

Renal Nerves Promote Sodium Excretion During Long-Term Increases in Salt Intake

Thomas E. Lohmeier, Drew A. Hildebrandt, W. Ashley Hood

Abstract—To determine whether the renal nerves contribute to sodium homeostasis during long-term increments in sodium intake, studies were conducted in conscious dogs subjected to unilateral renal denervation and surgical division of the urinary bladder into hemibladders to allow separate 24-hour urine collection from denervated and innervated kidneys. They were fed a low sodium diet and continuously infused with isotonic saline (350 mL/d) to provide a daily sodium intake of ≈ 60 mmol. After control measurements, sodium intake was increased to 470 mmol/d by increasing the rate of isotonic saline infusion to 3000 mL/d for 5 days; this was followed by a 5-day recovery period. Twenty-four-hour control values for mean arterial pressure and ratios for urinary sodium, potassium, and creatinine excretion from denervated and innervated kidneys (DEN/INN) were 96 ± 3 , 1.06 ± 0.04 , 1.00 ± 0.04 , and 1.01 ± 0.02 mm Hg, respectively. During the ≈ 8 -fold increase in sodium intake, there was no long-term change in mean arterial pressure, and daily sodium balance was achieved within 48 hours. Moreover, during the first day of high salt intake, there were significant reductions in the DEN/INN for sodium and potassium excretion, which persisted for the entire 5-day period of increased sodium intake; on day 5, the DEN/INN for sodium and potassium excretion was 0.86 ± 0.03 and 0.86 ± 0.04 , respectively. In contrast, the DEN/INN for creatinine excretion remained at control levels during high salt intake. Furthermore, similar long-term reductions in the DEN/INN for sodium and potassium excretion occurred in a second group of dogs administered adrenergic receptor–blocking agents for 5 days to interrupt the functional effects of the renal nerves. These data indicate that sustained renal sympathoinhibition promotes sodium and potassium excretion during long-term increments in sodium intake by inhibiting tubular reabsorption of these electrolytes. (*Hypertension*. 1999;33[part II]:487-492.)

Key Words: renal nerves ■ sodium excretion ■ sodium intake ■ sympathetic nervous system

Neural reflexes promote sodium excretion after short-term increments in body fluid volume. Elegant studies in conscious animals have shown that suppression of renal sympathetic nerve activity contributes to natriuresis in response to volume expansion and elevations in intracardiac pressures.^{1–6} Further, cardiac denervation, cervical vagotomy, or blockade of cardiac afferents by intrapericardial procaine administration markedly attenuates renal sympathoinhibition and impairs the excretion of sodium after a short-term volume load. This indicates that cardiopulmonary (probably cardiac) reflexes with vagal afferents decrease renal sympathetic nerve activity and enhance renal excretion of salt and water when intravascular volume increases.

Although there is a rather thorough understanding of the role of reflex mechanisms in the short-term regulation of intravascular volume, it is unclear whether the renal nerves play a role in long-term control of body fluid volume. On the basis of short-term neurally induced changes in sodium excretion, it is often assumed that baroreflex-induced alterations in renal sympathetic nerve activity promote long-term

changes in sodium excretion as well. However, this notion is incompatible with the observations that baroreflexes adapt to sustained changes in pressure.^{1,7} If adaptation is complete, baroreflexes would be unable to mediate long-term adjustments in renal sodium excretion during sustained alterations in body fluid volume. Therefore, if the renal nerves play a chronic role in sodium homeostasis, either baroreflexes (presumably cardiopulmonary baroreflexes) do not completely adapt or nonadapting baroreceptor-independent mechanisms account for volume-induced alterations in renal sympathetic nerve activity.

