Changes in Renal Vascular Sensitivity and Arterial Pressure Associated with Sodium Intake During Long-Term Intrarenal Norepinephrine Infusion in Dogs

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SUMMARY Experiments were performed on conscious uninephrectomized dogs to determine the comparative effects of chronic intrarenal and intravenous norepinephrine (NE) infusion (0.27 μg/kg/min) on the steady-state values for arterial pressure, plasma renin activity (PRA), and renal function at four levels of sodium intake (5, 40, 120 and 240 mEq/day). Arterial pressure was monitored continuously 24 hr/day with online computer techniques. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and plasma renin activity (PRA) were determined after sodium and water balance was achieved. During intrarenal NE infusion, ERPF and GFR decreased progressively from 15% to 30% and from 24% to 46% respectively, while renal vascular resistance increased progressively from 40% to 140% as sodium intake was increased from 10 to 240 mEq/day. Both ERPF and renal resistance, but not GFR, returned to control levels during intravenous NE infusion at each level of sodium intake and after terminating NE infusion. During intrarenal NE infusion the steady-state value for mean arterial pressure increased from a control of 105 to 118 mm Hg when the sodium intake was 10 mEq/day. Pressure then increased progressively from 118 to 135 mm Hg as the sodium intake was elevated from 10 to 240 mEq/day. Increases in arterial pressure associated with intravenous NE infusion were significantly smaller at each sodium level than those achieved with intrarenal NE infusion. At each level of sodium intake, PRA was elevated during intrarenal NE infusion and returned to control after NE infusion. Intravenous NE infusion did not increase PRA above control levels. The data are compatible with the concept that enhanced renal adrenergic activity could initiate and sustain hypertension chronically by basic alterations in renal function. (Hypertension 1: 549-558, 1979)

KEY WORDS • norepinephrine • hypertension • renal vascular sensitivity • arterial pressure • pressure diuresis • sodium balance • plasma renin activity

INCREASED sympathetic vasoconstrictor nerve activity is thought by many to be involved in the pathogenesis of certain forms of hypertension. There are increased levels of the sympathetic neurotransmitter norepinephrine (NE) in the plasma of some patients with essential hypertension,1, 2 and sympathetic inhibiting agents are effective antihypertensive agents in many types of hypertension. Reduction in renal excretory capacity is associated with many forms of hypertension. Since acute stimulation of renal sympathetic nerves can decrease sodium and water excretion3, 4 and increase the secretion of renin,5 it is possible that a persistent increase in renal adrenergic activity could produce alterations in renal function that would result in chronic hypertension.

Although considerable work has been done on the short-term effects of increased sympathetic nerve activity on renal function, little has been done to characterize the effects of chronic stimulation. In anesthetized dogs, renal sympathetic fibers, when acutely stimulated, can decrease renal blood flow6 and decrease excretion of sodium and water.7 There are only two studies reported in which the renal nerves were stimulated chronically; hypertension resulted in both studies.6, 7 Because of the technical difficulties inherent in chronic sympathetic nerve stimulation, long-term intrarenal infusion of NE has been used to mimic this condition.8 Although it is not possible to quantitatively compare receptor site NE concentration during renal sympathetic nerve stimulation and during NE infusion, the effects of intrarenal NE infusion would be expected to mimic those associated with increased nerve activity if comparable NE concentrations were achieved.

The present studies were performed on conscious uninephrectomized dogs to determine the comparative effects of chronic intrarenal and intravenous NE in-
fusions on arterial pressure, PRA, and renal function at four levels of sodium intake ranging from 5 to 240 mEq/day. The results indicate that during enhanced renal adrennergic activity, renal function is altered such that over a wide range of sodium intake, fluid and electrolyte balance is achieved only at an elevated level of arterial pressure.

