the specific primer and non-amplification of RNA after PCR reaction signify the absence of genomic DNA amplification. PCR efficiency was measured for each primer set and standard curves were generated. Then, to examine the expression of NRG-1 and PGC-1α, total RNA was extracted from the tissue samples using a commercial RNA extraction kit (FavorPrep™ Tissue Total RNA Mini Kit) made in Hong Kong.

Table 2. Training Protocol

Genes	Primer Sequences	Sizes (bp)
PGC1a	Forward: 5'- CAGAAGCAGAAAGCAATTGAAGA -3' Reverse: 5'- GTTTCATTCGACCTGCGTAAAG -3'	230
Nrg1 (neuregulin 1)	Forward: 5'- GCTGCCCCAGCCATTTT -3' Reverse: 5'- GTGGATGTCGATGTGGAAAGT -3'	299

2.6 Data analysis

Mean standard error of the means (SEM) represents the data values, which were analyzed using a two-way ANOVA (DIET×HIIT). We also ran a one-way ANOVA and Bonferroni's post hoc test to compare the groups in the HFD regimen. P<0.05 was set as the significance value.

3. Results

Based on the findings, diet had a significant effect (p=0.0001, F=49.67), decreasing PGC1 levels, also the results further showed that training had a significant effect (p=0.0001, F=19.41), increasing PGC1 levels, but the interactive effect of diet and training on PGC1 was not found to be statistically significant (p=0.63, F=0.232). It means that diet decreased and training increased PGC1. The effect of training in the high-fat diet group reduced the differences and led to non-significant results statistically.

High-fat diet had a significant and decreasing effect on NRG-1 (p=0.004, F=11.17).

Training did not have a significant effect (p=0.039, F=5.04) on NRG-1, although it increased NRG-1 levels. The interactive effect of diet and training on NRG-1 was not statistically significant (p=0.93, F=0.008). The findings indicate that diet reduced and training increased NRG-1 levels. In fact, the effect of training in the high-fat diet group reduced the differences and led to non-significant results statistically.

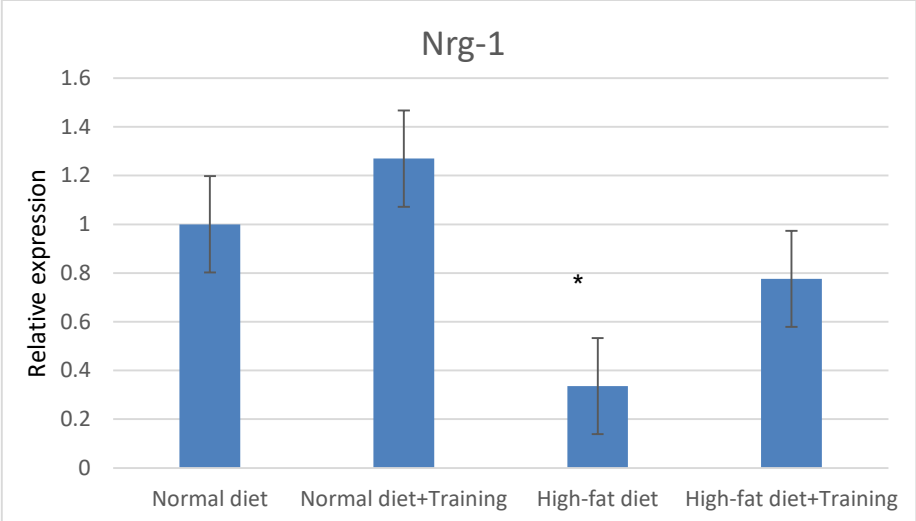

Figure 1. Nrg-1 levels in the heart tissue of rats in the research groups (*Significant decrease compared to the Normal diet group).

