Effect of Renal Denervation on Arterial Pressure in Rats with Aortic Nerve Transection

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SUMMARY The role of renal nerves in influencing the control of arterial pressure was studied in Wistar rats with aortic depressor nerve (ADN) transection. Renal denervation prevented or reversed the normal increase in arterial pressure seen after ADN transection. This effect was not due to an effect on the renin-angiotensin system, as the elevated arterial pressure after ADN section in rats with renal nerves intact was shown to be due to increased α-adrenergic activity. Food and water intake and urine output decreased significantly in both renal-denervated and sham-denervated rats after ADN section, suggesting that a pressure diuresis mechanism was not responsible for preventing the rise in pressure in renal-denervated rats. In another study, the concentration of norepinephrine in skeletal muscle and hypothalamus at 0 and 8 hours after inhibition of tyrosine hydroxylase with α-methyltyrosine was used as an index of norepinephrine turnover. Norepinephrine turnover in skeletal muscle was increased significantly over control values by ADN transection in sham renal-denervated rats, but was not significantly different from controls in renal-denervated rats with ADN section. In the hypothalamus, there was a significant difference between the turnover of norepinephrine in the two groups of ADN-sectioned rats. The results taken together suggest that renal denervation prevents the arterial pressure response to ADN transection by altering the central mechanisms governing sympathetic outflow. It is suggested that this effect may be due to elimination of information carried by afferent renal fibers. (Hypertension 5:468-475, 1983)

KEY WORDS • afferent renal fibers • efferent renal fibers • norepinephrine turnover • neurogenic hypertension • converting enzyme inhibitor

RENAL nerves and their possible role in the control of arterial pressure are topics of much interest in recent years. Several studies have shown that an enhanced noradrenergic influence on the kidney, produced by chronic intrarenal infusion of norepinephrine, may lead to chronically elevated arterial pressure. In addition, renal denervation has been shown to delay the development of genetic hypertension and DOCA-salt hypertension, and reverse the elevated arterial pressure associated with one- and two-kidney, one clip Goldblatt hypertension and one-kidney Grollman hypertension in rats.

Although most of the work in this area has been directed toward understanding the physiology of efferent renal nerves, there is a growing interest in the possible influence of afferent renal nerves on the mechanisms controlling water balance and arterial pressure. Recordati et al. have demonstrated the presence of several types of renal chemoreceptors, and several investigators have reported cardiovascular effects produced by electrical stimulation of afferent renal fibers. In addition, afferent renal fibers have been shown to project to medullary and hypothalamic nuclei known to be involved with fluid and circulatory homeostasis.

Recently, the rat with bilateral transection of the aortic depressor nerve (ADN) has been used as a 'neurogenic' model of hypertension. There are several lines of evidence suggesting that sympathetic activity is increased in these animals at least for the first few days after ADN transection. This preparation would seem to be ideal to test the effect of renal denervation on the control of arterial pressure, as there is evidence for an increased turnover of norepinephrine...
in the kidney as well as functionally increased renal sympathetic tone in these rats. In addition, as we have described changes in turnover of norepinephrine in the brain and other peripheral organs 3 days after sectioning the ADN, this preparation also provides the opportunity to test further the suggestion that afferent renal fibers play a role in determining the activity of central and peripheral noradrenergic systems under certain conditions.

Methods

Studies were done using male Wistar rats (Canadian Breeding Laboratories, St. Constant or Woodlyn Farms, Guelph, Ontario) weighing 250 to 300 g. The animals were randomly assigned to various experimental control groups described in the Results section, placed in individual cages in a room with a controlled 12-hour light cycle, and acclimated for 1 week before surgical or experimental maneuvers. Standard laboratory rat chow and water were available ad libitum. In one experiment, animals were housed in standard metabolism cages for measurements of water intake and urine output. Water bottles were fitted with Richter tubes to minimize spillage, and urine was collected in narrow-neck bottles using standard funnels attached to metabolism cages. Food intake was measured by using pulverized rat chow placed in cups with spill-resistant lids and screens. All measurements were taken for 24-hour periods. Urinary sodium excretion was calculated from urine volumes and urinary sodium concentration (determined by Radiometer Flame Photometer). Food, water, and urine measurements were not done on days on which arterial pressure was measured using the tail cuff technique, but reported values are those obtained for the 24 hours preceding the day shown.

