Sympathetic Nervous System in High Sodium One-Kidney, Figure-8 Renal Hypertension

Carmen Hinojosa-Laborde, Paula Guerra, and Joseph R. Haywood

The contribution of the sympathetic nervous system and vasopressin to the maintenance of arterial pressure was investigated in high sodium-fed rats 4 weeks after the induction of one-kidney, figure-8 renal wrap hypertension. Arterial pressure was significantly greater in renal-wrap hypertensive rats than in sham-operated animals. The contribution of the sympathetic nervous system was assessed functionally by measuring the arterial pressure response to ganglionic blockade and estimating the apparent rate of release of norepinephrine. The contribution of vasopressin was assessed by administration of the vascular antagonist d(CH2)5Tyr(Me)-AVP. Whole-animal vascular responsiveness and cardiac baroreceptor reflex sensitivity were determined by graded intravenous bolus injections of angiotensin II, vasopressin, and phenylephrine. Hypertensive rats demonstrated an exaggerated reduction in arterial pressure to autonomic blockade before and after blockade of vascular vasopressin receptors. There was a significant 27% increase in the apparent rate of release of norepinephrine into the plasma. Administration of d(CH2)5Tyr(Me)-AVP did not affect arterial pressure when given alone. However, after ganglionic blockade, inhibition of the vasopressin system elicited similar falls in blood pressure in both normotensive and hypertensive rats. Arterial pressure dose-response effects of phenylephrine, angiotensin II, and vasopressin were similar between renal-wrap and sham-operated animals; however, cardiac baroreceptor reflex sensitivity was suppressed in the hypertensive rats. These studies indicate that the maintenance of arterial pressure in chronic, high sodium renal-wrap hypertension is associated with an increased responsiveness to sympathetic nerve stimulation have been observed in hypertensive rats. This model of hypertension also is prevented by chemical sympathectomy. Consequently, the sympathetic nervous system has been linked closely with sodium-dependent hypertension. In spite of these findings, some investigators have not been able to demonstrate that sympathectomy prevents the development of DOC-saline hypertension.

The vasopressin system has also been implicated in sodium-related increases in arterial pressure. Elevated plasma vasopressin levels have been demonstrated in DOC-saline forms of hypertension. In some studies, hypertensive rats have been shown to experience a decrease in arterial pressure in response to a vascular vasopressin antagonist. In addition, vasopressin-deficient Brattleboro rats are also protected against the development of DOC-saline hypertension.

Recent findings in our laboratory have indicated that one-kidney, figure-8 renal wrap hypertension is also a model of sodium-dependent hypertension. This form of hypertension is prevented when rats are maintained on a low sodium intake, while the hypertension is exacerbated when the rats are fed a high sodium diet. An exaggerated fall in blood pressure following ganglionic blockade has also suggested that hypertension in normal sodium-fed hypertensive animals is supported by a functional activation of the sympathetic nervous system. The present study was designed to investigate the relationship between sodium and elevated arterial pressure.

Several experimental models of sodium-dependent hypertension have been used to investigate the relation between sodium and elevated arterial pressure. The work has revealed significant contributions of the sympathetic nervous system and vasopressin to the maintenance of chronic hypertension. Several indexes of augmented sympathetic nervous system function have been documented in sodium-dependent hypertension. In deoxycorticosterone (DOC)-saline hypertension in rats, an exaggerated depressor response to ganglionic blockade, elevations in plasma catecholamines, increases in norepinephrine turnover, and an augmented apparent rate of release of norepinephrine have been observed. In addition, peripheral chemical sympathectomy with 6-hydroxydopamine is effective in preventing this model of hypertension. In Dahl salt-sensitive rats, an augmented ganglionic blockade response, an elevation in splanchnic nerve activity, and increased responsiveness to sympathetic nerve stimulation have been observed in hypertensive rats. This model of hypertension also is prevented by chemical sympathectomy. Consequently, the sympathetic nervous system has been linked closely with sodium-dependent hypertension. In spite of these findings, some investigators have not been able to demonstrate that sympathectomy prevents the development of DOC-saline hypertension.

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contributions of the sympathetic nervous system and vasopressin to the maintenance of arterial pressure in chronically hypertensive high sodium–fed rats.

**Methods**

**General Methods**

Male Sprague-Dawley rats weighing 200–250 g were fed a sodium-supplemented rat chow that contained 1.2 meq sodium/g. Food and tap water were given ad libitum throughout the course of the experiment. Two weeks after initiation of the diet, the rats were anesthetized with methoxyflurane and subjected to renal wrap (n=15) or sham wrap (n=17) surgery. Hypertension was produced by the removal of one kidney and the placement of two ligatures around the poles of the remaining kidney as described by Grollman. The sham renal wrap consisted of unilateral nephrectomy only. All animals were studied 4 weeks after surgery.

