Science & Sports (2018) 33, 152—157

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ORIGINAL ARTICLE

Endurance training and LXR activation increased *LXRα* and *ABCA1* transcripts in Wistar male rats

L'entraînement en endurance et l'activation de LXR augmentent la transcription de LXRα *et* ABCA1 *chez le rat*

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Received 24 November 2015; accepted 11 February 2018
Available online 15 March 2018

KEYWORDS
ATP-binding cassette transporter A1;
Endurance training;
Liver X receptor;
Liver X receptor agonist;
Reverse cholesterol transport

Summary
Purpose. — LXR, belongs to the ligands activated transcription factors, regulates the expression of genes in cholesterol homeostasis. The aim of the present study was to examine combinatory effects of selective LXR activator-T0901317 and training on gene expression profiles of *LXRα* and *ABCA1*.
Material and methods. — To examine simultaneous effects of selective LXR activator-T0901317- and exercise on *LXRα* and *ABCA1* genes expression and lipids profile, Wistar male rats were assigned to four groups as animal models: Control group (Ctrl), trained group received exercise (Exc) on a motor-driven treadmill at 28 meter/min for 60 min/day, 5 days/week for 8 weeks, group receiving LXR agonist T0901317 (10 mg kg^{-1} day^{-1}) (Ago) for 1 week, group received both endurance training and LXR agonist T0901317 (Exc&Ago). Finally, rats were killed and blood was taken for lipids measurement. A portion of the liver was also excised for assessment of *LXRα* and *ABCA1* transcripts.

Abbreviations: ABCA1, ATP-binding cassette transporter A1; HDL-C, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; LRE, LXR response element; LXR, liver X receptor; RCT, reverse cholesterol transport; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element-binding protein-1c; TC, total cholesterol; TG, triglycerides.

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https://doi.org/10.1016/j.scispo.2018.02.005

Results. — A significant increase in *LXRα* and *ABCA1* transcripts was observed in Exc&Ago group when compared to other groups. However, there was not a synergistic response in plasma lipid and lipoprotein concentrations despite a significant increase in *LXRα* and *ABCA1* mRNA levels, possibly due to a physiological negative feedback loop, the response to exercise could be negated by the effects of the agonist in plasma lipid and lipoprotein profiles.

MOTS CLÉS
ATP-binding cassette transporter A1 ;
Entraînement en endurance ;
Récepteur X du foie ;
LXR ;
Agoniste LXR ;
Transport rétrograde du cholestérol

Résumé
Objectifs. — LXR qui appartient au groupe des facteurs de transcription activés par des ligands, contrôle l'expression des gènes impliqués dans l'homéostasie du cholestérol. Le but de cette étude est d'évaluer les effets combinés d'un activateur sélectif de LXR (T0901317) et de l'entrainement en endurance, sur l'expression des gènes *LXRα* et *ABCA1*.
Matériel et méthodes. — quatre groupes de rats Wistar mâles ont été constitués; groupe Contrôle (Ctrl), groupe Entraîné en endurance (Exc) soumis à un exercice sur tapis roulant à la vitesse de 28 m/min, pendant 60 min/j, 5 j/semaine, pendant 8 semaines, groupe recevant un agoniste activateur de LXR (T0901317, 10 $mg.kg^{-1}.day^{-1}$) (Ago) pendant 1 semaine, groupe soumis à la fois à l'entrainement, et recevant l'agoniste de LXR T0901317 (Exc&Ago). À la fin de l'expérimentation, les animaux sont sacrifiés, et leur sang prélevé afin de mesurer leur profil lipidique. Un fragment du foie est aussi prélevé afin de mesurer les transcrits spécifiques (mRNA) de *LXRα* and *ABCA1*.
Résultats. — Une augmentation significative des mRNA de *LXRα* and *ABCA1* est observée dans le groupe Exc&Ago, comparativement aux autres groupes expérimentaux. Cependant, cette augmentation de la transcription des gènes codant pour *LXRα* and *ABCA1* n'est pas associée à des effets associés de l'entraînement et de l'agoniste LXR sur le profil lipidique plasmatique. Ce résultat peut être lié à une boucle de rétro-contrôle négative, les réponses à l'exercice pouvant être annulées par les effets de l'agoniste de LXR sur le profil lipidique plasmatique.