Denervation Techniques

Surgical procedures for ADN transection were done using methoxyflurane anesthesia. A ventral midline incision was made in the neck, the ADN, and cervical sympathetic nerves were dissected free from the vagus nerves for approximately 1 cm, and cut bilaterally. The carotid arteries were also stripped of all connective tissue. Sham ADN surgery consisted of opening the neck and exposing the nerves and carotid arteries. For renal denervation, animals were anesthetized with sodium pentobarbital (60 mg/kg, i.p.). The abdomen was opened via a ventral midline incision and the abdominal vescera retracted to expose the kidneys. The renal arteries and veins were isolated and stripped free of neural and connective tissue, after which 95% alcohol was applied to the vessels. We have previously reported that this technique reduces renal norepinephrine concentration by over 90% by 3 days after surgery. A fluorescence assay for norepinephrine was used to verify that renal denervation was successful (see below). Sham-renal denervation surgery consisted of exposing the kidneys and vessels, but the vessels were not isolated and alcohol was not applied.

Measurement of Arterial Pressure

Arterial pressure was measured in conscious, pretrained, restrained rats (Narco Biosystems) using the indirect tail cuff technique for most experiments. Arterial pulsations and cuff pressure were recorded using a Grass piezolectric microphone connected to a balloon plethysmograph and a TPS preamplifier, on a Grass model 7 polygraph. Heart rate was determined using a tachograph triggered by the arterial pulsations. In one experiment, arterial pressure was measured directly via a chronically implanted femoral arterial cannula. The cannula, constructed of Tygon tubing (0.05 mm i.d. × 0.15 mm o.d.) with a 4.5 cm Teflon tip (0.05 mm i.d. drawn to fit into the Tygon tubing), was implanted in the abdominal aorta via the femoral artery of rats anesthetized with methoxyflurane. Cannulas were filled with a viscous solution of polyvinylpyrrolidone in heparin (8 g PVP-40, Sigma Chemical Company, St Louis, Missouri, added to 10 ml Heparin, 1000 U/ml) and flushed daily. A single dose of antibiotic (Pen-Di-Strep, Rogar/STB, 0.2 ml, i.m.) was given after implantation of the cannula. After 1 to 3 days of recovery, mean arterial pressure was recorded on a Grass model 7 polygraph in conscious, freely moving rats in their home cage by attaching the cannula to a Statham pressure transducer by a length of Tygon tubing. Control values were taken as an average of arterial pressure over a 15-minute period, after rats had been connected to the recording system for 30 to 45 minutes.

To assess the contribution of the renin-angiotensin system to the maintenance of arterial pressure in these rats with chronic cannulas, captopril (50 mg/kg, s.c.) was given, and the arterial pressure was measured after stabilization (usually within 15 minutes). This dose of captopril is known to block both the peripheral and central renin-angiotensin systems. Following this, phentolamine (10 mg/kg, i.p.) was given to assess the degree of α-adrenergic vasoconstrictor tone. This dose was shown to block the pressor effects of phenylephrine HCl (2 μg/kg, i.v.) completely. When arterial pressure stabilized, measurements were taken again. This first recording session was taken as Day — 1. ADN section was done the following day (Day 0), and the sequence of arterial pressure measurements was repeated on Day 3 after ADN section.

