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Effects of high intensity interval vs. low intensity continuous training on LXRβ, ABCG5 and ABCG8 genes expression in male wistar rats

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Original Article

Abstract

BACKGROUND: Liver X receptors (LXR) play an essential role in the regulation of cholesterol metabolism, and their activation increases ABCG5 and ABCG8 gene expression for the improvement of cholesterol excretion from the body during reverse cholesterol transport (RCT). The aim of this study was to investigate the effects of high-intensity interval (HIT) and low-intensity continuous (LIT) trainings on gene expression of these substances after a high-fat diet in Wistar rats.

METHODS: Fifteen male Wistar rats were divided into 3 groups: control group (n = 5), HIT exercise group (n = 5), and LIT exercise group (n = 5). All groups were fed a high-fat diet for 13 weeks, and the HIT and LIT groups performed the specific training program. The expression of LXRβ, ABCG5, and ABCG8 genes was measured after the training period.

RESULTS: Data analysis showed significantly higher levels of LXRβ, ABCG5, and ABCG8 gene expression in the HIT and LIT groups compared to the control group ($P \leq 0.05$).

CONCLUSION: HIT and LIT trainings after a high-fat diet have beneficial effects on RCT, preventing heart attacks. Additionally, HIT training may have a greater effect on cholesterol excretion during the reverse cholesterol transport mechanism than LIT.

Keywords: Liver X Receptor; Atherosclerosis; Endurance Training, Exercise, Stroke

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Introduction

Atherosclerosis caused by cholesterol deposition in coronary arteries is the leading cause of disability and mortality worldwide[1, 2]. High-density lipoprotein (HDL) is responsible for the transfer of excess cholesterol from the peripheral tissues to the liver during reverse cholesterol transport (RCT)[3]. Adenosine Triphosphate (ATP) Binding Cassette Transporters are involved in RCT, among which ABCA1 and ABCG1 are responsible for cholesterol transport in macrophages. Free cholesterol is also transmitted through ABCG5 and ABCG8 into the liver and intestine. The cardiovascular risk is higher in mice with mutations in the ABCG5 and ABCG8 genes[4-7].

Liver X Receptors (LXR) are known as cholesterol sensors that are involved in the prevention of atherosclerosis through overexpression of RCT-related genes such as ABCA1, ABCG1, ABCG5, ABCG8, and a variety of apolipoproteins[8]. LXR receptors include alpha (LXRα or NR1H3) and beta (LXRβ or NR1H2) variants. LXRα is found mainly in the liver, small intestine, adipose tissue, kidney, adrenal glands, and macrophages; whereas LXRβ is found in all body tissues. They bind to a Retinoid X Receptor (RXR) to form a heterodimer. The LXR/RXR complex is activated by LXR and RXR agonists such as 22-hydroxycholesterol[9-12].

The development of atherosclerotic plaque is a slow process that often takes decades. Because of the

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significant importance of cardiovascular disease, several studies have been conducted for a century to understand the molecular mechanisms involved in these diseases, and further research is needed. Since the activity of LXR receptors can stimulate the expression of ABCG5 and ABCG8 genes[13, 14], the effect of Low Intensity Continuous Training (LIT) and High Intensity Interval Training (HIT) on the expression of LXRβ, ABCG5, and ABCG8 genes in male Wistar rats after a high-fat diet was investigated in this study. What is the hypothesis?

Materials and Methods

This study was approved by the Ethics Committee of the Institute of Sport Sciences under code IR.SSRI.REC.1395.115. The present study was conducted in two stages: the obesity phase and the exercise phase. After one week of adaptation to the new environment, all rats, with a mean age of 5-6 weeks and an initial weight of 128.32 g on a normal diet, were divided into 3 groups after 13 weeks of a high-fat diet. The study groups in the second phase (exercise) included the control group (n = 5), the HIT exercise group (n = 5), and the LIT exercise group (n = 5).

All rats were housed in a cage under controlled laboratory conditions (ambient temperature 22 ± 2 °C, light cycle at 12:12 h, and 50 ± 5 percent humidity with appropriate ventilation). The high-fat diet consisted of 40% fat, 13% protein, and 47% carbohydrate[15]. The maximum speed and aerobic power of the exercise rats were measured before the start of the main exercise program and after one week of training as a treadmill orientation phase aimed at more precise planning according to the standard protocol. After 10 to 20 minutes of warming up at 40% to 50% of maximal oxygen consumption (VO2max), the treadmill speed was increased by 0.03 m/s (2 m/min) every 2 minutes until the animals were exhausted. The criterion for achieving VO2max was reaching fatigue (achieving maximum speed).

