Importance of the Renal Nerves in Established Two-Kidney, One Clip Goldblatt Hypertension

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SUMMARY Increased sympathetic nervous system activity has been demonstrated in established two-kidney, one clip hypertension in the rat. To determine the importance of the renal nerves in this model of hypertension, renal denervation of the clipped kidney (n = 15), renal denervation of the nonclipped kidney (n = 14), sham operation (n = 20), or unclipping (n = 12) was carried out 6 weeks after the onset of two-kidney, one clip hypertension. Normotensive age- and sex-matched rats were used as controls (n = 10). Sham operation or renal denervation of the nonclipped kidney produced no change in systolic blood pressure while renal denervation of the clipped kidney resulted in a significant decrease in systolic blood pressure (195 ± 7 to 150 ± 6 mm Hg; p < 0.01). Unclipping lowered systolic blood pressure to normotensive levels (126 ± 5 mm Hg). Eight days after operation, plasma norepinephrine and mean arterial pressure before and after ganglionic blockade with 30 mg/kg hexamethonium bromide were measured in conscious unrestrained resting animals as indices of peripheral sympathetic nervous system activity. Plasma norepinephrine was significantly higher in hypertensive sham-operated rats (347 ± 26 pg/ml) and nonclipped-kidney denervated rats (355 ± 27 pg/ml) compared to normotensive controls (228 ± 22 pg/ml) (p < 0.01). Both renal denervation of the clipped kidney and unclipping restored plasma norepinephrine to normal levels (215 ± 16 and 232 ± 19 pg/ml, respectively). Ganglionic blockade in hypertensive sham-operated and nonclipped-kidney denervated animals resulted in a significantly greater decrease in mean arterial pressure than that which occurred in clipped-kidney denervated, unclipped, or control rats. There was no difference in plasma renin activity, clipped-kidney renin activity, or blood pressure response to 250 μg SQ 20,881 administration among sham-operated, clipped-kidney denervated, or nonclipped-kidney denervated animals. The data indicate that the depressor effect of clipped kidney denervation or unclipping in the two-kidney, one clip hypertensive rat is associated with a decrease in sympathetic nervous system activity. These results support the hypothesis that the afferent renal nerves contribute to the maintenance of hypertension in this model by modulating the activity of the sympathetic nervous system. (Hypertension 4 (suppl II): II-166–II-174, 1982)

Key Words • rat • two-kidney, one clip hypertension • renal nerves • sodium balance • creatinine clearance • plasma norepinephrine • ganglionic blockade • hexamethonium bromide • unclipping • SQ 20,881 • plasma renin activity • kidney renin activity

While increased activity of the renin-angiotensin system has been implicated in the initial hypertensive response to clipping of the renal artery in a one-kidney or two-kidney rat, the renin-angiotensin system appears to play a diminishing role as hypertension becomes established in these models. Although there have been some reports to the contrary, there is increasing evidence suggesting participation of the sympathetic nervous system in the maintenance of these forms of renal hypertension. Since increases in efferent sympathetic nerve activity facilitate the retention of sodium and result in renin release, we previously studied the effect of renal denervation in the one-kidney renal hypertensive rat at a time when increased peripheral sympathetic nervous system activity was present. We found that renal denervation performed 2 weeks after clipping the renal artery or figure 8 wrapping the kidney resulted in a significant attenuation of the hypertension. The depressor effect of renal denervation, however, was not mediated by alterations in sodium or renin. Further studies revealed that the depressor effect of renal denervation in the one-kidney renal hypertensive rat was associated with a fall in...
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hypothalamic norepinephrine content to control levels and decreased activity of the peripheral sympathetic nervous system.11,12 Taken together, these results are compatible with the hypothesis that the afferent renal nerves play a role in one-kidney renal hypertension by modulating sympathetic nervous system activity. The objective of the current study was to examine the importance of the renal nerves during the established phase of hypertension in the two-kidney, one clip Goldblatt hypertensive rat.

Methods

Animal Preparation

Male Sprague-Dawley rats (n = 61) obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts, were subjected to clipping (0.35 mm silver clip) of the proximal left renal artery at 4 weeks of age. Renal denervation of the clipped kidney, renal denervation of the nonclipped kidney, sham operation, or unclipping was carried out 6 weeks after the onset of two-kidney one clip hypertension (7 weeks after clipping). The 61 animals were randomly assigned to either renal denervated, sham-operated, or unclipped groups and compared with 10 nonclipped age- and sex-matched normotensive controls. Renal denervation was accomplished through a flank incision by stripping the renal artery adventitia distal to the clip and painting the renal artery with 20% phenol (wt/vol) in ethanol. Care was taken not to disturb the position of the clip during the denervation procedure. The sham operation consisted of opening and closing the flank on the side of the clipped kidney.

