Running training attenuates blood pressure and norepinephrine responses to immobilization stress in spontaneously hypertensive rats

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Abstract We investigated the effects of 4 weeks of running training on the progressive changes in resting blood pressure (BP) and heart rate (HR) that occurred during that period, as well as on the increases in cardiovascular variables and catecholamine levels induced by a novel stress (immobilization stress) in spontaneously hypertensive rats (SHR) and control normotensive Wistar-Kyoto rats (WKY). In addition, rat sensitivity to exogenously infused norepinephrine (NE) was investigated by measuring the induced pressor response. BP was measured by a tail-cuff method (without heating), which is reportedly both sensitive and accurate for non-invasive measurement of BP in conscious rats. Increases in resting systolic BP over the 4-week period were significantly smaller in the trained SHR than in the untrained SHR, but the training had no effect on the changes in resting BP seen in WKY. After the 4-week running training, BP and NE responses to immobilization stress were reduced in the SHR, as was the increase in BP induced by intravenous (IV) infusion of NE. In the WKY, however, neither the BP response to the stress nor that to the IV infusion of NE was changed by running training. These results suggest 1) that such training was beneficial in the SHR, and 2) that the immobilization stress-induced activation of the sympathetic nervous system (as evidenced by the increase in plasma NE) and the sensitivity to NE (as evidenced by the increase in BP induced by exogenous NE) were each attenuated after the 4-week running training in the SHR, with a consequent reduction in the BP response to a novel stress.

Keywords: running training, stress, SHR, blood pressure, norepinephrine

Introduction

A host typically reacts to a stressful stimulus with an increase in the activity of the sympathetic nervous system, leading to rises in blood pressure (BP) and heart rate (HR)\(^1\).\(^2\). Furthermore, repeated stress-exposure (i.e., chronic stress-exposure) can result in the development of stress-related disorders such as hypertension\(^3\); and it is well known that appropriate lifestyle modifications, such as increased physical exercise, can have therapeutic effects on hypertensive patients. On the other hand, exercise itself can be a kind of stress, because the plasma level of ACTH may reportedly increase after exercise\(^4\). Therefore, it might be postulated that prolonged ("chronic") exercise can induce cross-adaptation to other stresses, an effect that could contribute to an amelioration of hypertension. Indeed, running training reportedly reduces the ACTH response to a novel stress in rats\(^5\).

Many reports have demonstrated the effects of chronic exercise on changes induced by a novel stress in cardiovascular variables such as BP and HR, and in the plasma concentrations of catecholamines. For example, spontaneous wheel-running in rats led to reduced pressor and tachycardiac responses to novel stresses (e.g., cage-switch stress and immobilization stress)\(^6\). On the other hand, a discrepant report found no effect of chronic swimming exercise on the BP response to a novel stress, tail shock, in rats\(^7\). As for the catecholamine responses to a novel stress, two reports detected no significant differences between chronically exercised and sedentary control rats\(^6\),\(^7\). The above findings, obtained from chronically exercised normotensive rats, may represent further discrepancies concerning the possible beneficial effects of exercise on the cardiovascular and catecholamine responses to a novel stress.

Several studies have examined the effects of chronic exercise on resting BP in spontaneously hypertensive rats (SHR); and some, but not all, investigators have observed that chronic exercise results in significant reductions in resting BP and HR in SHR\(^8\)-\(^10\). Actually, to our knowledge, only one report found no effect of chronic exercise on cardiovascular response to a novel stress in SHR\(^11\). No literature is available regarding modulation, by chronic exercise, of stress-induced catecholamine responses in SHR.
In this study on SHR and their normotensive controls, Wistar-Kyoto rats (WKY), we investigated the effects of chronic exercise (i.e., 4 weeks of running training) on progressive changes in resting BP and HR that occurred during that period, as well as on increases in cardiovascular variables and catecholamine levels induced by a novel stress. The rats’ sensitivity to exogenously infused norepinephrine (NE) was investigated too, by measuring the induced pressor response. Such examination of an animal’s sensitivity to an increase in the plasma catecholamine level (which in real life might result from activation of the sympathetic nervous system) is a way of investigating a possible mechanism underlying exercise-induced modulation of the BP response to stress. As mentioned above, cross-adaptation could play an important role in a chronic exercise-induced amelioration of hypertension. The main purpose of the present study was to examine whether cross-adaptation to a novel stress might actually occur in chronically exercised SHR. Use of WKY allowed investigation of the possibility of such cross-adaptation also occurring in normotensives.

