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Exaggerated Natriuresis in Experimental Hypertension[1] (42306)

GERALD F. DiBONA[2] AND LINDA L. SAWIN

Department of Internal Medicine, University of Iowa College of Medicine, and Veterans Administration Medical Center, Iowa City, Iowa 52242

Abstract. The exaggerated natriuretic response to intravenous isotonic saline volume expansion in conscious spontaneous hypertensive rats (SHR), compared to normotensive Wistar–Kyoto rats (WKY), is associated with an exaggerated inhibition of renal nerve activity. Following bilateral renal denervation, the natriuresis was significantly attenuated in SHR but unaffected in WKY. Thus, the exaggerated natriuretic response to intravenous isotonic saline in SHR is dependent on their enhanced inhibition of renal nerve activity. Conscious Dahl salt-sensitive rats, on either low or high salt diet, did not exhibit an exaggerated natriuretic response to intravenous isotonic saline volume expansion which may be explained by their known impairment of cardiopulmonary baroreceptor reflex mediated suppression of efferent sympathetic nerve activity during intravenous volume expansion. Conscious hypertensive DOCA-NaCl rats exhibited an exaggerated natriuretic response to oral but not to intravenous isotonic saline volume expansion, suggesting differences in gastrointestinal absorption of isotonic saline. It is concluded that enhanced inhibition of efferent renal sympathetic nerve activity via cardiopulmonary baroreceptor reflex activation contributes to the exaggerated natriuretic response to intravenous isotonic saline volume expansion in certain models of experimental hypertension.

When challenged with an intravenous isotonic saline volume expansion, patients with hypertension of diverse etiology excrete sodium at a faster rate than normotensive control subjects, an exaggerated natriuresis (1). When spontaneous hypertensive rats (SHR) are compared with normotensive Wistar–Kyoto rats (WKY), several investigators have observed that SHR have an exaggerated natriuretic response to either oral (2, 3) or intravenous (4–9) isotonic saline volume expansion while others have found no differences (10, 11). These discrepancies may reflect choice of appropriate controls, use and type of anesthesia, substrain variations, and route of isotonic saline administration (12–14). Recently, in studying conscious SHR and WKY, we observed that the exaggerated natriuretic response of SHR to intravenous isotonic saline volume expansion was associated with an exaggerated inhibition of renal nerve activity mediated via activation of the cardiopulmonary baroreceptor reflex (8). In view of the role of alterations in efferent renal sympathetic nerve activity to directly influence renal tubular sodium reabsorption in the proximal convoluted tubule (15) and thick ascending limb of Henle's Loop (16), we tested the hypothesis that the exaggerated natriuretic response of SHR to intravenous isotonic saline volume expansion is dependent on an enhanced withdrawal of efferent renal sympathetic nerve activity to the renal tubules. Since the DOCA–NaCl (17, 18) and Dahl S (19) hypertensive rats are also known to exhibit an exaggerated natriuretic response to oral isotonic saline volume expansion, these two experimental forms of hypertension of diverse environmental and genetic background were similarly studied as a contrast to the genetic background of the SHR.

Materials and Methods. Male WKY and SHR, ages 14–16 weeks, were placed in individual metabolism cages with free access to normal rat chow (Na 163 meq/kg, K 210 meq/kg) and tap water for 1 week. Then, under methohexital sodium anesthesia, 50 mg/kg ip, they were instrumented with carotid arterial, jugular venous and urinary bladder catheters

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[2] To whom all correspondence should be addressed.

