Effects of Chronic Exercise on Blood Pressure in Dahl Salt-Sensitive Rats


We tested the hypothesis that daily exercise would reduce directly measured arterial blood pressure (BP) and sympathetic nervous system support of BP in conscious, unrestrained, female Dahl salt-sensitive rats consuming 4.0% NaCl. Dahl S/Jr inbred rats were assigned to daily exercise (EX) or sedentary (SED) treatment conditions (n = 12/group) at 4 weeks of age. Rats in the EX group were housed in cages with attached running wheels. After 5 weeks of exercise, rats were running 10.3 ± 1.7 km/day. After at least 5 wks of treatment, all rats in both groups were placed on a 4.0% NaCl diet for 2 weeks to produce sodium-induced hypertension. Rats continued to either exercise daily or remain sedentary for an additional 2 weeks while consuming the high sodium diet. Carotid and jugular catheters were then implanted for measurements in conscious, resting, unrestrained rats on two separate days. Daily wheel running exercise for 7 to 9 weeks did not alter BP or HR in Dahl S/Jr rats consuming a 4.0% NaCl diet. However, acute arterial depressor responses to ganglionic blockade were less in EX rats. Furthermore, greater α-adrenergic (phenylephrine-induced) pressor responses were observed in the EX group while under ganglionic blockade. The findings suggest that overall resting sympathetic neural activity or cardiac β-adrenergic responsiveness to sympathetic activity is reduced in this model of hypertension by daily wheel running exercise. Am J Hypertens 1998;11:73–80 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Physical activity, exercise training, hypertension, vascular reactivity.

Participation in regular exercise for several weeks or longer (chronic exercise) is typically associated with lower blood pressure (BP) in hypertensive animals and humans. Interestingly, variable results have been obtained from exercise training studies using Dahl hypertensive rats. Treadmill training has been shown to reduce BP measured from anesthetized Dahl rats. In contrast, Tipton et al assessed systolic BP using the tail cuff method and did not observe reduced systolic BP with exercise training in conscious Dahl salt-sensitive rats. One purpose of this study was to determine the influence of chronic exercise on salt-induced hypertension using direct measures of BP in conscious, unrestrained Dahl rats. We hypothesized that chronic exercise would reduce the development of sodium-induced hypertension in the Dahl rat.

The mechanisms by which exercise training reduces BP are not established, but may include decreases in sympathetic nervous system activity. Reductions in resting plasma norepinephrine levels and norepinephrine spillover have recently been associated with...
reductions in resting BP produced by several weeks of exercise. Sodium-induced hypertension in Dahl rats is probably dependent on increases in efferent sympathetic activity. Thus, Dahl rats appear to be an appropriate model to examine the influence of chronic exercise on sympathetic nervous system regulation of BP during development of hypertension. A second purpose of this study was to test the hypothesis that physically active animals would have reduced tonic sympathetic nervous system support of BP. We quantified sympathetic nervous system support of BP by determining depressor responses to ganglionic blockade.

Quantification of the depressor response to ganglionic blockade is frequently used to assess the level of sympathetic nervous system support of BP. For example, greater depressor responses to ganglionic blockade may provide evidence for augmented sympathetic activity in many forms of experimental hypertension. However, differences in depressor responses to ganglionic blockade may also be due in part to differences in vascular and cardiac reactivity to a given level of sympathetic activity. Several studies have demonstrated decreased, unaltered, or increased vascular constrictor function after chronic exercise. To ascertain if there were differences in vascular reactivity between sedentary and chronically active rats, we also determined the pressor response to bolus administration of the a1 receptor agonist phenylephrine after ganglionic blockade.

METHODS

The protocols used in these experiments were approved by the Institutional Animal Care and Use Committee at Florida State University. Female rats (n = 24) of the Dahl salt-sensitive (S/Jr) inbred strain (Harlan Sprague-Dawley; Indianapolis, IN) obtained at 4 weeks of age were randomly assigned to sedentary (SED) or exercise (EX) groups. The inbred strain of the Dahl rat is very susceptible to the BP elevating effects of dietary sodium. In fact, only 4 weeks of 8% NaCl diet will elevate mean BP to > 200 mm Hg in these rats.

