Renal denervation supersensitivity revisited

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Lohmeier, Thomas E., Glenn A. Reinhart, H. Leland Mizelle, Maohao Han, and Mark M. Dean. Renal denervation supersensitivity revisited. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1239–R1246, 1998.—To determine whether the chronically denervated kidney is supersensitive to either physiological or pathophysiological plasma levels of norepinephrine (NE), studies were conducted in conscious dogs subjected to unilateral renal denervation and surgical division of the urinary bladder into hemibladders to allow separate 24-h urine collection from denervated and innervated kidneys. Plasma NE concentration was increased by chronic infusion of NE (4–5 days) at rates of 25, 100, and 200 ng·kg⁻¹·min⁻¹. Twenty-four-hour control values for mean arterial pressure (MAP), plasma NE concentrations, and ratios for urinary sodium and potassium excretion from denervated and innervated kidneys (Den/Inn) were 94 ± 4 mmHg, 145 ± 24 pg/ml, 1.05 ± 0.05, and 0.97 ± 0.07, respectively. With infusions of NE producing plasma levels of NE of up to ~3,000 pg/ml or plasma concentrations of NE at least threefold greater than present under most pathophysiological conditions and during acute activation of the sympathetic nervous system, there were no significant long-term changes in MAP or relative excretion rates of sodium and potassium from denervated and innervated kidneys. In marked contrast, pharmacological plasma levels of NE (~7,000 pg/ml) produced chronic increases in MAP (to 116 ± 2% of control) and sustained reductions in Den/Inn for urinary sodium and potassium excretion to 57 ± 4 and 68 ± 5% of control, respectively, indicating a lower excretion rate of these electrolytes from denervated vs. innervated kidneys. We conclude that the chronically denervated kidney does not exhibit an exaggerated antinatriuretic response to either physiological or pathophysiological levels of circulating NE. It is therefore unlikely that renal denervation supersensitivity is a confounding issue in studies employing chronic renal denervation to elucidate the role of the renal nerves in the regulation of sodium excretion.

renal nerves; norepinephrine; sodium excretion

RENAL DENERVATION is a method commonly used to study the role of the renal nerves in the control of sodium excretion. However, a potential criticism of studies employing renal denervation is that the chronically denervated kidney may be supersensitive to circulating levels of norepinephrine (NE), a response that could mask the effects of renal denervation. Indeed, several studies have shown that both the renal vasculature and tubules are supersensitive to exogenously administered NE (1, 11, 12, 20, 26, 28). This has been attributed to both prejunctional and postjunctional mechanisms (4, 29, 32). The prejunctional mechanism is a result of diminished reuptake of NE into sympathetic nerve terminals, whereas the postjunctional mechanism includes upregulation of postjunctional β-adrenergic receptors. Although the phenomenon of renal denervation supersensitivity to NE has been recognized for almost 50 years (1), it is still unclear whether chronically denervated kidneys are supersensitive to either physiological or pathophysiological levels of NE or whether exaggerated renal responses to NE occur only at supraphysiologic levels of NE.

Our interest in revisiting this issue stems from our studies using the split-bladder preparation in combination with unilateral renal denervation to elucidate the role of the renal nerves in the control of sodium excretion, particularly in the pathophysiological states of congestive heart failure and hypertension (14, 16, 17, 23). The split-bladder preparation, in combination with unilateral renal denervation, is a powerful technique for exposing a functional role of the renal nerves, because it controls for subtle changes in arterial pressure and humoral factors that could mask the effects of renal denervation on sodium excretion when responses of a kidney before and after renal denervation or responses in animals with bilateral renal denervation to those with intact innervation are compared. Because both kidneys are exposed to the same arterial pressure and humoral factors, any differences in urinary sodium excretion can be attributed to either the direct or indirect effects of the renal nerves on renal excretory function. However, despite this powerful technique for detecting neurally induced alterations in renal function, this model has failed to reveal a role for the renal nerves in chronically promoting sodium retention under conditions such as prolonged sodium depletion and experimentally induced heart failure (16–18). This is particularly disconcerting, since some studies, but not all, have shown that these chronic sodium-retaining states are associated with increased renal sympathetic activity (3, 4, 6, 25, 30). One possible explanation for the inability to demonstrate neurally induced sodium retention in studies employing the split-bladder preparation is that the chronically denervated kidney is supersensitive to either physiological or pathophysiological levels of circulating NE. A resolution of this issue is the primary objective of the present study.

