Renal Manifestations of NaCl Sensitivity in Borderline Hypertensive Rats

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Compared with the normotensive Wistar-Kyoto rat, the spontaneously hypertensive rat exhibits exaggerated alterations in renal sympathetic nerve activity and excretory function during volume expansion (exaggerated natriuresis) and environmental stress (antinatriuresis). The borderline hypertensive rat is the first filial offspring of the spontaneously hypertensive rat and the Wistar-Kyoto rat and develops hypertension with increased dietary NaCl intake. The present investigation sought to determine whether the dietary NaCl intake–induced transition from the normotensive state of the Wistar-Kyoto parent to the hypertensive state of the spontaneously hypertensive parent in the borderline hypertensive rat was accompanied by a similar transition of the renal sympathetic nerve activity and excretory responses to volume expansion and environmental stress. Borderline hypertensive rats fed a 1% NaCl diet remained normotensive and exhibited renal sympathetic nerve activity and excretory responses to volume expansion and environmental stress that were similar to those of their Wistar-Kyoto parent. Borderline hypertensive rats fed an 8% NaCl diet developed hypertension and exhibited responses that were similar to those of their spontaneously hypertensive parent. Thus, the dietary NaCl intake–induced transition from the normotensive state of the Wistar-Kyoto parent to the hypertensive state of the spontaneously hypertensive parent in the borderline hypertensive rat was accompanied by a similar transition of the renal sympathetic nerve activity and excretory responses to volume expansion and environmental stress. The results suggest that increased dietary NaCl intake is able to induce or unmask the capabilities for these responses, which are genetically conveyed to the borderline hypertensive rat by the spontaneously hypertensive rat parent in latent forms. (Hypertension 1991;17:44–53)

The central nervous system and the kidneys have long been thought to be critical in the pathophysiology of hypertension. Folkow1 has advanced the concept that primary hypertension derives from an interaction between genetic and environmental factors. Of the environmental factors, dietary sodium intake and environmental (psychosocial) stress are considered important. Our previous work2-3 has defined an interaction between environmental stress and dietary sodium intake in two experimental models characterized by genetic predisposition to hypertension, the spontaneously hypertensive rat (SHR) and the Dahl rat. In both instances, increased dietary sodium intake augmented the efferent renal sympathetic nerve activity (ERSNA) response to acute environmental stress, leading to a renal vasoconstrictor response in the SHR and more profound antidiuretic and antinatriuretic responses in both strains.

Exaggerated natriuresis is a phenomenon observed in hypertensive animals and humans whereby the natriuretic response to intravenous isotonic saline loading is enhanced over that seen in normotensive controls. Our previous work4-6 has demonstrated that the exaggerated natriuresis seen in SHR is accompanied by an exaggerated withdrawal of ERSNA; this exaggerated withdrawal of ERSNA contributes to the exaggerated natriuresis since it is attenuated by prior renal denervation. Dahl rats do not exhibit an exaggerated natriuresis, perhaps because they have impaired cardiopulmonary baroreceptor reflex inhibitory control over ERSNA.7

The borderline hypertensive rat (BHR) is a genetic model of environmentally induced hypertension. The BHR is the first filial offspring of SHR and the normotensive Wistar-Kyoto (WKY) rat and possesses genetic information from both a normotensive WKY and a hypertensive SHR parent. As described
by Lawler and colleagues,8-10,11 the BHR become permanently hypertensive when subjected to a time-limited period of exposure to environmental stress or to increased dietary sodium intake. Renal denervation, performed early but not late, can prevent the development of environmental stress-induced hypertension in BHR.12

Because increased dietary sodium intake causes the BHR to exhibit one characteristic of the phenotype of the hypertensive SHR parent (i.e., a sustained increase in arterial pressure), we sought to determine whether other features of the hypertensive SHR parent phenotype were also expressed by the increased dietary sodium intake. The two features examined were the exaggerated natriuretic response to intravenous isotonic saline loading and the ERNSA and renal excretory responses to acute environmental stress.