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by previously described methods (8) They were returned to their individual metabolism cages for a 4-day postoperative recovery period. On the day of study, they were placed in Lucite cylinders which permitted forward and backward motion. The carotid arterial catheter was attached to a Statham P23Db pressure transducer, zeroed at the center of the cylinder, which led to a Beckman R-611 dynograph recorder; mean arterial pressure was continuously recorded throughout each experiment. The jugular venous catheter was attached to a syringe pump which was set to deliver 50 μl/min 0.9% NaCl. The urinary bladder catheter was led, via a slit in the bottom of the Lucite cylinder, to mineral oil containing pretared beakers. Following 40 min equilibration and stabilization, consecutive 10 min urine collections were taken continuously. The first three urine collections constituted the control period. Then, 0.9% NaCl, 10% body wt, was given iv over 30 min. At the end of the experiment, each rat was anesthetized with methohexital sodium, 10–20 mg/kg iv, and bilateral renal denervation was performed through bilateral flank incisions. Using a dissecting microscope (25×) all visible nerve fibers in the neurovascular pedicle were dissected and cut; the neurovascular pedicle was coated with a solution of 10% phenol in absolute ethanol. We have previously demonstrated that this technique of renal denervation abolishes the renal vasoconstrictor response to direct electrical stimulation of the proximal renal nerve bundles or suprarenal lumbar sympathetic chain and virtually obliterates renal tissue norepinephrine content, whether measured biochemically or by fluorescence histochemistry (20, 21). In addition, this technique of renal denervation does not affect glomerular filtration rate or effective renal plasma flow (22). Sham renal denervation was accomplished by bilateral flank incisions alone. The animals were returned to their individual metabolism cages; when the rats were fully recovered (2–5 days), the isotonic saline volume expansion protocol was repeated.

Female rats from the salt-sensitive and salt-resistant Dahl strain were fed either a low (0.4% NaCl) or a high (8.0% NaCl) salt diet a few days after weaning and studied during the fifth week of diet feeding. They were chronically instrumented and subjected to the intravenous isotonic saline volume expansion protocol as described above for SHR and WKY.

Male Sprague–Dawley rats (age 12 weeks) were anesthetized with methohexital sodium, 50 mg/kg ip, and uninephrectomized via a flank incision. They were placed in individual metabolism cages with free access to normal rat chow and tap water for 1 week. Then, the drinking fluid was changed to 0.9% NaCl and the rats received DOCA (Percorten Pivalate, Ciba-Geigy Corporation, Summit N.J.) 50 mg/kg sc each week. Sham rats were also uninephrectomized but received an equal volume of DOCA vehicle sc each week and tap water. Both Sham and DOCA–NaCl rats were studied during the fifth week of treatment. For the intravenous isotonic saline volume expansion protocol, the rats were chronically instrumented and studied as described above for SHR and WKY. For the oral isotonic saline volume expansion protocol, arterial and urinary bladder catheters were chronically implanted. Following the control period of three consecutive 10 min urine collections, 6.0 ml of 0.9% NaCl was given by orogastric tube and urine collections continued for six additional periods.

Urine volume was determined gravimetrically and urinary sodium concentration (U_{Na}, meq/liter) was determined by flame photometry; urinary sodium excretion = $U_{Na}V$ (μeq/min) where V = urinary flow rate (μl/min). Data are presented in text and figures as means ± 1 SE. Statistical analysis of the data was performed using analysis of variance for repeated measurements (group comparisons) and the Bonferroni method for simultaneous multiple comparisons (23, 24). Changes are reported as significant if the P value was less than 0.05.

Results. *SHR and WKY.* The median age of the eight WKY was 15.7 ± 0.7 weeks and of the nine SHR was 15.9 ± 0.3 weeks. The body weight was 311 ± 4 g for WKY and 297 ± 8 g for SHR. With intact renal innervation, mean arterial pressure (MAP) was 122 ± 2 mm Hg in WKY and 173 ± 4 mm Hg in SHR ($P < 0.001$); after bilateral denervation (4 days in both WKY and SHR), MAP was 122 ± 3 mm Hg in WKY and 168 ± 3 mm Hg in SHR ($P < 0.001$, but not significantly different from intact renal innervation values). With intact renal innervation (Figs. 1A, B), $U_{Na}V$ was not different between WKY and SHR during the