Methods

Animal Preparation

Fifteen mongrel female dogs weighing 20.3 ± 1.0 kg were surgically prepared using sodium pentobarbital anesthesia (30 mg/kg) at 10 to 20 days prior to the start of the control period for fluid and electrolyte balances. All animals were uninephrectomized and equipped with chronic indwelling catheters inserted into the right femoral artery and vein, the renal artery, and the urinary bladder. The femoral artery and vein catheters were made of thick-walled Tygon tubing (Norton, Akron, OH) and fitted with a Silastic elbow to prevent kinking in the femoral area. Tapered Tygon catheters were implanted into the renal artery using the technique described by Herd and Barger.9 All vascular catheters were tunneled subcutaneously, brought out the interscapular region of the dog's back, and filled with 1000 USP units (U) heparin. The femoral catheters were flushed with sterile isotonic saline every third day and the renal artery catheter twice daily during the 7-day postoperative period. Prior to each flushing, the heparin was withdrawn from the catheters.

The bladder cannula was made from Silastic tubing (No. 601-325, Dow Corning, Midland, MI) and held in place with a Silastic end disk formed from a piece of flat uncured Silastic sheet (HH 6018, 0.4 Dow Corning). The end disk of the cannula was inserted through a single stab wound in the most ventral part of the bladder and held in place with a purse-string suture. Dacron cloth attached to a second disk located 5 mm from the end disk was loosely sutured to the outer bladder wall to enable fibrous tissue to grow around the point of entry. A 13-gauge stainless steel needle cut to 1 cm length, with the Luer-Lok hub remaining, was inserted into the Silastic tube, brought out through the abdominal wall, and sealed with a Luer-Lok cap (No. 223-586, Curtin Matheson, New Orleans, LA). The dogs urinated routinely through the urethra. However, the Luer-Lok cap could be removed at a fixed time each day to obtain any remaining urine in the bladder for precise 24-hour determinations of electrolyte and water excretion. Bladder and retrograde renal infection was not encountered. The dogs were given 1.2 million U Bicillin immediately following surgery and were maintained on 250 mg ampicillin twice daily for 1 week. Two days after surgery all dogs except those included in the pilot study (to be described) were fed daily two cans of heart/diet prescription dietary animal food (Riviana, Topeka, KS) which contained a total of 5 mEq sodium and 45 mEq potassium. Water was provided ad libitum. The dogs were maintained on this diet throughout the experiment protocol. Any additional sodium was administered intravenously as described in the following protocol.

Collection of Data

Fourteen days prior to the start of NE infusion, each dog was placed in a large, specially constructed metabolic pen measuring 5 X 6 X 6 feet. The dog was harnessed with a light aluminum saddle housing a small arterial pressure transducer at heart level. A strong flexible tubing was attached to the top of the saddle to protect the pressure transducer wires and all infusion lines. The tubing was brought out through the top of the pen and counter-weighted to a pulley system to maintain it in a vertical position at all times. Two guidelines from opposite ends of the saddle were attached to the sides of the pen to prevent the dogs from circling in the pen.

Arterial pressure was monitored continuously 24 hr/day using a stable solid-state model 7D Grass recorder (Grass Instrument Co., Quincy, MA). The analog signal of the mean arterial pressure from this recorder was sampled every 60 seconds using a PDP 11-70 Digital Corporation computer. On-line data was stored on disk for editing and reduction, using batch processing which provided hourly averages, statistics, and graphics. An example of a single experiment in which the average bi-hourly mean arterial pressure was plotted by the computer graphics terminal is seen in figure 1. This overall system was virtually free of drift as was demonstrated by undetectable changes over seven continuous days of computer monitoring of amplified output signals from the Grass recorder. These procedures have been modified from those described previously in our laboratory.10 The large size of the animal pen enabled sufficient movement of the dog for enough daily exercise to maintain good muscle tone and appetite for food. Renal clearance studies were performed by supporting the dog in a standing position by the guidelines attached to the saddle and simply attaching a light-weight polyurethane bottle to the Luer-Lok hub of the implanted bladder catheter. All infusion pumps were located remotely out of sight of the pen and could be manipulated without disturbing the animal. This permitted all clearance studies to be performed in the environment to which the dog had been accustomed.