Experimental limitations have impeded an understanding of the role of the renal nerves in long-term control of sodium excretion. One major obstacle is that it is difficult to monitor time-dependent changes in renal sympathetic nerve activity over periods of days to weeks, and therefore it is not clear whether the level of sympathetic activity to the kidneys is altered by long-term changes in body fluid volume. An even greater problem occurs in assessing the functional effects of the renal nerves under long-term conditions. There have been

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a few studies that have examined the long-term excretory responses of bilaterally denervated animals to changes in sodium intake, but the results have been conflicting.^{8–11} This is not entirely surprising because a confounding factor in the interpretation of all studies in which the renal nerves are totally removed is the possible compensatory mechanisms that may be activated to maintain sodium balance in the absence of the renal nerves. Changes in arterial pressure, circulating hormones, and other factors activated by the absence of the renal nerves may mask the influence of the renal nerves in controlling sodium excretion during long-term alterations in salt intake.

The split-bladder preparation combined with unilateral renal denervation is a powerful technique for exposing a functional role of the renal nerves because both kidneys are exposed to the same perfusion pressures and hormonal influences.^{10,12–15} Consequently, any differences in sodium excretion between the kidneys can be attributed to either the direct or indirect effects of the renal nerves on renal excretory function. In the present study, we used the split-bladder preparation in combination with unilateral renal denervation to test the hypothesis that in the long term, the renal nerves promote sodium excretion during sustained increments in salt intake.

Methods

Animal Preparation

Eleven female dogs weighing 18 to 23 kg were used in this study. All procedures are in accordance with National Institutes of Health Guidelines, approved by the Institutional Animal Care and Use Committee, and described further in recent communications.^{14,15} In brief, catheters made of Tygon microbore tubing were implanted in the lower abdominal aorta and inferior vena cava and exteriorized between the scapulae. Subsequently, the left kidney was denervated and the urinary bladder was surgically divided. Each half was then sutured to form hemibladders, and Silastic catheters were implanted to allow continuous 24-hour urine collection from each kidney. The catheters were exteriorized in the flank region and connected to sterile plastic bags that were changed daily.

Several days after surgery, the dogs were placed in metabolic cages in a room maintained at $22 \pm 3^\circ\text{C}$ with a 12:12-hour light-dark cycle. They were fitted with a specially designed harness containing a pressure transducer (model P23 ID, Statham Laboratories, Inc) positioned at heart level. Isotonic saline was infused continuously into a venous catheter with a Wiz peristaltic pump (Isco) at a rate of 350 mL/d. A disposable filter (Cathivex, Millipore) was connected in series with the infusion to prevent passage of bacteria and other contaminants.

During a 2-week training and equilibration period and throughout the study, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5-oz cans of prescription heart diet (H/D, Hill's Pet Products) supplemented with 5 mL of vitamin syrup (VAL Syrup, Fort Dodge Laboratories). Two cans of H/D provide ≈ 5 mmol of sodium and ≈ 60 mmol of potassium. Thus, with the intravenous saline infusion, sodium intake was ≈ 60 mmol/d. Water consumption was monitored daily, and 24-hour urine samples were collected at 10 AM, ≈ 1 hour before feeding. During this initial 2-week period, the dogs were trained to lie quietly in their cages for collection of blood samples. Subsequently, 3 days of control measurements preceded the experimental protocols described below. Arterial blood samples (≈ 5 mL) were taken at 9 AM on intermittent days throughout the experiments. Body temperature was measured each morning, and amoxicillin (250 mg), dicloxacillin (250 mg), and a trimethoprim (400 mg) and sulfamethoxazole (80 mg) combination were given prophylactically twice a day.

Measurement of Hemodynamics

Throughout the study, arterial pressure was monitored continuously from an arterial catheter connected to the pressure transducer in the harness and recorded on a Grass polygraph (model 7D, Grass Instruments). A microcomputer and customized software^{12,14,16} were used to sample the signal from the Grass recorder at 200 Hz for a duration of 12 seconds, once per minute, 24 hours per day. The digitized data for each 12-second burst were processed immediately to compute mean arterial pressure (MAP) and heart rate. The daily values for MAP and heart rate presented were determined from the average of 1260 sample points collected during the 21-hour period between noon and 8 AM. The hours excluded from the 24-hour analysis included the time required for flushing catheters, calibrating blood pressure transducers, feeding, and cleaning cages.