Methods

Animals. Male SHR (11 weeks old) or WKY (11 weeks old) purchased from Shimizu Laboratory Supplies Co. Ltd. (Kyoto, Japan) were housed in individual plastic cages (40 x 25 x 20 cm; length x width x depth) with wood-chip bedding in a room maintained at 25 ± 1°C. They experienced a photoperiod of 12 h light:12 h dark (lights on at 7:00 a.m.). All had ad libitum access to drink (tap water) and standard laboratory rat chow. The protocols were reviewed by the Committee on the Ethics of Animal Experiments in Tottori University Faculty of Medicine, and the experiments were carried out in accordance both with the Guidelines for Animal Experiments at Tottori University Faculty of Medicine and with the Federal Law (no. 221) and Notification (no. 6) issued by the Japanese Government.

This study comprised four studies (Studies 1 - 4), all on conscious rats. Each study consisted of two experiments, one using SHR and one using WKY. A given rat took part in only one study. Details of the experimental protocols are given below.

Drug. L-(-)-norepinephrine (+)-bitartrate (norepinephrine) (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile saline. The doses administered (in Study 4) is a sensitive and accurate approach to the noninvasive measurement of BP in conscious rats12). On a given day, measurement of BP and HR was performed three times (5 min apart) and the values were averaged. Delta BP and HR values were calculated. In addition, body weight was measured at the time of the cardiovascular measurements.

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) under resting conditions (Study 1)

Resting systolic BP and HR were measured (at 11:00 - 11:30 a.m.) one day before and one day after the 4-week period of running training. This was done by a tail-cuff method (without heating) in both trained and untrained rats (SHR or WKY) using an electrophysgomanometer (made by Muromachi Kikai; Model MK-2000). For the measurement, the rats needed to be restrained, but this was performed with as little force as possible. To accustomed rats to the measurement protocols, rats were slightly restrained by being placed in a small holder made of plexiglass (20 x 6.5 x 5.5 cm; length x width x depth) for 30 min/day, three times a week for 2 weeks. The rat had sufficient room (see next section) to make restricted movements. Furthermore, all rats were handled for up to 2 min every 2 or 3 days. These procedures were performed to avoid unwanted novel effects. The unheat-ed animal tail-cuff method used here has been reported to be a sensitive and accurate approach to the noninvasive measurement of BP in conscious rats12). On a given day, measurement of BP and HR was performed three times (5 min apart) and the values were averaged. Delta BP and HR values were calculated. In addition, body weight was measured at the time of the cardiovascular measurements.

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) under stressful conditions (Study 2)

Systolic BP and HR were measured by the above tail-cuff method in trained and untrained rats (SHR or WKY) under stressful conditions. Stress was induced in a given rat by immobilizing it within the small holder used for the measurement of cardiovascular variables (at 11:00 - 11:30 a.m.). First, the resting BP and HR were measured as described above. At that stage, there was a space (1.0 - 1.5 cm) in front of the rat’s nose (i.e., in the resting condition). Thereafter, the front end plate of the holder was moved backwards to immobilize the rat (i.e., there was then no space between the front end of the holder and the nose of the rat). Measurements of BP and HR were made at 5, 10, 15, 20, 25, and 30 min after the start of this stress exposure, and the six values so obtained were averaged. The evidence that the “immobilization stress” we used was actually stressful to the rats was that the BP of such observed each rat’s condition; if any rat showed signs of fatigue, the exercise was stopped. During the training program, animals in the control sedentary group (SHR and WKY) received only handling for ~2 min every 2 or 3 days.

