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# Endurance training enhances *LXR $\alpha$* gene expression in Wistar male rats

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**Abstract** Liver X receptor  $\alpha$  (*LXR $\alpha$* ) is a member of the ligand-activated transcription factor of nuclear hormonal receptor superfamily, whose activation leads to modulation in the expression of genes involved in cholesterol homeostasis including *ATP-binding cassette transporter A1* (*ABCA1*), which plays a crucial role in plasma high-density lipoprotein cholesterol (HDL-C) remodeling. The purpose of this study was to investigate whether endurance training enhanced the expression level of liver *LXR $\alpha$*  gene. Twelve adult male Wistar rats (200–220 g) were divided into control and training groups. Training group received exercise on a motor-driven treadmill at 28 m/min (0 % grade) for 60 min/day, 5 days/week for 8 weeks. Twenty-four hours after the last exercise session, the rats were killed and blood was taken from the right ventricle of each rat. Plasma was collected for HDL-C, low-density lipoprotein cholesterol (LDL-C), TC and TG measurements. Furthermore, a portion of the liver of each rat was excised and washed in ice-cold saline and frozen in liquid nitrogen for assessment of *LXR $\alpha$*  and *ABCA1* mRNA levels. Data

indicated significant increase in both *LXR $\alpha$*  and *ABCA1* mRNA levels in trained rats, compared to control rats. Plasma HDL-C concentration was significantly higher ( $P < 0.001$ ) in trained rats at the end of treadmill exercise. However, there was a significant decrease in LDL-C ( $P < 0.003$ ), TG, TC concentration, TC/HDL-C and LDL/HDL-C ratios in trained rats compared with those in the control group ( $P < 0.001$ ). In conclusion, we found that endurance training induced significant elevation in *LXR $\alpha$*  gene expression, which correlated with enhanced levels of *ABCA1* mRNA and plasma HDL-C concentration.

**Keywords** ATP-binding cassette transporter A1 · Endurance training · Gene expression · HDL-C · Liver X receptor  $\alpha$

## Abbreviations

ABCA1	ATP-binding cassette transporter A1
CAD	Coronary artery disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LXR	Liver X receptor
RCT	Reverse cholesterol transport
TC	Total cholesterol
TG	Triglycerides

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## Introduction

Coronary artery disease (CAD) is among one of the greatest causes of morbidity and mortality in most countries. The frequency of its incidence correlates well with increment in plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations. Moreover,

population studies have shown a significant reverse relation between high-density lipoprotein cholesterol (HDL-C) level and atherosclerotic cardiovascular onset in humans (Nagasawa et al. 2012). The protective effect of HDL-C against atherosclerosis is well defined in reverse cholesterol transport (RCT) (Cooney et al. 2009). In the RCT pathway, HDL mediates the excess free cholesterol efflux from the peripheral cells to the liver for excretion into the bile (Baranowski 2008; Zhao and Dahlman-Wright 2010). Therefore, the liver acts as a lipid-regulating organ through numerous receptors. One of these receptors which plays a key role in cholesterol metabolism is the liver X receptor (LXR) that was identified in the rat liver in 1994 (Apfel et al. 1994). LXRs are the ligand-activated transcription factors of the nuclear receptor superfamily consisting of two isoforms  $\alpha$  and  $\beta$ . Both are involved in regulation of the expression of genes in cholesterol homeostasis (Lehmann et al. 1997; Wójcicka et al. 2007; Beltowski and Semczuk 2010). LXRs exert their main function as intercellular sterol (especially cholesterol) sensors, which cause different adapting procedures in response to cholesterol overload. These mechanisms include: (a) the stimulation of the RCT pathway; (b) prevention of cholesterol synthesis; (c) inhibition of cholesterol absorption in the intestine; (d) stimulation of cholesterol efflux in the form of HDL and its transfer to the liver; (f) cholesterol conversion to biliary acids and its excretion (Lehmann et al. 1997; Wójcicka et al. 2007; Beltowski and Semczuk 2010). LXRs stimulate the RCT through mediating two different pathways: increasing *ATP-binding cassette transporter A1 (ABCA1)* gene expression and enhancing the availability of extracellular cholesterol acceptors including apoprotein E (Wouters et al. 2005; Sato et al. 2008). Several studies have shown that the natural and synthetic agonists of LXRs cause an increment in the gene expression of *ABCA1* and excretion of cholesterol from the cells. Hence, they may play a potential therapeutic role for preventing atherosclerosis (Zhao et al. 2008). During the last few years, many studies have been conducted for understanding the effect of physical activities on the HDL level. It has been well accepted that regular endurance exercises could cause an increase in plasma HDL (Lespessailles et al. 2010; Dabidi 2011) and a decrease in plasma LDL and triglycerides (TG) levels (Zhao et al. 2011). However, the number of studies that have focused on the genetic mechanisms of HDL increase is very limited. Considering the importance of the *LXR $\alpha$*  gene and since there has not been any studies on the effect of physical exercises on the expression of this gene in the rat liver, this study was designed to show for the first time whether regular endurance exercises could cause any changes in the mRNA level of *LXR $\alpha$* .

