Exercise Training Attenuates Stress-Induced Hypertension in the Rat

RONALD H. COX, JOHN W. HUBBARD, JAMES E. LAWLER, BRIAN J. SANDERS, AND VICKI P. MITCHELL

SUMMARY The ability of exercise training to block the generation of hypertension produced by chronic stress in the borderline hypertensive rat was tested. Twenty-three male borderline hypertensive rats, F1 offspring of spontaneously hypertensive and Wistar-Kyoto rats, were divided into three groups. Two groups (8 rats per group) were subjected to 2 hours of daily, predictable, uncontrollable tail shock for 12 weeks. One of these groups was also given 2 hours of daily swim stress (exercise trained). A third group served as a maturation control and received neither intervention (n = 7). After 12 weeks of stress, direct recording of blood pressure verified the pattern observed with tail cuff: shock only group, 180/118 ± 3/3 mm Hg; exercise-trained and shocked group, 166/108 ± 4/2 mm Hg; and control group, 160/98 ± 6/4 mm Hg (mean ± SEM). Systolic and diastolic blood pressures in the shock only group were significantly higher than in both the other groups (p < 0.05). The control group differed from the exercise-trained and shocked group only in diastolic BP (p < 0.05). During a short-term stress session plasma norepinephrine levels in the exercise-trained and shocked group were significantly lower than those in the shock only group (555 ± 56 vs 776 ± 84 pg/ml; p < 0.05). These results indicate that an alteration of autonomic function resulted from the exercise training, but its contribution to the resistance of the exercise-trained and shocked rats to stress-induced hypertension is unclear. (Hypertension 7: 747-751, 1985)

KEY WORDS • stress • rats • hypertension

DISEASES of the cardiovascular system are the leading cause of death in most industrialized nations. Efforts to combat this disorder have included a number of nonpharmacological approaches such as alteration of dietary cholesterol and sodium, weight loss, and an exercise program. The belief that regular exercise can influence the development or progression of cardiovascular disease rests heavily on its ability to reduce such risk factors as body weight, unfavorable lipoprotein profiles, and blood pressure. The latter effect, however, is not consistently observed. Another mechanism by which exercise training may contribute to the maintenance of cardiovascular health is by reducing the insult of potentially pathogenic agents. Exercise training can slow the hypertensive effect of sodium loading in a rat model of salt-sensitive hypertension, and though the mechanism responsible for this effect is unclear, a reduction in sympathetic nervous system activity is suggested. Exercise training might also attenuate the effects of stress, a putative risk factor for hypertension, through a similar mechanism.

A major problem plaguing the investigation of stress-induced hypertension is the elusiveness of the phenomenon. While chronic stress can result in an elevation in resting blood pressure, not all animals or strains become hypertensive when stressed. The lack of a suitable experimental model has made it difficult to test many popularized assumptions about stress-induced hypertension and agents that might blunt or exacerbate its effects. Consequently, investigations concerned with the potential of exercise training to modulate the effects of stress on blood pressure have few antecedents.

The first filial (F1) generation of spontaneously hypertensive rat and its normotensive control, Wistar-Kyoto rat, is a reliable subject for studies of stress-
induced hypertension. We studied the effects of stress and exercise training on this model because it does not show the relentless rise in blood pressure to hypertensive levels characteristic of its progenitor, the spontaneously hypertensive, unless chronically provoked. Thus, it offers a stable, but borderline, high level of blood pressure (hence the name borderline hypertensive rats) on which environmental perturbations can be assessed. We found that borderline hypertensive rats exposed to 2 hours of daily swimming, in addition to 2 hours of daily, predictable cutaneous electric shock, showed a significantly smaller increase in resting blood pressure than did rats subjected only to the predictable shock.