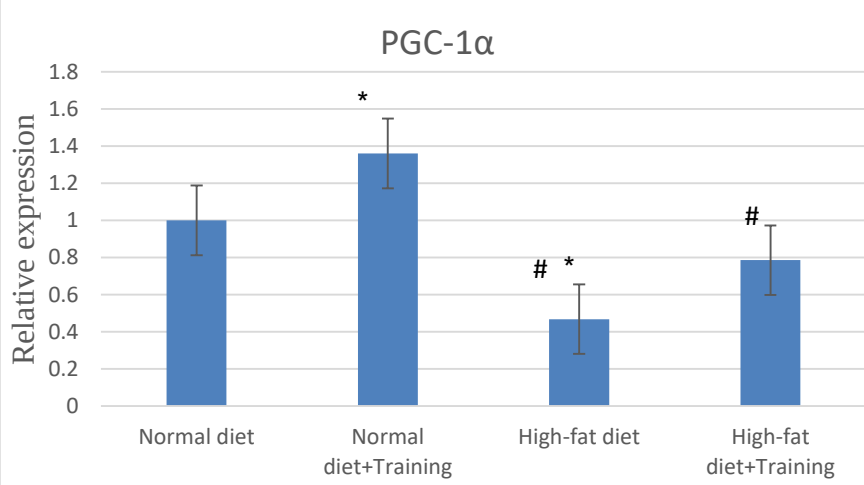

Figure 2. PGC-1α levels in the heart tissue of rats in the research groups (*Significant Increase compared to the Normal diet group; #*Significant decrease compared to the Normal diet group; #Significant decrease compared to the Normal diet group).

The high-intensity interval training (HIIT) consisted of 30-second bouts of high-intensity exercise followed by 30 seconds of active low-intensity rest. The training protocol included 20-meter sprints with varying repetitions over six weeks. Rest intervals between sprints ranged from 20 to 30 seconds. To ensure progressive overload and effectiveness of the training, the number of short-distance sprint repetitions was set at four in the first and second weeks, five in the third and fourth weeks, and six in the fifth and sixth weeks. Each session included a 5-minute warm-up and a 5-minute cool-down. The HIIT was performed three days a week for six weeks. At the end of the study, data were collected and analyzed using descriptive statistics (mean and standard deviation) and inferential statistics. Paired t-tests were used to compare pre-test and post-test values, and independent t-tests were used to compare differences between groups. All data analysis was conducted using SPSS version 26, with a significance level set at less than 0.05.

4. Discussion

NRG is expressed in the endothelial cells of the adult heart and plays an important role in the regulation, survival, hypertrophy, and proliferation of cardiomyocytes. In addition, NRG protects the heart against apoptosis and fibroblastic disorder (3). These factors emphasize the

importance of NRG in cardiovascular growth and supporting the heart throughout adulthood.

The results of the present study showed that eight weeks of high-intensity interval training along with a normal diet led to an increase in NRG expression in the hearts of aged mice. On the other hand, a high-fat diet led to disrupted expression of NRG and PGC-1α.

Increased levels of saturated fatty acids in the diet led to damage to the NRG signaling pathway. Saturated fatty acids lead to harmful effects on the insulin signaling pathway, which has common signaling pathway with NRG (25). Additionally, Miller (2009) showed that saturated fatty acids lead to the disruption of the NRG/ErbB signaling pathway in cardiac myocytes. To further investigate this issue, the present study examined the effect of a high-fat diet on NRG expression in the hearts of aged mice with the results showing that a high-fat diet led to a decrease in NRG expression in the mouse heart compared to a normal diet (13).

Ennequein (2015) found that a high-fat diet does not alter NRG/ErBb expression. In this study, the effect of a 16-week high-fat diet on NRG/ErBb expression was examined following a normal diet and eight weeks of endurance training, and no change was observed in NRG/ErbB expression (26). However, in the present study, the effect of a high-fat/normal diet and HIIT on NRG expression was examined with the results showing a positive effect for interval training and the damaging effect of a high-fat diet.

Exercise and a balanced diet are the cornerstones of overweight and obesity management (27). The results of the present study showed that the body weight of aged mice decreased after 8 weeks of HIIT.

Previous studies have examined the effect of endurance and resistance training on the expression of NRG/ErbB showing contradictory results. In our previous study we showed that six weeks of circuit resistance training led to an increase in plasma NRG/ErbB levels in young men, and this increase was greater at higher intensities (28). Further investigation is needed on the effects of different intensity levels of exercise training on NRG/ErbB expression.

Rohrbach et al. (2006) reported that energy restriction led to increased expression of NRG receptors and restoration of mitochondrial metabolism in the hearts of old mice. The receptors are sensitive to both interventional strategies in cardiac tissue (5).