Measurements

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured using standard clearance techniques with I125-iothalamate (Glofil) and p-aminohippuric acid (PAH). Three separate 20-minute collection periods were averaged for the daily value. The isotopes were counted with a Searle No. 1180 gamma counter (Tracor-Analytic, Inc., Chicago, IL), and PAH was determined using colorimetric procedures. Urinary and plasma electrolyte concentrations were determined by flame photometry.
Plasma renin activity (PRA) was analyzed by the method of Haber et al. using Squibb antibody and angiotensin standards.

**Experimental Protocol**

Once the dog was placed in a metabolic recording pen, the renal artery catheter was continuously infused with saline (2.5 ml/hr) during the 7- to 10-day control period, at the same infusion rate of saline used later to deliver NE. A disposable Millipore filter (Cathivex) was connected in series with the renal artery infusion line to prevent passage of bacteria and other contaminants. The bladder was washed with a nitrofurazone solution to prevent bacterial infection. Heparin was added to all intrarenal infusates yielding a concentration of 50 USP U/ml. Water consumption (ad libitum) and urine excretion were measured daily to determine fluid and electrolyte balance. Five days prior to any infusion, continuous 24-hour monitoring of arterial pressure was begun together with daily arterial blood sampling for measuring of sodium and potassium concentration and PRA.

**Preliminary Norepinephrine Dose-Response Studies**

To determine the intrarenal NE infusion rate most effective in producing stable benign hypertension, five dogs were infused 5 to 10 days at either 0.07 (N = 2), 0.14 (N = 3), or 0.27 (N = 2) μg/kg/min. These dogs were maintained on 80 mEq Na/day and 45 mEq K/day. It was determined from these studies that NE doses less than 0.27 μg/kg/min did not consistently produce hypertension, while higher doses frequently resulted in renal failure or malignant hypertension. This dose was therefore used in all of the following experiments.

**Chronic Intrarenal and Intravenous Norepinephrine Infusion**

Seven dogs were used to determine the comparative effects of intravenous and intrarenal NE infusions on the steady-state relationship between arterial blood pressure and sodium and water excretion. During the final 2 days of the control period, on the morning immediately prior to the start of NE infusion and on specified days to be later described, GFR and ERPF were determined. The general protocol is illustrated by the continuous pressure recording seen in figure 1. Following the control period, the dogs were maintained on the low sodium diet and then infused intrarenally for 4 days with NE at a rate of 0.27 μg/kg/min. On the fourth day of NE infusion, GFR and ERPF were measured and blood samples obtained for determination of PRA and plasma electrolyte concentration. Subsequently, the NE infusion was switched to the systemic intravenous catheter and continued for the next 3 days at the same rate and the
same low sodium intake. On the third day of intravenous NE infusion, blood sampling and renal clearance studies were repeated. The sodium intake was then increased to 40 mEq/day for 7 days and NE was again infused at the above rate, first intrarenally for 4 days and then intravenously for 3 additional days as described above. Similarly, blood samples and measurements of renal function were repeated on Days 4 and 3 of intrarenal and intravenous NE infusion, respectively. In each dog, this sequence was repeated at sodium intakes of 10, 40, 120, and 240 mEq/day using the NE infusion rate of 0.27 μg/kg/min at each sodium intake level. Sodium intake was increased by continuous intravenous infusion of isotonic saline using a Sage pump (Model 375A, Sage Instruments, Cambridge, MA). This sequence of altering the NE infusion between the renal artery and the vena cava at each level of sodium intake served as a type of intermittent control to detect any permanent changes in renal function that could have sustained hypertension independently of intrarenal NE infusion.

Following NE infusion at the highest level of sodium intake (240 mEq/day), NE was terminated while the high rate of saline infusion was maintained for the next 2 days to determine the effects of high sodium alone on the measured variables. Sodium intake was then decreased to the control level (10 mEq/day) for 5 days, and renal clearance determinations were repeated on Day 4 post-NE infusion. At autopsy the infused kidneys from each of the seven dogs were decapsulated, weighed, grossly examined, and then sent to pathology for routine histological sectioning with H and E staining.