1. Introduction

Over the last decade, both in vivo and in vitro studies have revealed that liver lipid and carbohydrate metabolism are modulated by nuclear receptors which function as ligand-activated transcription factors that bind to DNA and translate physiological signals into gene regulation [1]. Liver X receptor α (*LXRα*) is a member of such group 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 [2]. Generally, liver X receptors (LXRs) family of nuclear hormone receptors act as transcription factors for several classes of genes [3]. There are two known *LXR* subtypes termed α and β which upon activation form heterodimers with retinoid X receptor (RXR) and bind to LXR response element (LRE) found in the promoter region of the target genes [4]. These isoforms, *LXRα* and *LXRβ*, differ in distribution and function, the former being highly expressed in liver, intestine, and macrophages, where it is involved in lipid metabolism [5,6]. When LXR is activated by the respective agonist, it gains an ability to make a heterodimer with RXR, which subsequently this heterodimer binds to LRE regions in promoter sequences of different target genes and modifies the expression of target genes. [6]. Several endogenous compounds are accounted as LXR agonists including a number of oxidized cholesterol derivatives referred to as oxysterols [7]. Thus, LXRs were shown to function as sterol sensors protecting the cells from cholesterol overload by stimulating reverse cholesterol transport (RCT) and activating its conversion to bile acids in hepatocytes. In addition, synthetic LXR agonists including T0901317, promote hepatic lipogenesis via up-regulation of sterol regulatory element-binding protein-1c (SREBP-1c) [7]. Therefore, synthetic LXR activators up-regulate genes involved in cholesterol efflux also in liver indicating normal response to LXR stimulation [8]. To our knowledge, LXR stimulation is also involved in the modulation of the RCT, the process by which excess cholesterol is removed from extra-hepatic tissues and transported back to the liver [9]. This observation is supported by several distinct evidences: LXR agonists, through up-regulating *ABCA1* and *ABCG1* expression in cell culture, may stimulate cellular cholesterol efflux, the first step of RCT [10]. In this regard, several studies have revealed that treatment of mice with T0901317 or GW3965 induced a significant increase in circulating plasma triglyceride and phospholipid levels [11]. Because these lipoproteins have a well-established role in cholesterol efflux, we wondered whether LXR may promote RCT through the increase in the efflux potential of plasma. Hence, we selected the non-steroidal compound, T0901317, to activate LXRα. T0901317 has been already demonstrated to increase HDL plasma levels [11] and to suppress the development of atherosclerotic lesions [12] in mice. On the other hand, in our previous published paper, we elucidated that endurance training enhanced gene expression levels of *LXRα* and *ABCA1*. We showed that regular endurance exercises

could cause an increase in plasma HDL and a decrease in plasma LDL and triglycerides (TG) levels [13]. Thus, physical exercise is a well-recognized activity that modulates HDL-C and affects the RCT process. However, the combination of activation of LXRα with an induction in the respective gene by physical training on plasma levels of HDL, LDL and TG is not testified yet. In our previous study, we indicated that *LXR* expression up-regulated by an endurance training which subsequently triggered an enhancement in the expression level of *ABCA1*. In the present study, we aimed to examine the combinatory effects of a selective LXR activator-T0901317 and training on gene expression profiles of *LXR*α and *ABCA1*.

2. Materials and methods

2.1. Animals and study design

All experiments with animals were carried out according to the policy of the ethics committee of the University of Isfahan. Twenty-four Wistar male rats with an estimated weight of 200—230 g were kept under normal light conditions (12 h light/dark cycle), temperature of $23 \pm 1\,^{\circ}C$ and moisture of $50 \pm 3\%$ 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, a total of 24 animals were randomly divided into four groups: (1) Control group (Ctrl) ($n = 6$), (2) Trained group (Exc) ($n = 6$), (3) T0901317 group (Ago) ($n = 6$) and (4) Trained & T0901317 group (Exc&Ago) ($n = 6$).

