

PROTECTIVE EFFECT OF AEROBIC EXERCISE AGAINST L-NAME-INDUCED KIDNEY DAMAGE IN RATS

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Exercise, alone or combined with changes in lifestyle, can prevent or reduce the need for pharmacotherapy in patients with compromised endothelium-dependent function. The aim of this study was to examine the protective effect of aerobic exercise against (L-NAME)-kidney damage in male rats induced by N ω -nitro-L-arginine methyl ester (L-NAME). L-NAME was administered to rats intraperitoneally in doses of 10 mg kg⁻¹ six days a week over eight weeks. Rats exercised by running on a treadmill at the speed of (15 to 22) m min⁻¹, 25 min to 64 min per day, five days a week over eight weeks. The rats were killed 48 h after the last dose, and their kidneys removed and homogenised to measure the levels of heat shock protein70 (HSP70), superoxide dismutase activity (SOD), and thiobarbituric acid reactive substances (TBARS). We also measured serum nitrite/nitrate. Chronic administration of L-NAME significantly increased renal HSP70 and TBARS levels and decreased renal SOD activity and serum nitrites/nitrates. Training modified abnormal renal HSP70, lowered TBARS, and increased SOD and serum nitrite/nitrate. Our results have confirmed that regular aerobic exercise protects against nitric oxide deficiency-induced kidney damage by modifying HSP70, up-regulating SOD activity, and depleting TBARS.

KEY WORDS: *heat shock protein70, nitric oxide, renal injury, superoxide dismutase*

A number of epidemiological, clinical, and experimental studies have shown that physical exercise protects against cardiovascular diseases and often makes an important part of hypertension management (1, 2). Many health problems such as hypertension, atherosclerosis, and vascular diseases in humans, often correlating with cardiovascular mortality, are associated with severe endothelial dysfunction (1). Nitric oxide production is one of the most important defence mechanisms against hypertension (2).

However, the underlying protective mechanisms of exercise against nitric oxide (NO) deficiency-induced kidney damage are still unclear. Previous studies have shown that tubulointerstitial inflammatory infiltration and oxidative stress are the main signs of salt-sensitive hypertension (3). Cellular stress as a response to oxidative stress induces heat shock proteins (HSPs) (4). Heat shock proteins (or stress proteins) are part of an endogenous defence system within the body, which help to protect protein assembly and folding in stressed cells and to maintain cell

integrity by acting as molecular chaperones (5). When the cell is severely damaged or necrotic, HSPs are released into the cytoplasm to stimulate inflammatory cytokine generation (6). Of all HSPs, the HSP70 protein family is known to be the most inducible by stress (7), and the overexpression of renal HSP70 is associated with salt-sensitive hypertension induced by chronic angiotensin II and L-NAME administration (8-10).

Because of inherent physiological stress associated with it, physical exercise can beneficially affect a number of tissues (6). Endurance training up-regulates HSP72 expression in multiple organs, protecting them against heatstroke damage and/or it offsets some adverse effects of diabetes (11, 12). Campisi et al. (13) demonstrated that physically active rats had both greater and faster HSP72 responses to stress and physical activity. These responses may contribute to stress resistance at the cellular level. Conversely, underexpression of aortic HSP70 gene has been observed in spontaneously hypertensive rats after five weeks of voluntary exercise (4).

Exercise is one of the best physiological models to study molecular mechanisms of HSP induction and tissue protection (12). Even though several studies (2, 14) have evidenced that exercise lowers high blood pressure induced by nitric oxide synthase (NOS) inhibition, the effects of chronic exercise on renal HSP70 level, oxidative stress, and antioxidant enzyme activity in a pathological condition similar to compromised endothelium-dependent vasomotor function are still unknown. The aim of our study was therefore to determine the effects of exercise on renal HSP70 and oxidative stress in L-NAME-treated rats.

MATERIALS AND METHODS

Chemicals

L-NAME, ketamine, xylazine, sodium chloride (NaCl), Tris-HCl, NP40, glycerol, Phenylmethylsulfonyl fluoride (PMSF), leupeptin, sodium vanadate, and 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride (AEBSF) were obtained from Sigma-Aldrich Corp. (St. Louis, MO, USA). SOD, TBARS, and HSP70 test kits were purchased from Cayman Chemical Company (Ann

Arbor, MI, USA) and R&D Systems (Minneapolis, MN, Assaypro Co, USA).

Animals

The experiments were performed on male Wistar rats (200 g to 250 g, eight to ten weeks old) with free access to standard pellet diet and water. All animals were housed in polycarbonate cages (five per cage) at a temperature of (22 ± 2) °C and humidity of (50 ± 5) %, with 12 h:12 h dark/light cycles. The experimental protocol followed the US National Institutes of Health guidelines for the care and use of laboratory animals and was approved by the Institutional Animal Care and Use Committee (Approval number: No.H-101121404902003 1391 IAU).