Statistical analysis was performed by unpaired t test; probability values greater than 0.05 were considered nonsignificant.

Results

Intrarenal versus Intravenous Norepinephrine Infusion at Varying Salt States: Mean Arterial Pressure

Figure 1 shows the computer output of the bihourly mean arterial pressure obtained during the sequential renal artery and intravenous NE infusion. The control and entire experimental procedure required 38 days (900 hours) during which mean arterial pressure (MAP) in this dog, as in all others, was recorded continuously by on-line computer techniques. The route of NE delivery and the daily sodium intake are indicated at the top and bottom of each graph, respectively. After 6 days of continuous monitoring of arterial pressure, intrarenal NE infusion was started. Arterial pressure rose from 103 ± 1 to 110 mm Hg during the first 24 hours of NE infusion and then progressively climbed to 128 mm Hg on the second day and remained at that level through day 4. NE was then infused intravenously for 3 days; arterial pressure averaged 110 mm Hg over this 3-day period. Subsequently, sodium intake was increased to 40 mEq/day and NE again infused intrarenally for 4 days; arterial pressure averaged 122 mm Hg. During intravenous NE infusion at this same sodium intake, arterial pressure returned to control levels and remained there over the 3-day period. When sodium intake was next increased to 120 mEq/day, intrarenal NE infusion raised arterial pressure to an average value of only 117 mm Hg, and arterial pressure again returned to normal during the subsequent 3-day intravenous NE infusion. While the dogs were maintained on the highest level of sodium intake (240 mEq/day), intrarenal NE infusion increased arterial pressure to 135 mm Hg during the final 2 days of NE infusion; during intravenous NE infusion, arterial pressure fell to 110 mm Hg. During the 2 days following NE infusion when the dogs continued to receive 240 mEq Na/day, arterial pressure declined to an average value of 103 mm Hg. Arterial pressure decreased further to 100 mm Hg when sodium intake was returned to 10 mEq/day for the remaining 2 days of the experiment.

The top curve of figure 2 summarizes the average daily mean 24-hour arterial pressure values obtained from the seven dogs during alternating intrarenal and intravenous NE infusions at increasing levels of sodium intake. Arterial pressure rose from an average value of 105 ± 3 to 116 ± 3 mm Hg on Days 3 and 4 of intrarenal NE infusion during 10 mEq/day sodium intake. During intravenous NE infusion at this sodium intake, arterial pressure was not significantly different from control. At 40 mEq/day sodium intake, mean arterial pressure averaged 118 ± 2 mm Hg, and during intravenous NE infusion at 40 mEq/day sodium intake, arterial pressure again fell to control levels. At the next level of sodium intake (120 mEq/day), intrarenal NE infusion increased arterial pressure to an average of 125 ± 3 mm Hg. Intravenous NE infusion at this level of sodium intake resulted in an average arterial pressure of 112 ± 3 mm Hg, which again was not significantly different from control. During the highest level of sodium intake (240 mEq/day), arterial pressure increased to 135 ± 4 mm Hg during intrarenal NE infusion and to 118 ± 4 mm Hg during intravenous infusion. Only at this level of sodium intake was the elevation in arterial pressure during intravenous NE infusion statistically significant.

Arterial pressure fell to an average of 109 ± 5 mm Hg within 24 hours after terminating NE infusion while the dogs were maintained on the high 240 mEq/day sodium intake. When sodium intake was returned to 10 mEq/day, arterial pressure stabilized at 105 ± 3 mm Hg, which was the value recorded during the control period.

Renal Blood Flow and Renal Vascular Resistance

As illustrated in figure 2, during intrarenal NE infusion, ERPF decreased progressively at increasing levels of sodium intake from a control value of 155 ± 10 to 130 ± 10 ml/min at 10 mEq Na/day, 119 ± 10 ml/min at 40 mEq Na/day, 107 ± 18 ml/min at 120 mEq Na/day, and 94 ± 15 ml/min at 240 mEq Na/day. At all levels of sodium intake, ERPF returned to control levels during intravenous infusion of norepinephrine. Four days after NE infusion, ERPF
averaged 130 ± 23 ml/min, and this was not significantly different from control.