The rats were anesthetized with methoxyflurane, and indwelling catheters were implanted for the monitoring of arterial pressure, the administration of drugs, and the withdrawal of blood samples. Arterial catheters made of Tygon tubing (0.5 mm i.d.) with a 28-gauge Teflon tip (0.4 mm i.d.) were inserted into the femoral artery. A polyethylene catheter (0.6 mm i.d., PE-50) was inserted into the femoral vein. The catheters were tunneled subcutaneously and exteriorized at the back of the neck. The animals were permitted to recover for 24–48 hours before experimental protocols were performed. On the day of the experiment, the rats were brought to the laboratory and placed in plastic containers for acclimatization at least 1 hour before any interventions. The arterial catheters were attached to a strain gauge transducer through an extension of PE-50 tubing. Heart rate was monitored with a cardiotachometer triggered by the arterial pressure pulse. The venous catheter was also extended by a length of PE-50 tubing.

**Assessment of Sympathetic Nervous System and Vasopressin System by Pharmacological Blockade**

In one set of renal-wrapped (n=9) and sham-operated (n=10) rats, the functional contribution of the sympathetic nervous system and vasopressin pressor system was assessed with pharmacological antagonists. Baseline arterial pressure and heart rate were measured over 1 hour. Responses to sequential blockade of the two pressor systems were monitored in all animals on separate days by random selection. Sympathetic nervous system function was estimated by the administration of 0.2 mg/kg atropine sulfate, causing blockade of \\[\text{H}]\text{Norepinephrine and Determination of Apparent Rate of Release of Norepinephrine}\\

In a separate set of renal-wrapped (n=6) and sham-operated (n=7) rats, the clearance of [\text{H}]\text{Norepinephrine ([\text{H}]NE)} was determined in the manner described by Keeton and Biediger for an independent assessment of the activity of the sympathetic nervous system. [\text{H}]\text{Norepinephrine (specific activity, 38–44 Ci/mM, New England Nuclear, Boston) was infused at a rate of 0.13 [\text{Ci min}]^{-1} [\text{kg}]^{-1} (286,000 dpm min}]^{-1} [\text{kg}]^{-1}). On the day of the experiment, [\text{H}]\text{NE stock solution was added to saline containing 0.2N acetic acid, 0.5 mg/ml sodium sulfite, and 0.2 mg/ml reduced glutathione to prevent oxidation of the catecholamines. The solution was kept on ice until the time of infusion. Aliquots of the solution were taken for determination of the amount of [\text{H}]\text{NE infused into each rat. [\text{H}]NE was measured using liquid scintillation. The [\text{H}]\text{NE was infused at the rate of approximately 14 [\mu l/min (Harvard Apparatus, South Natick, Mass.) for 90 minutes to achieve a steady-state concentration of [\text{H}]\text{NE in the plasma. At the end of 90 minutes, during the [\text{H}]\text{NE infusion, 2–2.5 ml blood was withdrawn from the arterial catheter into a syringe containing 10 [\mu l sodium sulfite (100 mg/ml) and 75 [\mu l EGTA (60 mg/ml, pH=7) and reduced glutathione (90 [\mu g/ml). As the sample was collected, the blood was mixed with the solution in the syringe. The collected blood was kept on ice and promptly centrifuged for 10 minutes at 1,000g at 4°C. A 0.5-ml aliquot of plasma was taken for sequential column chromatography to separate the following fractions: [\text{H}]\text{NE, [\text{H}]\text{3,4-dihydroxyphenylglycol (DOPEG); [\text{H}]\text{3,4-dihydroxymandelic acid (DOMA); and the combined catechol-O-methyl transferase (COMT) metabolites [\text{H}]\text{3-methoxy-4-hydroxymandelic acid, [\text{H}]\text{normetanephrine (NMN), and [\text{H}]\text{3-methoxy-4-hydroxyphenylglycol (MOPEG). The recovery of [\text{H}]\text{NE was determined for the extraction procedure by subjecting a known amount of [\text{H}]\text{NE to the procedure along with each group of samples. The mean±SEM [\text{H}]\text{NE recovery was 80.8±0.9%. The amount of [\text{H}]\text{NE in the experimental plasma sample was corrected for recovery. The remaining plasma sample was stored at −70°C for later radioenzymatic assay of norepinephrine and epinephrine as described by Peuler and Johnson. The clearance of [\text{H}]\text{NE was determined as rate of infusion of [\text{H}]\text{NE divided by steady-state plasma [\text{H}]\text{NE concentration. Subsequently, the apparent rate of release of norepinephrine was calculated.**