After obtaining the mean maximal velocity in all rats in the exercise groups, 65% of the maximal velocity evaluated was considered the desired intensity in the LIT exercise group in the first week. The warm-up phase consisted of 3 minutes at 10 m/min followed by 2 minutes at 15 m/min, and after the main exercise in each group, rats performed a cooling protocol for 1 minute at 15 m/min and then for 2 minutes at 10 m/min. The LIT training protocol also started at 20 m/min for 15 minutes in the first week and gradually reached 25 m/min and 31 minutes at 12 weeks. No electrical shock or stimulation was used except for touching and rubbing the tail.

The HIT training protocol in the first week consisted of 7 × 1-minute attempts at 31 m/min and active rest (between each intense exercise), gradually progressing to 10 × 1-minute attempts at 55 m/min in the 12th week and active rest. The intensity was increased by an average of 2 m/min weekly. After 13 weeks of a high-fat diet (40%), the exercise protocol was started. Exercise was performed 5 days a week with 2 days rest between these 5 sessions for 12 weeks[15].

The rats were anesthetized by intraperitoneal injection of a combination of ketamine (70 mg/kg) and xylazine (3–5 mg/kg) about 48 hours after the last training session; then, fasting blood samples were taken from the vena cava. Blood samples were collected in Falcon tubes and stored in the refrigerator. Blood samples were centrifuged at a speed of 3000 rpm for 15 min. Serum or plasma were separated and transferred to a freezer at a negative temperature of -70 °C for subsequent stages of the study (measuring the desired variables). Real-Time Polymerase Chain Reaction (rtPCR) technique was used to evaluate the expression of LXRβ, ABCG5, and ABCG8 genes after training[15].

The data was entered into the software SPSS (IBM SPSS Statistics 25). Data were shown as mean ± standard deviation (SD). According to the results of the Shapiro-Wilk test, the distribution of LXRβ data was normal (P>0.05); so, a one-way ANOVA and LSD post-hoc tests were used to analyze the findings. According to the results of the Shapiro-Wilk test, the distribution of ABCG5 and ABCG8 data was not normal (P≤0.05) and therefore, nonparametric Kruskal-Wallis and Mann–Whitney U tests were used to compare groups. The significance level in all analyses was considered less than 0.05.

Results

The recorded data are presented in Table 1. One-way ANOVA test showed a significant difference between the mean values of LXRβ in the study groups (F = 10.254, P = 0.003); based on the LSD post-hoc test

Table 1. Comparison of the LXRβ, ABCG5 and ABCG8 Genes expression among the study groups

Groups	ABCG5 (Normalized)	ABCG8 (Normalized)	LXRβ (Normalized)
Control group	$99\times10^{-5} \pm 24\times10^{-5}$	$37\times10^{-10} \pm 11\times10^{-10}$	$378\times10^{-6} \pm 197\times10^{-6}$
HIT group	$79\times10^{-4} \pm 18\times10^{-4}$	$238\times19^{-9} \pm 74\times10^{-9}$	$2273\times10^{-6} \pm 866\times10^{-6}$
LIT group	$196\times10^{-5} \pm 21\times10^{-5}$	$49\times10^{-10} \pm 36\times10^{-10}$	$16\times10^{-4} \pm 7\times10^{-4}$
P value[1]	0.008**	0.008**	0.001*
P value[2]	0.008**	0.841**	0.014*
P value[3]	0.008**	0.008**	0.14*

1: The level of significance resulting from the comparison of two control and HIT groups
2: The significance level resulting from the comparison of two control and LIT groups
3: The level of significance resulting from the comparison of LIT and HIT groups
* P-value based on LSD test, ** P-value based on Mann Whitney U Test

results, the mean values of LXRβ were higher in the HIT group compared to the control group (P = 0.001) and higher in the LIT group compared to the control group (P = 0.014). LXRβ values in the HIT training group were higher than in the LIT group, but there was no significant difference in the mean values of LXRβ between these groups (P = 0.14).