**Methods**

**Animals**

The present study used age-matched male BHR, WKY rats, and SHR. The BHR were the first generation offspring of SHR females and WKY males purchased from Taconic Farms, Germantown, N.Y. The rats were weaned at 4 weeks of age. Standard laboratory rat chow and tap water were available to all rats until the dietary regimens were instituted as described below.

**Anesthesia**

The rats were anesthetized with methohexitnal (Brevital, 20 mg/kg i.p. supplemented with 10 mg/kg i.v. as needed; Eli Lilly and Co., Indianapolis, Ind.).

**Procedures**

**Renal denervation.** Renal denervation was performed via bilateral flank incisions by stripping the renal arteries and veins of adventitia, cutting the renal nerve bundles, and coating the vessels with a solution of 10% phenol in absolute ethanol. This renosteric nerve stimulation, prevents the antinatriuretic response to intravenous isotonic saline loading and the ERNSA and renal excretory responses to acute environmental stress.

**Renal sympathetic nerve activity recording electrode.** The left kidney was exposed through a left flank incision via a retroperitoneal approach. With the use of a dissecting microscope (x25), a renal nerve branch from the aorticorenal ganglion was isolated and carefully dissected free. The renal nerve branch was then placed on a bipolar platinum wire (Cooner Wire Company, Chatsworth, Calif.) electrode. Renal sympathetic nerve activity was amplified (10,000-50,000 times) and filtered (low 30 Hz; high 3,000 Hz) with a Grass P511 Bandpass Amplifier (Grass Instrument Co., Quincy, Mass.). The amplified and filtered signal was channeled to a Tektronix 5113 Oscilloscope (Tektronix, Inc., Beaverton, Ore.) and Grass Model 7DA polygraph for visual evaluation, to an audio amplifier/loudspeaker (Grass model AM 8 Audio Monitor) for auditory evaluation, and to a rectifying voltage integrator (Grass model 7P10) and a frequency discharge counter (Scope Raster/Stepper Model 140A, W-P Instruments, Inc., New Haven, Conn.). The integrated voltage, frequency discharge, and renal neurogram signals were displayed on the Grass polygraph. The quality of the renal sympathetic nerve activity signal was assessed by examining its pulse synchronous rhythmicity and the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor loading with an intravenous injection of norepinephrine (3 µg). After maximum inhibition by administration of norepinephrine, the remaining renal sympathetic nerve activity was similar to the background noise observed approximately 30 minutes post mortem; this value was subtracted from all experimental values of renal sympathetic nerve activity. When an optimal renal sympathetic nerve activity signal was observed, the recording electrode was fixed to the renal nerve branch with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie, Munich, FRG). The electrode cable was then secured in position by suturing it to the abdominal trunk muscles. Finally, the electrode cable was exteriorized and the flank incision closed in layers.

**Experimental Protocol**

At 6 weeks of age, all rats were individually housed and randomly assigned to one of two groups. One group received a 1% NaCl diet and the other received an 8% NaCl diet. At 12 and 18 weeks of age (6 and 12 weeks of each diet, respectively), half of the rats underwent bilateral renal denervation. Two to 5 days later, both the 12- and 18-week-old rats underwent chronic catheterization and implantation of a renal sympathetic nerve activity recording electrode.

After allowing 24 hours for recovery from surgery, rats were placed in rat holders, which permit forward and backward movement and collection of steady-state urine samples. An intravenous infusion (58 µl/min) of isotonic saline containing sufficient quan-
tities of inulin and para-aminohippurate (PAH) for determination of inulin and PAH clearance was then started and allowed to continue throughout the duration of the experimental protocol. Four to 6 hours after habituation and the start of isotonic saline infusion, the arterial catheter was flushed and attached to a pressure transducer (model P23Db, Statham, Oxnard, Calif.), and the urinary bladder catheter was led to a collection beaker. After stabilization of urinary flow rate, arterial pressure, and heart rate, the quality of the renal sympathetic nerve activity recording was again tested with an intravenous injection of norepinephrine (3 \text{ \mu g}) as previously described to ensure the absence of noise due to mechanical movement, respiration, or heart rate. If the quality of the renal sympathetic nerve activity recording was the same as that observed when the electrode was implanted, then the experiment commenced.