The SED rats were housed individually in standard hanging cages and EX rats were housed in cages equipped with attached running wheels (Lab Products; Aberdeen, MD). Animal quarters were maintained on a 12 h light/dark cycle (lights off: 6 PM to 6 AM) and a temperature of 22° to 23°C. Initially, rats were provided with deionized water and standard pelleted rat chow (Laboratory Rodent Diet 5001; PMI Feeds; St. Louis, MO; NaCl content = 0.96%) ad libitum. Daily volitional running activity was monitored for 5 to 7 weeks prior to providing all rats in both SED and EX groups with a 4.0% NaCl diet (Harlan Teklad; Madison, WI) to produce sodium-dependent increases in BP. Rats were maintained on the high sodium diet for 2 weeks while they continued to exercise or remain sedentary.

Surgery Rats were anesthetized with halothane for implantation of intravascular catheters into the right jugular vein and right carotid artery. The catheters were constructed of a 2-cm long intravascular segment of Teflon tubing (STT-28, Small Parts; Miami, FL) glued to an extravascular segment of Tygon (internal diameter 0.020 cm × outside diameter 0.060 cm) and filled with heparinized saline (100 U/mL). The catheters were secured in position, tunneled to the nape of the neck, exteriorized, and sealed with a stainless steel pin. All rats were housed individually in plastic cages after surgery and given ad libitum food and water. Rats in the EX group did not exercise after surgery for the duration of the study.

Experimental Protocols After an overnight recovery from surgery, the rats were weighed and their catheters connected to tygon extension lines filled with heparinized saline (100 U/mL). The arterial extension lines were attached to calibrated pressure transducers (TXX-R, Viggo-Spectramed; Oxnard, CA). Venous extension lines were attached to syringes for subsequent drug injections. The animals were placed in circular opaque testing chambers (diameter = 25 cm) containing wood chip bedding and rested for at least 3 to 4 h prior to recording pulsatile BP and heart rate (HR) for 45 min. At the conclusion of the recording period, the animals were disconnected from extension lines, the catheters were plugged, and the animals were returned to their home cages.

On the second day after surgery, measurements of baseline HR and BP were taken 3 to 4 h after rats were placed in testing chambers. Hexamethonium chloride (30 mg/kg intravenously; Sigma) and atropine methyl nitrate (0.1 mg/kg intravenously; Sigma) were administered in a volume of 1 mL/kg to produce ganglionic blockade. This procedure was used to quantify the level of sympathetic tone contributing to the maintenance of BP and to eliminate reflex buffering of BP. Maximum depressor responses to ganglionic blockade are generally observed within 5 min of injection. Vasopressin and angiotensin II are released in response to the hypotension produced by ganglionic blockade and may produce a partial compensatory increase in BP. However, combined angiotensin II receptor and vasopressin receptor blockade do not augment the initial depressor response to ganglionic blockade. This finding provides further support for using the depressor response to ganglionic blockade to quantify sympathetic support of BP. Five minutes after producing ganglionic blockade, bolus injections of phenylephrine (0.5, 1.0, and 2.0 μg/kg) were administered to evaluate the possibility that exercise may have influenced vascular reactivity. The efficacy of ganglionic
blockade was verified by the lack of reflex bradycardia during phenylephrine-induced pressor responses. At the conclusion of the experiments, the rats were euthanized with an overdose of sodium pentobarbital. Several tissues were obtained and weighed for determination of organ weight/body weight ratios.