Renal vascular resistance increased an average of 30% during intrarenal NE infusion at 10 mEq/day and thereafter increased progressively to 100% above control values at a sodium intake of 240 mEq/day (figs. 2 and 3). During intravenous NE infusion, renal vascular resistance was virtually unchanged except at the highest level of sodium intake (240 mEq/day). Post-infusion levels for renal vascular resistance were not statistically different from control.

GFR and Filtration Fraction

As also depicted in figure 2, GFR decreased from an average control value of 45 ± 3 ml/min to 34 ± 2, 32 ± 3, 30 ± 3, and 24 ± 5 ml/min, respectively, during intrarenal NE infusion at 10, 40, 120, and 240 mEq/day. During intravenous NE infusion, GFR decreased to 34 ± 3, 34 ± 3, 33 ± 3, and 29 ± 6 ml/min at the four levels of sodium intake.

Four days following NE infusion, GFR averaged 27 ± 6 ml/min. However, in three of seven dogs it returned to within 10% of control values following infusion. In the remaining four animals, it was nearly 50% of the control value by the fourth day after NE infusion.

Calculated filtration fraction tended to decrease with NE infusion but did reach statistically significant levels. In each instance, however, the average filtration fraction was higher during intrarenal NE infusion than during the associated intravenous infusion.

Plasma Renin Activity (PRA)

As seen in figures 2 and 4, PRA increased above the low sodium intake control level during intrarenal NE infusion even as sodium intake was increased to the very high levels. At all levels of sodium intake, PRA returned at least to control levels during intravenous NE infusion.

Daily Sodium and Water Excretion, and Sodium Balance

On the final day of each NE infusion period, at each level of sodium intake, daily sodium excretion closely reflected the amount of sodium infused (fig. 5). Urine excretion increased progressively with each level of
sodium intake, and no differences were obtained in these steady-state values between intrarenal and intravenous NE infusions.

Plasma Sodium and Potassium

Plasma sodium concentration was essentially unchanged except during the two periods that slight sodium retention was observed, that is, during intrarenal NE infusion at 40 and 120 mEq Na/day intake. Plasma potassium fell from 4.0 to 3.6 mEq/liter at the high level of sodium intake.

Steady-State Relationships Between Arterial Pressure and Sodium Excretion

Figure 6 plots the steady-state relationships between the average mean 24-hour arterial pressure level and daily sodium excretion during the three conditions summarized in figures 2 and 5: no NE infusion (saline control), intravenous NE infusion, and intrarenal NE infusion. With intrarenal NE infusion, the displacement of the curve far to the right indicates that at all levels of sodium excretion a higher level of arterial pressure was attained during infusion. In contrast, sodium balance was achieved with only slightly elevated pressures during intravenous NE infusion. In the absence of NE, steady-state urinary excretion of sodium increased from 11 ± 2 to 216 ± 20 mEq Na/day. Sodium intake was increased from 10 to 240 mEq/day while arterial pressure increased only 4 mm Hg. During intrarenal NE infusion, the rise in sodium excretion during sodium forcing increased from 15 ± 3 to 234 ± 17 mEq/day and was associated with a 16 mm rise in arterial pressure. A similar increase in arterial pressure was observed during intravenous infusion (16 mm Hg) as sodium excretion increased from 8 ± 2 to 244 ± 25 mEq/day. Thus, similar changes in renal function occurred during sodium forcing with both intrarenal and intravenous infusions of NE, but much higher levels of arterial pressure were sustained during intrarenal NE infusion.

Similar relationships were obtained between the steady-state mean 24-hour arterial pressure and daily urine volume, as seen in figure 7.

Postmortem Renal Morphology

The infused kidneys were characteristically hypertrophied, weighing an average of 65.5 ± 4 g compared to the previously removed contralateral kidneys, which weighed an average of 38 ± 3 g. Gross inspection of the kidneys subjected to infusion for over 34 days showed small scattered areas of scarring which were estimated to represent, at most, a 5% reduction in renal mass.