Materials and Methods

The male offspring of spontaneously hypertensive rat dams and male Wistar-Kyoto rats bred at the University of Tennessee animal facility were used in this study. Both inbred parent strains were purchased from Taconic Farms (Germantown, NY, USA). Pups were weaned 3 weeks after birth and housed four per cage until they were 8 weeks old, at which time they were individually caged. Systolic blood pressure was determined each week throughout the remainder of the study by the tail cuff method. Animals were placed in a rat holder with preheated base plate (39 °C) for 10 minutes before measurements were taken. A mean of seven artifact-free tracings was taken as the pressure for the week. A minimum of 24 hours was allowed to elapse after the last shock and/or swim session before blood pressures were determined.

At 11 weeks of age (average body weight, 291 g), the 23 animals were randomly assigned to three groups of eight, eight, and seven: maturation control (C; n = 7), shock stress only (S), and shock plus exercise (EX-S) groups. All animals were accustomed to handling before and during the course of the experiment.

Stress Procedures

The two groups of rats exposed to the shock stress paradigm received 2 hours of predictable, unavoidable tail shock 5 days a week for 12 weeks. The duration of the shock sessions increased progressively over a 2-week period until the full 2 hours was reached. This followed the same procedure as the home cage rest represented the average of these two recording days. Subsequent to measurement of resting systolic and diastolic blood pressure, all rats were exposed to a 30-minute session of the predictable, uncontrollable shock. This followed the same procedure as the 12-week chronic phase of the experiment with two exceptions: 1) the session was shorter (30 min vs 120 min) and 2) the C group was exposed to the tail shock for the first time. Blood for the assessment of resting plasma catecholamine measurements was obtained while the rat rested quietly in the home cage on the day following the last experimental measurement.

After 30 minutes of tail shock, a blood sample was withdrawn through the arterial catheter without further disturbing the rat. A 0.6-ml aliquot of blood was added to an ice-cold microfuge tube containing 1.1 mg of ethyleneglycol-bis(β-aminoethyl ether)-N,N′-tetraacetic acid and 0.72 mg of glutathione. The blood was
gently mixed and centrifuged in the cold for 15 minutes. The separated plasma was stored at -20 °C until assayed for catecholamines. Plasma samples were measured in duplicate by a modification of a radioenzymatic technique utilizing catechol-o-methyl transferase extracted by the method of Axelrod and Tomchick and tritium-labeled S-adenosyl methionine purchased from New England Nuclear (Boston, MA, USA). Internal standards of 100 pg of epinephrine and norepinephrine were run with each plasma sample. The coefficient of variation averaged 5%. Two separate assay runs were performed, one each for the rest and stress samples. Because assay blanks for epinephrine on the rest run were higher than normal, the sensitivity for rest samples was only 7 pg per tube. Consequently, accurate measures of epinephrine at rest (<100 pg/ml) were not possible. Assay sensitivity for stress samples was better than 2 pg per tube.

**Statistical Analysis**

Systolic blood pressure data generated by the weekly tail cuff measurements were subjected to analyses of variance for repeated measures. Analysis of simple main effects and post hoc follow-up t tests were used where appropriate. The plasma catecholamine values were compared and evaluated with t tests for independent groups.

For each animal, a single mean blood pressure and heart rate for the 30-minute shock session was generated by collapsing across all 6-second blocks. These data were also subjected to t tests for independent means to substantiate any observed differences. A chance level of 0.05 was used as the minimal level of statistical significance. All averages in the text and figures depict the mean ± SEM.

**Results**

At the time of the direct measurements of cardiovascular function the body weights of the two stressed groups were essentially the same; however, both were significantly lower than the controls (p < 0.05; Table 1).

![FIGURE 1. Mean (± SEM) tail cuff systolic blood pressure for each 2-week period before the stress manipulations (PRE), during the 2 weeks when the stress was being progressively lengthened (Training), and during the 12 weeks of daily swim and tail shock (Stress), in rats exposed to daily shock plus swim training (open circles), shock only (filled squares), or neither intervention (filled circles).](image)

The elevation of systolic blood pressure across weeks that occurred in the S group relative to both the EX-S and C groups is shown in Figure 1. Analysis of variance provided statistical confirmation of this difference. Separate analyses of variance comparing each pair of groups (C vs S, C vs EX-S, and S vs EX-S) across all weeks revealed that the EX-S group was essentially no different from the C group. In contrast, the S group showed a slow but steady increase in systolic blood pressure that was significantly different from the C and the EX-S group (p < 0.05). A comparison of each week with post hoc follow-up t tests indicated that the S group became significantly different from C animals at Week 9 (p < 0.05) and significantly different from EX-S at Week 10 (p < 0.05).