**Data Acquisition and Analysis** All data were obtained between 11 AM and 2 PM. Thus, experiments were conducted during the time of day at which BP and HR are at their minimum values during the normal circadian hemodynamic pattern of the rat. Pulsatile BP was recorded continuously during experimental protocols. BP transducers were connected to transducer amplifiers (PM-1000, DATAQ Instruments; Akron, OH) and interfaced with an AT-Codas data acquisition card (DATAQ) installed in a 486/33 PC. BP signals obtained from arterial catheters were sampled at 200 Hz. Mean arterial blood pressure (MAP) was determined by calculating an average of all BP values recorded during a given time period. Pulsatile BP signals triggered a cardiotachometer from which HR was recorded continuously. The values reported for ganglionic blockade are the lowest 15 sec averages for BPs observed during the first 5 min following injection.

Data were analyzed using ANOVA and Student’s t test procedures. Responses to phenylephrine and Student’s t test procedures. Responses to phenylephrine were evaluated using a 2 (groups) × 3 (doses) ANOVA with repeated measures for doses. Significant differences between individual means were determined using Tukey’s post hoc analysis. Student’s t test was used to analyze decrements in BP produced by ganglionic blockade and body weight/organ weight ratios. Statistical significance was set at \( P < .05 \).

**RESULTS**

All rats in the EX group were housed in cages with attached running wheels for at least 7 weeks. As indicated in Figure 1, running activity peaked after about 3 weeks at approximately 10 km/day. The range in running activity for the 12 rats studied was 6.8 to 13.6 km/day during the seventh week of activity. At the time of surgery, there were no differences in body weight between groups (SED: 238 ± 610 g; EX: 240 ± 4 g). There was significant weight loss after surgery in both groups (\( P < .05 \)); however, the weight loss stabilized on the second day after surgery and was not different between groups (SED: 217 ± 610 g; EX: 221 ± 4 g).

Resting BP and HR were determined by computer based averages of 45 min recordings obtained from conscious, undisturbed rats. All catheters were patent for BP and HR measurement on day 1; however, there was one catheter failure in each group on day 2. There were no significant differences in resting MAP between SED and EX groups on either day of measurement (Table 1). Group means for MAP on day 1 and 2 were very similar. ANOVA also revealed no significant treatment or time effect on resting HR (Table 1).

The sympathetic contribution to maintenance of resting MAP was quantified by determining the reduction in BP in response to ganglionic blockade produced by hexamethonium. The magnitude of the depressor response to ganglionic blockade (Figure 2) was significantly greater in the SED (−60 ± 3 mm Hg) than in the EX group (−50 ± 4 mm Hg). Five to ten minutes after ganglionic blockade, HR values were 358 ± 15 beats/min for EX and 393 ± 15 beats/min for SED. The efficacy of ganglionic blockade was verified by the lack of reflex bradycardia in response to increments in MAP produced by phenylephrine administration. For example, increases in MAP of 28 ± 4 mm Hg (SED group) and 36 ± 3 mm Hg (EX group)

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**TABLE 1. RESTING MEAN ARTERIAL PRESSURE (MAP) AND HEART RATE (HR) FOR SEDENTARY AND EXERCISE GROUPS**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
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<tbody>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>132 ± 2</td>
<td>129 ± 2</td>
</tr>
<tr>
<td>Exercise</td>
<td>136 ± 3</td>
<td>135 ± 3</td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>393 ±15</td>
<td>372 ± 9</td>
</tr>
<tr>
<td>Exercise</td>
<td>363 ± 9</td>
<td>357 ± 9</td>
</tr>
</tbody>
</table>

*Data are mean ± standard error, \( n = 12 \) for both groups on day 1 and \( n = 11 \) for both groups on day 2. Data were obtained from conscious, unrestrained rats during 45 min recording sessions on 2 consecutive days.*

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**FIGURE 1.** Daily volitional running activity in km/day for Dahl S/Jr rats (\( n = 12 \)). Activity increased significantly during the first 3 weeks of running and reached a plateau after 3 weeks. There were no significant changes in running activity after the third week of running.
produced average changes in HR of +3 ± 2 beats/min (SED group) and -2 ± 3 beats/min (EX group).