Light microscopic examination revealed focal cortical infiltrates of chronic inflammatory cells oc-
SODIUM INTAKE AND RENAL NOREPINEPHRINE SENSITIVITY/Cowley and Lohmeier

Figure 6. Relationship between steady-state mean 24-hour arterial pressure level and the measured 24-hour sodium excretion for the same period. The steep curve on the left (control) was obtained in the absence of norepinephrine infusion. The center curve (IV-NE) was obtained during intravenous infusion of norepinephrine at 0.27 µg/kg/min. The curve furthest to the right (RA-NE) was obtained during intrarenal infusion of norepinephrine at 0.27 µg/kg/min.

Figure 7. Relationship between steady-state mean 24-hour arterial pressure level and the measured 24-hour urine secretion for the same period. The steep curve on the left (control) was obtained in the absence of norepinephrine infusion. Center curve (IV-NE) was obtained during intravenous infusion of norepinephrine at 0.27 µg/kg/min. The curve placed furthest to the right (RA-NE) was obtained during intrarenal infusion of norepinephrine at 0.27 µg/kg/min.

cupying an average of approximately 7% of the renal parenchyma and ranging from an estimated 3% to 30% among the individual animals. This chronic inflammatory infiltrate was also seen beneath the epithelium of the calices. In the larger cortical foci this inflammatory infiltrate was occasionally accompanied by foci of calcification and tubular dilatation. Occasionally, scattered neutrophils were present. This process was interpreted as focal chronic active pyelonephritis.

Light microscopic examination did not reveal diffuse glomerular changes, and there was no intimal thickening observed in arteries or the arterioles. The tubules, except in the focal areas of pyelonephritis, showed no detectable changes. The presence of medial hypertrophy could not be evaluated properly without elaborate quantitative methods, but there was no obvious change in arterial or arteriolar walls.

No recent or organizing thrombi suggestive of emboli were seen in the renal arteries or arterioles. Only a single arteriole with a necrotic wall was observed. Several glomeruli in the areas of active pyelonephritis showed segmental necrosis of glomerular tufts; although these lesions could have resulted from microembolization, they were only occasionally seen and were interpreted as part of the pyelonephritic process.

Discussion

The role of the sympathetic nervous system in control of renal function has long been of interest to both physiologists and clinicians. Evidence indicates, however, that in the conscious resting state there is only modest renal sympathetic nerve activity, and pharmacological or surgical removal of nervous activity has little effect on renal function. In contrast, physiological stimulation of renal sympathetic nerves directly, reflexly, or centrally can significantly alter renal hemodynamics, glomerular filtration rate, and tubular reabsorption. On the basis of short-term studies, many physiologists believe that modification of renal function by the sympathetic nervous system can contribute significantly to the normalization of body fluid volume, electrolyte balance, and arterial pressure in situations of volume depletion and/or hypotension.
By the same logic, many investigators believe that chronic overactivity of renal sympathetic nerves can lead to hypertension. Although the role of the sympathetic nervous system in the etiology of essential hypertension remains unclear, evidence indirectly supports the belief that the autonomic nerves can produce chronic alterations in renal function and lead to hypertension. The present study and that of Katholi et al., demonstrate that chronically elevated renal adrenergic activity can lead to hypertension. Enhanced splanchnic and renal sympathetic activity has been observed in the spontaneously hypertensive rat, and evidence suggests the same may be true in early essential hypertension. Finally, it has been reported that renal denervation significantly decreases the rate of development of hypertension in the spontaneously hypertensive rat.

Ideally, enhanced renal adrenergic activity would be mimicked by the chronic stimulation of renal efferent sympathetic nerve fibers, a procedure which at present is technically unfeasible. Although we can only speculate as to the extent to which the intrarenal infusion of norepinephrine mimics increased sympathetic activity, a number of studies suggest the responses are similar. Although the distribution of adrenergic receptors need not necessarily coincide with the distribution of sympathetic nerve terminals, both whole kidney and micropuncture studies suggest that functionally they do coincide. The results achieved in the present study, therefore, are probably not unlike the changes that could occur under conditions of chronically enhanced renal sympathetic nerve activity and should be very similar to those accompanying adenal medullary tumors such as a pheochromocytoma.