Experimental Protocols

High Salt Intake

After control measurements were taken, 6 dogs were subjected to a 5-day period of increased salt intake. This was achieved by increasing the rate of isotonic saline infusion from 350 to 3000 mL/d. Subsequently, this ≈ 8 -fold increase in sodium intake (from 60 to 470 mmol/d) was returned to control levels during a 5-day recovery period. Throughout the control, experimental, and recovery periods, arterial blood samples were taken on intermittent days for determination of hematocrit, plasma renin activity (PRA), and the plasma concentrations of sodium, potassium, and protein.

Adrenergic Receptor Blockade

After control measurements were taken, 5 additional dogs were administered prazosin and propranolol for 5 days for long-term blockade of α - and β -adrenergic receptors, respectively. In this study, prazosin (Zenith Laboratories; 5 mg/kg per day, TID) was administered orally and *dl*-propranolol (Sigma; 10 mg/kg per day) was added to the continuous intravenous infusion of saline. The above doses of prazosin and propranolol greatly attenuated the blood pressure responses to bolus intravenous injections of phenylephrine (10 $\mu\text{g}/\text{kg}$) and isoproterenol (5 $\mu\text{g}/\text{kg}$). The 5-day period of adrenergic receptor blockade was followed by a 13-day recovery period. Arterial blood samples were taken throughout the experiment as described above.

Analytical Methods

PRA was measured by radioimmunoassay.¹⁷ Plasma and urine concentrations of sodium and potassium were determined by flame photometry (IL 943, Instrumentation Laboratories), plasma protein concentration by refractometry (American Optical), and hematocrit by a micromethod (Autocrit II). Urinary creatinine concentration was determined with a creatinine analyzer (model 2, Beckman).

Statistical Analysis

Results are expressed as mean \pm SEM. Experimental and recovery data were compared with control by ANOVA with Dunnett's *t* test for multiple comparisons.¹⁸ Statistical significance was considered to be $P < 0.05$. The relative excretion rates of sodium and potassium from denervated and innervated kidneys are expressed by the ratio DEN/INN.

Results

High Salt Intake

The changes in MAP, heart rate, and urinary electrolyte excretion in response to increased salt intake are illustrated in Figures 1 through 3. The average control values for MAP and heart rate were 96 ± 3 mm Hg and 66 ± 4 bpm, respectively. Average control values for urinary sodium excretion from denervated and innervated kidneys were 31 ± 1 and 30 ± 1 mmol/d, respectively; the corresponding values for urinary potassium excretion were 30 ± 1 and 30 ± 1 mmol/d,

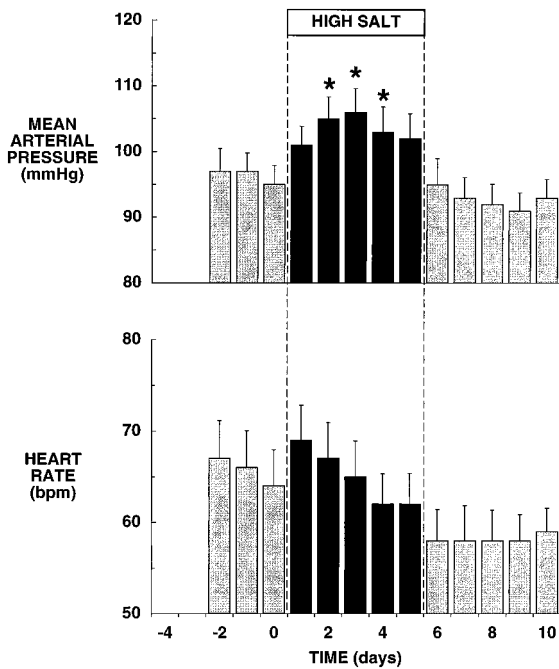


Figure 1. Effects of increased salt intake on mean arterial pressure and heart rate. Values are mean±SEM; n=6. *P<0.05.

and for urinary creatinine excretion, 3.4±0.2 and 3.4±0.1 mmol/d. As a result of the approximately equal excretion rates of these electrolytes and creatinine from denervated and innervated kidneys before high salt intake, the DEN/INN for sodium, potassium, and creatinine excretion during the control period was 1.06±0.04, 1.00±0.04, and 1.01±0.02, respectively.