The BP responses to graded doses of phenylephrine after ganglionic blockade were significantly greater in the EX group (Figure 3). ANOVA revealed a significant group main effect (SED v. EX) and post hoc tests indicated that the pressor response to phenylephrine was greater in the EX group at each dose administered.

Table 2 indicates the influence of chronic exercise on various organ weight/body weight ratios. We found that the EX group had greater heart, left ventricle, and soleus weight/body weight ratios (P < .05). These differences are indicative of adaptation to chronic exercise.

**DISCUSSION**

The results of this study indicate that daily wheel running exercise for 7 to 9 weeks did not alter BP or HR in Dahl S/Jr rats consuming a 4.0% NaCl diet. However, acute arterial depressor responses to ganglionic blockade were less in EX rats. Furthermore, greater a-adrenergic (phenylephrine-induced) pressor responses were observed in the EX group while under ganglionic blockade. The results suggest that overall resting sympathetic neural activity may have been reduced in the EX rats. However, because we did not directly assess β-adrenergic responsiveness or the cardiac output response to ganglionic blockade, we cannot rule out the possibility that daily exercise reduced the myocardial adrenergic responsiveness to nerve activity and that this contributed to smaller depressor response to ganglionic blockade.

**Chronic Exercise and Hypertension**

It is generally thought that chronic exercise reduces BP in hypertensive humans and in animal models. We are aware of three prior studies that used forced treadmill running as the mode of chronic exercise. We chose to use daily volitional wheel running in this study because it has been demonstrated to be an effective mode for lowering BP in hypertensive rats. Although BP was not reduced by daily wheel running exercise in the current study, greater heart weight and soleus weight in EX animals provides objective evidence of adaptation to daily wheel running in this study. Furthermore, several studies have provided ample evidence that daily wheel running exercise is a sufficient stimulus to produce physiological adaptations including increases in maximal oxygen uptake and alterations in baroreflex function. Therefore, it is unlikely that the absence of a blood pressure lowering effect from daily wheel running was due to an inadequate level of physical activity.

Shepherd et al found that treadmill training both delayed the development of hypertension and markedly reduced the magnitude of the hypertension in the Dahl-S rat. In this study, indirect systolic BP (tail-cuff method) was measured weekly from heated, ether anesthetized rats. Savage et al also used treadmill training, but obtained BP measurements at 4 week intervals from catheterized rats while under halothane...
anesthesia. In their study, chronic exercise reduced blood pressure of Dahl-S rats that were maintained on either a normal or a high salt diet. However, Tipton et al. did not find lower systolic blood pressures obtained via the tail cuff method from conscious, treadmill trained Dahl-S rats. In this study, we found no influence of chronic exercise on resting MAP representing an average of 45 min of recording obtained from conscious, unrestrained Dahl S/Jr.

It is not clear why there are discrepancies in the findings of these studies that have evaluated the effects of chronic exercise on development of sodium induced hypertension in Dahl rats. There are a number of methodological differences that complicate attempts to integrate the studies and draw conclusions. For example, prior exercise studies using Dahl rats have typically begun exercise and high salt feeding concurrently and followed the development of the hypertension. One consistent trend among these studies is that those using anesthesia found chronic exercise induced reductions in BP, whereas studies that measured BP from conscious animals did not find an effect of chronic exercise on resting BP. There is no clear explanation as to why the use of anesthesia would lead to the measurement of lower BP in chronically exercised salt-sensitive rats compared with sedentary controls. Clearly, various anesthetics produce an array of neural and humoral responses that are dependent on the type and depth of anesthesia. Both ether and halothane generally produce very dramatic and transient reductions in blood pressure. Interestingly, the hypotensive actions of ether in normotensive rats appear to be due to increases in vascular conductance, whereas depressor responses to halothane involve depressed cardiac output. Nonetheless, we believe that, given the marked influences of anesthetics on cardiovascular function, their use should be avoided during assessment of cardiovascular function whenever possible. Furthermore, future animal studies evaluating the role of chronic exercise on blood pressure in rats should use direct measures recorded for several hours from conscious, unrestrained rats. This is particularly important in light of reports suggesting that chronic physical activity does not consistently lower blood pressure in hypertensive subjects when 24-h ambulatory monitoring is used.