For reasons discussed below, previous acute studies have failed to resolve the issue of whether the chronically denervated kidney is supersensitive to either physiological or pathophysiological levels of circulating NE. Moreover, although the goal of many renal denervation studies has been to elucidate the role of the renal nerves in long-term control of sodium excretion, it has not been determined whether the chronically den-
uated kidney exhibits exaggerated antinatriuretic responses to prolonged increments in plasma NE concentration. Accordingly, the split-bladder preparation in combination with unilateral renal denervation was used in the present study to determine the long-term influence of elevated plasma levels of NE on the sodium excretory responses in intact vs. denervated kidneys. Increments in plasma NE concentration to levels present under physiological and pathophysiological conditions and to beyond levels commonly observed in experimental animals were achieved by chronic infusion of NE.

METHODS

Animal preparation. Seven female dogs weighing 20–23 kg were used in this study, and all procedures were in accordance with National Institutes of Health Guidelines and approved by the Institutional Animal Care and Use Committee. Before surgery, the dogs were administered atropine (0.05 mg/kg sc), sedated with acepromazine (0.15 mg/kg sc), and then anesthetized with either pentobarbital sodium (25 mg/kg iv) or isoflurane (1.5–2.5%). Catheters made of Tygon microbore tubing were implanted in the lower abdominal aorta and inferior vena cava via the femoral arteries and veins, respectively, and exteriorized between the scapulae. Subsequently, the urinary bladder was surgically divided, and each half was sutured to form hemibladders with Silastic catheters implanted to allow continuous 24-h urine collection from each kidney (14, 16, 17, 23). The catheters were exteriorized in the flank region and connected to sterile plastic bags. Finally, the left kidney was denervated through a flank approach. All visible nerves along the renal artery and vein were removed, the adventitia was stripped, and the vessels were painted for 20 min with a solution of 10% phenol in absolute ethanol. As we have reported in previous studies (16, 18, 23), this procedure produces a >30-fold difference in NE content between innervated and denervated kidneys, indicating pronounced depletion of NE in denervated kidneys. Postoperatively, the dogs were treated with antibiotics (cefazolin sodium, 0.5 g im bid) for 5 days and analgesics for the first 24–48 h (buprenorphine hydrochloride, 0.015 mg/kg im) or zoloflurane (0.5 g im bid). Catheters and various catheters were maintained by flushing with isotonic saline two to three times weekly and filling the catheters with heparin (1,000 U/ml). The urine collection bags were changed daily using sterile techniques.

Several days after surgery, the dogs were placed in metabolic cages in a room maintained at 22 ± 3°C with a 12:12-h light-dark cycle. They were fitted with a specially designed harness containing a pressure transducer (model P23 ID, Statham Laboratories, Hato Rey, PR) positioned at heart level. Isotonic saline was infused continuously into a venous catheter with a Wiz peristaltic pump (Isco, Lincoln, NE) at a rate of 350 ml/day. A disposable filter (Cathivex, Millipore) was connected in series with the infusion to prevent passage of bacteria and other contaminants.

During a 2-wk training and equilibration period and throughout the entire experiment, 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 meq of sodium and ~60 meq of potassium. Thus, with the intravenous saline infusion, sodium intake was ~60 meq/day. Water consumption was monitored daily, and 24-h urine samples were collected at 10 AM, ~1 h before feeding. Body temperature was measured each morning, and amoxicillin (250 mg), dicloxacillin (250 mg), and a trimethoprim (400 mg)-sulfamethoxazole (80 mg) combination were given prophylactically twice a day.

Measurement of hemodynamics. Throughout the study, arterial pressure was continuously monitored from an arterial catheter connected to the pressure transducer in the harness and recorded on a Grass polygraph (model 7D, Grass Instruments, Quincy, MA). A microcomputer and customized software (15, 16, 19, 27) were used to sample the signal from the Grass recorder at 200 Hz for a duration of 12 s, once a minute, 24 h/day. The digitized data for each 12-s burst were processed immediately to compute mean arterial pressure (MAP) and heart rate (HR). The daily values for MAP and HR presented were determined from the average of 1,260 sample points collected during the 21-h period between noon and 8:00 AM. The hours excluded from the 24-h analysis included the time required for flushing catheters, calibrating blood pressure transducers, feeding, and cleaning cages.