Measurement of Tissue Norepinephrine Concentration After Inhibition of Tyrosine Hydroxylase as an Index of Norepinephrine Turnover

The decline in tissue norepinephrine concentration after inhibition of tyrosine hydroxylase with α-methyl-p-tyrosine methyl ester HCl (300 mg/kg, i.p. every 4 hours; Aldrich Chemicals, Milwaukee, Wisconsin) was determined by measuring tissue levels of norepinephrine in groups of rats at 0 time and 8 hours after inhibition of tyrosine hydroxylase. We have previously used this method in control and ADN-sectioned rats and have shown this technique to yield linear decay curves between 0 and 8 hours when data are expressed...
as semi-log plots of percent norepinephrine remaining vs time. Rats were killed by cervical dislocation, and the brain, left kidney, and a piece of skeletal muscle from the hindlimb were quickly removed. The brain was sectioned on ice to remove the hypothalamus, which was defined for this study as the tissue from the optic chiasm to the mamillary bodies rostrocaudally, from the corpus callosum to the ventral surface dorsoventrally, and laterally to the edge of the optic tract. Tissue samples were weighed, homogenized in cold perchloric acid, and centrifuged at 30,000 × g for 15 minutes; supernatants were frozen at −75°C. Norepinephrine was assayed using an alumina extraction and fluorescence assay as previously described. All samples were corrected for percent recovery using internal standards, and results were expressed as ng/g wet weight.

**Data Analysis**

All data are reported as means ± SE. Data obtained over time were analyzed using an appropriate ANOVA. Post hoc comparisons between selected means were done with Duncan’s multiple range test when initial ANOVA indicated statistical differences between treatments. Comparisons involving only two means within or between groups were done using a t test. Differences in the turnover of norepinephrine were inferred by plotting the values for tissue concentrations of norepinephrine 8 hours after α-methyltyrosine as a percent of the average tissue concentration of norepinephrine in respective 0 time controls. A low percentage of norepinephrine remaining 8 hours after inhibition of tyrosine hydroxylase would imply a high turnover of norepinephrine in that tissue. Comparisons between these 8-hour values were done using Duncan’s test; p < 0.05 was considered to indicate statistical significance.

**Results**

**Effect of Renal Denervation on the Arterial Pressure Response to ADN Section**

Renal denervation 3 days prior to ADN section completely prevented the rise in arterial pressure normally seen after cutting the ADN (fig. 1). Heart rate responses were transient and variable, being increased by 53 ± 11 and 31 ± 9 bpm in the sham renal-denervated and renal-denervated groups, respectively, on Day 1, but returning to control levels by Day 4. Renal denervation 5 days after ADN section, when arterial pressure was significantly elevated, returned the arterial pressure to within normal levels by the next day (fig. 2). Arterial pressure remained at that level for the remainder of the experiment. Similarly, when renal denervation was done 19 days after ADN section, arterial pressure abruptly returned to control levels (fig. 2).

**Effect of Captopril and Phentolamine on Arterial Pressure in Rats with ADN Section**

Before ADN section, captopril had no significant effect on mean arterial pressure; however, phentola-
Effect of Renal Denervation and ADN Section on Fluid Balance

Table 2 summarizes the results of these studies using four groups of rats: 1) sham ADN + sham renal, a control group for both renal and ADN surgery; 2) ADN + sham renal, an experimental group to study the effects of ADN section on fluid balance; 3) sham ADN + renal, an experimental and control group to study the effects of renal denervation on fluid balance; and 4) ADN + renal, an experimental group to study the possible interaction between ADN section and renal denervation on fluid balance. Values for measurements obtained prior to and immediately after renal denervation are not shown, as by Day − 1 all variables had essentially returned to control levels.

As in the previous experiment, renal denervation completely prevented the rise in arterial pressure normally seen after ADN section. Water intake decreased significantly in all groups after ADN surgery, and, in particular, the average decrease in water intake was identical for the two groups with ADN section. Urine output did not change significantly in the two sham-ADN groups, but did decrease significantly in the two groups with ADN section. Urinary sodium excretion was similar among the groups, but in particular those with ADN section with and without renal denervation. Changes in food intake were similar to those seen for water intake. There were no significant changes in body weight after ADN surgery, but some animals in the two ADN section groups did lose up to 15 g by Day 1 (compared to their weight on Day 0).

