Long-term exercise training affects age-induced changes in HSP70 and apoptosis in rat heart

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Abstract. The aim of this study was to test the effects of age and long-term exercise training on antioxidant, heat shock protein 70 (HSP70) expression and apoptosis by comparing the hearts of sedentary and trained rats.

Training groups went under 3-, 6- and 9-months of regular exercise (25 m/min with a 0% slope, 60 min/day and 6 days/week).

Level of glutathione increased with age in trained and sedentary control rats but level of this factor unchanged by training. Activity of mitochondrial superoxide dismutase (mtSOD) increased in heart homogenates of 6- and 9-months trained animals as compared with their sedentary. The rates of apoptosis were increased with age but level of apoptosis in 9-months trained group was significantly lower than corresponding sedentary. Levels of HSP70 expression were significantly decreased with age while long-term training induced marked increase in HSP70 expression levels.

These results show that a long-term regular exercise affects age-induced changes in mtSOD, HSP70 and apoptosis as it increases mtSOD activities and HSP70 expression levels and elicits a marked reduction in apoptosis rate in rat myocardium. However, a shorter training program is not effective.

Key words: Antioxidant — Cell death — Cardiomyocyte — Exercise and HSP70

Introduction

Increased oxidative stress with age is a source of damage to cellular structure and function (Bar-Shai et al. 2008). Tissue with few or no cell divisions, such as heart is theoretically more susceptible to accumulative damage caused by oxidative stress (Rinaldi et al. 2006). In addition, the cardiac muscle may be particularly vulnerable to oxidative damage because it works continuously, it has a high VO₂ and its antioxidant defenses are less effective than those of other contracting muscles (Leeuwenburgh et al. 1999).

This stress can be occurred by an increase in oxidants, a decrease in antioxidant defenses or both of them (Rinaldi et al. 2006) which might result in apoptosis (Pollack et al. 2002). Apoptosis is a major factor contributing to the loss of myocytes as the heart ages (Kwak et al. 2006) and it has deleterious effects on cardiac structure and function (Centurione et al. 2002).

The myocardium uses enzymatic and non-enzymatic systems to neutralize reactive oxygen species (ROS) (Leeuwenburgh et al. 1999). Superoxide dismutase (SOD) and glutathione (GSH) systems are important antioxidant mechanisms involved in the elimination of ROS (Pollack et
Soufi et al. 2002). On the other hand, oxidative stress induces heat shock proteins (HSPs) expression (Snoeckx et al. 2001). Although HSP27 and HSP90, as well as other HSPs, have been associated with cellular protection against stress, evidence indicates that members of the 70-kDa family are the HSPs most responsible for cell protection (Powers et al. 2008). Apoptosis probably evolved in the context of HSP70 (Lindquist and Craig 1988). Recent studies have indicated that the heart survival promoting effects of HSP70 can be partly attributed to the suppression of apoptosis (Zhao et al. 2007; Powers et al. 2008) and enhancement of antioxidant capacity (Powers et al. 2008).

Protective cellular antioxidants have been reported to change with age and exercise (Kaul et al. 1993; Singal et al. 1998). Clinical studies have shown that regular exercise decreases cardiovascular morbidity and mortality in adults and in the elderly (Rinaldi et al. 2006), improves muscle performance even in old age (Bar-Shai et al. 2008) and delays the accumulation of cell damage and physiological dysfunction, which are characteristic of the aging process (Radak et al. 2002).

Many studies reveal that exercise training provides cardiac protection by enhancing antioxidant defense (Bar-Shai et al. 2008; Rinaldi et al. 2006; Powers et al. 2008) but only few of them employ the effect of long-term exercise training (more than 12 weeks) on cardiac antioxidants and HSPs specially (Kanter et al. 1985; Moran et al. 2004; Bar-Shai et al. 2008). Surprisingly, these few articles expressed that if intensity, duration of the daily sessions, and total duration of training program are not prolonged (more than 3 months), the total training volume might be insufficient to elicit adaptation, considering the low ability of myocardium to up-regulate its antioxidant defenses (Moran et al. 2004) or if the prolonged exercise (up to 21 months) is initiated at young age it has more benefits than the identical exercise regime is initiated at old age (Bar-Shai et al. 2008). Nonetheless, these reports alone do not provide definite evidence about the effect of regular exercise on the heart HSPs and antioxidants.