**Vasoclonstrictor and Baroreceptor Reflex Responses to Exogenous Pressor Stimuli**

To determine whether whole-body vascular responsiveness was altered in hypertensive rats, some of the animals that were subjected to pharmacological blockade were first challenged with vasoconstrictor drugs. Graded intravenous bolus doses of angiotensin II (30, 100, and 300 ng/kg), arginine vasopressin (5, 15, and 50 [\mu units/kg), and the α-adrenergic agonist phenylephrine (1, 3, and 10 [\mu g/kg) were administered to renal-wrapped (n=5) and sham-operated (n=8) rats. Heart rate was monitored to assess cardiac baroreceptor reflex function in both groups. For each animal and each drug, linear regression analysis was performed on resting mean arterial pressure and drug-induced increases in mean arterial pressure versus the resting heart period and the subsequent drug-induced change in heart period. The slope of the relation was taken as the cardiac baroreceptor reflex sensitivity for that animal.
using the clearance measurement and resting plasma norepinephrine concentration as $[^3H]NE$ clearance $\times$ plasma norepinephrine concentration.

**Statistics**

The data are expressed as mean±SEM. Student’s $t$ test for unpaired samples was used to compare single independent measurements between sham-operated and renal-wrapped rats. The responses to blocking drugs and dose–response data for pressor agents were evaluated by two-way analysis of variance with repeated measures and factorial analysis. A significant difference within a group was determined by one-way analysis of variance with repeated measures followed by Scheffe’s multiple range test to identify the significant comparisons.

**Results**

**Pharmacological Assessment of Contributions of Sympathetic Nervous System and Vasopressin to Arterial Pressure**

Twenty-eight days after surgery, resting mean arterial pressure was significantly greater in renal-wrapped rats than in sham-operated animals (160±4 versus 122±4 mm Hg, $p<0.05$). Resting heart rates were similar in both groups (405±4 versus 411±10 beats/min, respectively). The effects of ganglionic blockade followed by vasopressin receptor blockade on mean arterial pressure and heart rate are shown in Figure 1. Ganglionic blockade caused mean arterial pressure to decrease significantly in both sham-operated and renal-wrapped animals. The fall in blood pressure was greater in the hypertensive rats (57±4 versus 34±2 mm Hg, $p<0.05$; Figure 2), but arterial pressure was still significantly elevated in the wrapped animals after ganglionic blockade. Subsequent administration of $d(CH_2)_2Tyr(Me)$-AVP caused a further significant decrease in mean arterial pressure of 15±2 mm Hg in the hypertensive rats and 11±1 mm Hg in the normotensive animals. Combined blockade significantly reduced heart rate in both groups (Figure 1).

The effects of vascular vasopressin receptor blockade followed by ganglionic blockade on mean arterial pressure and heart rate are shown in Figure 3. The administration of $d(CH_2)_2Tyr(Me)$-AVP had little effect on mean arterial pressure or heart rate in either renal-wrapped or sham-operated rats. Subsequent ganglionic blockade resulted in significant ($p<0.05$) decreases in mean arterial pressure and heart rate in both groups. Mean arterial pressure fell 80±7 mm Hg in the wrapped animals and 49±3 mm Hg ($p<0.05$) in the sham-operated rats. Combined blockade of the sympathetic nervous system and the vasopressin pressor system reduced mean arterial pressure to similar levels regardless of the order of administration of the blocking agents.

**Pressor and Baroreceptor Reflex Responses to Vasoconstrictors**

The changes in mean arterial pressure in response to angiotensin II, vasopressin, and phenylephrine were similar in both normotensive and hypertensive rats (Table 1). However, reductions in heart rate were generally greater in the sham-operated rats. The baroreceptor reflex sensitivity data showed reduced sensitivity of the cardiac baroreceptor reflex in renal-wrapped animals compared with sham-operated rats for all pressor stimuli ($p<0.05$).
Clearance of $[3H]$Norepinephrine and Apparent Rate of Norepinephrine Release

Resting mean arterial pressure of the animals in which $[3H]$NE clearance was determined was 179±7 mm Hg for the hypertensive (n=6) and 134±3 mm Hg for the sham-operated (n=7) rats (p<0.05); heart rates in the respective groups were 424±19 and 407±7 beats/min. As previously demonstrated, the infusion of $[3H]$NE has no effect on the resting plasma total norepinephrine concentration using the infusion protocol outlined in this study. Total radioactivity of $[3H]$NE in the plasma of the hypertensive animals, however, was significantly greater than that in the normotensive rats (8,764±912 versus 5,733±445 dpm). The relative distributions of the radioactive tracer (Table 2) in the normotensive and hypertensive rats revealed that there was less radioactivity in the norepinephrine fraction and more in the COMT metabolite fraction in the renal-wrapped rats compared with the sham-operated animals.