Table 1. Effect of Captopril and Phentolamine on Mean Arterial Pressure in Conscious Rats (n = 7) Before and After ADN Transection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Day − 1†</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>106 ± 3</td>
<td>139 ± 3*</td>
<td></td>
</tr>
<tr>
<td>Captopril (50 mg/kg, s.c.)</td>
<td>103 ± 2</td>
<td>131 ± 2*</td>
<td></td>
</tr>
<tr>
<td>Phentolamine† (10 mg/kg, i.p.)</td>
<td>55 ± 2</td>
<td>55 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

†p < 0.05 compared with Day − 1.
†ADN transection done on Day 0.
†Phentolamine was given approximately 10-15 minutes after captopril.

Table 2. Effect of Renal Denervation and ADN Section on Fluid Balance

<table>
<thead>
<tr>
<th></th>
<th>Sham ADN + sham renal</th>
<th>ADN + sham renal</th>
<th>Sham ADN + renal</th>
<th>ADN + renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail cuff pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>128 ± 1</td>
<td>128 ± 2</td>
<td>122 ± 1</td>
<td>124 ± 2</td>
</tr>
<tr>
<td>Day 1</td>
<td>126 ± 2</td>
<td>150 ± 2*</td>
<td>122 ± 2</td>
<td>124 ± 1</td>
</tr>
<tr>
<td>Day 4</td>
<td>126 ± 2</td>
<td>151 ± 2*</td>
<td>123 ± 1</td>
<td>126 ± 2</td>
</tr>
<tr>
<td>Water intake (ml/24 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>36 ± 2</td>
<td>39 ± 2</td>
<td>34 ± 1</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Day 1</td>
<td>27 ± 1*</td>
<td>24 ± 2*</td>
<td>26 ± 2*</td>
<td>20 ± 2*</td>
</tr>
<tr>
<td>Day 4</td>
<td>40 ± 2</td>
<td>38 ± 1</td>
<td>39 ± 1</td>
<td>36 ± 1</td>
</tr>
<tr>
<td>Urine output (ml/24 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>13 ± 2</td>
<td>12 ± 2</td>
<td>9 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Day 1</td>
<td>12 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>8 ± 1*</td>
</tr>
<tr>
<td>Day 4</td>
<td>11 ± 2</td>
<td>8 ± 1*</td>
<td>12 ± 1</td>
<td>8 ± 1*</td>
</tr>
<tr>
<td>Urinary sodium excretion (meq/24 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>2.19 ± 0.11</td>
<td>2.29 ± 0.22</td>
<td>1.44 ± 0.42</td>
<td>2.39 ± 0.15</td>
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<tr>
<td>Day 1</td>
<td>2.17 ± 0.13</td>
<td>1.97 ± 0.10</td>
<td>1.90 ± 0.12</td>
<td>1.86 ± 0.03*</td>
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<tr>
<td>Day 4</td>
<td>2.57 ± 0.26</td>
<td>2.25 ± 0.24</td>
<td>2.82 ± 0.16*</td>
<td>2.33 ± 0.19</td>
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<tr>
<td>Food intake (g/24 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>18 ± 2</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>Day 1</td>
<td>15 ± 1*</td>
<td>13 ± 1*</td>
<td>14 ± 1*</td>
<td>12 ± 1*</td>
</tr>
<tr>
<td>Day 4</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
<td>23 ± 1*</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day − 1</td>
<td>297 ± 5</td>
<td>303 ± 3</td>
<td>287 ± 9</td>
<td>292 ± 9</td>
</tr>
<tr>
<td>Day 1</td>
<td>297 ± 6</td>
<td>300 ± 2</td>
<td>288 ± 8</td>
<td>286 ± 7</td>
</tr>
<tr>
<td>Day 4</td>
<td>315 ± 5*</td>
<td>319 ± 3*</td>
<td>303 ± 8</td>
<td>306 ± 8</td>
</tr>
</tbody>
</table>

n = 7 for all groups; renal denervation or sham-renal denervation was done on Day − 3. ADN transection or sham-ADN transection was done at Day 0.