Experimental protocol. During the 2-wk training and equilibration period, the dogs were trained to lie quietly in their cages for collection of blood samples. After a 3-day control period, five dogs were continuously infused with NE (Levoephed, Winthrop Pharmaceuticals) for 9 days by adding NE to the 24-h saline infusion. NE was infused at a rate of 25 and 100 ng·kg⁻¹·min⁻¹ on days 1–5 and 6–9, respectively. This initial chronic infusion of NE was followed by a 7-day recovery period. Subsequently, in three of the dogs, NE was infused for an additional 5 days at a higher rate of 200 ng·kg⁻¹·min⁻¹. In two additional dogs, a 5-day infusion of NE at 200 ng·kg⁻¹·min⁻¹ commenced immediately after 5 days of NE infusion at 50 ng·kg⁻¹·min⁻¹; responses to NE infusion at 50 ng·kg⁻¹·min⁻¹ were studied in only two dogs and are not reported here. The NE infusion was prepared fresh daily and contained ascorbic acid (1 mg/ml saline) as an antioxidant. In addition, the bags of saline containing the NE and the infusion lines were shielded from light to minimize photooxidation.

Analytic methods. Plasma renin activity (PRA) was measured by RIA (7). Plasma and urine concentrations of sodium and potassium were determined by flame photometry (IL 943, Instrumentation Laboratories), plasma protein concentration by refractometry (American Optical, Buffalo, NY), and hemato crit by a micromethod (Autocrit II, Clay Adams, Franklin, NJ). The plasma concentration of NE was determined by HPLC as previously described (15, 16, 21, 22, 27). Additionally, renal NE concentration was determined in three of the seven dogs by methods previously employed in our laboratory (16, 23).

Statistical analysis. Results are expressed as means ± SE. Experimental and recovery data were compared with control by using ANOVA with Dunnett’s t-test for multiple comparisons (5). 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/In.

RESULTS

The changes in MAP, HR, and urinary electrolyte excretion in response to chronic NE infusion at 25 and 100 ng·kg⁻¹·min⁻¹ are shown in Figs. 1–3. The average control values for MAP and HR were 94 ± 4 mmHg and 51 ± 2 beats/min, respectively. Average control values for urinary sodium excretion from denervated and innervated kidneys were 31 ± 2 and 29 ± 2, respectively; the corresponding values for urinary potas-
sium excretion were 26 ± 2 and 27 ± 2. As a result of the approximately equal excretion rates of these electrolytes from denervated and innervated kidneys before NE infusion, control values of Den/Inn for sodium and potassium excretion were 1.05 ± 0.05 and 0.97 ± 0.07, respectively.

As illustrated in Fig. 1, during thelowest rate of NE infusion (25 ng·kg⁻¹·min⁻¹), there was an initial transient decrease in HR but no significant changes in MAP. Although this rate of NE infusion tended to cause natriuresis and kaliuresis, there were no significant changes in the total excretion rates of either sodium or potassium during the 5-day infusion period (Fig. 2). Due to a small increase in sodium excretion in innervated kidneys from 31 ± 2 to 35 ± 3 meq/day on day 1 of NE infusion (there was no change in sodium excretion in denervated kidneys: 32 ± 2 and 32 ± 2 meq/day), there was a transient decrease in Den/Inn for sodium excretion from 1.03 ± 0.04 to 0.93 ± 0.04 (Fig. 3). Subsequently, Den/Inn for sodium (and potassium) excretion returned to control levels, and most importantly, there were no sustained changes in the relative excretion rates of these electrolytes from denervated and innervated kidneys, even though the plasma concentration of NE increased from 145 ± 24 to 775 ± 105 pg/ml, or to 5–6 times control (Fig. 3). Thus denervated kidneys did not exhibit exaggerated antinatriuretic (or antikaliuretic) responses to elevated circulating levels of NE as high as those commonly present under physiological and pathophysiological conditions (6, 10, 15, 21, 22, 24, 33, 34).