Experimental procedure

The rats were randomly divided into four groups consisting of 10 animals each and were treated as follows: the control group received no treatment; the sham group received normal saline (1 mL kg^{-1} body weight, intraperitoneally, i.p.) for six days a week over eight weeks; the L-NAME group received L-NAME in i.p. doses of 10 mg kg^{-1} body weight for six days a week over eight weeks; and the exercise plus L-NAME group received the same L-NAME doses, but performed aerobic exercises, as follows: the rats had first familiarised themselves with the treadmill (KN-73, Natsume Ltd., Tokyo, Japan) for a week. In the first week of the experiment, the treadmill was set to the speed of 15 m min^{-1} and the rats exercised 25 min a day for five days. Every week the running speed and exercise duration increased gradually until the rats ran at the speed of 22 m min^{-1} for 64 min a day by the end of the eighth week. This protocol was designed to correspond to maximum oxygen consumption. Before every exercise session, the animals warmed up by running at the speed of 7 m min^{-1} for 3 min and then we increased the speed by 2 m min^{-1} every next minute until the desired speed was reached. After the exercise, the animals would cool down as the treadmill speed decreased gradually back to the initial speed (15).

Anaesthesia and tissue collection

Forty-eight hours after the last received dose and overnight fasting (12 h), the animals were killed under anaesthesia with ketamine (60 mg kg^{-1} i.p.) and xylazine (5 mg kg^{-1} i.p.) (16). Blood samples were taken from a cardiac puncture and centrifuged at 604 g (3000 rpm) for 15 min. Serum was used for nitrite/

nitrate determination and kidneys removed, quickly frozen in liquid nitrogen, and stored at -70°C until they were homogenised.

Preparation of tissue homogenate

Whole kidney was homogenised in ice-cold lysis buffer (PBS, pH 7.4) containing $137\text{ mmol L}^{-1}\text{ NaCl}$, $20\text{ mmol L}^{-1}\text{ Tris-HCl}$ (pH 8.0), 1% NP40, 10% glycerol, $1\text{ mmol L}^{-1}\text{ PMSF}$, leupeptin ($1\text{ }\mu\text{g mL}^{-1}$), and sodium vanadate (0.5 mmol L^{-1}), AEBSF (100 mg mL^{-1}) and was centrifuged at 9660 g (12000 rpm) and 4°C for 30 min . Supernatants were removed and stored at -20°C until the assay (17).

Biochemical analysis

HSP70 was measured using the R&D Systems enzyme immunoassay (ELISA) kit according to the manufacturer's manual (Assaypro Co., St. Charles, MO, USA) (4). SOD activity in kidney homogenates was measured using a superoxide dismutase assay kit (18). TBARS, as a byproduct of lipid peroxidation,

was measured using a TBARS kit as described by Nabavi et al. (16, 17). Serum levels of nitrate/nitrite were determined using a colorimetric assay based on Griess reaction, as described elsewhere (19).