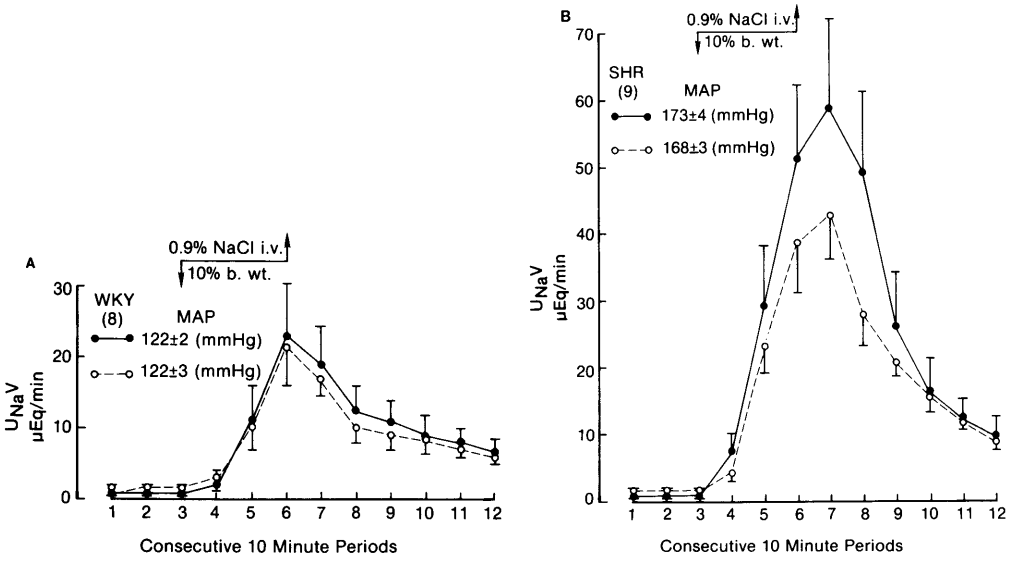

FIG. 1. Urinary sodium excretion ($U_{Na}V$) response to intravenous isotonic saline volume expansion in WKY (A, left panel) and SHR (B, right panel) rats before (●) and after (○) bilateral renal denervation.

control periods 1–3. With the onset of intravenous isotonic saline volume expansion (immediately after period 3), $U_{Na}V$ was significantly greater in SHR than in WKY in all periods ($P < 0.05$ for periods 4, 11, 12; $P < 0.01$ for period 10; $P < 0.001$ for periods 5–9). As shown in Table I, the peak $U_{Na}V$ ($P < 0.001$) and the total sodium excreted, either in absolute terms ($P < 0.01$) or as a percentage of the administered load ($P < 0.01$) was significantly greater in SHR than in WKY.

In WKY (Fig. 1A), bilateral renal denervation increased $U_{Na}V$ in control periods 1–3 (0.61 ± 0.09, 0.62 ± 0.11, 0.66 ± 0.10 vs 0.91 ± 0.10, 0.91 ± 0.11, 0.97 ± 0.09 μeq/min, respectively, $P < 0.05$) but there were no significant effects on the natriuretic response to intravenous isotonic saline volume expansion in periods 4–12. Likewise, as shown in Table I, there were no significant effects on the peak $U_{Na}V$ or the total sodium excreted, either in absolute terms or as a percentage of the administered load. In SHR (Fig. 1B), bilateral renal denervation increased $U_{Na}V$ in control periods 1–3 (0.62 ± 0.08, 0.58 ± 0.10, 0.57 ± 0.07 vs 0.99 ± 0.10, 1.02 ± 0.09, 1.04 ± 0.12 μeq/min, respectively, $P < 0.05$) and decreased the natriuretic response to intravenous isotonic saline volume expansion ($P < 0.05$ for period 4; $P < 0.01$ for periods 5 and 9; $P < 0.001$ for perids 6–8). The peak $U_{Na}V$ ($P < 0.05$) and the total sodium excreted, in ei-