On the other hand, there are few studies about the effect of regular exercise (up to 3 months) on the heart apoptosis rate (Siu et al. 2004; Quindry et al. 2005) and about the physiologic role of apoptosis in postmitotic muscle cells in young and adult healthy individuals during age progression (Centurione et al. 2002; Torella et al. 2004). Also, responsible mechanism of exercise cardioprotective effect on apoptosis rate is not well understood.

The aim of the present study was to investigate the role of long-term exercise training on antioxidant enzymes, HSP70 and apoptosis during the maturation and late maturation phases in rat heart. This study seeks to answer some questions relating to how exercise may attenuate the decline in cell loss as age progresses.

**Materials and Methods**

**Animals**

Seventy-two male Wistar rats (three months old and body mass of 230 ± 14 g) were recruited from The Laboratory Animal House in Tabriz University of Medical Sciences. Animals were housed at room temperature (22–28°C) with 12/12 h light/dark cycles and had access to food and water ad libitum. The study protocol was designed in accordance with the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication, No. 86-23, revised 1996) and approved by the Ethics Committee for the Use of Animals in Research at Tabriz University of Medical Sciences.

**Training program**

The rats were randomly divided into sedentary (n = 36) and trained groups (n = 36). Each group was divided into three subgroups (3-, 6-, and 9-month subgroups). All the rats in the trained group ran on a rodent motor-driven treadmill (Danesh Yakhteh Co. Tabriz, Iran) and performed 25 m/min with a 0% slope, 60 min/day and 6 days/week (Jain et al. 2000). The rats were initially exercised on a rodent treadmill at 10 m/min for 35 min. The volume and duration of running were increased 4 m/min and 5 min/day until animals were exercising at 25 m/min for 60 min/day. Whole experiment was done in the same period of the day cycle.

To account for the stress of handling, sedentary control rats were placed on a nonmoving treadmill daily. After 3, 6 and 9 months of training, trained rats and their sedentary counterparts belonging to the 3-, 6- and 9-month subgroups (at each subgroups, n = 12) were sacrificed, respectively.

**Tissue processing and homogenate preparation**

48 h after the last exercise-training session, the rats were anesthetized with ether and sacrificed by decapitation. The heart was quickly removed, washed with ice-cold saline, and blotted. Six hearts were assigned to apoptosis analysis and fixed in 10% formalin. Six remaining hearts were assigned to oxidative stress analysis and their atria and great blood vessels were trimmed. The ventricles were weighed and the apices were cut and quickly frozen in liquid nitrogen. For oxidative stress analysis, cardiac homogenates were prepared at 0–4°C as described by Rothermel et al. (2000). In brief, 50 mg of ventricle muscle were homogenized on ice in 1 ml of ice-cold lysis buffer (10 mmol/l NaCl, 1.5 mmol/l MgCl2, 20 mmol/l HEPES, 20% glycerol, 0.1% Triton X-100, 1 mmol/l dithiothreitol, pH 7.4). The homogenates were centrifuged at 1000 rpm for 1 min at 4°C. The supernatant containing the cytoplasmic protein fraction was collected and a protease...
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inhibitor cocktail (104 mmol/l AEBSF; 0.08 mmol/l apro-
tinin, 2 mmol/l leupeptin, 4 mmol/l bestatin, 1.5 mmol/l pepstatin A, and 1.4 mmol/l E-64) (PB340; Sigma-Aldrich, St. Louis, MO) was added to it and stored at ~80°C until use. Protein concentration of the supernatant was estimated using Bradford technique (Bradford 1976).

