Renal Nerves Affect Rate of Achieving Sodium Balance in Spontaneously Hypertensive Rats

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The spontaneously hypertensive rat (SHR) has an elevated efferent sympathetic nerve activity, suggesting that the renal handling of sodium and water may be altered. This study evaluated the renal neurogenic influence on the rate of achieving sodium balance in adult SHRs and Wistar-Kyoto (WKY) rats after either a step increase or step decrease in fixed sodium intake. Conscious, unrestrained rats with either innervated or denervated kidneys were initially placed on a low-sodium (0.3 mEq/d) or high-sodium (5.0 mEq/d) intake by intravenous infusion. Hourly urinary sodium excretion was determined 24 hours before and 72 hours after sodium intake had been increased from low to high or decreased from high to low. After either step change in fixed sodium intake, both innervated SHRs and innervated WKY rats achieved sodium balance within 24 hours. Similarly, the time course of achieving sodium balance was nearly identical between WKY rats with innervated and denervated kidneys after either switch in sodium intake. In SHRs receiving a step increase in sodium intake, both innervated and denervated kidneys increased urinary sodium excretion equally for 9 hours; however, at this time, innervated SHRs continued to increase sodium excretion rapidly, whereas denervated rats were delayed in a further response. Thus, differences in urinary sodium excretion did not result from concomitant changes in plasma renin activity or mean arterial pressure. These data suggest that in sodium depletion of SHRs and WKY rats, the mechanism for immediate regulation of urinary sodium excretion appears to be independent of renal sympathetic outflow, whereas the renal nerves do provide a rapid sodium excretory response to a step increase in sodium intake. (Hypertension 1993;22:1-8)

Key Words • water-electrolyte balance • hypertension, renal • sodium chloride • renin-angiotensin system

The spontaneously hypertensive rat (SHR) of the Okamoto-Aoki strain has gained wide acceptance as an appropriate model for studying essential hypertension. Although the precise mechanisms responsible for the development of hypertension in the SHR remain controversial, much evidence points to the involvement of the sympathetic nervous system. Early studies by Liard1 showed that bilateral renal denervation of 5-week-old SHRs delayed the onset of elevated blood pressure by 2 to 3 weeks; however, neither the rate of development nor the final level of hypertension was affected. Norman and Dziela2 subjected 4-week-old SHRs and Wistar-Kyoto (WKY) rats to bilateral renal denervation every 3 weeks for 16 weeks. This long-term renal denervation blocked 30% to 40% of the expected progressive elevation in blood pressure in the SHR, whereas arterial pressure of the WKY rat or sham-operated SHR was not affected. These studies clearly implicate the renal sympathetic nerves as one factor that may lead to the development of hypertension in the SHR; however, the mechanisms mediating this hypertension remain unclear.

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The elevated level of efferent sympathetic tone thought to exist in the SHR may alter the renal handling of sodium and water. In recent years, much evidence has accumulated suggesting an important role for the renal nerves in the regulation of urinary sodium excretion. Low-frequency renal nerve stimulation directly affects both proximal tubular sodium reabsorption and renin release in the absence of changes in renal hemodynamics.3,4 Furthermore, several investigators5,6 have observed that renal denervation results in an increased urine flow rate that is attributed to a decreased absolute and fractional reabsorption of sodium in the proximal convoluted tubule. To assess the role of the renal nerves in the development and maintenance of hypertension with regard to possible direct effects on tubular sodium reabsorption, Winternitz et al7 measured the sodium and water balance of SHRs before and after development of hypertension (7 through 18 weeks of age, respectively). The results indicated that the renal sympathetic nerves may contribute to hypertension in the SHR in part by causing enhanced sodium retention; however, in the adult SHR, renal denervation had no effect on urinary sodium excretion or arterial pressure.