TABLE I. SUMMARY OF DATA IN WKY AND SHR RATS

Strain	Treatment	MAP[a] (mm Hg)	Peak $U_{Na}V$ (μeq/min)	Sodium excreted/2 hr	
				meq	% Load
WKY (8)[b]	INN	122 ± 2	23 ± 8	1.0 ± 0.2	22 ± 4
	DNX	122 ± 3	22 ± 6	0.9 ± 0.2	20 ± 4
SHR (9)	INN	173 ± 4	59 ± 14	2.5 ± 0.4	56 ± 7
	DNX	168 ± 3	43 ± 7*	1.9 ± 0.2*	42 ± 6*

[a] MAP = mean arterial pressure; *$P < 0.05$ vs INN.
[b] Number of rats.

ther absolute terms ($P < 0.05$) or as a percentage of the administered load ($P < 0.05$), were significantly decreased by bilateral renal denervation. In comparing WKY and SHR following bilateral denervation, $U_{Na}V$ was not different during the control periods 1–3. With the onset of intravenous isotonic saline volume expansion, $U_{Na}V$ was higher in SHR than in WKY during periods 5–10 ($P < 0.05$ or greater) but was not different in periods, 4, 11, and 12. The peak $U_{Na}V$ ($P < 0.01$) and the total sodium excreted, in either absolute terms ($P < 0.01$) or as a percentage of the administered load ($P < 0.01$), were significantly greater in SHR than in WKY. The natriuretic response to intravenous isotonic saline volume expansion was not significantly affected by sham renal denervation in either WKY or SHR.

Mean arterial pressure tended to decrease during the volume expansion phase (periods 4–6) and gradually return to the control level over the subsequent experimental periods in both SHR and WKY as noted in our previous study (8). The maximum decreases were less than 10 mm Hg in SHR and less than 5 mm Hg in WKY. The magnitude of this decrease was not different between SHR and WKY, before or after renal denervation; in addition, renal denervation did not significantly affect this response in either SHR or WKY.

Dahl. The body weight of the 12 Dahl R rats on the low salt diet was 240 ± 5 g and of the 11 Dahl R rats on the high salt diet was 233 ± 7 g; the body weight of the 12 Dahl S rats on the low salt diet was 232 ± 7 g and of the 10 Dahl S rats on the high salt diet was 223 ± 8 g. As shown in Table II, the MAP of Dahl R rats on the low salt diet was 117 ± 3 mm Hg and of Dahl R rats on the high salt diet was 115 ± 2 mm Hg; the MAP of Dahl S rats on the low salt diet was 116 ± 4 mm Hg and of Dahl S rats on the high salt diet was 158 ± 5 mm Hg ($P < 0.001$ vs all other groups). During the control periods 1–3, $U_{Na}V$ in the Dahl R and S rats on high salt diet was greater than that in the same rats on a low salt diet ($P < 0.01$ for both, Figs. 2A and B). With intravenous isotonic saline volume expansion, $U_{Na}V$ was not different at any of periods 4–12 between the four groups of rats. As shown in Table II, there were no significant differences in peak $U_{Na}V$ or in total sodium excreted, either in absolute terms or as a percentage of the administered load.