Throughout the study, animals were housed in a room with constant temperature (24° ± 1°C), humidity (60± ± 5%), and light from 6 a.m. to 6 p.m. Systolic blood pressure of all animals was measured using the tail-cuff method without anesthesia (Narco Biosystems, Inc., Houston, Texas). Animals were weighed weekly.

Protocol

To examine the effects of renal denervation on blood pressure, sodium balance, peripheral sympathetic nervous system activity, renin-angiotensin system activity, and creatinine clearance in established two-kidney, one clip hypertension, 15 clipped-kidney denervated, 14 nonclipped-kidney denervated, 20 sham-operated clipped, 12 unclipped, and 10 sham-operated nonclipped rats were compared. To assess the effects of renal denervation and unclipping on sodium excretion, rats were housed in individual metabolic cages for measurement of sodium balance and creatinine clearance from 1 week before renal denervation, sham operation, or unclipping and continued until the end of the study. These animals remained in the cages continuously except for a brief period when they were removed for blood pressure measurement and weighing. They were given distilled water and a purified basal diet (0.29% sodium) (Ralston Purina Company, Richmond, Indiana) ad libitum.

Food intake was measured daily; 24-hour urine collections were analyzed for sodium determination on 6 of 7 days. In addition, at the end of each 24-hour collection period, the collection funnel of each cage was rinsed with 50 ml of distilled water and the rinse saved for analysis of sodium content. Daily sodium excretion was calculated as the product of urine volume and sodium concentration plus the product of the wash volume and wash sodium concentration. Daily sodium output was calculated as the fractional excretion of sodium (24-hour urinary sodium excretion divided by 24-hour sodium intake X 100).

Plasma norepinephrine concentration and blood pressure response to ganglionic blockade were used as indices of peripheral sympathetic nervous system activity. Plasma renin activity, kidney renin activity of the clipped kidney, and blood pressure response to SQ 20,881 were used as indices of renin-angiotensin system activity. Six days after renal denervation, sham operation, or unclipping, the rats were anesthetized with ether and then had 0.025 inch (i.d.) microline catheters placed in the femoral artery, brought under the skin, and externalized behind the neck. Forty-eight hours after catheter placement, tubing was connected to the catheter; at least 30 minutes was allowed to pass before 0.5 ml of blood was sampled from conscious unrestrained resting animals. In all animals, blood was taken at the same time of day under the same environmental conditions to avoid diurnal variation or ambient temperature influences on plasma norepinephrine. The blood was immediately placed on ice for measurement of plasma norepinephrine. After sampling, 0.5 ml of whole blood from a donor rat was infused as volume replacement. Two hours later under the same conditions, each animal's catheter was connected to a Statham P50 pressure transducer. After a stable mean arterial pressure was obtained (measured using Hewlett Packard recorder), 30 mg/kg of hexamethonium bromide was infused interarterially, and the maximum decrease in mean arterial pressure was recorded. This dose of hexamethonium bromide has been shown to interrupt sympathetic transmission controlling the cardiovascular system in the rat.13 On the following day, mean arterial pressure response to 250 μg SQ 20,881 was determined using the method described above. This dose of SQ 20,881 has been shown to produce more than 80% inhibition of the pressor response to a test dose of 100 ng of angiotensin 1/kg.14 Plasma norepinephrine was measured using a modification of the radioenzymatic method of Peuler and Johnson.14 Sodium concentration (mEq/liter) was measured by flame photometry (Instrumentation Laboratory Model 643, Lexington, Massachusetts). Two days later the animals were sacrificed by decapitation without anesthesia. Blood was collected in iced tubes containing EDTA (1 mg/ml) for determination of plasma creatinine and renin activity. Plasma renin activity was determined by radioimmunoassay of
generated angiotensin I according to the method of Haber et al. Kidneys were collected immediately, frozen in liquid nitrogen, and subsequently homogenized for measurement of kidney renin activity.