## Materials and methods

### Animals

All experiments with animals were carried out according to the policy of the Ethics Committee of the University of Isfahan. Twelve Wistar male rats with an estimated weight of 200–220 g under normal light conditions (12 h light–dark cycle), temperature of  $23 \pm 1$  °C and moisture of  $50 \pm 3$  % were kept in special cages. Animals were fed with pellet rodent diet ad libitum and had free access to the water. The whole study period was carried out by one person. After 2 weeks of work in the laboratory and human intervention, rats were randomly divided to training ( $n = 6$ ) and control ( $n = 6$ ) groups.

### Exercise training protocol

The training program began with adaptation of rats to the apparatus for 7 days by placing them on the motor-driven treadmill (School of Medicine, Isfahan University of Medical Sciences). The training protocol was as follows: first, rats were exercised on the treadmill at 16 m/min for 15 min. One week after starting the experiment, the time and speed of running were increased steadily to 60 min/day at 20 m/min. After this step, the experiment group received a progressive exercise. They were again made to run on a treadmill for 60 min/day, 5 days a week. During the first week of exercises, the speed was set to 20 m/min, while for the second, third and fourth weeks it was adjusted to 23, 25 and 28 m/min, respectively.

Running exercises were continued for the next 4 weeks with a speed of 28 m/min, 60 min in each session and five times per week. The angle of inclination was 0 % gradient during the whole period of the study. This condition corresponded to a moderate intensity of about 65 % of maximal oxygen consumption (Powers et al. 1993; Vincent et al. 2000).

### Liver biopsy and blood sample

Twenty-four hours after the last exercise session (eighth week), rats were anesthetized intraperitoneally with a mixture of ketamine (30–50 mg/kg of body weight) and xylazine (3–5 mg/kg of body weight). Three ml of blood was taken from the right ventricle of each rat and immediately transferred to a test tube. The blood samples were centrifuged for 15 min at 4,000 rpm to separate the serum. Obtained sera were inserted into the test tubes and kept in a deep freezer ( $-80$  °C) for future measurements.

After collecting the samples, abdominal part of rats were opened and a portion of the liver was excised and washed in ice-cold saline. Then they were immediately frozen in liquid nitrogen for extraction of *LXR $\alpha$*  mRNA. The frozen liver tissues were kept in  $-80^{\circ}\text{C}$  for further experiments.

#### Measurements of lipids and lipoproteins

To determine the concentration of TC, TG and HDL-C, enzymatic methods were used in a calibrated biochemical analyzer (Hitachi 902 Automatic analyzer, Roche Diagnostics, USA) as follows. TC and TG were measured by assessment of the produced  $\text{H}_2\text{O}_2$  (Parakh and Gank 1982). For measurement of the HDL-C content, chemical precipitation of lipoproteins containing apoprotein B was performed using dextran sulfate- $\text{Mg}^{2+}$ . Then HDL-C was measured by coupling the product of cholesterol oxidase reaction to an indicator reaction as described (Warnick et al. 1982). The amount of LDL-C was calculated with respect to the values for TC, TG and HDL-C (Demacker et al. 1984).

#### mRNA level assessment of *LXR $\alpha$* and *ABCA1*

To extract RNA, 50 mg of the frozen liver tissue was homogenized. Total RNA was isolated by the RNA-Plus kit (CinnaGen, Iran) according to the manufacturer's instruction. Then, the RNA solution was extracted and decontaminated from any DNA and destructive RNA enzymes using *RNase free DNaseI* (Fermentas, Germany). Two  $\mu\text{g}$  of RNA from each sample was used for synthesizing the first cDNA using the cDNA synthesis kit (Fermentas, Germany) utilizing the oligo dT primer. RT-PCR was performed using 2  $\mu\text{l}$  cDNA and 5 pmol of each primer (Table 1) in a total volume of 20  $\mu\text{l}$  PCR reaction mixture. Real-time (SYBRGreen) PCR was carried out in a thermal cycler (Biorad, USA) as suggested by the protocol (TaKaRa). The PCR mixture contained 10  $\mu\text{l}$  Rotor-Gene SYBR Green PCR Master Mix (TaKaRa), 3 pmol of each primer and 25 ng cDNA for each reaction in a final volume of 20  $\mu\text{l}$ .