DOCA–NaCl. For the intravenous isotonic saline volume expansion protocol, the body weight was 302 ± 7 for the nine DOCA–NaCl rats and 275 ± 8 for the ten sham rats ($P < 0.05$). MAP was 177 ± 7 mm Hg in DOCA–NaCl and 114 ± 4 mm Hg in Sham rats ($P < 0.001$). $U_{Na}V$ was greater in DOCA–NaCl rats than in Sham rats during control periods 1–3 ($P < 0.05$). However, with the onset of intravenous isotonic saline volume expansion, $U_{Na}V$ in DOCA–NaCl was numerically lower than that in sham although the difference was not significant. As shown in Table III, there was no significant difference in peak $U_{Na}V$ or in total sodium excreted. For the oral isotonic saline volume expansion protocol, the body weight was 307 ± 4 for the five DOCA–NaCl rats and 273 ± 6 for the five sham rats ($P < 0.05$). MAP was 196 ± 4 mm Hg in the DOCA–NaCl and 110 ± 3 mm Hg in the sham rats ($P < 0.001$). As with the intravenous isotonic saline volume expansion protocol, $U_{Na}V$ was greater in DOCA–NaCl rats than in sham

TABLE II. SUMMARY OF DATA IN DAHL R AND S RATS

Strain	NaCl diet	MAP[a] (mm Hg)	Peak $U_{Na}V$ (μeq/min)	Sodium excreted/2 hr	
				meq	% Load
Dahl R	Low (12)[b]	117 ± 2	88 ± 8	3.1 ± 0.3	84 ± 11
	High (11)	115 ± 2	95 ± 11	3.4 ± 0.4	93 ± 11
Dahl S	Low (12)	116 ± 4	79 ± 10	2.8 ± 0.3	78 ± 10
	High (10)	158 ± 5	82 ± 10	2.7 ± 0.3	79 ± 10

[a] MAP = mean arterial pressure.
[b] Number of rats.

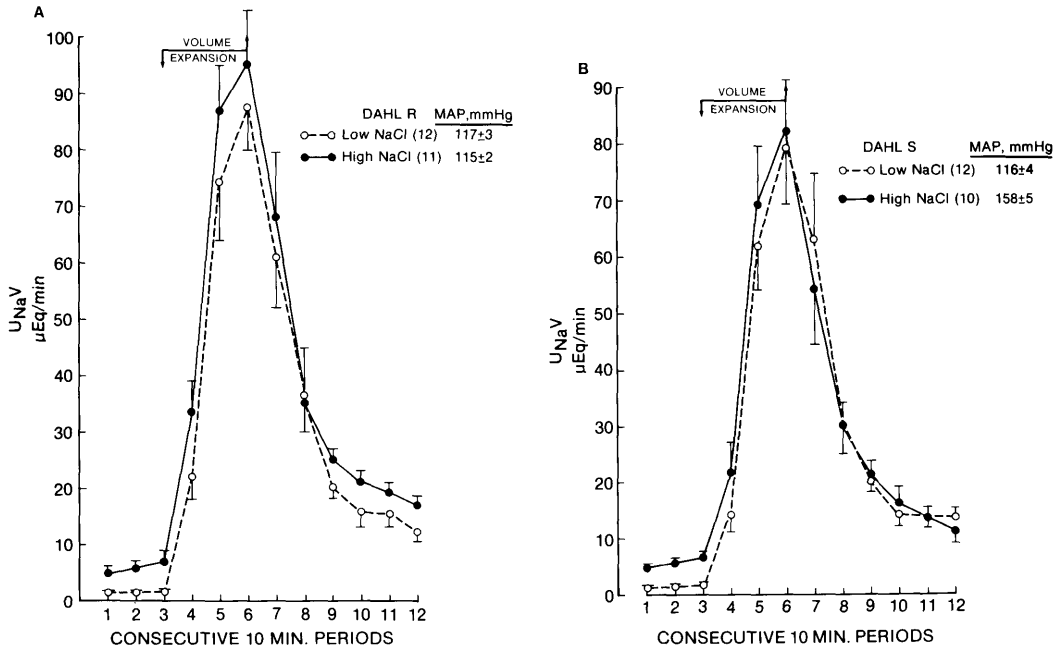

FIG. 2. Urinary sodium excretion ($U_{Na}V$) response to intravenous isotonic saline volume expansion in Dahl R (A, left panel) and Dahl S (B, right panel) rats.

rats during control periods 1–3 ($P < 0.05$). Following the oral isotonic saline load, as seen in Table III, the peak $U_{Na}V$ and the total sodium load excreted in absolute terms or in percentage of administered load were significantly greater in DOCA–NaCl than in sham.