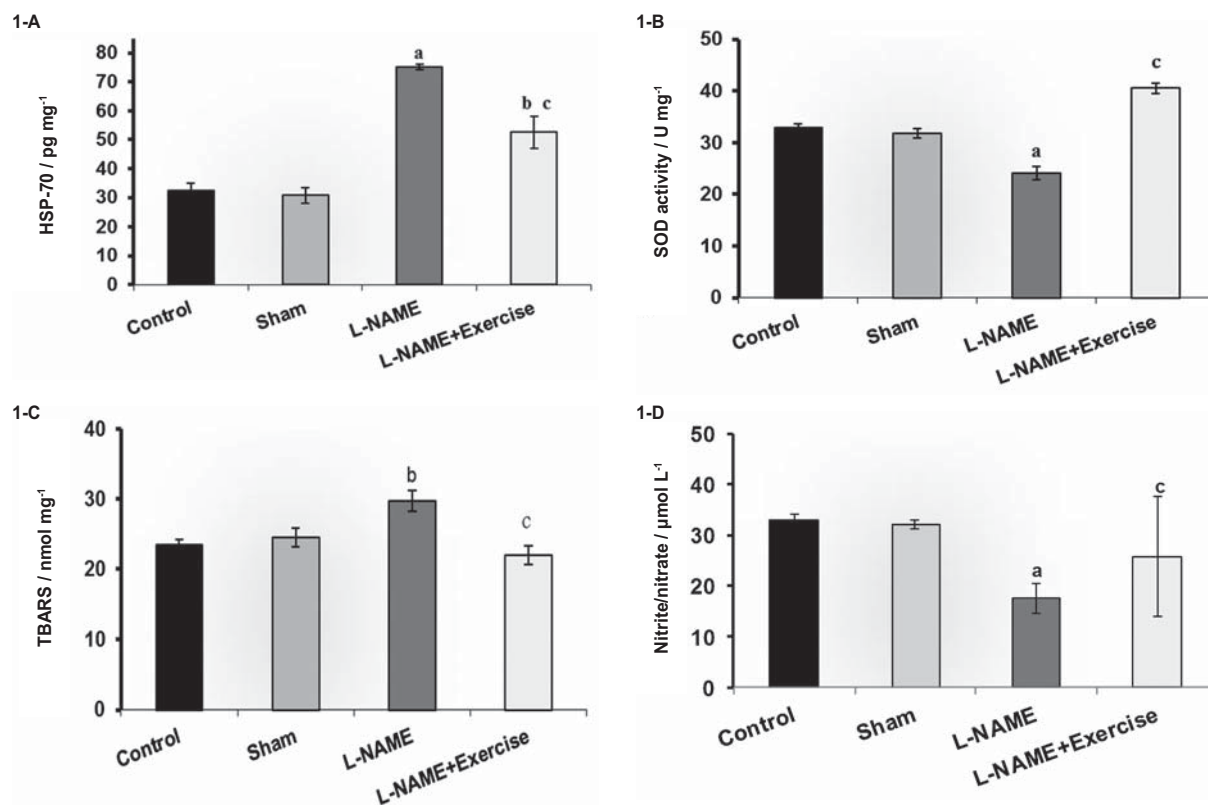
Statistical analysis

Data are shown as mean $\pm$ standard error of the mean (SEM). The groups were compared using the one-way analysis of variance (ANOVA) and the Tukey-Kramer post-hoc test. The level of significance was set at $p < 0.05$. All statistical tests were performed using the SPSS version 16.0 for Windows.

RESULTS

Chronic L-NAME administration significantly increased kidney HSP70 compared to the sham and control groups ($p < 0.001$). Eight-week aerobic exercise decreased kidney HSP70 in the L-NAME+exercise group ($p < 0.001$). However, it still had significantly

Figure 1 Mean renal HSP70 (A), SOD (B), TBARS (C), and serum nitrite/nitrate (D) by groups of Wistar rats after eight weeks of treatment



$a = p < 0.001$ vs. control and sham; $b = p < 0.05$ vs. control and sham; $c = p < 0.001$ vs. L-NAME

Values are means $\pm$ SEM for ten rats; L-NAME: N ω -nitro-L-arginine methyl ester; HSP70: heat shock protein 70; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances

higher HSP70 levels than shams and controls ($p<0.05$) (Figure 1A).

L-NAME-treated rats showed lower SOD activity than the rest, but exercise elevated it significantly ($p<0.001$) (Figure 1B). Moreover, it normalised TBARS levels (Figure 1C).

Serum nitrite/nitrate was significantly lower in the L-NAME group than in the sham and control group, while exercise increased it significantly ($p<0.001$; Figure 1D).

No significant difference was observed in any variables between controls and shams.

DISCUSSION

Endothelial dysfunction is involved in the development of cardiovascular diseases such as hypertension (20), and regular physical exercise is associated with improvements in endothelial function (1). In this study, we used an NOS inhibition model that is excellent for experimental induction of salt-sensitive hypertension (21, 22) and subtle acquired renal injury (22, 23). In this experiment, we found that chronic L-NAME administration in rats significantly increased renal HSP70 and TBARS levels. These pathophysiological changes were accompanied by a decrease in serum nitrite/nitrate and by downregulation of renal SOD activity, suggestive of high oxidative stress and impairment of antioxidant defences. Earlier studies (3, 24, 25) have established that NO deficiency-related excessive production of ROS by renal parenchymal cells, resident macrophages, infiltrating inflammatory cells, and persistent oxidative stress can impair renal antioxidant defence through inactivation of antioxidant enzymes. Similar changes have been reported in cardiac and/or aortic tissues of L-NAME-treated rats (14, 26). In contrast, Sainz et al. (27) reported an increase in renal SOD activity in L-NAME hypertensive rats, which was lowered by treatment with tempol. High renal SOD activity in this report may be a compensatory response to NO deficiency. Our findings further demonstrate that regular aerobic exercise depleted renal TBARS level and increased SOD activity in L-NAME-treated rats, and therefore counteracted renal oxidative injury. These results support the findings by Husain (26) and Husain and Hazelrigg (14), who demonstrated a significant increase in antioxidant defences and decreased lipid peroxidation in cardiac and aortic tissues in exercise-trained hypertensive rats. Asghar et al. (18) reported

that TBARS depletion caused an increase in antioxidant defences and alleviated inflammation in renal proximal tubules of trained rats. Although the exact mechanisms by which exercise counteracts L-NAME-induced renal injuries are unclear, they may involve increased NO bioavailability and enhanced responsiveness of the renal vascular smooth muscle to NO (28). In fact, under aerobic conditions, NO can inhibit TBARS formation by decomposing primary lipid peroxidation products (29).