The training program was carried out separately in SHR and WKY (7 weeks apart). Since this time lag (i.e., season-al difference) might have affected the results obtained in the studies below, training effects were examined either in SHR or in WKY (i.e., we did not make a comparison between SHR and WKY).
“stressed” rats was increased (see the Results section), reflecting an activation of the sympathetic nervous system. Since resting BP was lower in the trained SHR than in the untrained SHR (see below), delta BP and HR values were calculated.

Measurement of plasma concentrations of norepinephrine (NE) and epinephrine (E) in trained and untrained rats (SHR or WKY) under stressful conditions (Study 3)

To permit blood sampling, trained and untrained rats (SHR or WKY) were anesthetized with pentobarbital sodium (50 mg/kg IP), and a polyvinyl tube was inserted into the jugular vein so that its tip lay in the superior caval vein near the right atrium. The free end of the catheter was passed subcutaneously to the midscapular region, where it was exteriorized dorsally behind the neck. It was kept patent by flushing it every day with heparinized 0.9% saline (50 U/ml). This implantation was performed 3 days after the end of the 4-week running training and at least 3 days prior to the day of the experiment (which included blood sampling).

On the day of the experiment, the rats were subjected to 15 min of acute immobilization stress (11:00 - 11:15 a.m.), as described above. Blood samples were taken two times: at 90 min before the start of, and just after the end of the stress. Sampling for baseline measurements was done well before (i.e., 90 min before) the start of the stress to allow the rat time to recover (since the act of blood sampling itself from a rat held in the hands may be a kind of stress). On each occasion, about 0.8 ml of blood was withdrawn, collected into an ice-cooled test tube containing EDTA (1 mg/ml blood), and centrifuged at 3,000 r.p.m. for 10 min at 4 °C. The plasma was then transferred into a fresh test tube and stored at −80 °C until needed for the measurement of E or NE. The plasma concentration of E or NE was determined using a commercial ELISA kit (Labor Diagnostika Nord, FRG) with a lower detection limit of 0.00675 ng/ml or 0.0027 ng/ml, respectively. Since resting E was greater in the trained SHR than in the untrained SHR (see below), delta E and NE values were calculated.

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) receiving intravenous (IV) infusions of NE (Study 4)

For IV infusion, the IV cannulation method described above was employed in additional trained and untrained rats (SHR or WKY). This was done at least 3 days prior to the day of the experiment.

On the day of the experiment, resting systolic BP and HR were measured by the tail-cuff method described above in rats that were to receive an IV infusion of NE (1.5 µg/kg/min). NE was infused into the superior caval vein by means of a microsyringe pump (Model CMA/102; CMA Microdialysis AB, Kista, MA, Sweden). The doses of NE were chosen on the basis of previous reports.

NE dissolved in sterile saline (1.5 µg/kg/10 µl) was infused at a rate of 10 µl/min for 15 min (i.e., 1.5 µg/kg/min). Measurement of BP and HR was performed at 5, 10, and 15 min after start of infusion of NE (1.5 µg/kg/min), and the values obtained were averaged. Since resting BP was lower in the trained SHR than in the untrained SHR (see below), delta BP and HR values were calculated.

Statistical analysis. All results are expressed as mean ± S.E.M.

Comparisons were made between trained and untrained groups (of either SHR or WKY type). All data were analyzed for statistical significance by means of an unpaired Student’s t-test.

Differences were considered significant at p < 0.05.