Relative mRNA concentrations were calculated from takeoff point of reactions using the software provided by the manufacturer and normalized to  *$\beta$ -actin* expression level in the same samples. All measurements were done in

duplicate and data were assessed and reported according to the  $\Delta\Delta\text{Ct}$  method.

#### Statistics

All results were expressed as mean  $\pm$  SD (standard deviations). All variables were compared by independent *t* test. Correlation was calculated using the Pearson product moment correlation. All statistical analysis was performed using SPSS (Version 13). *P* values  $<0.05$  were considered to be significant.

#### Results

Data revealed that liver *LXR $\alpha$*  expression was significantly ( $P < 0.001$ ) higher in trained rats when compared with control rats (Fig. 1). A similar result was obtained for assessment of hepatic *ABCA1* expression level which was significantly ( $P < 0.05$ ) higher in trained rats (Fig. 2). Plasma HDL-C was also significantly ( $P < 0.001$ ) higher in trained rats (Table 2). However, plasma LDL-C was significantly ( $P < 0.003$ ) decreased in trained rats (Table 2). Furthermore, plasma TC, TG concentrations, TC/HDL-C and LDL/HDL-C ratios were significantly ( $P < 0.001$ ) decreased in trained rats following 8 weeks of treadmill running programs (Table 2) consistent with previous studies (Petridou et al. 2005; Karanth and Jeevaratnam 2009).

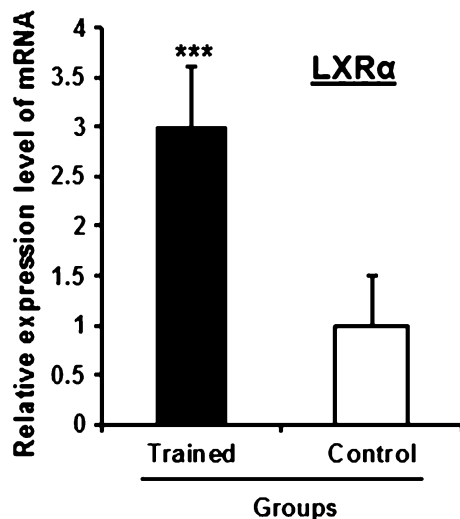
There were positive and significant correlations between liver *LXR $\alpha$*  mRNA expression and plasma HDL-C ( $r = 0.82$ ,  $P < 0.001$ ) concentrations, whereas a reverse significant correlation between *LXR $\alpha$*  mRNA expression and LDL-C ( $r = -0.66$ ,  $P < 0.01$ ), TG ( $r = -0.78$ ,  $P < 0.002$ ) and TC ( $r = -0.79$ ,  $P < 0.002$ ) was observed.

#### Discussion

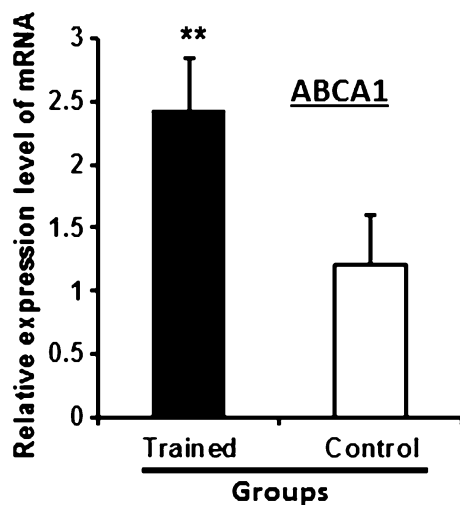
Physical exercise is a well-recognized activity that modulates HDL-C and affects the RCT process (Gupta et al. 1993; Leaf 2003; Olchawa et al. 2004). A recent study by Hong and coworkers has elucidated that *LXR $\alpha$*  plays an important role in the whole-body sterol homeostasis, mainly through the upregulation of genes involved in the