Numerical results are expressed as mean ± 1 SE. Statistical analysis of the blood pressure data was performed using analysis of variance based on a split plot in time model. Regression analysis was used to establish a linear relationship between mean arterial blood pressure and plasma norepinephrine. The changes in arterial pressure with hexamethonium and SQ 20,881 were compared to the control using analysis of variance in conjunction with Dunnett's test. Changes are reported as significant if the p value was less than 0.05.

Results

Hypertension

After clipping, the 61 rats that subsequently would undergo unilateral renal denervation, sham operation, or unclipping were observed for changes in blood pressure over 9 weeks. As shown in figure 1, clipping the renal artery produced a rise (p < 0.01) in systolic blood pressure from 125 ± 7 to 155 ± 7 mm Hg by 1 week; the pressure continued to rise reaching a plateau of 194 ± 7 mm Hg by 2 weeks. Thereafter, the systolic blood pressure remained elevated over the subsequent weeks of observation. Sham operation and nonclipped kidney denervation 7 weeks after clipping resulted in a significant sustained decrease in systolic blood pressure from 195 ± 7 to 150 ± 6 mm Hg (p < 0.01). Unclipping the renal artery resulted in a decrease in systolic blood pressure to baseline (preclip) levels, which was significantly lower (p < 0.05) than the pressure of clipped-kidney denervated animals.

Ten control two-kidney sham-operated nonclipped rats were observed for 9 weeks. Baseline systolic blood pressures of these animals were not significantly different from the baseline systolic blood pressures of the animals that were subsequently clipped. Over the subsequent 9 weeks of observation, systolic blood pressure ranged between 120 ± 4 and 128 ± 4 mm Hg in this control group, representing no significant change from baseline. There were no significant differences in weekly weight gain among the groups during the 9 weeks of observation.

Urinary Sodium Excretion Studies

The time course of development and degree of hypertension in those animals housed in individual metabolic cages beginning 6 weeks after clipping were similar to those observed for the larger groups shown in figure 1. As shown in figure 2, animals that subsequently underwent sham operation, renal denervation, or unclipping excreted 91% ± 5% of the ingested sodium at a time the hypertension was at a plateau. During the week after operation, there was no change in fractional excretion of urinary sodium in sham
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Before Operation (n=29)
- Sham (n=10)
- D-Nonclip (n=6)
- D-Clip (n=6)
- Unclipped (n=7)

**D**-Nonclip (n=6)

![Graph showing fractional urinary sodium excretion](https://hyper.ahajournals.org/)

**FIGURE 2.** Daily fractional urinary excretion of sodium intake in two-kidney one clip rats with established hypertension before and after sham operation, renal denervation (D), or unclipping. Arrow indicates the time of intervention (6 weeks after onset of the hypertension). Asterisks represent p < 0.05 comparing fractional urinary sodium excretion after operation to before operation.

(90% ± 6%), nonclipped-kidney denervated (90% ± 5%), or unclipped (87% ± 5%) animals. In contrast, there was a significant decrease (p < 0.05) in fractional excretion of urinary sodium of clipped-kidney denervated animals (80% ± 4%) seen the first 24 hours after operation. Thereafter, sodium excretion in all animals returned to preoperative levels. During the week of observation after operation, there was no significant difference in daily sodium intake among sham-operated, renal-denervated, or unclipped animals.

Plasma Norepinephrine

Eight days after operation (renal denervation, sham operation, or unclipping), plasma norepinephrine was measured in conscious unrestrained resting animals. As shown in table 1, there was no significant difference in plasma norepinephrine among clipped-kidney denervated animals and normotensive unclipped or control animals. In contrast, plasma norepinephrine values of sham-operated and nonclipped kidney-denervated hypertensive animals were significantly (p < 0.01) greater than those of the clipped-kidney dener-

<table>
<thead>
<tr>
<th>Rat group</th>
<th>No.</th>
<th>NE (pg/ml)</th>
<th>MAP (mm Hg) Pre-Hex</th>
<th>MAP (mm Hg) Post-Hex</th>
<th>Absolute decrease MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>9</td>
<td>347 ± 26*</td>
<td>148 ± 7*</td>
<td>78 ± 4†</td>
<td>70 ± 5*</td>
</tr>
<tr>
<td>D-nonclip</td>
<td>7</td>
<td>355 ± 27*</td>
<td>150 ± 7*</td>
<td>76 ± 4†</td>
<td>74 ± 5*</td>
</tr>
<tr>
<td>D-clip</td>
<td>6</td>
<td>215 ± 16</td>
<td>122 ± 5†</td>
<td>77 ± 4†</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>Unclipped</td>
<td>6</td>
<td>232 ± 19</td>
<td>107 ± 4</td>
<td>68 ± 4</td>
<td>39 ± 4</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>228 ± 22</td>
<td>102 ± 4</td>
<td>65 ± 4</td>
<td>37 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE. D = denervated.
* p < 0.01.
† p < 0.05.
vated, unclipped, or control rats. There was a highly significant \( p < 0.0001 \) positive correlation between mean arterial pressure and the plasma norepinephrine measured in renal-denervated (clipped and nonclipped side) and sham-operated rats (fig. 3). The prediction equation relating mean arterial pressure (MAP) to plasma norepinephrine (NE) level was \( \text{MAP} = 75.89 + 0.21 \text{NE} \). The t test for nonzero slope was significant at the less than \( p < 0.0001 \) level.