Exaggerated natriuresis. The control period consisted of three consecutive 10-minute urine collections. Then, a volume of isotonic saline equivalent to 10\% body weight was given intravenously over 30 minutes during which three consecutive 10-minute urine collections (volume expansion period) were made. After the acute intravenous isotonic saline load, six consecutive 10-minute urine collections were made (recovery period). Venous blood samples (200 \mu l) were taken during the midpoint of the control, volume expansion, and recovery periods. For experiments with renal sympathetic nerve activity recordings, the quality of the renal sympathetic nerve signals was again assessed with intravenous injections of norepinephrine (3 \text{ \mu g}) after completion of the protocol. The rat was then killed and postmortem renal sympathetic nerve activity was continuously recorded for 30 minutes as a measure of background noise. The kidneys were removed, decapsulated, drained, and weighed.

Acute environmental stress. The control period consisted of two consecutive 10-minute urine collections. The acute environmental stress was applied for 20 minutes using air jet stress. Five minutes was allowed after the start of air jet stress before collecting two consecutive 10-minute urine specimens (air jet stress period). Five minutes was allowed after cessation of air jet stress before collecting two consecutive 10-minute urine specimens (recovery period). Venous blood samples (200 \mu l) were taken during the midpoint of the control, air jet stress, and recovery periods. Acute environmental stress stimulation consisted of an air jet delivered to the top of the rat’s head through a tube located 4–5 cm in front of the rat. Repeated applications of air jet stress in the same rat result in similar increases in heart rate, mean arterial pressure, and efferent renal sympathetic nerve activity and in decreases in urinary flow rate and sodium excretion.\textsuperscript{2,15–20} For experiments with renal sympathetic nerve activity recordings, the quality of the renal sympathetic nerve signals was again assessed with intravenous injections of norepinephrine (3 \text{ \mu g}) after completion of the protocol.

\textbf{Results}

\textbf{Exaggerated Natriuresis}

\textbf{Six-week diet.} Figure 1 summarizes the mean arterial pressure (MAP) data. While consuming a 1\%
As seen in Figure 2 (top panel), while consuming a 1% NaCl diet, only SHR demonstrated an exaggerated natriuretic response to intravenous isotonic saline loading (p<0.05 versus all others). After renal denervation, the natriuretic response of SHR was significantly decreased and not different from the responses of both WKY rats and BHR, whether innervated or denervated. While consuming an 8% NaCl diet (Figure 2, bottom panel), both SHR and BHR demonstrated an exaggerated natriuretic response to intravenous isotonic saline loading (p<0.05 versus all others). After renal denervation, the natriuretic responses of both SHR and BHR were significantly decreased and not different from the response of WKY rats, whether innervated or denervated.

As summarized in Table 1, glomerular filtration rate and renal plasma flow were similar among WKY rats, SHR, and BHR in the control period and slightly, but not significantly, increased by intravenous isotonic saline loading with a return toward the control period values in the recovery period. The pattern was similar in WKY rats, SHR, and BHR, and there were no significant differences between the NaCl diet for 6 weeks, SHR (172±5 mm Hg) had significantly higher MAP than both BHR (137±4 mm Hg, p<0.01) and WKY rats (119±3 mm Hg, p<0.01); also, BHR had higher MAP than WKY rats (p<0.05). Renal denervation did not affect MAP in WKY rats, SHR, or BHR. Consumption of an 8% NaCl diet for 6 weeks did not change MAP in WKY rats, SHR, or BHR from MAP values observed on the 1% NaCl diet; renal denervation did not affect MAP in WKY rats, SHR, or BHR.

These changes are more easily appreciated in Figure 3, which summarizes the data for percent excretion of sodium (% ENa), the percent of the sodium load excreted over 2 hours. Only the SHR demonstrate an exaggerated natriuretic response while consuming a 1% NaCl diet (Figure 3, top panel), with % ENa of 81±5%, and after renal denervation, this is reduced to 66±5%, which is similar to the level seen in WKY rats and BHR, whether innervated or denervated. While consuming an 8% NaCl diet (Figure 3, bottom panel), both SHR (84±2%) and BHR (83±2%) demonstrate an exaggerated natriuretic response, and after renal denervation, the natriuretic responses are reduced to 70±4% and 68±5%, respectively, which are similar to the levels seen with WKY rats whether innervated or denervated.