**Table 1** List of the primers

Genes	Forward primer (5'-3')	Reveres primer (5'-3')	Product size (bp)
<i>LXR<math>\alpha</math></i>	CCTGATGTTTCTCCTGACTC	TGACTCCAACCCTATCCTTA	147
<i><math>\beta</math>-Actin</i>	GGAGAAGATTTGGCACACAC	GGATGGCTACGTACATGGCTG	164
<i>ABCA1</i>	CTTGCTCCGTTATCCAACCTCCAG	GCTGTAATGTTCTCAGGACCTTGTG	162



**Fig. 1** The percentage of mRNA liver *X receptor α* (*LXRα*) gene expression with respect to *β actin* gene in trained and control groups. *Triple asterisks* indicate significant difference between trained and control groups at  $P < 0.001$



**Fig. 2** The percentage of mRNA *ATP-binding cassette transporter A1* (*ABCA1*) gene expression with respect to *β actin* gene in trained and control groups. *Double asterisks* indicate significant difference between trained and control groups at  $P < 0.05$

reverse RCT process (Hong et al. 2012). Furthermore, the activation of *LXRα* increased fatty acid utilization during exercise and prevented the fatigue caused by glucose insufficiency (Baranowski et al. 2011). It has been already indicated that low-intensity exercises caused an enhancement in *LXRα* gene expression in human leukocytes (Butcher et al. 2008). However the effect of physical activity, especially endurance exercise, on *LXRα* expression level in the liver has remained obscure. Thus, the present study was designed to address whether endurance

**Table 2** Lipid and lipoprotein profiles, and TC/HDL-C and LDL/HDL-C ratio in control and trained Wistar male rats

Variables	Training group	Control group	<i>P</i> value
HDL-C (mmol/L)	1.383 ± 0.119	0.922 ± 0.081	<0.001
LDL-C (mmol/L)	0.133 ± 0.077	0.271 ± 0.042	<0.003
TG (mmol/L)	0.306 ± 0.052	0.598 ± 0.066	<0.001
TC (mmol/L)	1.103 ± 0.062	1.642 ± 0.173	<0.001
TC/HDL-C	0.797 ± 0.113	1.780 ± 0.152	<0.001
LDL-C/HDL-C	0.096 ± 0.051	0.293 ± 0.046	<0.001

Data are expressed as mean ± SD in each group ( $n = 6$ ). Differences between contents of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol (TC) of training and related control groups are shown to be significant at  $P < 0.003$

training modulated *LXRα* expression level in the liver. Our data revealed a significant increase in *LXRα* expression level in the liver, resulting from performing endurance training. Furthermore, we found a positive significant correlation between liver *LXRα* mRNA expression and plasma HDL-C. The possible cause of plasma HDL-C increment following physical activities is that several modulations happen with respect to exercise such as an enhancement in the activity of several enzymes including lipoprotein lipase, lecithin:cholesterol acyltransferase and hepatic lipase, as well as in the content of phospholipid transport protein, cholesterol esteryl transport protein and ATP-binding cassette transporters family (Olchawa et al. 2004; Roth et al. 2011). Particularly in the latter group, activities of *ABCA1* and *ABCG1* are regulated by *LXRα* (Tang et al. 2012). Studies have shown that regular endurance exercises may also cause an increase in hepatic *ABCA1* gene expression (Khabazian et al. 2008; Ghanbari-Niaki et al. 2007). Numerous studies have shown that *LXRα* may activate *ABCA1* gene expression (Brunham et al. 2006; Fukumoto et al. 2002; Zhou et al. 2010). Here, we have shown that endurance exercise enhanced hepatic *ABCA1* mRNA level, implicating an increase in *LXRα* content and its activity may cause such enhancement. These modulations could affect an alteration in HDL content and therefore speed up the process of RCT. Very recently, in contrast to our results, Cote et al. (2013) have indicated that exercise did not increase hepatic *LXRα* transcripts. This discrepancy may be reflected by the effect of different intensities and various modes of exercise. The condition of exercise in the present study corresponded to a moderate intensity of about 65 % of maximal oxygen consumption versus 75 % of  $VO_2$  max, which was reported by Cote et al. However, more investigations are required to clarify the effect of different conditions of exercise on the contents of hepatic *LXRα* transcripts.

## Conclusion

Data indicated that treadmill running induced elevation in hepatic *LXR $\alpha$*  expression levels, which correlated well with an enhancement in hepatic *ABCA1* expression level and plasma HDL-C and decreased levels of plasma LDL-C, TG and TC.

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**Conflict of interest** None of the authors has any conflicts of interest to disclose and all authors support submission to this journal.

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