The above evidence suggests that although the renal nerves do not appear to be involved in the maintenance of hypertension in the adult SHR, urinary sodium excretion may be inherently different in these animals as a result of an elevated level of sympathetic tone. This in turn may influence the way in which the SHR responds...
to alterations in sodium intake. Studies in conscious, normotensive rats have suggested that intact renal innervation may play an important role in allowing a rapid sodium excretory response to alterations in sodium intake. DiBona and Sawin\(^5\) found that rats with innervated kidneys were able to achieve sodium balance within 1 or 2 days after sodium restriction; however, after renal denervation, rats exhibited a progressively negative sodium balance for 3 to 4 days after sodium restriction. In contrast, other investigators\(^6\) have found no difference in sodium excretion between conscious rats with denervated kidneys and innervated control rats. Previous studies in our laboratory have shown that the renal nerves may influence the rate of achieving sodium balance after a step increase in sodium intake.\(^7\) The possibility that such neurogenic regulation of sodium balance may be altered in the SHR has not been previously evaluated.

Therefore, the main objectives of the present study were to determine (1) if adult SHRs and WKY rats differ in their ability to achieve sodium balance after a step change in fixed sodium intake and (2) whether the presence of intact renal nerves affects the rate at which sodium balance is achieved in these rats after a step change in fixed sodium intake.

**Methods**

**Animals**

Male SHRs and WKY rats aged 12 to 13 weeks were purchased from Sasco King, Omaha, Neb. Animals were housed individually in metabolic pens (Animal Resource Center of the Medical College of Wisconsin, certified by the American Association for Accreditation of Laboratory Animal Care) with a 12-hour light/dark cycle (lights on at 6 AM). Rats were fed standard laboratory chow (Purina Rat Chow) until the time of catheter implantation, when sodium-free chow (Dyets, Inc, Bethlehem, Pa) and water were provided ad libitum, with sodium intake controlled by intravenous infusion as indicated.

**Surgical Preparation**

Rats were anesthetized with ketamine (Ketaset, 60 mg/kg), xylazine (Rompun, 6 mg/kg), and acepromazine maleate (0.9 mg/kg) by intraperitoneal injection. In some rats, a dorsal midline incision was made, and the muscle was separated from the fascia on either side of the spine to expose each kidney. With the use of a dissecting microscope, all visible nerves were stripped from the renal pedicle, then was painted with a 10% fibrinolysin in 1000 U/mL heparin to prevent clotting. The bladder was exposed via a ventral midline incision. A small hole was made near the dome of the bladder, and a chronic indwelling catheter was inserted and secured with nylon suture for the continuous collection of urine. This bladder catheter was constructed from two 1-cm, 20-gauge stainless-steel pins soldered to a 0.125-in.-diameter stainless-steel disk and attached by a silicone elastomer (Silastic) cuff to two lengths of microbore tubing (2 ft each and 0.05-in. id x 0.09-in. od and 0.02-in. id x 0.06-in. od, respectively). The larger of these lines was used for urine withdrawal, and the other line served as a vent to the atmosphere. A 0.45-μm-pore Millipore filter (Acrodisc, Gelman Sciences, Inc, Ann Arbor, Mich) was attached to the vent line to prevent microbial infection from incoming air. These catheters were exteriorized in a manner similar to that described above.

All catheters were placed in a spring fastened to a Dacron-covered stainless-steel plate. This Dacron plate then was sutured to the muscles of the back. All incisions were closed, and the rats received 20 000 U im penicillin G. After recovery from the anesthesia, rats were housed individually in metabolic cages, and the springs were attached to a three-channel swivel (Alice King Chatham, Medical Arts) to allow freedom of movement. Chloramphenicol (200 mg iv) was administered daily.

**Protocol**

Immediately after instrumentation, rats were infused with either a low (0.3 mEq/d) or high (5.0 mEq/d) sodium intake (25.0 μL/min iv); sodium-free chow and drinking water were allowed ad libitum. This infusion rate provides for each solution being hypotonic in a total daily water infusion of 36 mL. Urine was continuously collected with a roller pump connected to the bladder catheter. A minimum 3-day period was allowed to ensure both full recovery from surgery and that experiments were not begun until urinary sodium excretion was equal to sodium intake (ie, zero sodium balance). A 24-hour control period was followed by either a step increase (0.3 to 5.0 mEq/d) or a step decrease (5.0 to 0.3 mEq/d) in sodium intake. The new level of sodium intake was maintained for 72 consecutive hours. Thus, the following eight sodium-switch groups were established: SHRs (n=8) and WKY rats (n=7) with innervated kidneys (INN) and SHRs (n=6) and WKY rats (n=6) with denervated kidneys (DNX) all receiving the step increase in sodium intake; INN SHRs (n=7) and INN WKY rats (n=6); and DNX SHRs (n=5) and DNX WKY rats (n=6) all receiving the step decrease in sodium intake.