As shown in Figure 1, there was little or no change in MAP and heart rate during high salt intake. MAP did increase ≈10 mm Hg by day 3 of high salt, but on day 5, MAP (102±4 mm Hg) was not significantly different from control (96±3 mm Hg). There were no significant changes in heart rate during high salt intake.

Figure 2 illustrates the changes in urinary sodium excretion during increased salt intake. By day 2, total sodium excretion from both kidneys (467±5 mmol/d) equaled intake (470 mmol/d) and remained at this level for the duration of high salt; this represents an ≈8-fold increase in sodium excretion from control levels (60±2 mmol/d), a change commensurate with the increase in sodium intake. Moreover, and most importantly, the DEN/INN for sodium excretion decreased abruptly on day 1 of high salt, and this response was sustained throughout the entire 5-day period of increased sodium intake. On day 5, the DEN/INN for sodium excretion was reduced to 0.86±0.03 (control=1.06±0.04). Thus there was a 15% to 20% greater increase in sodium excretion from innervated (day 5=261±3 mmol/d) versus denervated (day 5=223±6 mmol/d) kidneys during high salt intake. During the recovery period, total urinary sodium excretion and the DEN/INN for sodium excretion returned to control levels within 2 days. These results indicate that the renal nerves chronically promoted sodium excretion during increased sodium intake.

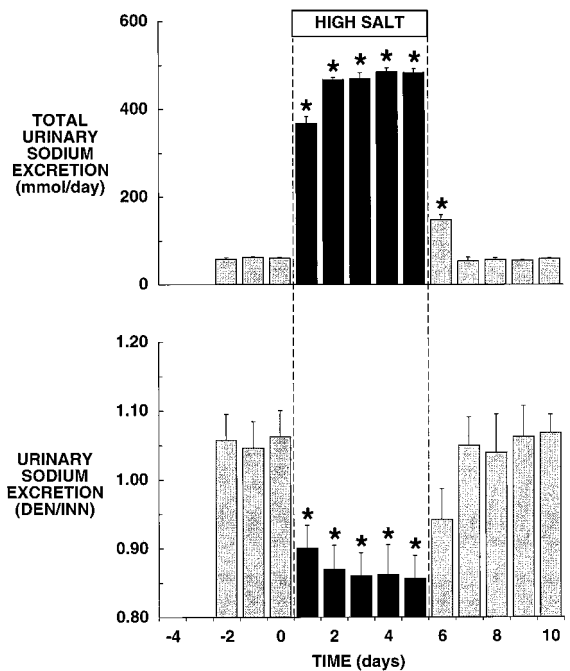


Figure 2. Daily sodium excretion from denervated and innervated kidneys and changes in DEN/INN for sodium excretion during increased salt intake. Sodium intake was increased from 60 to 470 mmol/d during high salt intake. Values are mean±SEM; n=6. *P<0.05.

Although there were no significant changes in total potassium excretion during increased salt intake, the DEN/INN for potassium excretion decreased in parallel with the fall in the DEN/INN for sodium excretion (Figure 3). On day 5 of high salt intake, the DEN/INN for potassium excretion was re-