Subsequently, as illustrated in Fig. 3, when the rate of NE infusion was increased from 25 to 100 ng·kg⁻¹·min⁻¹ at the end of day 5, plasma NE concentration increased further to ~20 times control (2,997 ± 105 pg/ml), or to levels rarely seen under physiological or pathophysiological conditions. In association with this extremely high plasma concentration of NE, MAP increased ~6 mmHg on days 6–8 before falling to control levels on the last day of NE infusion (day 9); during this 4-day period of NE infusion, HR was 10–15% below control levels (Fig. 1). Although there were no significant changes in the total excretion rates of either sodium or potassium during the 4-day infusion period (Fig. 2), there were significant transient reductions in Den/Inn for sodium and potassium excretion in parallel with increments in MAP on days 6–8 of NE infusion (Fig. 3). Most notably, on the 1st day of this
higher rate of NE infusion (day 6), sodium excretion decreased in denervated kidneys from 35 ± 3 to 30 ± 4 meq/day but increased in innervated kidneys from 32 ± 2 to 36 ± 4 meq/day; as a result, Den/Inn for sodium excretion decreased from 1.11 ± 0.03 (day 5) to 0.84 ± 0.05 (day 6). However, concomitant with a waning hypertensive response to NE, Den/Inn for sodium and potassium excretion returned toward basal levels by day 9 of NE infusion. Thus this rate of NE infusion also had no significant sustained effects on either MAP or the relative excretion rates of sodium and potassium from denervated and innervated kidneys.

During the 24-h period that followed termination of NE infusion, MAP decreased and HR increased ~5 mmHg and ~20 beats/min, respectively; final recovery values for MAP and HR were not significantly different from control. In association with these changes in arterial pressure and HR on day 1 of the recovery period, there were striking increments in Den/Inn for both sodium and potassium excretion to above control levels, presumably due to arterial baroreflex activation of the renal nerves. The transient increase in Den/Inn for sodium excretion from 0.98 ± 0.04 (day 9) to 1.65 ± 0.08 (day 10) was primarily due to a decrease in sodium excretion in innervated kidneys; during this time, sodium excretion decreased in innervated kidneys from 32 ± 1 to 20 ± 4 meq/day, whereas it was unchanged in denervated kidneys (31 ± 2 and 32 ± 6 meq/day). Over the next few days, the relative and absolute excretion rates of sodium and potassium from denervated and innervated kidneys returned to control levels.

The highest rate of NE infusion (200 ng·kg⁻¹·min⁻¹) increased plasma NE concentration to supraphysiological levels (Fig. 4). Responses after 5 days of NE infusion at 200 ng·kg⁻¹·min⁻¹ are illustrated in Fig. 4 and indicate that plasma NE concentration increased to 7,091 ± 289 pg/ml, or to ~50 times control. For comparison, responses on the final days of NE infusion at 25 and 100 ng·kg⁻¹·min⁻¹ are also illustrated in Fig. 4. Unlike the lower rates of NE infusion, infusion of NE at 200 ng·kg⁻¹·min⁻¹ produced a sustained increase in MAP (to 116 ± 2% of control), confirming previous observations (8). Moreover, the pharmacological levels of NE associated with this highest rate of NE infusion
produced not only chronic hypertension but also striking and sustained reductions in Den/Inn for sodium and potassium excretion (to 57 ± 4 and 68 ± 5% of control, respectively), indicating a lower excretion rate of these electrolytes from chronically denervated kidneys vs. kidneys with intact innervation. Once again, and most importantly, these sustained changes in the relative excretion rates of sodium and potassium from denervated and innervated kidneys did not occur at physiological or pathophysiological levels of circulating NE.

There were no significant changes in PRA or plasma concentrations of sodium and potassium during NE infusion; control values were 0.35 ± 0.12 ng ANG I·ml⁻¹·h⁻¹, 144 ± 1 meq/l, and 4.3 ± 0.1 meq/l, respectively. Hematocrit (control = 36 ± 1) and plasma protein concentration (control = 6.3 ± 0.2 g/dl) tended to increase at elevated plasma levels of NE; at the highest rate of NE infusion, increments in both hematocrit (to 40 ± 1) and plasma protein concentration (to 6.8 ± 0.2 g/dl) were statistically significant. Finally, in accordance with the results from our previous studies, there was a >30-fold difference in NE content between innervated and denervated kidneys. As in our earlier studies, NE concentration in denervated kidneys (15 ± 7 pg/mg tissue) was ~20 pg/mg tissue.