Urine was collected hourly into preweighed tubes by means of a fraction collector, beginning at the start of the control period and continuing throughout the experiment for a total of 96 consecutive hours of urine...
collection. Urinary sodium concentration was measured by flame photometry. Mean arterial pressure (MAP) was determined daily from 10 AM to 4 PM from the femoral arterial catheter. MAP was monitored by means of a pressure transducer (Statham P23id) connected to a direct-writing oscillograph (Grass polygraph). Arterial blood samples (150 μL) were drawn during hour 23 of the control day and at 24, 48, and 72 hours after the switch in sodium intake (a total of 600 μL over 4 days). Samples were centrifuged and plasma was frozen for later determination of plasma renin activity (PRA) by radioimmunoassay of the generated angiotensin I (Ang I) after a 3-hour incubation period (37°C). At the conclusion of each experiment, kidneys were rapidly removed and quick-frozen on dry ice. Tissue catecholamine content then was determined by radioenzymatic assay to verify denervation.

Statistics

Data were calculated as the mean±SEM. Data from hourly urine samples were summated at 3-hour intervals and are presented as the 3-hour average. Multiple comparisons within animals were conducted by two-way analysis of variance. Multiple comparisons between INN and DNX rats were conducted by one-way analysis of variance. Mean differences were determined by the Student-Newman-Keuls procedure. The .05 level of probability was used as the criterion of significance.

Results

Innervated Spontaneously Hypertensive Rats Versus Innervated Wistar-Kyoto Rats

Figs 1A and 1B depict hourly urinary sodium excretion rate (UNaV) of SHRs and WKY rats with intact renal innervation. In rats receiving a step decrease in sodium intake from high to low (5.0 to 0.3 mEq/d) (Fig 1A), average UNaV was similar between SHRs and WKY rats during the 24 hours of control (SHR, 2497±160 nEq/min; WKY, 2917±121 nEq/min). After the switch to low sodium intake, both rat groups significantly decreased UNaV within 3 hours and achieved sodium balance at the new level of sodium intake within 24 hours.

Rats subjected to a step increase in sodium intake from low to high (0.3 to 5.0 mEq/d) exhibited a similar time course for achieving sodium balance, again with no differences observed between SHRs and WKY rats (Fig 1B). During the 24 hours of control on low sodium intake (208 nEq/min), UNaV was not different between SHRs and WKY rats (244±38 nEq/min). After sodium intake was increased (3472 nEq/min), both groups significantly elevated UNaV within 9 hours, and by 24 hours, each group had achieved sodium balance at the new level of sodium intake.

PRA was elevated in both SHRs and WKY rats after the step decrease in sodium intake (Fig 2A). After the step increase in sodium intake, WKY rats suppressed PRA within 24 hours, whereas in SHRs a significant decrease in PRA was not observed until 48 hours (Fig 2B). Despite this difference in time course, there were no significant differences between SHRs and WKY rats in the renin responses for either step change in sodium intake, and the time course of UNaV elevation was very similar between the two groups as discussed above.

Daily MAP for each group of rats is shown in Fig 3. Control MAP of INN SHRs was significantly greater than that of INN WKY rats in both the high-to-low (Fig 3A) and low-to-high (Fig 3B) sodium-switch experiments. Both SHRs and WKY rats maintained MAP constant throughout the experimental period in both studies, with the exception that WKY rats receiving the step decrease in sodium intake showed a small but significant decrease in MAP on day 3 of the experiment (from 115±5 during control to 103±3 mm Hg on day 3 of low Na+), Fig 3A).

Innervated Versus Denervated Wistar-Kyoto Rats

Hourly UNaV for INN and DNX WKY rats is shown in Figs 4A and 4B. In WKY rats receiving a step decrease in sodium intake (Fig 4A), renal innervation had no influence on the rate at which sodium balance was achieved, as both INN and DNX WKY rats followed an almost identical time course for reducing UNaV after the switch to low sodium intake. In both
FIG 2. Bar graph shows plasma renin activity (PRA, nanograms angiotensin I [AI] generated per hour per milliliter) measured during control and at 24, 48, and 72 hours after step change in fixed sodium intake in spontaneously hypertensive rats (SHRs) and Wistar-Kyoto (WKY) rats with intact renal innervation. Panel a: Step decrease in sodium intake from high (3472 nEq/min) to low (208 nEq/min); panel b: step increase in sodium intake from low (208 nEq/min) to high (3472 nEq/min). INN, rats with innervated kidneys. *P < .05 from control.