Sodium-Intake and Norepinephrine Vascular Sensitivity

Intrarenal norepinephrine infusion was associated with increased renal vascular resistance in all animals. Moreover, this change in resistance appeared to be directly related to the daily sodium intake as demonstrated in figure 3. This sodium related increase in resistance was most apparent during the intrarenal infusion of NE but was also observed to a lesser extent during intravenous infusion. The progressive increase in resistance with increased sodium intake does not appear to be attributable to non-specific factors such as embolization of the kidney nor to a time-dependent renal deterioration, since vascular resistance returned to control values following NE infusion when sodium intake was returned to its initial state.

Estimation of the changes in segmental renal resistance was calculated at each level of sodium intake based on the analysis described by Gomez, and Huss et al. These calculations suggested that changes in NE sensitivity of both afferent and efferent resistance vessels were affected by sodium intake, but the major effect appeared to be on the afferent vessels.

The mechanism for this increased vascular sensitivity to norepinephrine is unclear, but Dietz et al. recently observed a similar increase in hindlimb vascular reactivity to norepinephrine in spontaneously hypertensive rats on a high-salt diet. Conversely, sensitivity to norepinephrine was reduced on a sodium-restricted diet.

Glomerular Filtration Rate

The rate of glomerular filtration decreased 25% to 45% during both intrarenal and intravenous NE infusions and tended to remain below control values following infusion, despite a return of effective renal plasma flow to normal. An even larger decrease in filtration rate during intrarenal NE infusion was probably prevented by the rise in arterial blood pressure. Further, the changes in GFR were fairly independent of sodium intake except at the highest level of sodium intake. Since ERPF was unchanged during intravenous NE infusion while GFR was depressed, the data suggest that chronically elevated levels of NE may alter GFR by causing changes other than alterations in renal vascular resistance. In contrast, Katholi et al. observed little change in glomerular filtration with similar rates of NE infusion.

Failure of GFR to return to control levels following intrarenal NE infusion has been observed recently by Cronin et al. In this model of acute renal failure, NE infused intrarenally for 40 minutes at three times the dose used in the present study produced a sustained decrease in insulin clearance to 50% of control value when GFR was measured 8 weeks after the NE infusion.

Histological examination of the kidneys showed that decreased GFR was probably not a result of persistent flushing of microemboli to the kidney parenchyma or other factors related to the infusion procedures. The observed changes in renal function cannot be readily explained on the basis of the light microscopic changes, which were focal and involved only approximately 7% of the parenchyma. We cannot eliminate the possibility that ultrastructural changes are present, or that evaluation by elaborate quantitative morphometric techniques might reveal changes not appreciated on routine histological examination.

Prolonged intrarenal infusion of angiotensin using similar procedures did not result in any permanent changes in GFR, again suggesting that norepinephrine per se was responsible for these changes rather than a nonspecific factor such as microembolization.

Finally, it should be pointed out that the observed alterations in renal morphology alone were not sufficient to produce hypertension, since arterial pressure returned to normal following the end of the infusion. The shift of the renal function curve to the right appears to be directly related to the presence of high renal norepinephrine concentrations and not to
any permanent renal damage from experimental procedures.

Relationship Between Norepinephrine Infusion, Sodium Intake, and Renin Secretion

Some of the changes observed during chronic intrarenal infusion of NE may in part be attributed to enhanced plasma renin activity. Figure 4 emphasizes the stimulatory effects of intrarenally infused NE on plasma renin activity, which were observed despite large increases in sodium intake. In contrast, during intravenous NE infusion, plasma renin activity decreased to nearly undetectable levels as sodium intake was increased, and this renin response was similar to that observed in the absence of NE infusion (control infusions). It should be noted that the elevated levels of plasma renin activity produced by intrarenal NE infusion remained inappropriately elevated but progressively decreased as sodium intake was increased from 10 to 240 mEq/day. This decrease paralleled that observed in the absence of NE infusion and during intravenous NE infusion. This seems to suggest that the adrenergic mechanisms for the control of renin release are independent from those mechanisms influenced by sodium intake.