Analysis of data for ABCG5 showed that the mean values of this variable were significantly different between the three groups (P ≤ 0.05), with the highest gene expression in the HIT group and the lowest in the control group. For ABCG8, gene expression was higher in the HIT group than in the LIT group (P = 0.008) and higher in the HIT group than in the control group (P = 0.008); however, the difference in gene expression between the LIT and control groups was not significant (P = 0.841).

Discussion

Main findings of this study were significant elevation of ABCG5, ABCG8, and LXRβ gene expression after training, with the highest levels in the HIT group and the lowest in the control group. The discussion of these findings, along with our hypothesis and existing literature, is presented below.

LXRβ

Analysis of the results showed that the mean values of LXRβ gene expression were higher (i) in the HIT group than in the LIT group and (ii) in the LIT group than in the control group (Figure 1). This finding was similar to the findings of Baranowski et al. (2011)[16], Hajighasem et al. (2018)[17], and Parsa et al. (2021)[18], but not similar to those of Cote et al. (2013)[19], Ghanbari-Niaki et al. (2015)[20], and Sahin et al. (2018)[21]. One reason for the discrepancy between the findings of this study and those of Sahin et al. (2018)[21], Cote et al. (2013)[19], and Ghanbari-Niaki et al. (2015)[20] was the exercise duration. In this study, the training duration was 12 weeks, while in the aforementioned research, the training durations were only 8 weeks, 7 weeks, and 8 weeks, respectively[19–21]. LXRβ gene expression is affected by various stimuli. Cholesterol conversion to oxysterol due to the action of Sterol 27-Hydroxylase (CYP27A1), improved insulin sensitivity, increased vitamin A derivatives, increased activation of CCAAT/Enhancer-Binding Proteins (CEBP), increased Cyclic Adenosine Monophosphate (cAMP) mechanisms, increased Tumor Necrosis Factor Alpha (TNFα), and activation of Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB) are the driving factors of LXRβ gene expression[22–28]. LIT exercise increases oxLDL, which is a PPARγ activator. PPARγ also enhances LXR activity, which directly stimulates ABCA1, ABCG1, ABCG5, and ABCG8 gene expression and is effective in RCT[29].

ABCG5 and ABCG8

Results showed that ABCG5 and ABCG8 gene expression after HIT training was significantly higher than after LIT (Figure 1). The findings for ABCG5 were consistent with those of Cote et al. (2013)[19], Sadeghi Fazel et al. (2022)[30], Bagheri et al. (2020)[31], and Ghanbari-Niaki et al. (2013 and 2014)[32, 33], but inconsistent with the findings of Meissner et al. (2010)[34] and Ngo Sock et al. (2014)[35]. For ABCG8, the results of this study contrast with those of Ghanbari-Niaki et al. (2012)[34] and are consistent with the results of Meissner et al. (2010)[35], Ngo Sock et al. (2014)[36], and Cote et al. (2013)[21]. The type of intervention, gender, intensity, and duration of the exercise are possible reasons for the inconclusive results of these studies. For example, in the

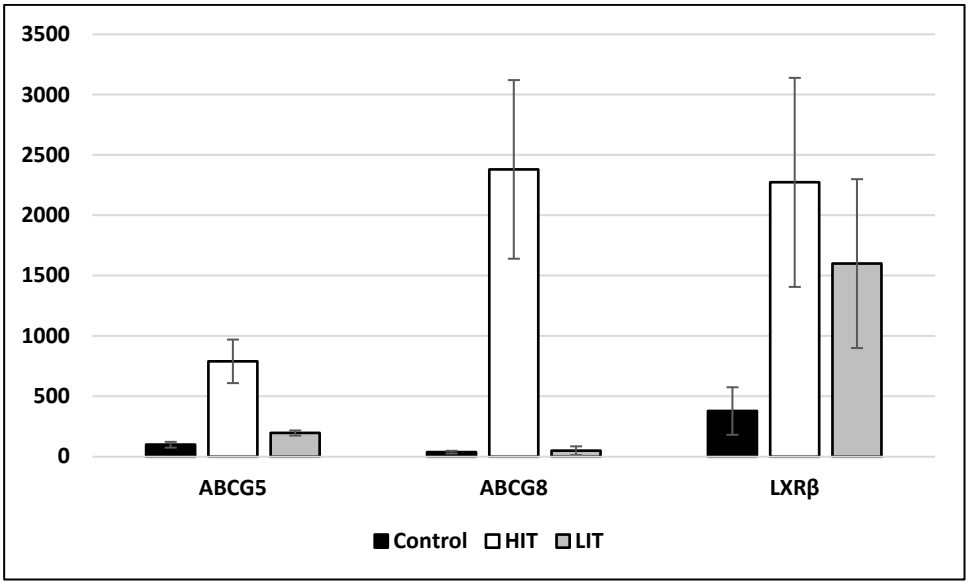

Figure 1. Levels of Gene Expression of ABCG5, ABCG8 and LXRβ in all Groups After Trainings