Discussion. In these experimental animal models of hypertension, we have compared the natriuretic response to a standard intravenous isotonic saline volume expansion of the hypertensive animal with that of the appropriate normotensive control. Thus, the SHR has been compared with WKY, the Dahl S with the Dahl R and the DOCA–NaCl with the sham. Therefore, although all four groups of Dahl rats excreted a larger percentage of the standard intravenous isotonic saline load over two hours (78–93%) than the SHR (42–56%), we do not consider that the Dahl S rats exhibited an exaggerated natriuresis because these rats did not excrete more than the appropriate normotensive Dahl R control rats. On the other hand, it is clear that the SHR exhibited an exaggerated natriuresis because they did excrete more than the appropriate normotensive WKY control rats (20–22%).

TABLE III. SUMMARY OF DATA IN DOCA–NaCl AND SHAM RATS

Treatment	Group	MAP[a] (mm Hg)	Peak $U_{Na}V$ (μeq/min)	Sodium excreted/2 hr	
				meq	% Load
iv NaCl	DOCA–NaCl (9)	177 ± 7	44 ± 8	2.0 ± 0.2	43 ± 6
	Sham (10)	114 ± 4	55 ± 6	2.5 ± 0.2	58 ± 7
po NaCl	DOCA–NaCl (5)	196 ± 4	6.6 ± 2.8*	0.31 ± 0.10*	34 ± 11*
	Sham (5)	110 ± 3	2.7 ± 0.5	0.12 ± 0.03	13 ± 3

[a] MAP = mean arterial pressure. *$P < 0.05$ vs Sham.
[b] Number of rats.

These studies confirm the presence of an exaggerated natriuretic response to intravenous isotonic saline volume expansion in SHR compared to WKY in the conscious state. Our previous studies, employing a similar chronically instrumented preparation and experimental protocol in conscious rats, demonstrated that the exaggerated natriuresis was associated with an exaggerated inhibition of simultaneously measured renal nerve activity in SHR compared to WKY (8). In those studies, at the peak of the natriuresis, $U_{Na}V$ was approximately 40% greater in SHR than WKY while renal nerve activity was approximately 20% lower in SHR than in WKY. Since reflex decreases in efferent renal sympathetic nerve activity are known to directly produce decreases in renal tubular sodium reabsorption and increases in urinary sodium excretion (25), it was proposed that the exaggerated natriuretic response to intravenous isotonic saline volume expansion in SHR is partly explained by the accentuated reflex inhibition of renal nerve activity resulting in a greater decrease in renal tubular sodium reabsorption. Quantitatively, reflex decreases in efferent renal sympathetic nerve activity of approximately 40% resulted in increases in urinary sodium excretion of approximately 80%. In the current studies employing a paired experimental design in conscious rats, bilateral renal denervation attenuated the natriuretic response to intravenous isotonic saline volume expansion in SHR but had no effect in WKY; sham renal denervation had no effect in either SHR or WKY. It is of interest that renal clearance studies in human essential hypertensive (26, 27) have identified the ascending limb of Henle's loop as the renal tubular segment responsible for their exaggerated natriuretic response to intravenous isotonic saline volume expansion. Since there is dense neuroadrenergic innervation of the thick ascending limb of Henle's loop (28) and alterations in efferent renal sympathetic nerve activity directly influence sodium chloride reabsorption in this nephron segment (16), it is reasonable to suggest that the exaggerated natriuretic response of conscious SHR to intravenous isotonic saline volume expansion is partly mediated by an accentuated inhibition of efferent renal sympathetic nerve activity (8) which is responsible for decreased sodium chloride reabsorption in the thick ascending limb of Henle's loop. This is consistent with our previous micropuncture study in anesthetized SHR which showed that the exaggerated diuretic and natriuretic response to intravenous isotonic saline volume expansion was caused by a decreased reabsorption in the loop of Henle (4).