**Chronic Exercise and Sympathetic Activity** Several studies suggest that exercise training induced reductions in resting sympathetic nervous system activity may be responsible for decreasing BP in hypertensive subjects. Chronic exercise has been shown to reduce directly measured renal sympathetic nerve activity in conscious, normotensive rats. Because increased sympathetic nervous system activity is a component of sodium-induced hypertension, we speculated that chronic exercise might provide some protection against sodium-induced elevations in sympathetic nervous system activity and BP. We found that the depressor response to ganglionic blockade was less in EX animals, suggesting reduced sympathetic influence on BP; however, there was no difference in resting BP between the groups. Although this approach is frequently used to assess tonic sympathetic support of BP, it is clear that differences in the reduction in BP after administration of ganglionic blockade between groups of animals may be due to mechanisms other than efferent sympathetic nerve activity. For example, it was possible that chronic exercise reduced the depressor response to ganglionic blockade in this study because of decreases in vascular responsiveness. To check for this possibility we administered phenylephrine after ganglionic blockade. In fact, the pressor response to phenylephrine was augmented in the trained group. Thus, it appears that the smaller depressor response to ganglionic blockade in EX rats cannot be explained by depressed vascular reactivity.

Although phenylephrine injection provided an indication of $\alpha$-adrenergic responsiveness, this approach does not permit assessment of $\beta$-receptor function. The support of blood pressure by sympathetic activity is clearly the sum of stimulation of all adrenergic receptors. This is potentially an important issue because 1) high salt feeding increases cardiac ventricular $\beta$-receptor number in Dahl S rats and 2) exercise training may decrease the number of these receptors. Several studies have reported that treadmill or swimming exercise reduces myocardial $\beta$-receptor number in normotensive rats. Furthermore, training has been shown to decrease inotropic and chronotropic responses to $\beta$-adrenergic stimulation in pigs. Thus, a limitation of the current study is the lack of information concerning cardiac $\beta$-adrenergic responsiveness. It is possible that a reduction in such responsiveness

### Table 2. Organ Weight/Body Weight Ratios (mg/kg) of Dahl S/Jr Rats

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>LV</th>
<th>Kidney</th>
<th>Soleus</th>
<th>Plantaris</th>
<th>Adrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SED</td>
<td>3.58  ± 0.14</td>
<td>2.51 ± 0.11</td>
<td>4.03 ± 0.21</td>
<td>0.31 ± 0.02</td>
<td>1.03 ± 0.05</td>
<td>0.20 ± 0.02</td>
</tr>
<tr>
<td>EX</td>
<td>4.35  ± 0.12*</td>
<td>3.01 ± 0.09*</td>
<td>4.41 ± 0.13</td>
<td>0.39 ± 0.01*</td>
<td>1.08 ± 0.02</td>
<td>0.20 ± 0.01</td>
</tr>
</tbody>
</table>

Data are mean ± standard error, n = 12. Values are calculated organ weight/body weight ratios in mg/kg for the sedentary (SED) and exercise (EX) groups. LV, left ventricle; *Indicates significantly different from sedentary (P < .05).
could explain a portion of the differences in the depressor response to ganglionic blockade between EX and SED animals.