Despite the similar UNaV profiles of INN and DNX WKY rats receiving the low-to-high sodium switch, a suppression of PRA after the step increase in sodium intake was observed only in INN WKY rats (Fig 5B). PRA in these animals fell from 7.11±2.91 during control to 1.92±0.44 ng Ang I/mL per hour within the first 24 hours after sodium intake was increased, and this suppression of PRA was maintained for 72 hours. The DNX WKY rats, however, exhibited relatively low levels of PRA during control (2.66±0.61 ng Ang I/mL per hour), and PRA did not change significantly within the 72-hour period after the step increase in fixed sodium intake.
**Fig 4.** Plots show hourly urinary sodium excretion rates (UNaV, nanoequivalent per minute) during control (24 hours before 0) and for 72 hours after step change in fixed sodium intake in Wistar-Kyoto (WKY) rats with innervated (INN) and denervated (DNX) kidneys. Each point represents average hourly sodium excretion over a 3-hour period. Panel a: Step decrease in sodium intake from high (3472 nEq/min, hours —24 to 0) to low (208 nEq/min, hours 0 to 72); panel b: step increase in sodium intake from low (208 nEq/min, hours —24 to 0) to high (3472 nEq/min, hours 0 to 72). +P<.05 at time when UNaV becomes different from control.

In the control sodium-deplete state before the step increase in sodium intake, the average MAP of INN WKY rats was greater than the MAP of DNX rats (Fig 3B). Despite these differences, MAP remained unchanged in both groups after the step increase in sodium intake (Fig 3B).

**Innervated Versus Denervated Spontaneously Hypertensive Rats**

Hourly UNaV of INN and DNX SHRs is depicted in Fig 6. In SHRs receiving the high-to-low switch in sodium intake, renal denervation did not alter the reduction of UNaV after the step decrease in sodium intake (Fig 6A). UNaV during control (high sodium intake, 3472 nEq/min) averaged 2497±160 and 2860±128 nEq/min in INN and DNX SHRs, respectively. Both groups reduced UNaV within 3 hours after the switch to low sodium intake (208 nEq/min), and sodium balance was achieved at this new level of intake within 24 hours.

When SHRs were subjected to a step increase in fixed sodium intake (208 to 3472 nEq/min), a significant difference in the renal excretory response was observed between INN and DNX rats (Fig 6B). During the control period (low sodium intake), hourly UNaV was slightly but not significantly higher in DNX SHRs over approximately 6 of the 24 hours. Furthermore, neither group exhibited UNaV significantly different from the fixed sodium intake. Both INN and DNX SHRs rapidly increased sodium excretion after the switch to high sodium intake. However, after 9 hours of elevated sodium intake, INN SHRs continued to rapidly increase urinary sodium excretion, whereas DNX SHRs did not continue to increase sodium excretion until hour 24. Consequently, INN SHRs were able to achieve sodium balance at the new level of intake within 27 hours, whereas this did not occur in DNX SHRs until hour 45.

Significant elevation and inhibition of PRA was observed in SHRs after the switches from high to low and low to high sodium intakes, respectively. However, these responses were not different between INN and DNX SHRs (Figs 7A and 7B).

In INN SHRs, MAP did not change appreciably from control when sodium intake was switched to either low...
or high; however, MAP of DNX SHRs was much more labile with changes in sodium intake. When sodium intake was switched from high to low, MAP of DNX SHRs fell from 150±4 to 123±2 mm Hg after 2 days (Fig 3A). Despite this, there was no difference in the time course of UNaV reduction between INN and DNX SHRs. With the step increase in sodium intake (Fig 3B), MAP of DNX SHRs rose from a control value of 116±1 to 133±2 mm Hg on the second day after the switch from low to high sodium intake, although this increase in MAP was not sustained. Furthermore, this increase in MAP occurred significantly later (day 3) than the elevation of UNaV (days 1 to 2).