In our study, exercise significantly downregulated renal HSP70 in L-NAME-treated rats (Figure 1A). However, several authors (8-10) observed overexpression of renal HSP70 in the tubulointerstitial areas in which inflammation and oxidative stress were associated with the development of hypertension (9, 10). Some authors have suggested that autoimmune reaction to HSP70 persistently produces low-grade inflammatory infiltrates in the tubulointerstitial areas of a hypertensive kidney (3, 8). L-NAME-induced oxidative stress can stimulate HSP70 and renal tubulointerstitial inflammation by activating NF- κ B (3, 23). Conversely, HSP70, intra-renal T cell, and macrophage infiltration may contribute to oxidative stress-mediated inflammation and renal injuries (3, 4). Although HSP plays a beneficial role prior to a proinflammatory condition, in proinflammatory condition it is toxic. These paradoxical roles of HSP are a result of its differing actions in intracellular and extracellular conditions (30). Moderate expression of HSP70 had a protective role under stress (31).

Hägg et al. (4) have also demonstrated that exercise downregulates overexpression of aortic HSP70 in spontaneously hypertensive rats (4), and Ding et al. (31) found a reduction in renal expression of HSP70 and in cell apoptosis in kidney-impaired rats. De Moraes et al. (28) proposed that increases in cardiac output during exercise, associated with renal vasoconstriction and upregulation of endothelial NOS, could enhance blood flow velocity and shear stress in kidney circulation. In addition, they have shown that renal hyperaemia occurring immediately after exercise inactivates vascular ROS and consequently prevents ROS interaction with NO by upregulating free-radical scavenger systems. Therefore, the renoprotective effect of long-term aerobic exercise may be attributed to decreased HSP70 and consequently attenuated oxidative stress and inflammation, and upregulated renal antioxidant defence systems.

As shown in Figure 1D, exercise increased serum nitrite/nitrate level in L-NAME-treated rats. This

suggests a decrease in systemic oxidative stress and higher bioavailability of NO (2). Previous studies have also demonstrated that exercise lowers blood pressure in L-NAME-treated rats by increasing NOS activity, improving NO bioavailability, and by inducing the NO-dependent relaxation pathway (2, 32). NO bioavailability increased by exercise could be the result of increased activity/expression of eNOS and/or the diminished degradation of NO due to reduced interaction with ROS (33). This phenomenon could be attributed to an elevation of shear stress-induced vasodilation during exercise accompanied by increased blood flow (20, 28, 33).

In conclusion, aerobic exercise attenuates NO deficiency-induced renal oxidative injuries while simultaneously improving vascular NO bioavailability. It seems likely that these renoprotective effects of exercise are mediated by reduced lipid peroxidation, downregulated HSP70, and upregulated antioxidant enzyme activity.

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Sažetak

AEROBNE VJEŽBE KAO ZAŠTITA BUBREGA OD OŠTEĆENJA KOJE UZROKUJE L-NAME U ŠTAKORA

Tjelovježba kao takva ili u kombinaciji s promjenama u životnim navikama može smanjiti potrebu za uzimanjem lijekova u bolesnika s kompromitiranom endotelnom funkcijom. Cilj je ovog istraživanja bio utvrditi zaštitno djelovanje aerobnog vježbanja od oštećenja bubrega koje uzrokuje metil (2S)-2-amino-5-[[amino(nitramido)metiliden]amino]pentanoat (L-NAME) u Wistar štakora. L-NAME se davao štakorima osam tjedana intraperitonealno u dozi od 10 mg kg⁻¹ na dan, šest dana u tjednu. U tih osam tjedana, štakori su trčali na traci brzinom od 15 m min⁻¹ do 22 m min⁻¹, 25 min do 64 min na dan, pet dana u tjednu. Četrdeset osam sati po primitku posljednje doze L-NAME-a štakori su žrtvovani, a njihovi bubrezi uklonjeni i homogenizirani radi mjerenja razina HSP70, SOD-a i TBARS-a. Također smo mjerili koncentraciju nitrita/nitrata u serumu. Dugotrajna primjena L-NAME značajno je povećala razine HSP70 i TBARS-a te smanjila aktivnost SOD-a u bubrezima odnosno razine nitrita/nitrata u serumu. Vježbanje je smanjilo povišene razine HSP70 i TBARS-a, a povećalo aktivnost SOD-a i razinu nitrita/nitrata u serumu. Naši rezultati potvrđuju da redovito vježbanje štiti od oštećenja bubrega uzrokovanog nedostatkom dušikova oksida, tako što mijenja razine HSP70, potiče aktivnost SOD-a, te smanjuje razine TBARS-a.

KLJUČNE RIJEČI: *dušikov oksid, HSP70, SOD, tjelovježba*

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