*p < 0.05 when compared to Day − 1 value for same group (Duncan's test).
Effect of Renal Denervation and ADN Section on Index of Norepinephrine Turnover in Hypothalamus and Skeletal Muscle

Arterial pressure on Day 2 after ADN section was increased significantly only in the rats with ADN section + sham renal denervation (fig. 3 A). In addition, rats that received renal denervation and sham ADN section had a significantly lower tail cuff pressure when compared to the surgical control group. On Day 3, the data imply that norepinephrine turnover was increased significantly in the skeletal muscle of rats with ADN section plus sham renal denervation when compared to all of the other groups (fig. 3 B). Rats with only renal denervation had a significantly larger percentage of norepinephrine remaining in skeletal muscle 8 hours after α-methyltyrosine when compared to the surgical control group. Rats with ADN section plus renal denervation had a significantly lower percentage of norepinephrine remaining in skeletal muscle when compared to the sham ADN plus renal-denervated group, but were not different when compared to the surgical control group.

This relationship is shown more clearly in figure 4. Note that the lines are essentially parallel, suggesting that renal denervation did not prevent the response to ADN section. In the hypothalamus there was a significant difference between the two ADN section groups; however, the ADN plus sham renal group was not significantly different from the surgical control group (Duncan's least significant difference = 7.7 for p < 0.05; actual difference = 6.7). Only data for the sham renal groups are given for turnover of norepinephrine in kidney, as renal denervation reduced kidney norepinephrine concentration in this and other experiments to less than 10% of normal. The data suggest that norepinephrine turnover was increased significantly in the kidneys of rats with ADN section plus sham renal denervation.

The reciprocal relation between arterial pressure recorded on Day 2 and the index of norepinephrine turnover in skeletal muscle measured on Day 3 suggested a possible correlation between these two variables. Figure 5 shows the results of such a plot and the best-fit line calculated by linear regression analysis. There was a significant correlation between the turnover of norepinephrine in skeletal muscle and arterial pressure under the conditions of this experiment.
Discussion

Results of this study clearly showed that renal denervation, done either before or after ADN section, completely prevented or reversed the arterial pressure response to cutting the ADN. The response was not due to elimination of influence of the renin-angiotensin system on arterial pressure in these rats, as administration of captopril showed that there was little if any difference between the contribution of the renin-angiotensin system to the maintenance of arterial pressure in rats before and after ADN section. On the other hand, α-adrenergic blockade with phentolamine produced a much larger decrease in arterial pressure after ADN section when compared to the response seen in the same rats prior to ADN section. These results, which are in agreement with those of Fink et al., obtained 1 month after aortic baroreceptor denervation in rats, further support the idea that the elevated arterial pressure in ADN-sectioned rats is primarily due to increased α-adrenergic activity.

Of particular interest is the fact that renal sympathetic nerve activity appears to be increased after ADN transection. According to the prediction made by Guyton et al., increased renal sympathetic nerve activity could produce increased arterial pressure as a result of neurally-mediated changes in the ability of the kidney to excrete urine. In the present study, if the effects of renal denervation were due solely to the removal of efferent sympathetic fibers, then pressure diuresis and natriuresis should have occurred.