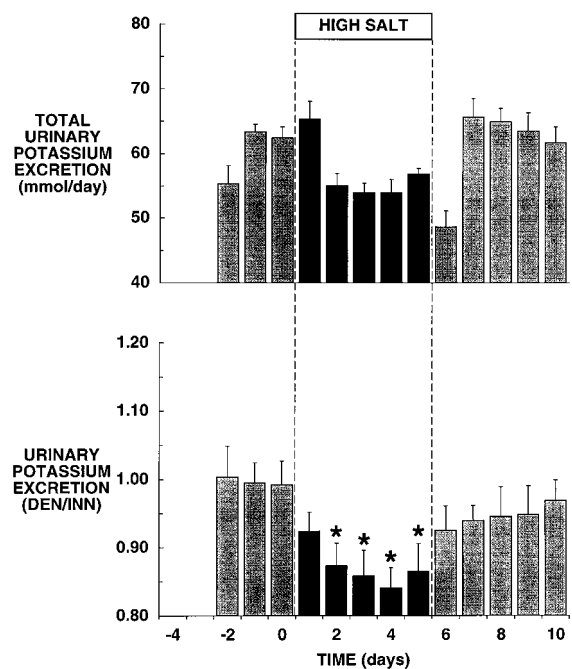


Figure 3. Daily potassium excretion from denervated and innervated kidneys and changes in DEN/INN for potassium excretion during increased salt intake. Potassium intake was 60 mmol/d. Values are mean±SEM; n=6. *P<0.05.

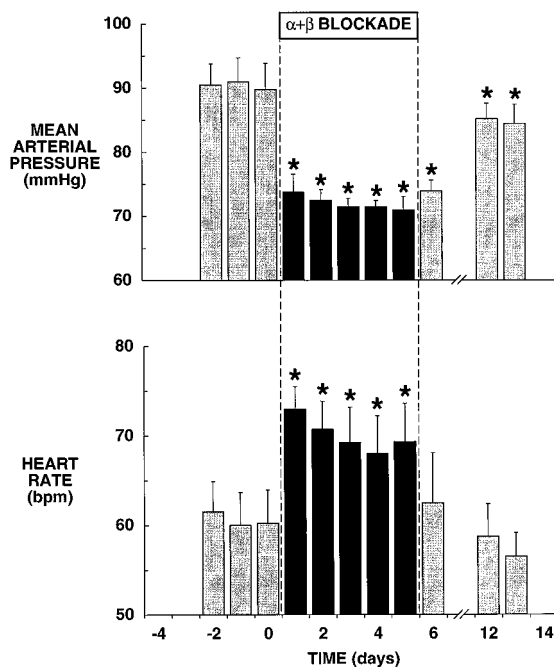


Figure 4. Changes in mean arterial pressure and heart rate during adrenergic receptor blockade. Values are mean \pm SEM; $n=5$. * $P<0.05$.

duced to 0.86 ± 0.04 (control = 1.00 ± 0.04), indicating that the innervated kidneys (day 5 = 31 ± 1 mmol/d) excreted $\approx 15\%$ more potassium than denervated kidneys (day 5 = 26 ± 1 mmol/d). During the recovery period, the DEN/INN for potassium excretion returned to control levels. Thus the renal nerves promoted the excretion of potassium as well as sodium during high salt intake.

During increased sodium intake there were no significant changes in total creatinine excretion. Further, in marked contrast to the fall in the DEN/INN for sodium and potassium excretion during high salt intake, there were no significant changes in the DEN/INN for creatinine excretion. On day 5 of high salt intake and on day 5 of the recovery period, the DEN/INN for creatinine excretion was 1.02 ± 0.03 and 1.02 ± 0.03 , respectively (control = 1.01 ± 0.02). This indicates that during increased sodium intake, neurally induced sodium and potassium excretion occurred in the absence of changes in glomerular filtration rate (GFR).

Whereas there were no significant changes in plasma electrolyte concentration (control: plasma sodium concentration = 146 ± 1 mmol/L; plasma potassium concentration = 4.2 ± 0.1 mmol/L), hematocrit, plasma protein concentration, and PRA all decreased during high salt intake. Control values for hematocrit and plasma protein concentration were $38 \pm 2\%$ and 6.3 ± 0.2 g/dL, respectively; on day 5 of high salt intake, the corresponding values were $34 \pm 1\%$ and 5.9 ± 0.2 g/dL. During increased sodium intake, PRA decreased from a control value of 0.46 ± 0.21 nmol angiotensin I \cdot L \cdot h $^{-1}$ to undetectable levels.