As summarized in Table 1, glomerular filtration rate and renal plasma flow were similar among WKY rats, SHR, and BHR in the control period and slightly, but not significantly, increased by intravenous isotonic saline loading with a return toward the control period values in the recovery period. The pattern was similar in WKY rats, SHR, and BHR, and there were no significant differences between the
TABLE 1. Summary of Glomerular Filtration Rate and Renal Plasma Flow Data in Wistar-Kyoto, Spontaneously Hypertensive, and Borderline Hypertensive Rats on 1% and 8% NaCl Diets During Isotonic Saline Volume Expansion Protocol

<table>
<thead>
<tr>
<th>Measure</th>
<th>WKY 1% NaCl</th>
<th>WKY 8% NaCl</th>
<th>SHR 1% NaCl</th>
<th>SHR 8% NaCl</th>
<th>BHR 1% NaCl</th>
<th>BHR 8% NaCl</th>
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<tr>
<td>GFR</td>
<td>1.15±0.07</td>
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<td>3.35±0.21</td>
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<tr>
<td>SEM</td>
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<td>C</td>
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<td>0.80±0.06</td>
<td>1.28±0.07</td>
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<td>1.25±0.08</td>
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<tr>
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<td>4.45±0.15</td>
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<td>4.54±0.21</td>
<td>4.33±0.21</td>
</tr>
</tbody>
</table>

C, control; VE, volume expansion; R, recovery; WKY, Wistar-Kyoto rat; GFR, glomerular filtration rate (ml/min/g kidney wt); RPF, renal perfusion rate (ml/min/g kidney wt); SHR, spontaneously hypertensive rat; BHR, borderline hypertensive rat.

1% or 8% NaCl diet condition or the innervated and denervated condition.

Simultaneously recorded ERSNA in BHR consuming an 8% NaCl diet for 6 weeks (n=4) showed a maximum decrease of 46±8% compared with a maximum decrease of 30±5% in BHR consuming a 1% NaCl diet for 6 weeks (n=4). This difference did not achieve statistical significance (0.10>p>0.05).

Twelve-week diet. BHR consuming an 8% NaCl diet for 12 weeks had significantly higher MAP than BHR consuming a 1% NaCl diet for 12 weeks: 164±4 mm Hg versus 138±7 mm Hg. Renal denervation did not affect MAP.

As shown in Figure 4, BHR consuming 8% NaCl for 12 weeks demonstrated an exaggerated natriuretic response to intravenous isotonic saline loading compared with BHR consuming 1% NaCl for 12 weeks. After renal denervation, the natriuretic response of BHR consuming 8% NaCl but not 1% NaCl for 12 weeks was decreased. As summarized in

![Figure 4](http://hyper.ahajournals.org/)[in T4F.png]
Figure 5, % ENa was greater in BHR consuming 8% NaCl for 12 weeks than in BHR consuming 1% NaCl for 12 weeks, 84±6% versus 61±5%, p<0.05. After renal denervation, % ENa in BHR consuming 8% NaCl (72±3%) but not 1% NaCl (60±3%) for 12 weeks was decreased (p<0.05). As illustrated in Figure 6, simultaneously recorded ERSNA decreased to a greater extent (p<0.05) in BHR consuming 8% NaCl for 12 weeks (maximum decrease 52±6%) than in BHR consuming 1% NaCl for 12 weeks (maximum decrease 29±3%).