Animals in Ago group were received T0901317 (Santa-Cruz Biotechnology, California, USA; $10\,mg\,kg^{-1}\,day^{-1}$, suspended in 0.5% carboxymethylcellulose) for 1 week. The solutions were administrated once daily by an oral gavage. The chosen dose of the drug was previously found to be the highest that can be administered to rats without affecting sharp changes on appetite and weight of the animals [14]. Exc&Ago group, first received exercise on a motor-driven treadmill at 28 meter/min (0% grade) for 60 min/day, 5 days/week for 8 weeks, then were treated with selective liver receptor agonist, T0901317 ($10\,mg\,kg^{-1}\,day^{-1}$) for 1 week. Twelve hours after treatment, animals were killed and blood was taken from the right ventricle of each rat. Plasma was collected for HDL-C, 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*α and *ABCA1* mRNA levels.

2.2. Exercise training protocol

The training program began with adaptation of trained group 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 meter/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 meter/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 meter/min, while for the second, third and fourth weeks it was adjusted to 23, 25 and 28 meter/min, respectively. Running exercises were continued for the next 4 weeks with a speed of 28 meter/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 [15,16]. Liver biopsies and blood samples of rats were taken twenty-four hours after the last exercise session (eighth week) from those who were anesthetized with intraperitoneal injection of 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. Sera were inserted into the test tubes and kept in a deep freezer ($-80^{\circ}C$) for future measurements.

After collecting the samples, abdominal part of rats was 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*α mRNA. The frozen liver tissues were kept in $-80^{\circ}C$ for further experiments.

2.3. 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 H_2O_2 [17]. For measurement of the HDL-C content, chemical precipitation of lipoproteins containing apoprotein B was performed using dextran sulfate-Mg^{2+}. Then HDL-C was measured by coupling the product of cholesterol oxidase reaction to an indicator reaction as described [18]. The amount of LDL-C was calculated with respect to the values for TC, TG and HDL-C [19].

2.4. Gene expression analysis by real-time PCR

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 μg 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 μL cDNA and 5 pmol of each primer (Table 1) in a total volume of 20 μL PCR reaction mixture. Simultaneously, RT — control sample was prepared to ensure elimination of all traces of DNA from the samples. Real-time (SYBRGreen) PCR was carried out in a thermal cycler (Biorad, USA) as suggested by the protocol (TaKaRa). The PCR mixture contained 10 μL 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 μL. Relative mRNA concentrations were calculated from takeoff point of reactions using the software provided by the manufacturer and normalized to β-*actin* expression level in the same samples. All measurements were done in duplicate and data were assessed and reported according to the $\Delta\Delta$Ct method.

Table 1 List of the primer sequences.

Genes	Forward primer (5′—3′)	Reverse primer (5′—3′)	Product size (bp)
LXRα	CCTGATGTTTCTCCTGACTC	TGACTCCAACCCTATCCTTA	147
ABCA1	CTTGCTTCCGTTATCCAACTCCAG	GCTGTAATGTTCTCAGGACCTTGTG	162
β-actin	GGAGAAGATTTGGCACCACAC	GGATGGCTACGTACATGGCTG	164

2.5. Statistical analysis

All data are presented as means ± standard error of mean (SEM). A two-way analysis of variance (ANOVA) was used to determine the main effects of exercise, the effects of Ago administration and interactions (Exercise × Ago administration) for all parameters. Also results were analyzed statistically by Pearson correlation for between *LXRα* and *ABCA1* mRNA levels. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Gene expression analysis