Antioxidant

Activity of mitochondrial SOD (mtSOD) was determined spectrophotometrically by the method described by Marklund and Marklund (1974), with minor modifications. In brief, an adequate amount of protein (2 mg tissue wet weight) was incubated at 25°C with 1 mmol/l N,N-bis[2-(bis(carboxymethyl)amino)-ethyl] glycine in 50 mmol/l Tris-HCl, pH 8.2, in 1 ml final volume. The reaction was initiated with 1 mmol/l KCN and 0.3 mmol/l pyrogallol, which auto-oxidation rate was recorded at 420 nm. One unit of activity was defined as the amount of enzyme necessary to inhibit the rate of pyrogallol auto-oxidation by 50%.

The GSH content of the ventricles was determined by the method described by Griffith (1980) in homogenates prepared as follows. The ventricles’ apices were homogenized in 5 vol. of 1% trichloroacetic acid (w/v), after which the homogenates were centrifuged at 18,000 × g for 10 min. For total GSH (tGSH) content, an aliquot of the supernatant was diluted 1 : 50 and 100 μl of this preparation was added to a mixture containing 0.21 mmol/l NADPH, 0.6 mmol/l 5, 5’-dithio-bis(2-nitrobenzoic acid) (DTNB), 5 mmol/l EDTA, and 0.5 U of GSH reductase in 100 mmol/l sodium phosphate buffer, pH 7.5, in a final volume of 1 ml. The absorbance at 412 nm was recorded. GSH content was calculated by comparing the rate observed with a standard curve generated with predetermined amounts of GSH. Oxidized GSH (GSSG) content was determined in supernatant aliquots by the same method after derivatization of GSH with 3.88% 2-vinylpyridine (v/v).

Western blotting

HSP70 expression was assayed by the method described by Always (1997), with minor modifications. Forty micrograms of extracted cytoplasmic fractions were boiled for 5 min at 100°C in Laemmli buffer, loaded on each lane of a 12% polyacrylamide gel, and separated by SDS-PAGE for 1.5 h at 20°C. The gels were blotted to PVDF membranes and stained with Ponceau S red (Sigma) to confirm equal loading and transfer of proteins to the membrane in each lane. Similar loading between the lanes was further verified by loading gels in duplicate with one gel stained with Coomassie blue. The membranes were blocked in 5% nonfat milk in Tris-buffered saline with 0.05% Tween 20 at room temperature for 1 h and probed with anti-HSP70 mouse monoclonal antibody (Abcam, ab6535; Cambridge, UK) at a dilution of 1 : 5000 for 1 h at room temperature. Immunodetection of the primary antibody was carried out with peroxidase-labeled rabbit anti-mouse antibody (Abcam, ab6728), at a dilution of 1 : 3500. The blots were washed and the reactions were visualized using 3,3-diaminobenzidine substrate. Quantification was performed in the linear absorption range by computerized densitometry using commercially available software (Scion Image 4.0; Frederick, Maryland, USA). For comparison between blots, one aliquot of the same homogenate was loaded as a standard in each gel to allow data normalization.

Quantification of apoptosis

The left ventricle was immersion-fixed in 10% neutral formalin and embedded in paraffin. Serial sections of 4-μm thicknesses were prepared. Cardiomyocyte apoptosis was evaluated via the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) method with the use of In Situ Cell Death Detection Kit, POD (Cat. No. 1684817; Roche, Germany) according to manufacturer’s instructions, with some modifications (Xu et al. 2005). Briefly, the tissue sections were dewaxed and rehydrated by heating at 60°C, followed by washing in xylene and rehydration through a graded series of ethanol and double distilled water. Then, the sections were incubated for 30 min at 21–37°C with proteinase K working solution (20 μg/ml in 10 mmol/l Tris-Cl, pH 7.6). The sections were rinsed with PBS and incubated with the TUNEL reaction mixture for 1 h at 37°C in a humidified chamber. As a positive control, sections were treated with DNase I (1 mg/ml; Sigma) for 10 min to introduce nicks in the genomic DNA. After converter peroxidase was added, the sections were incubated for 30 min at 37°C in a humidified chamber. Then the 3,3-diaminobenzidine substrate was added for the visualization of nuclei with DNA nick end labeling. The sections were counter-stained with toluidine blue to show normal nuclei. The percentage of myocytes with DNA nick end labeling was analyzed by counting the cells exhibiting brown nuclei at ×40 magnification in 5 randomly chosen fields (1 mm²) in triplicate plates. The number of TUNEL-positive cardiomyocytes was counted by double-blinded observation.