**DISCUSSION**

The major finding of the present study is that the chronically denervated kidney does not exhibit exaggerated antinatriuretic responses to either physiological or pathophysiological plasma levels of NE, including the plasma levels of NE (~1,000 pg/ml or less) that occur either in chronic sodium-retaining states, such as sodium depletion and heart failure (3, 6, 15, 24), or acutely during sympathetic activation induced by postural changes, hypotensive hemorrhage, exercise, and insulin-induced hypoglycemia (10, 21, 22, 33, 34). Consequently, renal denervation supersensitivity is not a confounding issue in studies employing chronic renal denervation to elucidate the role of the renal nerves in regulation of sodium excretion in physiological and pathophysiological states. On the other hand, the fall in Den/Inn for sodium excretion at supraphysiological levels of NE, which chronically increased arterial pressure, is consistent with previous findings of renal denervation supersensitivity at pharmacological levels of NE (1, 11, 12, 20, 26, 28).

Previous studies have determined the renal excretory responses to acute infusions of NE in conscious and anesthetized dogs with one chronically denervated kidney and the contralateral kidney intact (1, 20, 26). In these earlier studies, acute infusions of NE decreased sodium excretion in the denervated kidney while producing considerably milder antinatriuresis or even increasing sodium excretion in the kidney with intact innervation. Hence, a fall in Den/Inn for sodium excretion in these experiments is consistent with the possibility of renal denervation supersensitivity. However, because substantial pressor responses occurred during NE infusion, it is likely that supraphysiological plasma levels of NE were achieved in these experiments. Furthermore, because infusion of NE increased MAP, one cannot discount the possibility that arterial baroreceptor reflex suppression of renal sympathetic nerve activity influenced sodium excretion in the innervated kidney in a direction opposite to the direct antinatriuretic effects of circulating NE. Thus one cannot discern from these studies whether the fall in Den/Inn for sodium excretion in response to NE was due to renal denervation supersensitivity, renal sympathoinhibition, or a combination of these influences.

To eliminate the confounding effects of reflex alterations in renal sympathetic nerve activity on the renal responses to acute NE infusion, Krayacich et al. (11, 12) subjected anesthetized rats with one innervated and one chronically denervated kidney to ganglionic blockade before acute NE infusion. Although the interpretation of these studies is confounded by substantial alterations in baseline values for MAP, renal hemodynamics, and sodium excretion as well as striking reductions in renal hemodynamics in response to NE, they do support the contention that the chronically denervated kidney is supersensitive to supraphysiological levels of NE in the circulation. Taken together, however, these studies as well as those discussed above in dogs fail to clarify the critical issue of whether the chronically denervated kidney is supersensitive to either physiological or pathophysiological plasma levels of NE.