The total plasma concentration of norepinephrine was slightly, but not significantly, higher in the hypertensive rats (p=0.09, Figure 4). The plasma epinephrine concentration was not different between the renal-wrapped and sham-operated rats (226±36 versus 202±43 pg/ml). The clearance of $[3H]$NE was also similar in normotensive and hypertensive rats. However, the calculated apparent rate of release of norepinephrine was significantly elevated, by 27%, in the hypertensive rats (68.3±5.4 versus 53.7±4.2 ng min$^{-1}$•kg$^{-1}$).

Discussion

The principal finding of the present study is that the elevated arterial pressure in chronic one-kidney, one figure-8 renal-wrapped rats maintained on a high sodium intake is the result of an augmented contribution by the sympathetic nervous system. The neural component that contributed to the hypertension was assessed by two independent methods: by measuring the mean arterial pressure response to ganglionic blockade and by measuring the clearance of $[3H]$NE and calculating the apparent rate of release of norepinephrine. An enhanced fall in mean arterial pressure after ganglionic

### Table 1. Changes in Mean Arterial Pressure and Cardiac Baroreceptor Reflex Response to Intravenous Angiotensin II, Arginine Vasopressin, and Phenylephrine in Chronic, High Sodium One-Kidney, Figure-8 Renal Hypertensive, and Normotensive Sham-Operated Rats

<table>
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<th>Vasoconstrictor</th>
<th>Dose</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Baroreceptor reflex sensitivity (msec/mm Hg)</th>
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<tr>
<td>Wrap</td>
<td>ΔMAP</td>
<td>-15±3</td>
<td>18±2</td>
<td>32±4</td>
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<tr>
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<tr>
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<td>41±4</td>
<td>55±4</td>
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MAP, mean arterial pressure; HR, heart rate. Values are mean±SEM.

$^*$Low, medium, and high doses of angiotensin II were 30, 100, and 300 ng/kg, respectively.

$^†$Low, medium, and high doses of vasopressin were 5, 15, and 50 microunits/kg, respectively.

$^€$Low, medium, and high doses phenylephrine were 1, 3, and 10 μg/kg, respectively.
blockade in hypertensive rats suggested a greater functional contribution of the sympathetic nervous system in these animals than in normotensive rats. In addition, an increase in the apparent rate of release of norepinephrine into the circulation of hypertensive animals provided evidence for an enhanced release of norepinephrine into the neuroeffector junction, resulting in a greater spillover into the blood in these animals compared with normotensive rats.

Each observation supports other data showing that sodium-dependent hypertension is maintained by the sympathetic nervous system. Studies using ganglionic blockade to assess the functional contribution of the sympathetic nervous system to blood pressure have shown that DOC-saline-treated rats and Dahl salt-sensitive rats fed a high sodium diet respond to ganglionic blockade with greater depressor responses than their respective controls. In addition, hypertension in DOC-saline-treated rats and Dahl salt-sensitive rats fed a high sodium diet can be prevented by the depletion of peripheral catecholamines with 6-hydroxydopamine or guanethidine pretreatment. Reductions in the norepinephrine content in the heart and kidney, as a result of an increase in the rate of turnover of norepinephrine, have been reported in DOC-saline hypertensive rats and in figure-8 renal-wrapped rats. An increase in the rate of norepinephrine turnover has also been reported in the renal cortex and atri of Dahl salt-sensitive rats fed a high sodium diet. Finally, Bouvier and de Champlain have shown an elevated apparent rate of release of norepinephrine into the plasma in established DOC-saline hypertensive rats. Thus, the present findings are consistent with the view that sympathetic nervous system function is enhanced in sodium-dependent hypertension.