Data analysis

Data were expressed as mean ± SD and were analyzed by a two-way ANOVA. To test for the two main effects (exercise training and protocol duration) and for the interaction between them, a standard computerized statistical program, SPSS13.0 for Windows software, was used (SPSS Inc., Chicago, IL, USA). When a significant p-value was obtained, a post hoc Tukey test was employed to determine the differ-
ences between the groups. A $p$-value of $<0.05$ was considered statistically significant.

**Results**

**Effect of age and training on body and left ventricle weights**

Table 1 depicts body and left ventricle weights and left ventricle to body weight ratio of the all sedentary and trained groups. As expected, older animals had a higher body weight and left ventricle weight as compared to younger animals. Exercise program resulted in a lower body weight in trained animals compared to their sedentary groups. Accordingly, the left ventricle to body weight ratio was smaller in sedentary than trained rats because of the training induced decrease in body mass.

**Antioxidant**

The results obtained for tGSH and GSSG content and mtSOD activity are summarized in Figure 1. Statistical analysis for tGSH and GSSG failed to demonstrate a significant main effect for the training factor. However, significant increase was observed when comparing the 6- and 9-month subgroups with their 3-month counterparts ($p < 0.01$). Statistical analysis revealed a significant main effect for the training factor ($p < 0.05$), as mtSOD activity increased when comparing the 6- and 9-month trained animals with their sedentary controls ($p < 0.05$). In addition, a significant main effect for age factor was observed ($p < 0.05$), as mtSOD activity was enhanced in both the long-term trained subgroup and its sedentary control subgroup in comparison to their corresponding 3-month subgroup.

**HSP70 expression level**

The HSP70 content in heart homogenates was estimated by Western blot analysis. Figure 2 shows that age significantly reduced HSP70 level in sedentary 6- and 9-month subgroups.

**Table 1. Body and left ventricle weights in sedentary and trained rats**

<table>
<thead>
<tr>
<th>Protocol duration</th>
<th>Group</th>
<th>Body weight (g)</th>
<th>Left ventricle weight (g)</th>
<th>Left ventricle /body weight ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Sedentary</td>
<td>373 ± 41</td>
<td>0.91 ± 0.09</td>
<td>2.43 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Trained</td>
<td>311 ± 29 *</td>
<td>0.82 ± 0.1</td>
<td>2.63 ± 0.3</td>
</tr>
<tr>
<td>6 months</td>
<td>Sedentary</td>
<td>491 ± 38</td>
<td>1.11 ± 0.06</td>
<td>2.26 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Trained</td>
<td>401 ± 21 *</td>
<td>1.05 ± 0.08</td>
<td>2.61 ± 0.2 **</td>
</tr>
<tr>
<td>9 months</td>
<td>Sedentary</td>
<td>618 ± 51 **</td>
<td>1.32 ± 0.1 **</td>
<td>2.11 ± 0.1 **</td>
</tr>
<tr>
<td></td>
<td>Trained</td>
<td>498 ± 33 **</td>
<td>1.27 ± 0.1 **</td>
<td>2.55 ± 0.1 **</td>
</tr>
</tbody>
</table>

Values are mean ± SD ($n = 12$ rats). Symbols: * $p < 0.05$ and ** $p < 0.01$, significantly different from the corresponding sedentary group; * $p < 0.05$ and ** $p < 0.01$, significantly different from the corresponding 3-month group; * $p < 0.05$, significantly different from the corresponding 6-month group.
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(29 and 30%, respectively) when compared with their corresponding 3-month subgroup (p < 0.01), but in corresponding trained subgroups, HSP70 level significantly increased (21 and 30%, respectively) compared with their corresponding 3-month subgroup (p < 0.05 and ** p < 0.01, respectively). Moreover, HSP70 level was significantly higher in 6- and 9-month trained subgroups (63 and 73%, respectively) when compared with their corresponding sedentary subgroups (p < 0.01), but the increase in the 3-month trained subgroup was not significant.