The results of the present study indicate that the chronically denervated kidney is not supersensitive to either physiological or pathophysiological levels of circulating NE. The lowest rate of NE infusion (25 ng·kg⁻¹·min⁻¹) increased plasma NE concentration to 700–800 pg/ml (to 5–6 times control) or to levels as high as those achieved in decompensated heart failure (15); this plasma concentration of NE is considerably higher than present chronically in most physiological and pathophysiological states believed to be associated with increased sympathetic activation including sodium depletion and compensated heart failure (3, 6, 15, 24). Importantly, at this rate of NE infusion, there were no significant changes in Den/Inn for sodium excretion, other than a transient decrease on day 1 of NE administration. Although central venous pressure was not measured in the present study, one would expect NE infusion to increase cardiac filling pressures acutely because NE increases venous as well as arterial tone and decreases the capacitance of the circulation. Therefore the transient increase in sodium excretion from innervated kidneys leading to an acute fall in Den/Inn for sodium excretion on day 1 of NE infusion (in absence of a rise in MAP) may have been due to cardiopulmonary baroreflex suppression of renal sympathetic nerve activity. Presumably, increments in central venous pressure were not chronically sustained because of loss of body fluid volume, as reflected by the tendency for total urinary sodium excretion to increase during NE infusion. In any event, the results clearly indicate that there were no sustained alterations in Den/Inn for sodium excretion in response to high
Furthermore, there were no significant long-term alterations in Den/Inn for sodium excretion even when the rate of NE infusion was increased further to produce a plasma NE concentration of \(\sim 3,000\) pg/ml, or a level of circulating NE at least three times higher than observed during acute activation of the sympathetic nervous system by hypotensive hemorrhage, exercise, and insulin-induced hypoglycemia (10, 21, 22, 33, 34). However, once again, transient reductions in Den/Inn for sodium excretion did occur during the initial days of this higher rate of NE infusion (100 ng·kg\(^{-1}\)·min\(^{-1}\)). Furthermore, at this infusion rate of NE, the initial reductions in Den/Inn for sodium excretion were more prolonged than at the lowest rate of NE infusion and occurred in parallel with transient elevations in arterial pressure. This would suggest that the greater excretion rate of sodium from innervated vs. denervated kidneys during the initial 3 days of NE infusion at 100 ng·kg\(^{-1}\)·min\(^{-1}\) was primarily due to arterial baroreflex-mediated inhibition of renal sympathetic nerve activity, particularly in light of the simultaneous time-dependent return in Den/Inn for sodium excretion and arterial pressure to control levels during the more chronic phase of NE infusion. The failure of this rate of NE infusion to produce chronic hypertension was expected because of the relatively weak sodium-retaining effects of circulating NE, particularly compared with ANG II (9, 13, 22). Most importantly, these results indicate that, under long-term conditions, chronically denervated kidneys do not exhibit exaggerated antinatriuretic responses to circulating levels of NE found under even extreme physiological or pathophysiological conditions.

In marked contrast to the absence of sustained alterations in arterial pressure and the relative excretion rates of sodium from innervated and denervated kidneys at the two lowest rates of NE infusion, hypertension and a substantial reduction in Den/Inn for sodium excretion were persistent effects of the highest rate of NE infusion, which produced supraphysiological levels of NE (\(\sim 7,000\) pg/ml). The relatively lower rate of sodium excretion from denervated vs. innervated kidneys is consistent with previous findings of renal denervation supersensitivity at pharmacological levels of NE (1, 11, 12, 20, 26, 28). However, another possibility is that the greater rate of sodium excretion from innervated vs. denervated kidneys at supraphysiological levels of NE was due to suppression of renal sympathetic nerve activity, with the renal nerves serving as the efferent limb of a feedback mechanism for the chronic regulation of arterial pressure. That chronic renal sympathoinhibition and attendant loss of sodium might be a long-term compensatory response to the hypertension is consistent with our earlier findings in dogs chronically infused with ANG II (2, 14). In these experiments, ANG II hypertension was associated with a sustained reduction in Den/Inn for sodium excretion and suppression of renal NE spillover, an index of renal sympathetic nerve activity (6). Because of the possibility that chronic renal sympathoinhibition promoted sodium excretion and contributed to the differential excretion of sodium in innervated and denervated kidneys at hypertensive levels of circulating NE, one cannot assess the relative importance of this mechanism vs. renal denervation supersensitivity to the fall in Den/Inn at pharmacological levels of NE. In either case, however, the present results indicate that the chronically denervated kidney is not supersensitive to either physiological or pathophysiological levels of circulating NE.