Measurement of tissue catecholamine content by radioenzymatic assay showed that the renal tissue of DNX SHRs and WKY rats contained less than 2% of the norepinephrine concentration found in INN SHRs and WKY rats (corresponding values in picograms per milligram tissue: INN SHR, 179.9±4.9; INN WKY, 152.7±6.7; DNX SHR, 2.34±0.81; DNX WKY, 0.90±0.18).

**Discussion**

The present study evaluated the time course for achieving sodium balance after either a step increase or step decrease in sodium intake in the adult SHR and the normotensive WKY rat. These responses were also studied in INN and DNX SHRs and WKY rats. Sodium intake was fixed by intravenous infusion, and urine was continuously withdrawn from the bladder by a chronic indwelling catheter. With these two applications, precise determinations of sodium excretion, sodium intake, and consequently sodium balance were determined on an hourly basis. The experiments were performed in conscious, freely moving rats to avoid the possible confounding influence of anesthesia and behavioral stresses associated with animal restraint.

With a step decrease in sodium intake (high, 5.0 mEq/d to low, 0.3 mEq/d), all four groups studied significantly reduced UNaV within 3 hours and achieved sodium balance at the new level of intake within 24 hours (Figs 1A, 4A, and 6A). Thus, despite a significant disparity in MAP (Fig 3A), there were no differences between SHRs and WKY rats in the rate of reducing urinary sodium loss immediately after sodium restric-
tion. Furthermore, renal denervation had no effect on the ability of either SHRs or WKY rats to rapidly adjust UNaV in response to a step decrease in sodium intake.

When fixed sodium intake was increased from low to high, SHRs and WKY rats again exhibited virtually identical UNaV profiles over the time course of achieving sodium balance and both rat strains were able to achieve sodium balance within 24 hours (Fig 1B). Similarly, the rate at which UNaV was elevated was not different between INN and DNX WKY rats (Fig 4B). However, in SHRs, renal denervation significantly impaired the ability to rapidly increase UNaV after a step increase in sodium intake. Consequently, INN SHRs were able to achieve sodium balance a full 18 hours before DNX SHRs when sodium intake was increased (Fig 6B). Although this effect of renal denervation was not seen in WKY controls, it was observed in Sprague-Dawley rats, as we reported previously. In fact, the UNaV profiles of INN and DNX Sprague-Dawley rats subjected to this step increase in sodium intake very clearly did not match the present UNaV profiles of INN and DNX SHRs. It is not clear why the WKY rat did not also demonstrate a delayed renal excretory response with renal denervation; however, other investigators have also observed that WKY rats and SHRs do not respond similarly to changes in renal neural input. Rudd et al found that, although acute renal denervation resulted in increases in sodium and water excretion in SHRs, Sprague-Dawley rats, and Munich-Wistar rats, WKY rats exhibited no diuretic or natriuretic responses. Taken together with the present findings, these results suggest that in response to step changes in sodium intake, the relative influence of renal sympathetic outflow on sodium balance is substantially different between Sprague-Dawley and WKY rats.

Despite their delayed response, DNX SHRs were not completely inhibited in their ability to respond to a step increase in fixed sodium intake. As postulated previously, these results suggest that slower, nonneural mechanisms may be primarily responsible for the regulation of UNaV in these animals in which neurogenic mechanisms are absent. Such nonneural mechanisms that regulate UNaV in DNX SHRs remain speculative. It is possible that suppression of PRA may have allowed DNX rats the partial response observed; but if so, PRA suppression is clearly too slow to provide the rapid elevation of UNaV seen in rats with intact renal nerves. In contrast, however, activation of the renin-angiotensin system may be a possible nonneural mechanism mediating the UNaV response to sodium restriction. PRA was significantly elevated in both INN and DNX SHRs, as well as in both INN and DNX WKY rats, within 24 hours after fixed sodium intake was decreased. It is difficult to speculate whether this stimulation of renin release could have occurred within the first 3 hours, thus allowing these animals the rapid sodium excretory response observed within this time. However, it is known that the renin-angiotensin system can become fully activated within 20 minutes of initial intense stimulation.