LXRα and *ABCA1* mRNA expressions in liver were examined in male rats. There were main effects for exercise on *LXRα* and *ABCA1* mRNAs where trained animals had higher *LXRα* and *ABCA1* mRNAs than non-trained animals ($F = 287.88$, $P < 0.001$) ($F = 231.6$, $P < 0.001$), respectively (Supplemental figure 1, 4). There were main effects for Agonist on *LXRα* and *ABCA1* mRNAs where Ago-treated animals had higher *LXRα* and *ABCA1* mRNAs vs. non-Ago-treated animals ($F = 1417.74$, $P < 0.001$) ($F = 1123.69$, $P < 0.001$), respectively (Supplemental figure 2, 5) and there were interactions between exercise and Agonist for *LXRα* ($F = 13.37$, $P = 0.002$) and ABCA1 mRNAs where post hoc testing revealed Agonist increased these gene expressions in exercised rats ($F = 17.74$, $P < 0.001$) (Table 2) (Supplemental figure 3, 6). Transcriptional levels of these genes enhanced significantly in Exc&Ago group compare with the other groups. Furthermore there was a synergistic response to exercise and Ago administration on *LXRα* and *ABCA1* mRNAs. Of note, there were positive and significant correlations between *LXRα* mRNA and *ABCA1* mRNA expression levels ($r = 0.91$, $P < 0.001$) [Supplemental table].

3.2. Analysis of lipid profile modulations

There were main effects for exercise on HDL ($F = 4.24$, $P = 0.05$), LDL ($F = 5.7$, $P = 0.02$), TC ($F = 13.77$, $P = 0.001$), TG ($F = 837.73$, $P < 0.001$) where trained animals had higher HDL than non-trained animals, but trained animals had lower LDL, TC and TG vs. non-trained animals. There were main effects for Agonist on HDL ($F = 33.98$, $P < 0.001$), LDL ($F = 7.52$, $P = 0.01$), TC ($F = 7.4$, $P = 0.01$), TG ($F = 1372.85$, $P < 0.001$) where Ago-treated animals had higher HDL and TG than non-Ago-treated animals, but Ago-treated animals had lower LDL and TC vs non-Ago-treated animals. There were interactions between exercise and Agonist on amount of HDL ($F = 29.27$, $P < 0.001$), LDL (10.71, $P = 0.004$), TC ($F = 16.16$, $P = 0.001$), TG ($F = 342.53$, $P < 0.001$) (Table 3). Furthermore, there was an antagonistic response to exercise and Ago administration in plasma lipid and lipoprotein concentrations [Supplemental table].

3.3. Analysis of body weight changes

Body weight of rats was measured after treatment. There were main effects for exercise in body weight where trained animals had lower body weight than non-trained animals ($F = 4.9$, $P = 0.03$) and There were main effects for Agonist in body weight where Ago-treated animals had lower body weight than non-Ago-treated animals ($F = 10.73$, $P = 0.004$) and there were interactions between exercise and Agonist for body weight ($F = 5.09$, $P = 0.03$) (Table 3). Furthermore, there was an antagonistic response to exercise and Ago administration in body weight [Supplemental table].

4. Discussion

In this study, we delineated the increased transcript levels of *LXRα* and *ABCA1* in the liver of the trained rats, as compared to the non-trained rats, and these gene expressions were significantly higher in Ago-treated rats, as compared to non-Ago-treated counterparts. Further studies demonstrated that *LXRs* regulate expression of genes involved in cholesterol transport and metabolism including *ABCA1*, which plays a crucial role in HDL-C remodeling [7,20]. LXR plays important roles in the metabolism of cholesterol, glucose, and fatty acids. Since activation of LXR can accelerate the reverse transport of cholesterol via increasing the expression of *ABCA1* and *ABCG1*, this nuclear receptor has been recognized as a potential target for treatment of atherosclerosis [21,22].

Despite the growing information about the role of LXR agonist in increased *ABCA1* expression and enhanced RCT process [23,24], there are few studies focused on synergistic effects of endurance training and liver X receptor activation on *LXRα* and *ABCA1* genes expression. Here, we demonstrated this synergism caused an enhancement in expression levels of aforementioned genes.