The fluid balance experiments surprisingly suggested that there were no significant differences among any of the variables measured between renal-denervated and sham-denervated animals with ADN section, except for arterial pressure. It is possible that, because of the time periods of collection and errors inherent in this type of metabolism study, transient differences in urinary sodium and volume may have occurred, but if anything, both groups with ADN section tended to excrete less urine volume after ADN section than before. This decrease in urine output, plus the marked decreases in food and water intake, in rats with ADN section is similar to that reported by Werber and Fink. However, unlike their study, the control groups in this study also showed significant decreases in water and food intake, presumably reflecting the effects of surgery on Day 0. It is possible that cutting the cervical sympathetic nerves and ADN may have effects on water intake apart from the effects of surgery, as the changes in water intake were nearly twice as large for the two experimental groups when compared to the sham groups. The reduction in water intake does not seem to be a result of or a response to the elevated arterial pressure after ADN section, as suggested by Werber and Fink, as arterial pressure was not elevated in rats with renal denervation and ADN section. Similarly, since water intake was reduced in both groups with ADN section, decreased water intake cannot be the mechanism whereby renal denervation prevents the increase in arterial pressure in ADN-sectioned rats. The reduced water intake may, in fact, be related to sectioning of the cervical sympathetic nerves and have no relation to arterial pressure.

In recent studies, Katholi et al. have shown that the decrease in arterial pressure after renal denervation in one- and two-kidney, one clip Goldblatt hypertension was not due to a pressure natriuresis and diuresis. They found that renal denervation normalized a previously elevated plasma NE concentration and proposed that increased activity of renal afferent fibers may be responsible for the enhanced peripheral sympathetic tone in these animals.
It is clear from several studies that electrical stimulation of afferent renal fibers in anesthetized animals produces cardiovascular effects. Recent studies have shown that afferent renal fibers project to hypothalamic and medullary sites known to influence neurohormonal control of the circulation and that renal denervation alters the concentration of catecholamines in specific brain nuclei. In addition, Calaresu and Ciriello have shown that a majority of single units in the hypothalamus and medulla that respond to stimulation of afferent renal fibers also respond to electrical stimulation of arterial baroreceptor afferent fibers. Therefore, it is conceivable that removal of afferent renal fibers may affect the baroreceptor control of sympathetic outflow.

To test this hypothesis, we used the turnover of norepinephrine in skeletal muscle as an index of sympathetic activity in ADN-sectioned rats. As reported previously, ADN section caused a significant increase in norepinephrine turnover in skeletal muscle; however, the turnover of norepinephrine in skeletal muscle was entirely normal in rats with combined renal nerve and ADN section. The exact mechanism whereby renal denervation produces these effects is not clear; however, two observations should be noted: 1) renal denervation alone significantly decreased the turnover of norepinephrine in skeletal muscle; and 2) ADN section in renal-denerverated animals did increase the turnover of norepinephrine in skeletal muscle when compared to the renal denervated control group. These results suggest that the removal of afferent renal fibers does not prevent the noradrenergic response to ADN section, but that afferent renal fibers may have a tonic influence on sympathetic outflow to skeletal muscle. That this effect may be important, at least over the short term during which these experiments were done, is illustrated in general by the significant correlation obtained between the index of norepinephrine turnover and arterial pressure, and specifically by the complete prevention of the arterial pressure response to ADN section in renal-denerverated rats. A similar correlation between peripheral sympathetic activity and blood pressure was shown by Katholi et al. However, they did not report data for animals that had received renal denervation only.

Changes in the turnover of norepinephrine in the hypothalamus are less clear, possibly as a result of using a large area known to influence and respond to many different organ systems. However, it is interesting that there was a significant difference between the turnover of norepinephrine in the two groups of ADN-sectioned rats, again illustrating an effect of renal denervation. These results agree in principle with Wintertonitz et al., who showed that renal denervation decreased arterial pressure in one-kidney, one clip Goldblatt hypertensive rats, while normalizing a previously elevated concentration of norepinephrine in the hypothalamus.

The effect of renal denervation on noradrenergic mechanisms in ADN-sectioned rats is presumably caused by removal of afferent renal fibers; however it is not clear what relative roles both renal efferent and afferent fibers may play in the overall response to ADN section. Further elucidation of these mechanisms will require selective destruction of renal efferent or afferent fibers.

Acknowledgments

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