It may be argued that prior bilateral renal denervation, by eliminating efferent renal sympathetic nerve activity, should have maximally "inhibited" efferent renal sympathetic nerve activity. Therefore, it might be anticipated that surgical removal of efferent renal sympathetic nerve activity would be at least as effective as reflex inhibition of efferent renal sympathetic nerve activity and that the natriuretic response to intravenous isotonic saline volume expansion of SHR with prior bilateral renal denervation would be at least as great as that of SHR with intact renal innervation. However, there are two major differences that must be considered. First, at the onset of the intravenous isotonic saline volume expansion, intact SHR have a finite level of efferent renal sympathetic nerve activity whereas denervated SHR have none; this is reflected by a significantly greater $U_{Na}V$ in denervated SHR than in intact SHR during the control period. Therefore, in denervated SHR, the contribution of a decrease (to zero) in efferent renal sympathetic nerve activity to changes in net renal tubular sodium reabsorption (decrease) and urinary sodium excretion (increase) has already occurred prior to the onset of the intravenous isotonic saline volume expansion. Second, during the time course of the intravenous isotonic saline volume expansion, intact SHR show a progressive concurrent decrease in efferent renal sympathetic nerve activity (8) which is known to mediate a decrease in net renal tubular sodium reabsorption resulting in an increase in urinary sodium excretion (25). However, denervated SHR cannot further decrease their efferent renal sympathetic nerve activity and there is no concurrent contribution of decreases in this variable to changes in net renal tubular sodium reabsorption and urinary sodium excretion during the time course of the intravenous isotonic saline volume expansion. Therefore, it seems that a portion of the exaggerated natriuretic response to intravenous isotonic saline volume expansion in SHR is dependent on

the presence of a finite level of efferent renal sympathetic nerve activity at the onset of the intravenous isotonic saline volume expansion and a progressive concurrent decrease in efferent renal sympathetic nerve activity during the time course of the intravenous isotonic saline volume expansion which results in a decrease in net renal tubular sodium reabsorption and an increase in urinary sodium excretion.

It may be argued that prior renal denervation produced changes in glomerular filtration rate, renal plasma flow, and plasma aldosterone concentration which may have contributed to the altered natriuretic response to acute intravenous isotonic saline volume expansion. Although these variables were not measured in this study, such an explanation seems unlikely because it has been demonstrated that chronic renal denervation does not affect the glomerular filtration rate and renal plasma flow responses to acute intravenous isotonic saline volume expansion (29) or the physiologic regulation of plasma aldosterone concentration by changes in dietary sodium intake in conscious rats (30).

It has been postulated that abnormalities in plasma aldosterone concentration may contribute to the exaggerated natriuresis of SHR. Compared to age-matched WKY, SHR had significantly higher plasma aldosterone concentrations than WKY at 5, 10, and 20 days of age but there are no significant differences at 15, 25, or 30 days (31). However, SHR were found to have lower plasma aldosterone concentrations than WKY at both 7 (32) and 12 (3) weeks of age. At 12 weeks of age, it appears that the preexisting depressed level of plasma aldosterone concentration in SHR can contribute to the exaggerated natriuresis seen in SHR (3). Although plasma aldosterone concentrations were not measured in this study, the complex pattern of age-related changes in plasma aldosterone concentration in SHR relative to WKY would seem to be no a priori reason to anticipate a reduced plasma aldosterone concentration in the 14- to 16-week-old SHR used here.

Since both the basal level (33) and the decrease in efferent renal sympathetic nerve activity during intravenous isotonic saline volume expansion (8) are less in WKY than in SHR, it is likely that the removal, by renal denervation, of this quantitatively smaller component in WKY is not translated into an observable change in the natriuretic response to volume expansion in WKY.