It is clear that the difference in UNaV response between INN and DNX SHRs can be attributed purely to neurally mediated sodium reabsorption and not to differences in PRA. PRA decreased appropriately when SHRs were switched from low to high sodium intakes, and PRA was not different between INN and DNX SHRs at any time sampled (Fig 7B). Furthermore, in DNX WKY rats, PRA was not suppressed at any time after a step increase in sodium intake (Fig 5B), yet these animals were able to increase UNaV at a rate similar to INN controls (Fig 4B). Thus, the major mechanisms involved in the rapid renal excretory response to elevation of sodium intake observed in INN rats do not appear to be renin dependent.

One of the most striking aspects of the results of this study is the disparity in UNaV response that exists between decreasing and increasing sodium intake in INN versus DNX SHRs. Rats subjected to a sudden sodium load were clearly dependent on intact renal innervation in order to rapidly increase sodium excretion and reestablish sodium balance. In the case of sodium depletion, however, the regulatory mechanism does not appear to involve the renal sympathetic nerves as part of its efferent limb. These results are corroborated by similar observations made in INN versus DNX Sprague-Dawley rats receiving either a step increase10 or step decrease11 in sodium intake. This difference suggests that there is a dichotomy in the mechanisms for immediate regulation of UNaV in response to sodium depletion versus sodium load. Two possible explanations exist for this dichotomy: (1) There may be two separate mechanisms that control UNaV responses to increasing and decreasing changes in sodium intake, or (2) nonneural sodium-retaining mechanisms may be more quickly activated to allow sodium retention than suppressed to allow sodium loss. Although other investigators have examined the role of the renal nerves in the renal excretory responses to sodium restriction in the conscious rat, these studies have met with conflicting results. This, together with a lack of information regarding the role of the renal nerves in the renal excretory response to pure sodium excess, warrants further evaluation of the unique mechanistic dichotomy reported in the present study.

It is fairly well established that although renal denervation in young SHRs can delay the elevation of arterial pressure, this manipulation cannot prevent the ultimate development and maintenance of hypertension in these animals. Nevertheless, evidence suggests that adult SHRs have higher levels of basal renal sympathetic nerve activity than WKY rats, presumably because of an inherent elevation of central sympathetic drive. It was thus hypothesized in this study that such an elevation of basal sympathetic tone may affect the rate at which the adult SHR reestablishes sodium balance after step changes in fixed sodium intake. However, no difference was observed between SHRs and WKY rats, and renal denervation in SHRs produced the same results observed in Sprague-Dawley rats. Although renal denervation enhanced the sodium sensitivity of MAP in the SHR, the level of hypertension in these animals was not significantly diminished compared with INN SHRs on each day of the study (Fig 3). Furthermore, the change in MAP from control that occurred in DNX SHRs did not become significant until 48 hours after the respective changes in sodium intake. This, however, occurred after the critical period of change in UNaV (Fig 6).

Other investigators have found that normalization of arterial pressure by aortic constriction significantly blunts the ability of the SHR to excrete sodium and water in response to an acute saline load compared with
control SHRs and WKY rats. This evidence, together with the present findings, supports the hypothesis that the kidneys of SHRs require a higher pressure than those of normotensive rats to excrete a given amount of sodium and water. Some investigators argue that this is the result of impaired autoregulation; however, others observed no such impairment of autoregulation and suggest that this phenomenon is an indication of inherently heightened tubular reabsorption in the SHR. In either case, the notion that renal function in the SHR necessarily operates within a higher pressure range is substantiated by evidence for resetting of both left atrial receptors as well as central baroreceptor reflexes.

In conclusion, the renal nerves appear to play an important role in the immediate urinary sodium excretion response to a pure sodium load in SHRs. However, the onset of the antinatriuretic response to sodium restriction does not appear to be neurogenically mediated in the SHR or WKY rat. These renal responses to chronic changes in sodium intake are not different from those in Sprague-Dawley rats as previously observed in our laboratory; however, they are different from the antinatriuretic responses of conscious dogs. Thus, any elevation of sympathetic tone that may exist in the SHR does not appear to be manifested as an alteration in the regulation of daily sodium balance but rather as a requirement to sustain MAP at a level consistent with other controllers of urinary sodium excretion.

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