Adrenergic Receptor Blockade

As illustrated in Figure 4, long-term α - and β -adrenergic receptor blockade produced sustained hypotension and

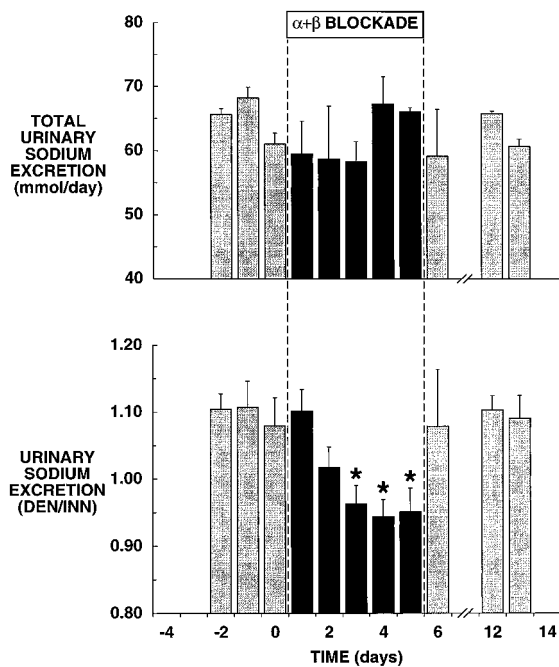


Figure 5. Daily sodium excretion from denervated and innervated kidneys and changes in DEN/INN for sodium excretion during adrenergic receptor blockade. Sodium intake was 60 mmol/d. Values are mean \pm SEM; $n=5$. * $P<0.05$.

tachycardia. By day 5 of prazosin with propranolol administration, MAP decreased from a control value of 91 ± 4 to 71 ± 2 mm Hg and heart rate increased from 60 ± 3 to 69 ± 4 bpm.

The sodium excretory responses to long-term adrenergic receptor blockade are shown in Figure 5. Despite the fall in MAP, there was no significant change in total excretion of sodium from both kidneys during administration of prazosin with propranolol. Importantly, however, during adrenergic receptor blockade, the DEN/INN for sodium excretion decreased from a control value of 1.10 ± 0.03 to 0.95 ± 0.04 (day 5). This indicates that compared with control conditions, $\approx 15\%$ more sodium was excreted from innervated than denervated kidneys during long-term adrenergic blockade. During the recovery period, the DEN/INN for sodium excretion returned to control levels. Thus during long-term adrenergic receptor blockade, the relative changes in sodium excretion between innervated and denervated kidneys mimicked those that occurred during increased sodium intake.

There was no significant change in potassium balance during long-term adrenergic receptor blockade, but the DEN/INN for potassium excretion decreased in parallel with the DEN/INN for sodium excretion (Figure 6). As with sodium excretion, there was an $\approx 15\%$ decrease in the DEN/INN for potassium excretion (control = 1.07 ± 0.06) by day 5 of adrenergic receptor blockade. Thus during adrenergic receptor blockade, there was a relatively greater excretion rate of potassium as well as sodium in innervated versus denervated kidneys.

Control values for hematocrit, PRA, and the plasma concentrations of sodium, potassium, and protein were $37 \pm 2\%$, 0.38 ± 0.20 nmol angiotensin I \cdot L \cdot h $^{-1}$, 145 ± 1 mmol/L,