Why were there no differences in resting BP between the EX and SED groups when sympathetic nervous system influence on BP appears to have been reduced by chronic exercise? One possibility is that blood volume was significantly greater in the EX group. Unfortunately, we did not measure blood volume in this study. Blood volume is elevated during the early stages of high sodium consumption in Dahl rats and may be additionally elevated by chronic exercise. It is possible that the combination of chronic exercise and sodium consumption produced significantly elevated blood volumes, which offset the influence of decreased sympathetic nervous system activity in determining resting BP. Another possible reason why chronic exercise did not reduce BP in spite of evidence for reduced sympathetic activity is suggested from the phenylephrine results. Since chronically exercised Dahl rats exhibited greater phenylephrine induced elevations in blood pressure, it is possible that increased vascular responsiveness partially opposed a reduction in sympathetic activity, yielding no change in resting BP. As discussed below, a number of studies have addressed the influence of physical activity on vascular responsiveness.

**Chronic Exercise and Vascular Reactivity** We observed enhanced pressor responses to phenylephrine after ganglionic blockade in physically active animals compared with sedentary controls. Interestingly, Evans et al also found substantially greater pressor responses to phenylephrine after ganglionic blockade in conscious trained normotensive dogs compared with sedentary controls. However, there appears to be no consensus view of the influence of chronic exercise on the reactivity of the vasculature to substances that increase smooth muscle tension. For example, Lash et al found no effect of exercise training on the steady state BP response to phenylephrine infusion in anesthetized rats pretreated with hexamethonium and captopril. Furthermore, Delp et al recently reported no influence of chronic exercise on phenylephrine induced increases in tension of vascular rings from the conduit aorta from treadmill trained rats. Others have demonstrated a decrease, no change, or an increase in vascular constrictor function due to chronic exercise. This heterogeneity of experimental findings may stem in part from differences in 1) modes of chronic exercise (swimming, treadmill running, voluntary running, and electrical stimulation); 2) methods of assessment (vascular rings, vascular strips, in vivo microcirculatory studies, hindlimb preparation, or in vivo systemic pressor responses with or without ganglionic blockade); and 3) constricting agents (norepinephrine, phenylephrine, methoxamine, and KCl). For example, some studies suggest that trained animals have a reduced vasoconstrictor response to norepinephrine. Delp has hypothesized that trained animals may have an enhanced nitric oxide release via norepinephrine binding to endothelial $\alpha_2$ receptors. Phenylephrine does not interact with $\alpha_2$ receptors. Thus, the discrepancies in experimental results may be due, at least in part, to differences in choice of vasoconstrictor agent. Future studies evaluating the effects of chronic exercise on vascular reactivity would be strengthened by utilizing both in vivo and in vitro approaches.

A clear limitation to our experimental approach is the inability to discern specific sites or potential mechanisms for our observation of enhanced pressor responses to the $\alpha_1$-agonist phenylephrine. If the response is restricted to $\alpha_1$-agonists, then increases in receptor number, receptor affinity, or postreceptor mechanisms leading to increased intracellular $Ca^{2+}$ could be involved. It is important to note that we do not know if the augmented pressor response is restricted exclusively to $\alpha$-agonists, or if it would also be observed with other pressor agents such as angiotensin II. Hudlicka and Fronek have noted that the increased vascular reactivity after long-term stimulation of muscle may be due to hypertrophy of the vascular wall. If this were the case, then we would predict greater responses to both angiotensin II and phenylephrine. We did not examine this possibility.

**Summary and Conclusions** Daily wheel running exercise for 7 to 9 weeks did not alter BP or HR in Dahl S/Jr rats consuming a 4.0% NaCl diet. However, acute arterial depressor responses to ganglionic blockade were less in EX rats. Furthermore, greater $\alpha$-adrenergic (phenylephrine induced) pressor responses were observed in the EX group while under ganglionic blockade. The results suggest that overall resting sympathetic neural activity may have been reduced in the EX rats. However, because we did not directly assess $\beta$-adrenergic responsiveness or the cardiac output response to ganglionic blockade, we can not rule out the possibility that daily exercise reduced the myocardial adrenergic responsiveness to nerve activity, and that this contributed to smaller depressor response to ganglionic blockade.

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