Results

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) under resting conditions (Study 1)

Fig. 1 shows the effects of running training on the delta changes in resting BP and HR that occurred progressively during the experimental period in SHR (A and B) or WKY (C and D). BP and HR were measured before and after the 4-week training period. Systolic BP and HR increased during this 4-week period in the untrained rats (whether they were SHR or WKY). Comparison of the delta BP (Fig. 1A) and delta HR (Fig. 1B) values between the trained and untrained SHR revealed: (a) the increase in BP was smaller in the former group, while (b) the increase in HR seen in the untrained SHR was replaced by a fall in HR in the trained ones (p < 0.05 for both [a] and [b]; Student t-test). In contrast, the training had no effect (p = 0.67) on the increase in BP in WKY (Fig. 1C), although the increase in HR was significantly (p < 0.05) smaller in the trained WKY than in the untrained WKY (Fig. 1D). This lack of an effect of training on the delta BP value suggests that the smaller HR increase in the trained (vs. untrained) WKY might have been partially or completely compensated for by a larger increase in total peripheral resistance during training in the WKY.

No significant differences were observed in body weight, before or after the training period, between the trained (before, 270.3 ± 3.66 g; after, 321.5 ± 5.09 g) and untrained (before, 275.0 ± 2.66 g; after, 324.3 ± 4.98 g) SHR.

No significant differences were observed in body weight, before or after the training period, between the trained (before, 285.8 ± 2.87 g; after, 346.0 ± 2.85 g) and untrained (before, 284.7 ± 3.02 g; after, 354.2 ± 5.63 g) WKY groups.

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) under stressful conditions (Study 2)

As shown in Fig. 2A and B, the trained SHR exhibited
significantly (p < 0.05) smaller BP increases than the untrained SHR under stress, but no difference in the HR changes was detected between the two groups. In the trained WKY, systolic BP (Fig. 2C) and HR (Fig. 2D) responses to 30 min of immobilization stress were similar to those in the untrained WKY.

Measurement of plasma concentrations of NE and E, in trained and untrained rats (SHR or WKY) under stressful conditions (Study 3)

Plasma concentrations of NE and E were increased by 15 min of immobilization stress in both trained and untrained rats (whether they were of the SHR or WKY type). The NE response to the stress was significantly (p < 0.05) smaller in the trained SHR than in the untrained SHR (Fig. 3A), but this was not true of the E response (p = 0.13) (Fig. 3B). The trained WKY showed a significantly (p < 0.05) smaller NE response than the untrained WKY (Fig. 3C). There was no significant (p = 0.054) difference in the E response between the two groups of WKY (Fig. 3D).

Measurement of systolic BP and HR in trained and untrained rats (SHR or WKY) receiving intravenous (IV) infusions of NE (Study 4)

As shown in Fig. 4, IV infusion of NE induced an increase in BP and a decrease in HR in both the trained and the untrained rats (whether they were of the SHR or WKY type). Trained SHR had significantly (p < 0.05) smaller BP responses to IV infusion of NE than untrained SHR (Fig. 4A). The HR response to IV infusion of NE was significantly (p < 0.05) smaller in trained SHR than in untrained SHR (Fig. 4B). Student’s t-test detected no significant difference in either the BP (p = 0.0611) or HR response between the two groups of WKY (Fig. 4C and D).

Discussion

The present results demonstrate (a) that after running training lasting for 4 weeks, SHR exhibited reduced BP and NE responses to immobilization stress, and (b) that the BP increase induced by IV infusion of NE was smaller in trained than in untrained SHR. By contrast, the HR and E responses to the stress underwent no alteration as a result of the training. The absence of a training-induced change in the HR response to the stress suggests that the training had no effect on the activity of the sympathetic innervation of the heart in the stressed rats. Collectively, these results may be interpreted as indicating: 1) that the reduction in the stress-induced BP response seen in the trained SHR was mainly due to an attenuated contractility of resistance vessels and, therefore, 2) that the stress-induced activation of the sympathetic nervous system (as

![Graph A](image1.png)

![Graph B](image2.png)