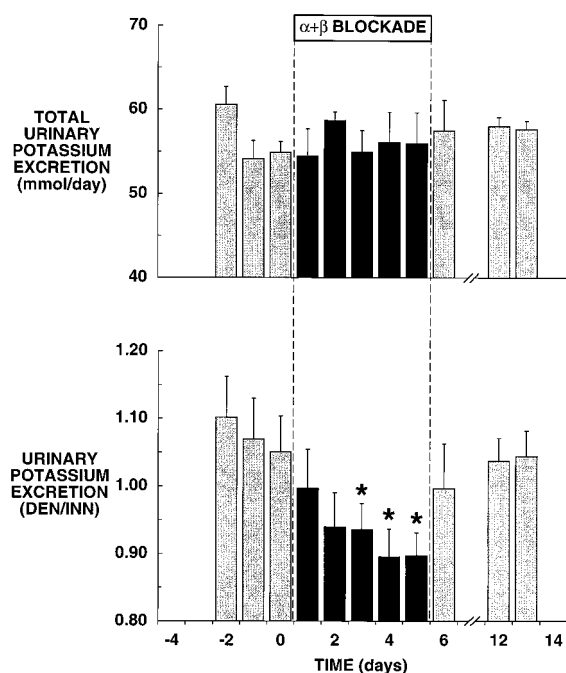


Figure 6. Daily potassium excretion from denervated and innervated kidneys and changes in DEN/INN for potassium excretion during adrenergic receptor blockade. Potassium intake was 60 mmol/d. Values are mean \pm SEM; $n=5$. * $P < 0.05$.

4.3 ± 0.1 mmol/L, and 6.7 ± 0.3 g/dL, respectively. There were no significant changes in any of the above during long-term adrenergic receptor blockade.

Discussion

The major finding of this study is that the renal nerves chronically promoted sodium excretion during sustained increments in sodium intake. Furthermore, because long-term adrenergic receptor blockade mimicked the influence of the renal nerves to promote sodium excretion during increased sodium intake, these results support the hypothesis that renal sympathoinhibition is a long-term compensatory mechanism for the regulation of body fluid volume during volume excess. Thus this study, along with earlier findings from our laboratory,^{14,15,19} provides direct evidence that the sympathetic nervous system plays a role in long-term regulation of body fluid volume by affecting changes in renal sympathetic nerve activity which, in turn, influence sodium excretion.

The few earlier studies that have examined the role of the renal nerves in adaptation to long-term alterations in sodium intake have produced conflicting results. In long-term balance studies, DiBona and Sawin⁸ reported that bilaterally denervated rats were unable to maintain sodium balance when challenged with a low sodium intake. In contrast, others have shown that bilateral renal denervation in rats⁹ and dogs¹⁰ does not affect the ability to achieve and maintain sodium balance after sodium restriction. Further, to our knowledge, there has been only 1 long-term study (3 days) that has evaluated the influence of the renal nerves on the sodium excretory response to increments in sodium intake.¹¹ In that study, daily sodium balance was achieved within 3 days of high salt intake but in association with greater net retention of sodium

in rats with bilateral renal denervation than in rats with renal nerves intact. Therefore it was concluded that the renal nerves may serve as a rapid controller of sodium excretion.

It is difficult to draw any conclusions regarding the role of the renal nerves in the long-term regulation of sodium excretion from studies in animals subjected to bilateral renal denervation. Clearly, total renal denervation may produce compensatory changes that could obscure conclusions regarding the importance of the renal nerves in long-term control of sodium excretion. For example, during increased salt intake, a greater rise in arterial pressure in animals with bilateral renal denervation than in intact controls could mask the normal natriuretic influence of the renal nerves. Therefore, to control for differences in arterial pressure and humoral agents, we used the split-bladder preparation in combination with unilateral renal denervation. With this experimental design, any compensatory responses would be similar in both kidneys because both kidneys are exposed to the same arterial pressure and humoral factors. Thus differences in sodium excretion between the kidneys during increased sodium intake must be due to the renal nerves. Importantly, with this powerful experimental design, we were able to demonstrate a long-term natriuretic influence of the renal nerves during increased sodium intake.