Apoptosis

The results obtained for TUNEL estimated rate of apoptosis in heart (Figure 3) indicated that the rate of apoptosis was significantly lower after 9 months of training compared with their sedentary controls (p < 0.01). In addition, a significant main effect for protocol duration was observed, as apoptosis rate was enhanced in both the long-term trained subgroup and its sedentary control subgroup compared to their corresponding 3-month counterparts.

Discussion

In our previous study, we showed that age progression was associated with increased cardiac lipid peroxidation, which is a well-known marker of oxidative stress, but it is not associated with significant changes in the catalase and GSH peroxidase levels (Ahmadiasl et al. 2007). The age-related
increase in oxidative stress would be expected to boost antioxidant defense mechanism (Bar-Shai et al. 2008). Since myocardium uses enzymatic and non-enzymatic systems to neutralize ROS (Leeuwenburgh et al. 1999), in the present study we measured mtSOD activity, tGSH, GSSG and HSP70 protein expression levels in rat left ventricles. The main finding of the present study is that long-term (6 and 9 months) treadmill training induces: i) an increase in myocardial antioxidant defenses activity, as evidenced by the enhancement in mtSOD activity; ii) a significant increase in HSP70 level; and iii) a marked decrease in apoptosis rate in the trained animals. In contrast, a shorter (3 months) training protocol of the same intensity did not modify these parameters significantly.

A large number of previous studies have analyzed the influence of exercise training on myocardial antioxidant systems but the overall results are controversial (Atalay and Sen 1999). Only two previous studies (Kanter et al. 1985; Moran et al. 2004) have evaluated the adaptive response of antioxidant defense mechanism to a long-term training protocol (24 and 21 weeks, respectively) in rats and only one of them measured the level of HSP72 (Moran et al. 2004). However, to the best of our knowledge, no other study has used a training program of nine months. The current investigation expands the work of Moran et al. (2004) and confirms their results about levels of HSP70, GSH, GSSG and the activity of mtSOD.

Numerous studies indicate that exercise training (up to 3 months) promotes an increase in myocardial antioxidants, however, variability exists regarding which of them increased after exercise training (for more study see Powers et al. 2008). The results of the present study support the idea that a prolonged training protocol is required to increase heart antioxidant defense activity (Moran et al. 2004). It should be considered that the rats from the long-term subgroups were more likely to suffer oxidative stress because of their older age which, in turn, would increase the need for improved antioxidant defenses to cope with the stress associated with exercise sessions (Moran et al. 2004). Our results are consistent with this hypothesis since mtSOD and GSH levels were higher in long-term trained and sedentary subgroups than in corresponding short-term subgroups (3 months). The increase in GSSG content suggests an augmented utilization of GSH likely to protect protein thiol groups against oxidative damage or because of GSH peroxidase activity (Moran et al. 2004). Therefore, a compensatory mechanism, such as enhanced GSH synthesis in the heart or GSH import from the liver, may account for the maintenance of the redox status of GSH (Moran et al. 2004). These modifications suggest that maturing of the rats throughout the study might have induced sufficient oxidative stress in the heart to elicit an adaptive response of some antioxidants to avoid greater cellular oxidative damage. Training alone did not modify levels of tGSH and GSSG in cardiac homogenates. This observation is consistent with the results of previous studies (Leeuwenburgh et al. 1997; Moran et al. 2004). The results of our previous study (Ahmadiasli et al. 2007) suggested that training program was insufficient to raise the basal levels of oxidative stress.