![Graph C](image3.png)

![Graph D](image4.png)

Fig. 1  Study 1: effects of running training on the progressive changes in systolic BP and HR occurring during the experimental period in rats (SHR or WKY) under resting conditions.
Delta values (mean±S.E.M.) obtained for systolic BP and HR in trained and untrained rats of either the SHR (A and B) or WKY (C and D) strain under resting conditions. Each parameter was measured 1 day before (week 0) and 1 day after (week 4) the 4-week period of running training. For trained and untrained SHR at week 0: mean values for baseline BP (±S.E.M.) were 189.8±2.06 and 195.0±3.10 mmHg, respectively; mean values for baseline HR (±S.E.M.) were 409.3±11.8 and 362.5±14.2 beats/min, respectively. For trained and untrained WKY at week 0: mean values for baseline BP (±S.E.M.) were 107.3±2.43 and 103.8±4.24 mmHg, respectively; mean values for baseline HR (±S.E.M.) were 361.7±7.4 and 355.0±10.2 beats/min, respectively. *P<0.05 vs. untrained rats of the same strain.
**Fig. 2** Study 2: effects of running training on changes in systolic BP and HR in rats (SHR or WKY) under stressful conditions.
Delta values (mean±S.E.M.) for systolic BP and HR obtained from trained and untrained rats of either the SHR (A and B) or WKY (C and D) strain exposed to a novel stress (immobilization stress; see details in “Methods”). For trained and untrained SHR before exposure to the stress: mean values for baseline BP (±S.E.M.) were 212.0±4.36 and 223.2±3.86 mmHg, respectively; mean values for baseline HR (±S.E.M.) were 376.2±18.73 and 412.4±9.37 beats/min, respectively. For trained and untrained WKY before exposure to the stress: mean values for baseline BP (±S.E.M.) were 113.5±1.84 and 113.7±5.53 mmHg, respectively; mean values for baseline HR (±S.E.M.) were 363.2±7.72 and 382.5±13.60 beats/min, respectively. *P<0.05 vs. untrained SHR.

**Fig. 3** Study 3: effects of running training on changes in plasma concentrations of NE and E in rats (SHR or WKY) under stressful conditions.
Delta values (mean±S.E.M.) for NE and E obtained from trained and untrained rats of either the SHR (A and B) or WKY (C and D) strain exposed to a novel stress (immobilization stress; see details in “Methods”). For trained and untrained SHR before exposure to the stress: mean values for baseline NE (±S.E.M.) were 71.2±7.88 and 69.7±9.44, respectively; and mean values for baseline E (±S.E.M.) were 54.6±3.17 and 37.3±5.89, respectively. There was a significant difference in the baseline E level between the two groups. For trained and untrained WKY before exposure to the stress: mean values for baseline NE (±S.E.M.) were 52.4±5.15 and 55.5±5.20, respectively; and mean values for baseline E (±S.E.M.) were 26.4±2.72 and 38.3±7.90, respectively. *P<0.05 vs. untrained rats of the same strain.
In the present study, the systolic BP in the untrained SHR under resting conditions rose during the 4 weeks, but the change was significantly smaller in the SHR undergoing training. This finding is in good accord with previous reports. By contrast, running training had no effect on the resting BP in the WKY. These data, taken together, may indicate that chronic exercise could indeed have a therapeutic potency leading to a decrease in BP in hypertensive individuals, but no such effect in normotensive ones. However, such a preventive effect of chronic exercise on hypertension still needs further investigation.

It should be noted that in the present study the resting BP of untrained WKY rose during the 4-week training period (like that of untrained SHR). This is in agreement with a report by Nagai et al. showing an increase in the resting BP of WKY from 4 to 20 weeks of age.