**TABLE 1.** Body Weights and Norepinephrine (NE) Levels During Rest and Heart Rate (HR) and Systolic and Diastolic Blood Pressure During Rest and Shock in Rats Exposed to Daily Shock plus Swim Training (EX-S), Shock Only, or Neither Intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (g)</th>
<th>HR (beats/min)</th>
<th>Blood Pressure (mm Hg)</th>
<th>NE (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Rest</td>
<td>400 ± 8</td>
<td>319 ± 5</td>
<td>160 ± 6</td>
<td>98 ± 4</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EX-S</td>
<td>361 ± 6*</td>
<td>287 ± 6*,†</td>
<td>166 ± 4†</td>
<td>108 ± 2*,†</td>
</tr>
<tr>
<td>Shock only</td>
<td>363 ± 10*</td>
<td>323 ± 7</td>
<td>180 ± 3*</td>
<td>118 ± 3*</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
<td>495 ± 9</td>
<td>184 ± 8†</td>
<td>114 ± 6</td>
</tr>
<tr>
<td>EX-S</td>
<td>—</td>
<td>454 ± 11*</td>
<td>199 ± 4</td>
<td>134 ± 3*</td>
</tr>
<tr>
<td>Shock only</td>
<td>—</td>
<td>477 ± 7</td>
<td>208 ± 3</td>
<td>136 ± 2*</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p < 0.05 (difference from control group), †p < 0.05 (difference from shock only group).
The direct measurements of blood pressure confirmed the tail-cuff findings (see Table 1). The systolic blood pressure of the EX-S group during rest was not statistically distinguishable from the C group, but it was significantly lower than the S group \( (p < 0.03) \). The systolic blood pressure of the S rats was significantly higher than that of the controls \( (p < 0.003) \). Furthermore, the diastolic pressure in S rats was significantly elevated above both the C \( (p < 0.0001) \) and EX-S rats \( (p < 0.01) \). However, the EX-S group was not totally refractory to the stress. They exhibited a diastolic blood pressure significantly higher than that of the C rats \( (p < 0.02) \).

A resting bradycardia was evident in the swim-trained group (Table 1), while no significant differences in resting heart rate were evident between the C and S groups. Low resting heart rates were associated with low plasma norepinephrine levels \( (r = 0.453, df = 21, p < 0.05) \).

The plasma catecholamine response to the 30-minute stress session is depicted in Figure 2. The naive C animals exhibited the greatest elevations in both epinephrine and norepinephrine. The epinephrine response in the EX-S and S groups was practically identical \( (868 \text{ vs } 818 \text{ pg/ml respectively}) \); however, the difference in norepinephrine levels between the EX-S and S animals was statistically significant \( (p < 0.05) \). Again, an association between heart rate and norepinephrine levels was observed \( (r = 0.678, df = 21, p < 0.001) \). The blood pressure levels attained during the shock stress by the EX-S and S groups were statistically indistinguishable, though both were higher than the C group. The parity of the EX-S and S groups appears to be a result of the greater change from rest in the EX-S group; however, the only change score difference to achieve statistical significance was that between EX-S and C on diastolic blood pressure \( \text{average change from rest } 27 \text{ vs } 16 \text{ mm Hg respectively}; \ t = 2.4, df = 13, p < 0.05) \).