Previous studies suggest that proteases play an important role in the release of NRG from the membrane and activation of its receptors, initiating intracellular signaling cascades (29). However, a decrease in the TIMP3 protein has been reported. The results of Enneqein et al.'s study revealed that protein levels of the ADAM17 protease increased significantly only in the exercise and normal diet group (26). These results strongly suggest that ADAM17 activity increases in skeletal muscle of obese individuals following exercise. ADAM17 expression is sensitive to nutritional interventions, especially moderation of dietary fat intake (30).

On this basis, considering the results of the present study, the increase in neuregulin following interval training and a normal diet may be due to increased ADAM17 levels. Previous results on mouse myoblasts support the relationship between these two components. ADAM17 can trigger NRG odomain cleavage from the membrane and increase NRG phosphorylation (26, 31).

Lebresseur (2005) reported that acute exercise stimulates NRG in mice and humans. In contrast, chronic resistance training had no effect on NRG in human skeletal muscle (31).

NRG plays an important role in improving mitochondrial biogenesis (7). It is produced by myoblast cells and initiates an autocrine signaling pathway that enhances myogenic differentiation (32).

Chronic treatment with NRG promotes the reprogramming of gene expression, leading to increased expression of genes related to the respiratory chain and beta-oxidation in cardiomyocytes (33). Additionally, the notion that NRG regulates mitochondrial gene expression has led to the suggestion that reduced NRG/ErbB signaling in cardiomyocytes is a contributive factor in mitochondrial dysfunction (1).

Canto, et. al (2007)showed that NRG stimulates the expression of PGC-1α and PPAR, and that neuregulin is necessary for increasing cellular mitochondrial content (7). The increased expression of PGC-1α observed in the present study is attributable to the effect of increased NRG.

NRG also increases insulin sensitivity through the upregulation of PPAR and PGC-1α, stimulating mitochondrial biogenesis, and enhances glucose uptake through the translocation of GLUT4 to the cell membrane. Canto (2007) also reported a similar relationship between increased insulin sensitivity and increased mitochondrial metabolism following the response to the presence of NRG in skeletal muscle cells, consistent with the role of mitochondrial metabolism in insulin sensitivity (7).

In Vincent's study (2015), it was reported that two weeks of HIT exercise led to increased PGC-1α expression. It was

suggested that extending the HIT training duration to six weeks or more may increase the total PGC-1α protein content in the muscles of healthy young individuals by up to 100% (34). Therefore, considering the effect of HIT training on improving mitochondrial capacity, the increase in PGC-1α expression observed after eight weeks of HIIT training may be due to the effect of the exercise.

5. Conclusion

The results of the present study showed that eight weeks of HIIT training, along with a normal diet, led to an increase in the expression of neuregulin in the heart tissue of aged mice. Additionally, the expression of PGC-1α also increased following the HIIT. This increase can be attributed to the increased neuregulin expression, leading to improved mitochondrial biogenesis. This mechanism may contribute to the improved energy metabolism that is regularly observed following dietary and exercise interventions. On the other hand, a high-fat diet led to a decrease in the expression of neuregulin and PGC-1α in the heart tissue, and HIIT improved these two variables compared to the high-fat diet group without training.

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Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.M. conceptualized the study, designed the research methodology, and supervised the experimental procedures involving the rats. M. M. was responsible for data collection, analysis, and interpretation. They also contributed significantly to drafting and revising the manuscript for intellectual content. P. N. provided expertise and guidance in the design of the animal experiment protocols, particularly focusing on the dietary aspects and biochemical analyses related to NRG-1 and PGC-1α expressions. P.N. played a crucial role in interpreting the biochemical results and integrating them into the broader context of aging and cardiovascular health. N. R. contributed to the experimental design and execution, particularly in the implementation of the high-intensity interval training protocols and monitoring the physiological responses of the rats. N. R. also assisted in data analysis and interpretation, ensuring the accuracy and reliability of the findings related to HIIT effects on NRG-1 and PGC-1α. Together, the authors collaborated in discussing the results, critically reviewing the manuscript, and approving the final version for submission. Their combined efforts contributed to advancing the understanding of how exercise and diet interventions influence molecular markers associated with cardiovascular health in aging rats.

Data Availability Statement

Data are available for research purposes upon reasonable request to the corresponding author.

Ethical Considerations

This research was conducted with the approval of the Ethics Committee with the number: IR.ILAM.REC.1402.020.

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