**Acute Environmental Stress**

These studies were conducted in BHR that had been consuming either 1% or 8% NaCl for 12 weeks. MAP in the 8% NaCl BHR (148±4 mm Hg) was significantly higher than in the 1% NaCl BHR (136±4 mm Hg). The responses to acute environmental stress are summarized in Figures 7 and 8. Air jet stress produced significant increases in heart rate, MAP, and urine flow rate in both groups. The increases in MAP and heart rate were significantly greater in the 8% NaCl than in the 1% NaCl BHR, 11±3 versus 4±1 mm Hg and 70±9 versus 41±9 beats/min, respectively, while the increase in urine flow rate was significantly greater in the 1% NaCl than in the 8% NaCl BHR, 15±3 versus 8±2 μl/min/g kidney wt. ERSNA and urinary sodium excretion (UNaV) did not significantly change in 1% NaCl BHR, 17±11% and -0.09±0.03 μeq/min/g kidney wt, respectively, whereas ERSNA was significantly increased (62±24%) and UNaV was significantly decreased (0.45±0.07 μeq/min/g kidney wt) in 8% NaCl BHR. Glomerular filtration rate and renal plasma flow were not changed in either 1% or 8% NaCl BHR.

In separate experiments, prior bilateral renal denervation did not affect the UNaV response to air jet stress in 1% NaCl BHR (n=6). In 8% NaCl BHR (n=6) prior bilateral renal denervation abolished the antagonistic response to air jet stress (UNaV in μeq/min/g kidney wt: control 3.31±0.49, air jet stress 3.34±0.50, recovery 3.11±0.52).

**Discussion**

The present studies have identified a major role for dietary NaCl intake in the pathophysiology of NaCl-inducible hypertension in BHR. BHR, when maintained on a 1% NaCl diet, do not exhibit an increase in arterial pressure, an exaggerated natriuretic response to isotonic saline loading, or an augmented...
response to acute environmental stress. In contrast, BHR given an 8% NaCl diet demonstrate an increase in arterial pressure in association with an exaggerated natriuretic response to isotonic saline loading. The exaggerated natriuresis is associated with an exaggerated withdrawal of ERSNA, and prior renal denervation diminishes the exaggerated natriuresis response, indicating its dependence, in part, on the withdrawal of ERSNA. In addition, they demonstrate an augmented response to acute environmental stress with greater increases in heart rate, MAP, and ERSNA and a greater decrease in $U_{\text{Na}V}$, which is dependent on intact renal innervation.

The responses that occurred in BHR given an 8% NaCl diet are similar to those previously observed in their hypertensive parent, the SHR. The SHR exhibit an exaggerated natriuretic response to isotonic saline loading in association with an exaggerated withdrawal of ERSNA. Prior renal denervation diminishes the exaggerated natriuresis, demonstrating its dependence, in part, on the decrease in ERSNA. This phenomenon, the dependence of the natriuretic response to isotonic saline loading on withdrawal of ERSNA, is not limited to the hypertensive state. Prior studies in conscious normotensive rats, dogs, and monkey have all demonstrated that renal denervation attenuates the magnitude of the natriuretic response to intravenous isotonic volume expansion. These studies indicate that the decrease in ERSNA that occurs during the volume expansion contributes to the natriuresis observed by directly decreasing renal tubular sodium reabsorption. Furthermore, it is not characteristic of all forms of experimental hypertension since neither Dahl salt-resistant nor Dahl salt-sensitive rats on either low or high NaCl diet exhibit an exaggerated natriuretic response to isotonic saline loading. This may relate to the documented defect in cardiopulmonary baroreceptor reflex inhibitory control over peripheral (renal) sympathetic nerve activity. Because this response was elicited in BHR by 8% but not 1% NaCl diet, the results suggest that the increased dietary NaCl intake is able to induce or unmask this mechanism, which is genetically conveyed to the BHR by the hypertensive SHR parent in a latent form.