In agreement with the previous studies, we observed that treatment of mice with T0901317 induced a significant increase in circulating HDL [11,12,25]. The similar outcome was observed when endurance training was subjected on mice [26,27]. However, surprisingly both LXR agonist treatment and endurance training uncooperatively increased amount of HDL while antagonistic effect was observed when both interventions were performed. Similar observations were attained for total cholesterol. Results

Table 2 Two way ANOVA test for RNA expression.

Parameters	Groups				Main effect		Interaction
	Ctrl	Exc	Ago	Exc & Ago	Exercise	Agonist	
LXRα	1 ± 0.01	3.48 ± 0.27	7.34 ± 0.67	11.23 ± 0.62	$P < 0.001$	$P < 0.001$	$P = 0.002$
ABCA1	1 ± 0.006	2.90 ± 0.13	6.22 ± 0.75	9.73 ± 0.4	$P < 0.001$	$P < 0.001$	$P < 0.001$

Differences between mRNAs expression of all groups are shown to be significant at $P < 0.05$.

Table 3 Two way ANOVA test for lipid profile and body weight.

Parameters	Groups				Main effect		Interaction
	Ctrl	Exc	Ago	Exc&Ago	Exercise	Agonist	
HDL (mmol/L)	35.66 ± 3.1	53.5 ± 4.6	62.5 ± 7.8	54.5 ± 6.6	$P = 0.05$	$P < 0.001$	$P < 0.001$
LDL (mmol/L)	10.5 ± 1.6	5.16 ± 2.9	4.83 ± 2.3	5.66 ± 2	$P = 0.02$	$P = 0.01$	$P = 0.004$
TC (mmol/L)	63.5 ± 6.7	42.66 ± 2.4	45.33 ± 7.2	46.16 ± 8.4	$P = 0.001$	$P = 0.01$	$P = 0.001$
TG (mmol/L)	53 ± 5.9	27.16 ± 4.6	183.16 ± 6	72.16 ± 6.4	$P < 0.001$	$P < 0.001$	$P < 0.001$
Body weight (g)	285.16 ± 37.7	234.66 ± 27.3	222.66 ± 9.1	223.16 ± 28.4	$P = 0.03$	$P = 0.004$	$P = 0.03$

Differences between lipid profile and body weight of all groups are shown to be significant at $P < 0.05$.

have shown that regular endurance exercises and LXR agonist reduce TC.

On the other hand, previous studies with synthetic LXR agonists described increased plasma levels of triglycerides in response to LXR activation [11]. This conclusion is mediated by up-regulation of SREBP-1c and other enzymes involved in fatty acid and triglyceride synthesis. However, recent study by Baranowski and coworkers has elucidated that in rats who were pre-treated with T0901317, there was a marked alteration in lipid and carbohydrate metabolism during exercise as LXR activation spared muscle glycogen and enhanced consumption of intramuscular triacylglycerol [28]. To our knowledge plasma TG content decreases upon endurance training [13]. This phenomenon explains why in Exc&Ago mice; plasma TG level was not increased to the same level as Ago group. Furthermore, there was an antagonistic response to exercise and Ago administration in plasma TG concentration.

5. Conclusion

Data indicated that both endurance training and LXR agonist induced elevation in hepatic *LXRα* and *ABCA1* genes expression levels and plasma HDL-C concentration. Also, exercise and LXR agonist induced a decrease in plasma LDL-C and TC. Although, we did not measure other plasma factor, which are involved in HDL-C remodeling, but an endurance training and T0901317 induced RCT has to in consideration. Further investigation is required clarifying the synergistic effect of different dose of T0901317 and endurance training on *LXRα* and *ABCA1* transcript levels. It is possible that there is a negative feedback loop in which the physiological responses to exercise is somehow negating the effect of the agonist. Importantly, there was not a synergistic response in plasma lipid and lipoprotein concentrations despite a significant increase in *LXRα* and *ABCA1* mRNA levels. It is necessary to mention that one of the limitations of this study was lack of protein measurement of the aforementioned genes due to the financial constraints. However, it would be quite interesting to get a confirmation in the protein levels of such genes, as we propose to carry out in the future experiments.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.scispo.2018.02.005.

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