The plasma norepinephrine concentration tended to be elevated. This was not owing to a reduction in the clearance of norepinephrine from the circulation. Rather, it appeared to be due to an increase in the apparent rate of release of norepinephrine into the plasma in the renal-wrapped rats. An increase in the apparent rate of release of norepinephrine may represent a possible elevation in sympathetic nerve activity. Alternatively, an elevated apparent rate of norepinephrine release may be the result of an enhanced presynaptic modulation of norepinephrine release, such as has been demonstrated for angiotensin II or a reduced α2-adrenergic receptor-mediated inhibition of neurotransmitter release. The kinetic disposition of [3H]NE in the hypertensive rats suggests an enhanced cycling of norepinephrine and supports an increased release of norepinephrine in these animals. The reduction in the [3H]NE level and an increase in the levels of tritium-labeled COMT metabolites of norepinephrine may represent an increase in norepinephrine uptake, particularly by extraneuronal sites where the enzyme COMT is primarily located. It should be noted that the apparent rate of release actually represents spillover of norepinephrine into the plasma. It does not reflect only the release of neurotransmitter in the neuroeffector junction because circulating norepinephrine may originate from the adrenal medulla.

The augmented spillover of norepinephrine into the plasma as a result of activation of the sympathetic nervous system supports the observation that the functional contribution of the sympathetic nervous system, as assessed by ganglionic blockade, was also enhanced in hypertensive rats. Greater depressor responses to hexamethonium and atropine were observed before and after administration of the vascular vasopressin antagonist d(CH2)5Tyr(Me)-AVP. However, in both normotensive and hypertensive rats the fall in mean arterial pressure was greater after d(CH2)5Tyr(Me)-AVP, suggesting that vasopressin compensated for the decrease in arterial pressure and blunted the depressor effect of ganglionic blockade. Although this phenomenon has been previously demonstrated by several investigators, these findings indicate that vasopressin release did not obscure the differences between normotensive and hypertensive rats.

A number of studies have demonstrated a role for vasopressin in the maintenance of sodium-dependent hypertension. DOC-saline hypertensive rats have been shown to have elevated plasma vasopressin levels and augmented depressor responses to the administration of vasopressin receptor antagonists. Similar observations have been made in reduced renal mass hypertension. In the present study, d(CH2)5Tyr(Me)-AVP alone had no effect on blood pressure or heart rate in either hypertensive or normotensive rats. When d(CH2)5Tyr(Me)-AVP was given after ganglionic blockade, significant decreases in arterial pressure were observed in both groups. However, the responses to d(CH2)5Tyr(Me)-AVP either alone or after ganglionic blockade were the same in normotensive and hypertensive rats, suggesting that vasopressin was not contributing significantly to the elevated arterial pressure in the hypertensive rats. These observations are in contrast to our previous findings in the early stage (3 days after wrap) of this model of hypertension, in which vasopressin was shown to contribute significantly to the maintenance of blood pressure. In those studies, the contribution of the sympathetic nervous system to blood pressure maintenance was the same in the two groups of rats. However, circulating levels of vasopressin were elevated in hypertensive rats compared with normotensive rats. Thus, it appears that the stage of the hypertension has a significant bearing on the mechanism responsible for
pressed baroreceptor reflex function in hypertensive
ports previous findings by several investigators of sup-
pressive agents demonstrated that cardiac reflex function was
sensitive to vasopressin but not angiotensin II. 28 Analysis of
sodium-fed hypertensive rats, which were more sensi-
tive pressor agent. This is in contrast to 3-day high
sodium intake in Dahl strain of genet-
ic hypertensive rat. 29

In summary, the results of this study reveal that the
sympathetic nervous system contributes to the elevated
arterial pressure in chronic high sodium-fed, renal-
wrapped rats while the contribution of vasopressin to
the maintenance of arterial pressure is the same in
normotensive and hypertensive rats. In the context of
our previous work, these current findings also suggest
that during the course of the hypertension there is a
transition in the maintenance of arterial pressure from
the vasopressin system to the sympathetic nervous
system.

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Keeton and Robert Gomez is appreciated for measurement
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FIGURE 4. Bar graph of plasma norepinephrine (NE) concen-
tration, NE clearance rate, and apparent rate of release of
NE for renal-wrapped and sham-operated rats. *p<0.05
different from wrap.

animals, which may contribute to the augmented sympa-
thetic nervous system function. 42–44 Finally, the reflex
responses to vasopressin were greater than those ob-
served with other pressor agents for a given change in
arterial pressure. This finding agrees with other re-
ports 45, 46 showing that vasopressin elicits a more pro-
found bradycardia than either angiotensin II or phen-
ylephrine; however, reflex sensitivity was similar in
normotensive and hypertensive animals.

The whole-body vascular responsiveness was similar
in normotensive and hypertensive rats for each exoge-
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or agents demonstrated that cardiac reflex function was
reduced in the hypertensive rats. This observation sup-
ports previous findings by several investigators of sup-
pressed baroreceptor reflex function in hypertensive


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