Acute environmental stress, using air jet, is known to produce a cardiovascular response pattern characteristic of the defense reaction in the SHR. There is tachycardia with an increase in arterial pressure; regional blood flow to the renal and mesenteric vascular beds is decreased while that to the skeletal muscle (hindquarters) vascular bed is increased. There is antidiuresis, antinatriuresis, and an increase in renin release in association with an increase in ERSNA; glomerular filtration rate and renal plasma flow are unchanged. The antidiuresis, antinatriuresis, and increase in renin release are abolished by prior renal denervation. These findings were not observed in WKY rats exposed to the same acute environmental stress. When dietary NaCl intake was increased for 4 weeks, the SHR but not the WKY rats responded with an augmented renal sympathoexcitatory response to acute environmental stress, which was sufficient to produce renal vasoconstriction with decreased renal plasma flow and glomerular filtration rate. Compared with BHR fed a 1% NaCl diet, BHR fed an 8% NaCl diet responded to acute environmental stress with a greater rise in heart rate and MAP. ERSNA was increased in association with a decrease in $U_{\text{Na}V}$ in BHR fed 8% NaCl, whereas ERSNA and $U_{\text{Na}V}$ were unchanged in BHR fed 1% NaCl. Prior bilateral renal denervation did not affect the $U_{\text{Na}V}$ response to air jet stress in 1% NaCl BHR but abolished the antinatriuretic response to air jet stress in 8% NaCl BHR. Thus, the overall response to acute environmental stress of BHR fed 1% NaCl was similar to that of WKY rats, whereas the overall response of BHR fed 8% NaCl was similar to that of SHR. Previous studies have shown that BHR fed 8% NaCl responded with an antinatriuresis, a de-
increase in renal plasma flow, and no change in glomerular filtration rate in response to tail-shock stress, whereas BHR fed 1% NaCl exhibited no changes in U_{\text{GFR}}, glomerular filtration rate, or renal plasma flow. Again, the results suggest that increased dietary NaCl intake is able to induce or unmask the potential for these cardiovascular and renal responses to acute environmental stress, which are genetically conveyed to the BHR by the hypertensive SHR parent.

The time course of the influence of increased dietary NaCl intake is noteworthy. At 6 weeks of diet, the MAP of BHR fed 1% and 8% NaCl was similar and somewhat higher than WKY rat but considerably less than SHR. At similar MAP, BHR fed 8% NaCl exhibited SHR-type responses to isotonic saline loading; whereas BHR fed 1% NaCl exhibited WKY-type responses. At 12 weeks of diet, the MAP of BHR fed 1% NaCl had not changed significantly from that at 6 weeks of the same diet (Δ=1 mm Hg), whereas the MAP of BHR fed 8% NaCl had increased significantly from that at 6 weeks of the same diet (Δ=27 mm Hg). Again, the hypertensive BHR fed 8% NaCl exhibited SHR-type responses to isotonic saline loading, whereas normotensive BHR fed 1% NaCl exhibited WKY-type responses. These results suggest that the influence of increased dietary NaCl intake in BHR on central neural control of efferent renal sympathetic nerve activity in the regulation of renal excretory function precedes and may be separate from that on arterial pressure.

In the current studies, 8% NaCl BHR with hypertension had significantly greater increases than 1% NaCl BHR with normotension in arterial pressure (11±3 versus 4±1 mm Hg) and heart rate (70±9 versus 41±9 beats/min) during an acute episode of air jet stress. Previous work had suggested that BHR made hypertensive by either exposure to environmental stress or increased dietary NaCl intake showed very little further increase in arterial pressure or heart rate in response to an acute episode of stress. BHR with hypertension induced by increased dietary NaCl intake had similar increases in plasma norepinephrine and epinephrine concentrations in response to cold stress as those seen in BHR on a normal dietary NaCl intake and in SHR and WKY rats on either normal or increased dietary NaCl intake. In addition, these hypertensive BHR did not show significant increases in arterial pressure to an acute episode of tail-shock stress. When hypertension was induced with environmental stress (tail-shock stress) in BHR, they showed increases in arterial pressure (12±6 mm Hg) and heart rate (approximately 100 beats/min) that were similar to those of nonstressed BHR control rats (6±2 mm Hg, approximately 100 beats/min) during an acute episode of foot-shock stress. However, significant changes in arterial pressure to an acute episode of foot-shock stress did not occur when increased dietary NaCl intake was used to produce hypertension in BHR. The augmented arterial pressure and heart rate responses to acute air jet stress herein observed in BHR made hypertensive with increased dietary NaCl intake compared with normotensive BHR on a normal dietary NaCl intake may reflect differences related to the type of acute stress used, air jet stress versus tail-shock or foot-shock stress.

