Cardiac Volume Receptor Reflex in Borderline Hypertensive Rats

Gerald F. DiBona and Susan Y. Jones

With increased dietary NaCl intake (8% NaCl), borderline hypertensive rats (BHR) develop hypertension and exhibit an exaggerated natriuresis in response to intravenous isotonic saline volume expansion. The exaggerated natriuresis is mediated by the concurrent exaggerated withdrawal of efferent renal sympathetic nerve activity since prior renal denervation eliminates the exaggerated natriuretic response. It was the objective of the present study to examine cardiac volume receptor reflex control of efferent renal sympathetic nerve activity in BHR made hypertensive by increased dietary NaCl intake. BHR were fed either 1% or 8% NaCl from age 4 to 16 weeks. BHR fed 8% NaCl were hypertensive (148±9 mm Hg) compared with BHR fed 1% NaCl (115±6 mm Hg, p<0.05). In one protocol, measurements of right atrial pressure and efferent renal sympathetic nerve activity were made in sinoaortic-denervated BHR before and during a 10% body weight intravenous isotonic saline volume load. Compared with 1% NaCl BHR, 8% NaCl BHR showed both a greater maximal inhibition of efferent renal sympathetic nerve activity (−67±4% versus −31±3% of control, p<0.05) and gain (−22.0±2.3 versus −9.7±1.7%/mm Hg, p<0.05). In a second protocol, measurements of efferent renal sympathetic nerve activity were made in sinoaortic-denervated BHR before and during graded frequency stimulation of the central portion of the sectioned vagus nerve. Compared with 1% NaCl BHR, 8% NaCl BHR showed a greater inhibition of efferent renal sympathetic nerve activity over the entire frequency range (e.g., −47.5±5.6% versus −29.3±5.4% at 2 Hz, p<0.05). Thus, 8% NaCl BHR exhibit increased cardiac volume receptor reflex suppression of efferent renal sympathetic nerve activity, which is associated with an increase in the gain of the central/efferent component of the reflex. (Hypertension 1993;21:222-226)

Key Words • kidney • sympathetic nervous system • cardiac volume • sympathectomy • rats, borderline hypertensive

The borderline hypertensive rat (BHR) is a genetic model of environmentally induced hypertension. The BHR is the first generation offspring of a mating between a female spontaneously hypertensive rat (SHR) and a male 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,1-3 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.6

Increased dietary sodium intake causes the BHR to exhibit characteristics of the phenotype of the hypertensive SHR parent. In addition to the development of sustained hypertension, BHR subjected to increased dietary sodium intake also manifest exaggerated natriuretic and renal sympathoinhibitory responses to intravenous isotonic saline loading compared with BHR on a normal dietary sodium intake.7 The exaggerated natriuresis is mediated by the exaggerated renal sympathoinhibition because it does not occur in BHR with renal denervation. These responses are similar to those of the hypertensive SHR parent.8,9 The described alterations in cardiac volume receptor reflex control of efferent renal sympathetic nerve activity (ERSNA) in SHR are such that, in response to a standardized intravenous volume load, there is a greater renal sympathoinhibition in SHR compared with WKY rats.10-16 The current study was performed to examine cardiac volume receptor reflex control of ERSNA in BHR fed either 1% or 8% NaCl for 12 weeks from age 4 to 16 weeks.

Methods

Animals

The current study used male BHR that 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. All animal procedures were in accordance with the
guidelines of the University of Iowa Animal Care and Use Committee.

Anesthesia

The rats were anesthetized with pentobarbital (Nembutal, 50 mg/kg i.p., supplemented with 10 mg/kg i.v. as needed; Abbott Laboratories, North Chicago, III.).

Procedures

Catheterization. The rats were instrumented with polyethylene catheters in the right atrium via the right jugular vein for measurement of right atrial pressure (RAP), the left femoral vein for infusion of isotonic saline (0.05 ml/min maintenance), and the abdominal aorta via the left femoral artery for measurement of mean arterial pressure (MAP). RAP has a positive linear correlation with left atrial pressure during blood volume expansion in rats.15

Sinoaortic denervation. All rats underwent sinoaortic denervation (SAD) by the method of Krieger.17 Efficacy was assessed by noting the absence of a bradycardia in response to a 50 mm Hg increase in MAP produced by an intravenous bolus injection of norepinephrine (3 μg).

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 (×25), a renal nerve branch from the aortirogenal 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; high, 3,000 Hz) with a bandpass amplifier (model P511, Grass Instrument Co., Quincy, Mass.). The amplified and filtered signal was channeled to a Grass S9 stimulator (model 5113, Tektronix, Inc., Beaverton, Ore.) and to a rectifying voltage integrator (Grass model 7P10). The integrated voltage was displayed on the Grass polygraph. The quality of the renal sympathetic nerve activity signal was assessed from its pulse synchronous rhythmicity and by examining the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor loading (performed before SAD) with an intravenous bolus injection of norepinephrine (3 μg). The renal sympathetic nerve activity remaining after maximum inhibition following norepinephrine administration was similar to the background noise observed approximately 30 minutes postmortem; this value was subtracted from all experimental values of renal sympathetic nerve activity. When an optimal renal sympathetic nerve activity signal (pulse synchronous rhythmicity, abolition by norepinephrine-induced arterial pressure increase) was observed, the recording electrode was fixed to the renal nerve branch with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie, Munich, Germany). The electrode cable was then secured in position by suturing it to the abdominal trunk muscles. The flank incision was closed in layers.