research by Meissner et al. (2010)[35] and Ngo Sock et al. (2014)[36], different methodologies were used compared to the present study, and a high-fat diet was not given to the subjects. Additionally, in the study by Cote et al. (2013)[21], similar to the present study, subjects consumed high-fat diets, and the results were consistent with the findings of this study. This illustrates the importance of diet, especially high-fat diet, in cholesterol metabolism and the RCT process.

The main mechanism involved in the expression of ABCG5 and ABCG8 genes is LXR activity[37]. Regulation of ABCG5 and ABCG8 gene expression is not only a function of LXR but also involves factors such as Hepatocyte Nuclear Factor 4 Alpha (HNF4α), GATA Binding Protein 4 (GATA4), and Liver Receptor Homolog-1 (LRH1), which together increase ABCG5 and ABCG8 gene expression[38]. Improvement in lipid profile and increased expression of ABCG5 and ABCG8 genes in this study may also be due to the reduction of inflammatory processes and factors such as C-Reactive Protein (CRP), Interleukin-6 (IL6), and Tumor Necrosis Factor-Alpha (TNFα)[39].

Orphan Nuclear Receptor Liver Receptor Homolog-1 (LRH1), also known as Cyp7a1 Promoter Factor (CPF) and Alpha-Fetoprotein Transcription Factor (αFTF), is a transcription factor that directly activates both ABCG5 and ABCG8 genes. It binds to position 134-142 in the ABCG5 / ABCG8 intergenic region, and mutation at this site substantially reduces the activity of ABCG5 and ABCG8 promoters. LRH1 also directly stimulates LXR activity[40].

Another mechanism associated with increased ABCG5 and ABCG8 gene expression in subjects may be a reduction in inflammation from exercise training, as inflammation can be a potential source of HDL and RCT suppression. During HDL inflammation, HDL undergoes several structural changes that make it an acute phase HDL, relatively rich in fatty acids, triglycerides, serum amyloid A, and apolipoprotein AIV, while cholesterol esters and anti-inflammatory enzymes such as Paraoxonase-1 decrease. In addition, inflammation induces myeloperoxidase secretion, which modifies Apo A1 and impairs its ability to accept cholesterol. Inflammation eventually negatively affects the expression of genes involved in the consumption, secretion, and excretion of cholesterol in the liver (such as ABCG5 and ABCG8)[34].

On the other hand, improving the lipid profile, especially HDL-suppressing inflammation itself, will eventually increase ABCG5 and ABCG8 gene expression. The precise mechanism is that increased HDL as well as increased cholesterol withdrawal from the cell negatively affect the quasi-transcriptional and CD14 receptors and signaling cascades that stimulate NFkB and MAPK to produce inflammatory cytokines and thus reduce the rate of

inflammation, which could ultimately have a positive effect on the increased expression of ABCG5 and ABCG8[41]. Additionally, interferon-gamma, a pre-atherogenic inflammatory substance, can suppress the expression of ABCG5 and ABCG8 genes. This decrease in inflammation following exercise training in this study may have been involved in the increased expression of ABCG5 and ABCG8[42].

Conclusion

Overall, the findings of this study showed that 12 weeks of HIT training increased the expression of the LXRβ, ABCG5, and ABCG8 genes in male Wistar rats, while LIT training only resulted in increased expression of the LXRβ and ABCG5 genes. This suggests that exercise training may have a greater effect on ABCG5 gene expression than on ABCG8, and that HIT training may have a more significant impact on cholesterol excretion during the reverse cholesterol transport mechanism than LIT.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

SJ: Scientific help about biology of atherosclerosis, ABCG5, ABCG8 and LXR; Laboratory analysis: Article writing; Training Protocol.

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