**Ganglionic Blockade**

Table 1 shows the mean arterial pressure before and after administration of 30 mg/kg hexamethonium bromide. Before ganglionic blockade, the mean arterial pressures of sham-operated and renal-denervated (clipped and nonclipped side) animals was significantly higher than that of unclipped or control animals. Ganglionic blockade resulted in a significant decrease in mean arterial pressure in all groups \( p < 0.01 \). The absolute decrease in mean arterial pressure (table 1) and the percentage decrease in mean arterial pressure (fig. 4) were significantly greater \( p < 0.01 \) in sham-operated and nonclipped-kidney denervated hypertensive animals compared to clipped-kidney denervated, unclipped or control animals. Postganglionic blockade mean arterial pressure (table 1) of control and unclipped animals were significantly lower \( p < 0.05 \) than those of sham-operated or renal-denervated animals.

**Response to SQ 20,881**

Table 2 shows the mean arterial pressure before and after administration of 250 \( \mu \)g SQ 20,881. Before SQ

![Figure 3. Regression analysis of the relationship between plasma norepinephrine and mean arterial pressure in sham-operated and renal-denervated (D) two-kidney, one clip hypertensive rats.](image)

![Figure 4. Effect of ganglionic blockade with hexamethonium bromide (30 mg/kg) on mean arterial pressure 8 days after operation. Asterisks represent \( p < 0.01 \) comparing sham-operated, renal-denervated (D), and unclipped animals to normotensive age and sex-matched controls.](image)
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20,881 administration, the mean arterial pressures of sham-operated and renal-denervated animals were significantly higher than those of unclipped or control animals. In response to SQ 20,881, the absolute and percentage decreases in mean arterial pressure in sham-operated and renal-denervated animals were significantly greater (p < 0.05) than those of unclipped or control animals; yet the mean arterial pressures (table 2) remained significantly higher than those of unclipped and control animals.

**Plasma and Kidney Renin Activity**

Shown in figure 5 are values for plasma and kidney renin activity 10 days following sham operation, renal denervation, or unclipping. The plasma renin in renal-denervated (clipped or nonclipped side) animals was not significantly different from that in sham-operated rats. Values for all of these experimental hypertensive groups were significantly greater (p < 0.01) than those in unclipped and nonclipped normotensive controls. Kidney renin content (fig. 5) of the clipped kidney was no different in sham-operated or renal-denervated compared to unclipped or nonclipped normotensive animals. Kidney renin content of the nonclipped kidney of sham-operated and renal-denervated animals was significantly (p < 0.001) lower than those of nonclipped normotensive control animals.

**Creatinine Clearance**

There were no significant differences in creatinine clearance among clipped kidney denervated (1.16 ± 0.18 ml/min; n = 14), nonclipped-kidney denervated (1.09 ± 0.17 ml/min; n = 12), sham-operated (1.12 ± 0.19 ml/min; n = 18), and unclipped (1.23 ± 0.22 ml/min; n = 12) animals. Creatinine clearances of renal-denervated, sham-operated, and unclipped animals were significantly lower than those in two-kidney normotensive controls (1.86 ± 0.18 ml/min; n = 10; p < 0.001).