The present results, as well as earlier findings from our laboratory,^{14,15,19} provide compelling evidence that suppression of renal sympathetic nerve activity and attendant increments in renal excretory function serve as compensatory mechanisms for the long-term regulation of sodium balance and arterial pressure in response to sustained increments in body fluid volume and some forms of hypertension. In the present study, the magnitude of the fall in the DEN/INN for sodium excretion indicated that 15% to 20% more sodium was excreted chronically from innervated versus denervated kidneys during high salt intake. In a previous study, the renal nerves exerted an even more pronounced natriuretic response when hypertension was induced by long-term infusion of angiotensin II.¹⁴ Furthermore, measurements of renal norepinephrine overflow (an index of renal sympathetic nerve activity) are consistent with the contention that the natriuresis induced by the renal nerves during angiotensin II-hypertension is mediated by renal sympathoinhibition.¹⁹ Because changes in renal sympathetic nerve activity in response to increased sodium intake have not been reported, a second group of dogs was subjected to long-term adrenergic receptor blockade in the present study. Long-term adrenergic receptor blockade produced sustained hypotension and tachycardia (presumably caused by reduced parasympathetic activity). Moreover, long-term adrenergic receptor blockade led to a greater increase in sodium excretion in innervated versus denervated kidneys, as would be expected from interrupting the functional effects of the renal nerves. That the same relative changes in sodium excretion occurred in denervated and innervated kidneys during increased salt intake supports the notion that the long-term natriuretic effects of the renal nerves during high salt are mediated by sustained suppression of renal sympathetic nerve activity.

The present findings are consistent with our previous observations of the split-bladder preparation and indicate that

the long-term natriuretic effects of the renal nerves are associated with parallel changes in potassium excretion and are mediated by actions on tubular function.^{14,15} Since the relative 24-hour excretion rates of creatinine in denervated and innervated kidneys were unchanged during increased salt intake, it is likely that the sustained effects of the renal nerves to promote sodium excretion were mediated by tubular events. This resembles the natriuretic response mediated acutely by baroreflex suppression of renal sympathetic nerve activity in that increments in sodium excretion occur in the absence of changes in GFR.^{1,2} Further, if the proximal tubule is the predominant site of neurally induced alterations in sodium reabsorption under long-term as well as short-term conditions, impaired sodium transport in this nephron segment could readily account for the greater excretion rate of potassium in innervated versus denervated kidneys during high salt intake (and long-term adrenergic receptor blockade). This is because potassium reabsorption is closely coupled to sodium reabsorption in the proximal tubule, and potassium secretion is strongly dependent on distal sodium delivery.²⁰

Apparently, intrarenal mechanisms other than suppression of renal sympathetic nerve activity contributed to the differential excretion rates of sodium in denervated and innervated kidneys during increased sodium intake. During chronically increased sodium intake in the present study, as well as during renal sympathoinhibition associated with short-term volume expansion,^{4,21} more sodium was excreted from innervated versus denervated kidneys. This would suggest a persistent, compensatory salt-retaining effect induced by renal denervation that is not reversible by either short-term or long-term expansion of extracellular fluid volume. Although the factors that account for the defective natriuresis in denervated versus innervated kidneys during volume expansion have not been identified, the present findings during adrenergic receptor blockade, as well as other recent findings from our laboratory,¹⁵ indicate that renal denervation supersensitivity is not involved in the renal compensation that impairs sodium excretion after renal denervation.

The results of the present study are novel because they clearly demonstrate a sustained influence of the renal nerves to promote sodium excretion during increased sodium intake. Furthermore, these results contribute to an emerging body of evidence from long-term studies that indicates that neurally induced sodium excretion plays a compensatory role in long-term regulation of body fluid volume and arterial pressure during volume excess and hypertension.^{14,15,19} An important objective in future studies will be to determine whether baroreflex mechanisms, which mediate reflex changes in renal sympathetic nerve activity under short-term conditions, also account for sustained renal sympathoinhibition during long-term volume expansion. Resolution of this issue will be particularly relevant to understanding whether abnormal baroreflex control of renal sympathetic nerve activity plays a causal role in promoting salt and water retention

in salt-sensitive hypertension and in congestive heart failure or whether the reported baroreflex dysfunction in these disease states is merely an associated finding.^{1,2}

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