The reduction in natriuretic response in SHR produced by bilateral renal denervation, as a percentage of the increment of innervated SHR over either innervated or denervated WKY (Table I) was approximately 40%. Therefore, bilateral renal denervation did not totally abolish the exaggerated natriuresis and the remaining portion, approximately 60%, must be ascribed to other important differences between WKY and SHR, two prominent ones being the level of arterial pressure (4) and aldosterone metabolism (3).

In a previous study we observed that despite the presence of an exaggerated natriuresis in SHR, there was no difference between WKY and SHR in the magnitude of the decrease in efferent renal sympathetic nerve activity during intravenous isotonic saline volume expansion (7). However, the experimental conditions differed in an important aspect. In contrast to the current and other (8) experiments which were performed in conscious unrestrained rates, those (7) experiments were performed in acutely anesthetized surgically operated rats. Although the exaggerated natriuresis is evident under both experimental conditions (4–9), as discussed previously (8, 15), anesthetic and surgical stress may have a profound and independent influence on the efferent renal sympathetic nerve activity responses.

With respect to Dahl rats, it had previously been reported that on a low salt diet, Dahl S rats have an exaggerated natriuretic response to oral isotonic saline volume expansion as compared to Dahl R rats; however, on a high salt diet, the natriuretic response of Dahl R and S rats was not different (19). In view of the generally unpredictable influences of variable gastrointestinal absorption and subsequent distribution of an oral isotonic saline load, the natriuretic response to a standard intravenous isotonic saline load was evaluated. Dahl S rats did not exhibit an exaggerated natriuresis, a finding similar to that of Roos *et al.* (34). Since an identifiable portion of the natriuretic response to intravenous isotonic saline volume expansion is mediated by inhibition of efferent renal sympathetic nerve

activity via cardiopulmonary baroreflex activation (35, 36), it is of interest that cardiopulmonary baroreflex inhibition of efferent sympathetic nerve activity is impaired in Dahl S rats (37). Therefore, the impaired cardiopulmonary baroreflex suppression of efferent renal sympathetic nerve activity may explain the lack of an exaggerated natriuresis in Dahl S rats.

With respect to DOCA–NaCl rats, our studies demonstrate that they exhibit an exaggerated natriuretic response to oral isotonic saline volume expansion and confirm previous observations (17, 18). However, the data also indicate that the exaggerated natriuresis is dependent on the route of isotonic saline administration since an exaggerated natriuresis was not observed following intravenous isotonic saline volume expansion. These findings focus on the possibility of altered gastrointestinal absorption and subsequent distribution of the oral isotonic saline load, either a delay in sham rats or an increase in DOCA–NaCl. In the evaluation of exaggerated natriuresis, we have viewed gastrointestinal absorption as part of the overall input versus output response pattern. It is known that administration of mineralocorticoid, either DOCA (38) or aldosterone (39), increases sodium, chloride, and water absorption in the rat colon. The intravenous route would bypass these two factors.

In summary, the exaggerated natriuretic response of SHR (compared to WKY) to intravenous isotonic saline volume expansion is partially dependent on an exaggerated withdrawal of efferent renal sympathetic nerve activity to the renal tubules, probably the thick ascending limb of Henle's loop, with decreased renal tubular sodium reabsorption. The lack of an exaggerated natriuretic response to intravenous isotonic saline volume expansion in Dahl S rats (compared to Dahl R rats, low or high salt diet) may be attributed to an impairment of the cardiopulmonary baroreflex wherein intravenous volume expansion produces a lesser inhibition of efferent (renal) sympathetic nerve activity. The presence of an exaggerated natriuretic response to oral but not intravenous isotonic saline volume expansion in DOCA–NaCl rats supports an abnormality in the gastrointestinal absorption and/or distribution of the fluid load.

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