In the present WKY, neither the cardiovascular responses to stress nor those to IV infusion of NE were changed by running training. However, the stress-induced increase in the plasma level of NE was smaller in the trained WKY than in the untrained WKY. We would expect the BP response to the stress to be decreased in the trained WKY, since the stress-induced activation of the sympathetic nervous system was attenuated while the sensitivity to exogenous NE was unchanged in those rats. However, other factors involved in cardiovascular regulation may have been affected in the trained WKY as well. For example, it has been reported that running training results in a decrease in the mRNA level of a vasodilator, atrial natriuretic peptide (ANP), in the left atrium. Since, ANP is produced in both endothelium and vascular smooth muscle, the production of vascular ANP might also be lowered after running training, a possibility that should be tested in the near future.

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limited potential in SHR for BP to increase in response to NE. In other words, the increases in BP in SHR may have approached “a ceiling”. On the other hand, a training-induced reduction in the BP response to NE was observed only in the SHR. The consequence of this may be that trained SHR with a high baseline BP are protected against a deleterious increase in BP in response to stress.

The present study revealed that the plasma concentration of E was significantly higher in the trained than in the untrained SHR in the resting condition, although there was no difference in the resting plasma NE between the two groups (see legend to Fig. 3). Since the changes in resting BP during the 4 weeks and the BP response to exogenous NE were both smaller in the trained SHR than in the untrained SHR, the decreased sensitivity to NE might have affected resting BP much more than the increased level of circulating E in the trained SHR. Indeed, it is widely accepted that NE has a much greater BP-elevating potency than E. In addition, it should be noted that in this study, trained SHR and trained WKY showed an apparent, though insignificant (p > 0.05), reduction in the E response to the stress (see Fig. 3) as compared with the respective untrained control group. We cannot exclude the possibility that increasing the number of the experimental animals in each group might lead to a significant difference being shown between trained and untrained rats in terms of the stress-induced E response.

The present results show that the BP and NE responses to immobilization stress are attenuated by 4 weeks of running training in SHR, as are the increases in BP induced by IV infusion of NE. These findings suggest that the running training reduced both the stress-induced activation of the sympathetic nervous system and the sensitivity of resistance vessels to the secreted NE, leading to the observed decrease in the stress-induced BP response. It has been reported that the operation of the baroreceptor reflex is improved after chronic exercise in SHR, which could lead to a decrease in BP. This seems a likely scenario since in our hands, the BP response to stress was decreased in the trained SHR, while the stress-induced HR response underwent no training-related alteration. The underlying changes that presumably occur in pathways involved in cardiovascular regulation in the brain during chronic exercise need to be clarified. For example, sympathetic premotor neurons in the brain can be detected by injecting retrograde tracer into the intermediolateral nucleus of the thoracic spinal cord. The activities of those neurons, as revealed by their expression of Fos protein, could be compared between trained and untrained SHR after exposure to a novel stress. The technique required for this experiment is an established one. For example, Nakamura et al. administered retrograde tracer into the raphe nucleus of rats and identified prostaglandin receptor-expressing hypothalamic neurons innervating the nucleus. Furthermore, sympathetic premotor neurons have been identified in the dorsal medulla in cats on the basis of retrograde transport of horseradish peroxidase following its injection into the intermediolateral nucleus. Using this technique, if the novel stress-induced changes in the activities of the sympathetic premotor neurons in a certain brain region were found to be decreased in chronically exercised animals, those neurons might be candidates for contributors to the effect of chronic exercise that leads to a reduction of the deleterious influences of stresses on BP. However, this is a complex issue, and would need considerable study. Finally, the attenuated BP and NE responses to immobilization stress seen here indicate that, in SHR, cross-adaptation may occur between chronic exercise and novel stress. It is widely accepted that acute stress elicits an increase in BP and that when animals are repeatedly exposed to stresses, they often develop hypertension. Chronic exercise is well known to have therapeutic effects on hypertension, and cross-adaptation between exercise and stresses might partly underlie such a contribution of chronic exercise to an improvement in hypertensive states.

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