Because glomerular filtration rate and renal plasma flow were not measured in the present study, we cannot determine whether either the transient or sustained differential effects of NE on sodium excretion in denervated vs. innervated kidneys were mediated via renal hemodynamic or tubular mechanisms. However, several observations support tubular mechanisms. First, the rates of NE infused in the present study do not produce either acute or long-term changes in glomerular filtration rate or renal plasma flow (8, 9, 20). Second, in dogs with one innervated and one chronically denervated kidney, NE infusion at 125 ng·kg\(^{-1}\)·min\(^{-1}\) (a rate intermediate to highest infusion rates in present study) acutely decreased Den/Inn for sodium excretion in the absence of hemodynamic changes in either kidney (20). This response was interpreted to indicate that "the chronically denervated kidney is hypersensitive to NE-stimulated fluid reabsorption." Finally, reductions in Den/Inn for sodium excretion during ANG II hypertension occurred in the absence of differential renal hemodynamic effects in denervated vs. innervated kidneys, suggesting that renal sympathoinhibition impaired sodium reabsorption (14). We speculate that, during NE infusion, a similar reflex mechanism was operative in response to both transient and sustained increments in cardiac and/or arterial pressures. Furthermore, if the proximal tubule is the predominant site of baroreflex-mediated alterations in sodium reabsorption under chronic as well as acute conditions, then an increased rate of sodium delivery to the distal nephron could account for the greater excretion rate of potassium as well as sodium in innervated vs. denervated kidneys during elevations in plasma NE concentration. Certainly, a similar intrarenal mechanism could account for the parallel fall in Den/Inn for sodium and potassium excretion at pharmacological rates of NE infusion if the proximal tubules of denervated kidneys are supersensitive to supraphysiological levels of NE in the circulation.

In conclusion, the novel approach taken in this study to address the long-standing unresolved issue of renal denervation supersensitivity strongly indicates that chronically denervated kidneys do not exhibit exaggerated antinatriuretic responses to circulating levels of NE normally present under either physiological or pathophysiological conditions. Thus it is unlikely that renal denervation supersensitivity is a confounding issue in studies employing chronic renal denervation to elucidate the role of the renal nerves in the regulation of sodium excretion under conditions associated with
either acute or chronic activation of the sympathetic nervous system. On the other hand, the sustained fall in Den/Inn for sodium excretion at suprapathophysiological levels of NE that produced chronic hypertension is consistent with previous findings of renal denervation supersensitivity at pharmacological levels of NE. Additionally, the higher excretion rate of sodium from innervated vs. denervated kidneys at suprapathophysiological plasma levels of NE is also consistent with our recent findings during chronic ANG II infusion, indicating that sustained renal sympathoinhibition and attendant loss of sodium may be a long-term compensatory response to the hypertension.

Perspectives

A role for the sympathetic nervous system in long-term control of body fluid volumes and arterial pressure is controversial for several reasons, including the difficulty in assessing the functional effects of the renal nerves under chronic conditions. For reasons discussed above, we believe the split-bladder preparation in combination with unilateral renal denervation is a powerful technique for investigating the role of the renal nerves in long-term (and short-term) control of sodium excretion during normal alterations in body fluid volumes and in pathophysiological states such as hypertension and heart failure. Indeed, our published and preliminary findings demonstrating sustained reductions in Den/Inn for sodium excretion during chronic increments in salt intake and ANG II hypertension indicate that renal sympathoinhibition plays a compensatory role in chronically increasing sodium excretion in states of volume expansion and hypertension. On the other hand, in the absence of elevations in Den/Inn for sodium excretion in dogs subjected to chronic sodium depletion and heart failure (16–18), our studies fail to support the notion that increases in renal sympathetic nerve activity play a homeostatic role in the chronic regulation of sodium excretion. The present results are therefore especially important because they indicate that these earlier negative findings were not due to renal denervation supersensitivity. If it is assumed that renal sympathetic nerve activity is elevated in the above sodium-retaining states, it is quite possible that neurally induced renin secretion obscures the importance of the renal nerves in promoting sodium retention in the split-bladder preparation with unilateral renal denervation. Thus, during chronic activation of the renal nerves, high circulating levels of ANG II would be expected to exert pronounced sodium-retaining effects on the contralateral denervated kidney as well as on the kidney exposed to increased renal sympathetic nerve activity. As a result, there would be little or no difference in sodium excretion between the two kidneys (little or no increase in Den/Inn for sodium excretion). This hypothesis is supported by the rise in PRA and the delayed but pronounced antinatriuresis in the denervated kidney during prolonged (3-h) renal sympathetic stimulation of the contralateral innervated kidney (31). The hypothesis that the ANG II plays a dominant role in indirectly promoting antinatriuresis during prolonged renal adrenergic stimulation is also consistent with reports that blockade of the renin-angiotensin system substantially attenuates sodium retention during postural changes (21) and completely eliminates the hypertensive response to long-term infusion of NE directly into the renal artery (22).

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