Central Vagal Stimulation

Via a midline cervical incision, the right cervical vagus was isolated, placed on a bipolar platinum wire (Cooner Wire Company) electrode, and affixed with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie). The electrode was connected to a Grass S9 stimulator via a Grass SI5 S stimulation isolation unit.

Experimental Protocol

At 4 weeks of age the rats were randomly assigned to one of two dietary groups, 1% or 8% NaCl, with tap water drinking solution ad libitum. At 16 weeks of age, rats from each dietary group underwent two protocols.

Volume loading. Rats were anesthetized, intubated, and mechanically ventilated with room air, catheterized, instrumented with a renal sympathetic nerve activity recording electrode, and subjected to SAD. A 60-minute postsurgical equilibration period followed. Thereafter, control measurements of MAP, ERSNA, and RAP were made for 5 minutes. Then, isotonic saline was infused intravenously in a volume equal to 10% body weight at 2.0 ml/min with continuous measurement of MAP, ERSNA, and RAP. In some rats, a prolonged recovery period was made to allow the isotonic saline load to be excreted and MAP, ERSNA, and RAP to return to basal levels. Then, bilateral cervical vagotomy was performed, and the intravenous isotonic saline volume load was repeated after a 30-minute equilibration period.

Central vagal stimulation. Rats were anesthetized, intubated, mechanically ventilated with room air, catheterized, instrumented with a renal sympathetic nerve activity recording electrode and a stimulating electrode on the central portion of the sectioned right vagus nerve, and subjected to SAD. A 60-minute postsurgical equilibration period followed. Thereafter, continuous measurements of MAP and ERSNA were made during consecutive 5-minute periods in which electrical stimulation of the central portion of the sectioned right vagus was alternated with control observations. The stimulation parameters were 4 V, 2.0 msec, and 0 (control), 1, 2, 4, 8, and 16 Hz.

Analysis

Data acquisition (MAP, RAP, integrated ERSNA) was performed with an analog-to-digital convertor (model DT2801, Data Translation Inc., Marlborough, Mass.) using LATECH NOTEBOOK 4.2 software (Laboratory Technologies Corp., Wilmington, Mass.) and an IBM PC-XT computer. In the volume loading protocol, ERSNA was expressed as percentage of control and plotted against RAP. In the central vagal stimulation protocol, ERSNA and MAP were expressed as percentage of change and plotted against stimulation frequency. Statistical analysis was conducted either with repeated-measures analysis of variance for main effects and interactions or Scheffe’s test for pairwise comparisons among means. For single comparisons between the two groups, 1% NaCl BHR and 8% NaCl BHR, the t test was used.21 Statistical significance was taken as p<0.05.

Results

Volume Loading

Twelve weeks of increased dietary NaCl intake increased MAP (measured under anesthesia before SAD) from 114±5 mm Hg in 1% NaCl BHR (n=8) to 144±9
mm Hg in 8% NaCl BHR (n=8) (p<0.05). Baseline RAP was not significantly different (-1.26±0.15 mm Hg in 1% NaCl BHR versus -0.82±0.28 mm Hg in 8% NaCl BHR). Body weights were not significantly different (410±12 g for 1% NaCl BHR versus 436±17 g for 8% NaCl BHR).

Figure 1 represents a single run in a 1% NaCl BHR (Figure 1A) and an 8% NaCl BHR (Figure 1B). In response to volume loading-induced increases in RAP, ERSNA decreased; both the slope of decrease in ERSNA and the minimum value of ERSNA achieved were greater in 8% NaCl BHR than in 1% NaCl BHR. Data for the entire group are shown in Table 1. The standardized intravenous isotonic saline volume load produced a similar increment in RAP in the two groups. The minimum value of ERSNA achieved was significantly greater in 8% NaCl BHR than in 1% NaCl BHR. The slope gain, relating the change in ERSNA to the change in RAP, was significantly greater in 8% NaCl BHR than in 1% NaCl BHR. The three 1% NaCl BHR rats and three 8% NaCl BHR rats were subjected to a repeat intravenous isotonic saline volume load after bilateral vagotomy. Despite similar increases in RAP, no decrease in ERSNA was observed in any of the SAD plus vagotomy rats.

Central Vagal Stimulation

Twelve weeks of increased dietary NaCl intake increased MAP (measured under anesthesia before SAD) from 115±7 mm Hg in 1% NaCl BHR (n=6) to 147±9 mm Hg in 8% NaCl BHR (n=6) (p<0.05). Body weights were not significantly different (442±12 g for 1% NaCl BHR versus 481±15 g for 8% NaCl BHR).