The training-induced increase in myocardial mtSOD activity observed in the present study probably represents an important defense mechanism against oxidative stress. The enhancement in mtSOD activity suggests that its activation results from augmented exercise-linked mitochondrial superoxide radical production (Moran et al. 2004). It is interesting to note that the training-induced increase in mtSOD activity only reached statistical significance in long-term trained rats; hence exercise-linked mitochondrial superoxide generation might be greater in the long-term than in the 3-month trained rats due to their older age. As mtSOD is the first line of defense against mitochondrial superoxide, the increase in mtSOD activity observed in our long-term trained animals might have reduced the exposure to superoxide and even to the hydroxyl radicals formed via Haber-Weiss reaction (Moran et al. 2004). Therefore, the increase in mtSOD activity induced in the long-term trained rats might be sufficient to protect myocardium from exercise-related oxidative stress since our previous study showed that long-term exercise training does not modify catalase and GSH peroxidase activity in the heart (Ahmadiasli et al. 2007).

HSPs are induced in the cell by a variety of stressful conditions, such as oxidative stress, and protect the cells against injury. Moreover, exercise has also been shown to increase HSPs expression independently from other stressors (Locke and Noble 1995; Kilgore et al. 1998). There is evidence that stress-induced synthesis of HSP70 decreases in the aged cardiovascular system (Starnes et al. 2005). Our data indicate that HSP70 expression probably decreases with age and maybe support the hypothesis that anti-stress activity is diminished in aging myocardial cells, thereby contributing to oxidative damage. It is widely accepted that exercise induces an increase in the expression of stress proteins (HSP70) in the cardiac muscle (Noble et al. 1999; Samelman 2000; Harris and Starnes 2001). The significant increase in HSP70 content found in our longer-term trained animals, which is consistent with the results of a previous study (Moran et al. 2004) suggests that long-term exercise training might have induced some type of stress over the rats' myocardium. In this regard, HSP70 has been demonstrated to protect cells against oxidative stress injury (Polla et al. 1996). Mitochondria were probably important ROS sources in the myocardium of 6- and 9-month trained rats, as evidenced by the increase in mtSOD activity observed in heart homogenates. Therefore, the enhanced levels of HSP70 detected in the long-term trained animals might have protected cardiac mitochondria against exercise-linked ROS overproduction, complementing the function
of antioxidant enzymes. On the other hand, there are no significant increases in HSP70 level and mtSOD activity in the hearts of 3 months trained rats. These findings suggest that training duration and age of animals might be critical factors in boosting myocardial defense systems, enzymatic antioxidants and HSPs.

The results of the present study indicate that exercise training attenuates apoptosis rate in cardiac muscles when measurements are made 48 h after the last exercise bout. Our results are shown that apoptosis rate increased with age and long-term exercise training decreased apoptosis progression. The influence of exercise training on apoptosis has not been clearly defined, and insufficient data exists to describe the influence of exercise training on cardiac tissue (Siu et al. 2004; Quindry et al. 2005; Kwak et al. 2006). For example Siu and his colleagues have demonstrated that the protein content of mtSOD increases (39%) and apoptosis rate decreases in the trained animals ventricle muscles compared to control animals after 8 weeks of endurance training. They have suggested that exercise training might attenuate muscle apoptosis. In the present study, we have demonstrated that long-term exercise training reduced apoptosis rate in the cardiac muscles when compared with sedentary control animals. This is consistent with the results of our previous study, which showed that a 3-month exercise training protocol does not attenuate apoptosis rate in rat heart. Our data suggest that an increased antioxidant capacity due to exercise training might be associated with lower apoptosis rate.

Our study depicts that the exercise training affects the age-induced changes in the animals, increases the mtSOD activity and the HSP70 expression in the heart, followed by the decrease in the apoptosis. However, the exercise training does not affect the GSH level in the tissue. These effects were more prominent in the animals with 9-month training; the shorter program was less effective.

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