**Discussion**

The observations reported here replicate previous efforts that produced chronic and substantial elevations of blood pressure in the borderline hypertensive rats exposed to chronic stress. \(^{10,11} \) In addition, as far as we can determine, they are the first experimental demonstration that exposure to repeated exercise can exert a prophylactic effect on stress-induced hypertension. The protection was not total, however, in that the EX-S rats did not escape all the deleterious consequences of chronic stress. The reduced sensitivity of swim-trained animals to the hypertensinogenic effects of daily exposure to predictable, uncontrollable shock was manifested primarily in systolic blood pressure. The elevation of diastolic blood pressure, though significantly less than that of the S group, was nonetheless higher than that of the control group. This finding may indicate that more than one hypertensive process is activated by chronic stress and that exercise training is differentially effective in interfering with these processes. Additional work characterizing the hemodynamic alterations produced by chronic stress and the effect of exercise training on it will be required to clarify this effect.

An additional feature of the data concerns the apparent alteration in sympathetic nervous system function, as reflected by plasma catecholamine levels, \(^{21} \) in the EX-S rats. This change was observed during both rest and stress. The reduction of plasma catecholamine levels in response to an emotional stress in trained rats is in contrast to the negative results reported with human beings (unpublished observations). \(^{2,23} \) We believe our success here in demonstrating a generalization of a training effect to the tail shock is related to the previous exposure of the trained rats to that stress. Previous studies in our laboratory indicate that trained rats unfamiliar with the shock stress do not exhibit reduced norepinephrine levels in this situation. \(^{24} \) The novelty apparently overwhelms any tendency to exhibit an attenuated response. The tremendous response observed in the naive control animals is consistent with the potency of the novelty effect and may explain the discrepancy between the present results and those in the human studies.

The mechanisms responsible for this alteration of sympathetic nervous system activity after training have not been elucidated in human or animal models. Possible contributing factors consistent with our observations are a reduction in food intake, \(^{23} \) an unloading of cardiac low pressure receptors as a consequence of the training-induced bradycardia, \(^{28} \) which is presumably a vagally mediated phenomenon, or changes in the nervous system itself, which are presently ill-defined (e.g., changes in receptor number or sensitivity or both).
EXERCISE AND STRESS/Cox et al.

Whether the apparent alterations observed in sympathetic nervous system function bear any relation to the prophylactic effect produced by exercise training is a matter of speculation. The low plasma levels of catecholamines at rest in the S and EX-S rats clearly indicate that high sympathetic nervous system activity was not responsible for the elevated blood pressure. However, this does not preclude the involvement of the sympathetic nervous system at some point in the pathogenesis of the hypertension. Adrenergic mechanisms may be a contributing factor or trigger in the early stages of the hypertension. As the disease progresses, the influence of this component may gradually subside. A similar scheme has been proposed for other experimental models of hypertension in which early sympathetic nervous system involvement is critical but later abates. If exercise training attenuates sympathetic nervous system activity during the early exposures to stress, a potentially prophylactic effect may be obtained. The present observations are limited by having a sample period only after the establishment of the hypertension. However, considering the rapidity with which training adaptations become manifest, the possibility that attenuation of sympathetic nervous system activity in EX-S rats would be observed during stress at an earlier, critical period is not unlikely.

The practical importance of clarifying the behavioral and environmental contributions to the genesis or prevention of hypertension has stimulated both a scientific and lay interest in exercise and stress. An association between regular exercise and a reduced blood pressure is an increase in the ability to withstand the hypertensive effects of stress. The identification of the mechanisms underlying this effect remain an interesting problem.

References

1. Marx J, Kolta G. Combating the #1 killer: the science report on heart research. Washington, DC: American Association for the Advancement of Science, 1978:3-4
26. Mancia G, Donald DE. Demonstration that the atria, ventricles and lungs each are responsible for a tonic inhibition of the vasomotor center in the dog. Circ Res 1975;36:310-312
Exercise training attenuates stress-induced hypertension in the rat.
R H Cox, J W Hubbard, J E Lawler, B J Sanders and V P Mitchell

Hypertension. 1985;7:747-751
doi: 10.1161/01.HYP.7.5.747
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/7/5/747

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/