Chronic Steady-State Renal Function Curve

The data from the present experiment can be used to derive a general understanding of the effects of NE on the ability of the kidneys to excrete sodium and water. These effects are seen by examining the relationship between mean arterial pressure and urinary sodium excretion seen in figure 6 and urinary volume excretion in figure 7. It should be recalled that these data were obtained only after a steady state had been reached between sodium and water intake and renal excretion. It is clear that the curves labeled "RA-NE" are displaced to the right of the normal "control" curves. The two curves are relatively parallel at the lower levels of sodium excretion. Similar relationships were obtained with intravenous NE infusion, but with only a minimal displacement of the curve.

Although the theoretical and experimental justification of these "renal function curves" has been presented elsewhere, it is important to clarify the meaning of these relationships. These graphs are not intended to represent a cause-and-effect relationship between arterial pressure and urinary excretion, but rather demonstrate that for each level of sodium and water excretion a higher level of arterial pressure was obtained for the same sodium output than was observed in the absence of norepinephrine. Although a direct relationship between arterial pressure and urine excretion can be demonstrated in acute experiments using isolated perfused kidney preparations, in the chronic state a number of other physical, humoral, and neural factors may intervene to modify these relationships. With these qualifications in mind, the displacement of the curve to the right in the presence of NE may be explained by assuming that the constriction of renal afferent arterioles with a decrease in glomerular filtration rate would necessitate a higher aortic pressure to maintain adequate filtration and excretion. Indeed, transient measurements obtained in three dogs during the first hour of NE infusion before the onset of any significant elevation of arterial pressure showed that GFR and sodium excretion were decreased to greater than twice that later observed in the chronic hypertensive state. Even in the chronic state, however, glomerular filtration remained below normal. It is unclear how normal sodium excretion was achieved at that time. Similar conditions have been observed in established essential hypertension.

The relatively parallel shift of the renal function curve to the right is not unlike that which has been observed in the rat during chronic renal artery stenosis and in the Okamoto strain of spontaneously hypertensive rats. It is, however, in marked contrast to the changes observed by DeClue et al. In their studies, chronic infusion of angiotensin II (5.0 ng/kg/min) resulted in an increasingly higher arterial level with progressive increases in sodium intake. The slope of the renal function curve decreased to less than one-tenth the "normal" curve in contrast to about a two-third reduction observed with norepinephrine. Based on these studies the mild decrease in slope in the present study may, therefore, have resulted from increased circulating levels of angiotensin.

The steepness of each of the respective renal function curves indicates the extent to which these types of hypertensive models will be affected by sodium intake. The present results therefore indicate that hypertension initiated by enhanced renal adrenergic activity is only moderately sensitive to changes in sodium intake.

Conclusions

The basis of the hypertension appears to be renal in origin since the same amount of NE infused intravenously had little effect on arterial pressure. The results suggest that chronic adrenergic stimulation of the kidney alters renal function so that salt and water balance are achieved only at a higher level of arterial pressure. The arterial pressure in this form of hypertension is only moderately sensitive to changes in sodium intake compared to angiotensin-induced hypertension. The results further indicate that sodium intake in some way increases the renal vascular sensitivity to circulating levels of catecholamines. Chronic renal adrenergic stimulation also appears to cause a sustained increase in renin release and this stimulus is not overridden by large sodium loads. Finally, the data are compatible with the concept that enhanced renal sympathetic activity could initiate and sustain chronic hypertension.
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References

1. DeQuattro V, Chan S: Raised plasma catecholamines in some patients with primary hypertension. Lancet 1: 806, 1972
34. Selkurt EE: Effects of pulse pressure and mean arterial pressure modification on renal hemodynamics and electrolyte and water excretion. Circulation 4: 541, 1951
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