Figures 2 and 3 show the changes in MAP and ERSNA produced by graded frequency stimulation of the central portion of the sectioned right vagus nerve. For MAP (Figure 2), the decreases in MAP in 1% NaCl BHR were statistically significant (p<0.05) from control at all frequencies; the responses were similar at all frequencies above zero. However, in 8% NaCl BHR the responses were not significant from control nor from those seen in 1% NaCl BHR at the same frequency. For ERSNA (Figure 3), the decreases in ERSNA in both 1% NaCl and 8% NaCl BHR were statistically significant (p<0.05 for both) from control at all frequencies.

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The results from the volume-loading protocol demonstrate that intravenous isotonic saline volume loading produces a greater maximal inhibition of ERSNA in 8% NaCl BHR than in 1% NaCl BHR. In addition, the slope gain, relating the decrease in ERSNA to the increase in RAP, was also greater in 8% NaCl BHR than in 1% NaCl BHR. Since these experiments were performed in rats with SAD, the observed decreases in ERSNA are not due to alterations in MAP operating via the sinoaortic baroreceptors to reflexly alter ERSNA. Further, since intravenous isotonic saline volume loading produced no changes in ERSNA after bilateral cervical vagotomy, the renal sympathoinhibition observed may be ascribed to activation of a cardiac volume receptor reflex subserved by vagal afferents. The results indicate that the gain of this overall reflex is increased in 8% NaCl BHR compared with 1% NaCl BHR. This could be due to increases in the gain of the afferent component, the relation between changes in cardiac chamber pressure and afferent vagal activity, or in the gain of the central/efferent component; the relation between changes in afferent vagal activity (input) and ERSNA (output).

To evaluate the gain of the central/efferent component, a central vagal stimulation protocol was used. By using electrical stimulation parameters of voltage and duration that are known to selectively activate the predominantly nonmyelinated cardiac vagal afferent in the rat,18-20 the afferent vagal input was standardized using similar stimulation frequencies for both 1% NaCl and 8% NaCl BHR. At the same level of afferent vagal input, renal sympathoinhibition and the gain of the central/efferent component were greater in 8% NaCl BHR than in 1% NaCl BHR.

The gain of the overall cardiac volume receptor reflex was approximately 2.3 times greater in 8% NaCl BHR than in 1% NaCl BHR, and the gain of the central/efferent component was approximately 1.5 times greater in 8% NaCl BHR than in 1% NaCl BHR. Although these observations derive from different groups of animals studied under different protocols, it may be speculated that the gain of the afferent component relating cardiac chamber pressure to afferent vagal activity may also be increased in 8% NaCl BHR compared with 1% NaCl BHR inasmuch as the increase in the gain of the overall reflex is not fully accounted for by the increase in the gain of the central/efferent component.

Although BHR and SHR each exhibit an exaggerated natriuretic response to intravenous isotonic saline volume loading that is mediated by the concurrent exaggerated inhibition of ERSNA, it appears that the nature of the alterations in the cardiac volume receptor reflex is different between BHR and SHR. In SHR, the gain of the overall cardiac volume receptor reflex is decreased compared with WKY.10 This is partly because cardiac receptors are reset to a higher pressure in SHR such that approximately twofold greater increases in left atrial pressure are required to produce similar increases in afferent vagal activity in SHR compared with WKY rats.12 Thus, the gain of the afferent component is also decreased in SHR compared with WKY rats. The gain of the central/efferent component does not seem to be different between SHR and WKY rats. However, these changes are overcompensated for by the fact that in response to a standardized intravenous volume load, there is a twofold to threefold greater increase in left atrial pressure in SHR compared with WKY rats.11,14 This has been attributed to a combination of decreased left atrial distensibility11,14 and decreased distensibility of peripheral capacitance vessels15 in SHR compared with WKY rats. This latter change results in a greater distribution of an intravenous volume load into the central blood volume in SHR compared with WKY rats.15 The net result is that, in response to a standardized intravenous volume load, there is a greater renal sympathoinhibition in SHR compared with WKY rats.8,13

These differences may be ascribed to several factors. In SHR, increasingly severe hypertension progresses from early in life without the necessity for an increase in dietary NaCl intake. The hypertension leads to structural cardiovascular alterations that can account for the decreased gain of the afferent portion of the cardiac volume reflex, including the alterations in distensibility of both the left atrium14 and peripheral capacitance vessels.22 In BHR, modest hypertension ensues only after exposure to increased dietary NaCl intake; thus, it seems likely that there will be less structural cardiovascular alterations related to both the duration and severity of hypertension in BHR compared with SHR. However, increased dietary NaCl intake is known to influence the function of central nervous system centers involved in the reflex regulation of peripheral sympathetic nerve activity.23-25 This would appear to be a potentially important mechanism contributing to the observed increased gain of the central/
The relation of an enhanced cardiac volume receptor reflex suppression of ERSNA to the development of NaCl-induced hypertension in BHR is unclear. However, the study of cardiac volume receptor reflex regulation of ERSNA is conducted using an acute intravenous volume load, whereas the development of NaCl-induced hypertension in BHR occurs with oral intake of increased NaCl diet for 12 weeks. Thus, the differences in both the time course and the route of NaCl administration make the analysis complex.

References
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