It is known that both environmental stress and increased dietary NaCl intake increase MAP in BHR. The BHR becomes hypertensive when subjected to tail-shock stress; this hypertension is permanent after cessation of the environmental stress and is associated with hypertensive pathological changes in the heart. Increased dietary NaCl intake also increases MAP in BHR. When BHR were randomly allocated to either an 8% or an 0.8% NaCl diet at 8 weeks of age, directly measured arterial pressure (systolic/diastolic) at 16 weeks of age was 186±2/129±2 mm Hg in 8% NaCl BHR and 161±2/105±2 mm Hg in 0.8% NaCl BHR. BHR were randomly allocated to either an 8% or an 0.8% NaCl diet at 8 weeks of age, directly measured MAP at 13 weeks of age was 156±3 mm Hg in 8% NaCl BHR and 143±4 mm Hg in 0.8% NaCl BHR. Recent studies strongly suggest that there is a neural component to the hypertension induced in BHR by environmental factors, psychosocial stress, and increased dietary NaCl intake. BHR subjected to 5 weeks of tail-shock stress before bilateral renal denervation failed to develop hypertension in response to continued stress. However, BHR subjected to 11 weeks of tail-shock stress before bilateral renal denervation exhibited a temporary decrease in arterial pressure after denervation, but arterial pressure returned to its elevated level in response to continued stress. These observations suggest that there may be a critical period during which the renal nerves are necessary for the expression of stress-induced hypertension in BHR. Lesions of the anteroventral third ventricle (AV3V), a maneuver that prevents the development of many forms of experimental hypertension, prevented the development of both stress- and NaCl-induced hypertension in BHR.

After 12 weeks of tail-shock stress, the MAP of AV3V-lesioned BHR was 126±5 mm Hg, which was significantly lower than the MAP of sham-lesioned BHR of 153±3 mm Hg. In addition, AV3V lesions kept MAP in stressed rats (126±5 mm Hg) at levels not significantly different from nonstressed control BHR (133±4 mm Hg). After 10 weeks of 8% NaCl diet, the MAP of AV3V-lesioned BHR was 128±5 mm Hg, whereas the MAP of sham AV3V-lesioned BHR was 148±4 mm Hg. Although the hypertension induced by stress is thought to be related to exaggerated responsiveness of the sympathetic nervous system and that induced by maintained increased dietary NaCl intake to volume expansion, these results suggest that the AV3V region is a common central neural substrate for both environmentally induced forms of hypertension.

Oparil has described a mechanism whereby increased dietary NaCl intake may increase arterial pressure via an action in the anterior hypothalamic.
area that results in increased peripheral sympathetic nerve activity. The collected data suggest that increased dietary NaCl intake causes a reduction in noradrenaline release in the anterior hypothalamus with a reduction in the noradrenergic input to depressor neurons in the anterior hypothalamic area. This should result in an increase in arterial pressure due to withdrawal of peripheral sympathoinhibition with associated upregulation of α2-adrenergic receptors in the anterior hypothalamic area. Studies have confirmed that increased dietary NaCl intake increases α2-adrenergic receptor number in the anterior hypothalamic area. Functional studies have demonstrated that dietary NaCl intake enhances the depressor, bradycardic, and renal sympathetic nerve inhibitory responses to administration of the α2-adrenergic receptor agonists, clonidine and guanabenz, into the anterior hypothalamic area, the lateral cerebral ventricle, or intravenously.

Therefore, increased dietary NaCl intake can act in central nervous system sites to result in alterations in the regulation of the peripheral sympathetic nervous system activity. These can result in increased arterial pressure and changes in the central neural regulation of renal sympathetic neural control of renal function, which may be observed in the responses to acute isotonic saline volume expansion and air jet stress. The expression of these responses in BHR made hypertensive by 8% NaCl dietary intake, similar to those observed in the hypertensive SHR parent, but not in normotensive BHR on a 1% NaCl dietary intake or the normotensive WKY parent, suggests that these dietary NaCl-inducible responses are hereditary.

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References


**KEY WORDS** • kidney • sympathetic nervous system • sodium • borderline hypertensive rat
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