**Discussion**

Our study has demonstrated that: 1) clipped kidney denervation during the established phase of two-kidney one clip hypertension in the rat attenuates the severity of hypertension while unclipping the renal artery normalizes the blood pressure; 2) nonclipped kidney denervation in this model produces no change in blood pressure; 3) the depressor effect of clipped kidney denervation or unclipping is associated with a decrease in peripheral sympathetic nervous system activity from the increased levels present in sham-operated hypertensive animals to levels comparable to those found in control normotensive rats; and 4) plasma norepinephrine, an index of peripheral sympathetic nervous system activity, is significantly correlated with mean arterial pressure in sham-operated and renal-denervated (clipped and nonclipped kidney) groups. These observations extend our previous find-

**Table 2. Mean Arterial Pressure (MAP) Before and After Administration of 250 μg SQ 20,881 Measured 9 Days After Operation in Conscious Unrestrained Resting Rats**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MAP (mm Hg)</th>
<th>Absolute decrease MAP (mm Hg)</th>
<th>Percent change MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-SQ</td>
<td>post-SQ</td>
<td></td>
</tr>
<tr>
<td>Sham (n = 8)</td>
<td>148 ± 6*</td>
<td>15 ± 2†</td>
<td>10 ± 2†</td>
</tr>
<tr>
<td>D-nonclip (n = 7)</td>
<td>147 ± 6*</td>
<td>13 ± 2†</td>
<td>9 ± 2†</td>
</tr>
<tr>
<td>D-clip (n = 6)</td>
<td>124 ± 5†</td>
<td>12 ± 2†</td>
<td>10 ± 2†</td>
</tr>
<tr>
<td>Unclipped (n = 6)</td>
<td>103 ± 4</td>
<td>5 ± 2</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>100 ± 4</td>
<td>4 ± 2</td>
<td>4 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. D = denervated.
*p < 0.01.
‖p < 0.05.

\[\text{Control (n=7)}\]
\[\text{Unclipped (n=7)}\]
\[\text{Sham (n=18)}\]
\[\text{D-Nonclip (n=10)}\]
\[\text{D-Clip (n=15)}\]

**Figure 5. Plasma renin activity (PRA) and kidney renin activity (KRA) of animals sacrificed 10 days after operation. Asterisks refer to p < 0.01 comparing PRA of sham, renal-denervated (D), or unclipped groups to normotensive animals. Within KRA bars N = nonclipped kidney value; C = clipped kidney value. The crosses refer to p < 0.001 comparing KRA of nonclipped kidney in hypertensive animals with that seen in normotensive control animals.**
ings suggesting that afferent renal nerves from a clipped kidney are important in the maintenance of increased blood pressure in one-kidney renal hypertension in the rat by modulating sympathetic nervous system activity.10-13

The indices of peripheral sympathetic nervous system activity used in these experiments were plasma norepinephrine levels and the mean arterial pressure response to ganglionic blockade with hexamethonium bromide.16 Plasma norepinephrine in the conscious resting unrestrained rat is principally derived from neurotransmitter released from noradrenergic nerve endings and appears to correlate well with other indices of sympathetic function.18 We therefore interpret the elevation of plasma norepinephrine observed in the two-kidney, one clip hypertensive rat as a consequence of increased sympathetic nervous system activity. Our finding of elevated norepinephrine levels in the two-kidney, one clip hypertensive rat is consistent with the observations of others implicating increased sympathetic nervous system activity in the maintenance of hypertension in this model. Plasma norepinephrine levels were decreased in clipped-kidney denervated animals in comparison to sham-operated or non-clipped-kidney denervated hypertensive rats, suggesting that clipped kidney denervation caused an attenuation in the level of peripheral sympathetic nervous system activity. The decrease in sympathetic activity following clipped kidney denervation was not related to differences in the activity of the renin-angiotensin system or glomerular filtration rate. These are important negative findings because there is evidence to suggest that angiotensin II facilitates the release of norepinephrine.20 Further, a significant decrease in urinary norepinephrine excretion could result in elevated plasma levels.21 The diminished hypotensive response to ganglionic blockade in clipped-kidney denervated rats compared to hypertensive animals gave further evidence that the depressor effect of clipped kidney denervation in this model is associated with a decrease in peripheral sympathetic nervous system activity.

Denervation of the clipped kidney in this model resulted in a decrease in blood pressure associated with retention of sodium, suggesting that the reduction in pressure was not due to loss of sodium or leftward shift in the blood pressure-sodium excretion curve.22 In addition, there was no difference in the intake of sodium or renal function in these animals compared to sham-operated rats to explain the fall in blood pressure after renal denervation. The transient retention of sodium was likely due to a carotid baroreflex-mediated increase in efferent renal sympathetic nerve activity in the nonclipped kidney induced by the decrease in blood pressure.23

Denervation of the clipped kidney in this model also did not alter the activity of the renin-angiotensin system. The lack of an observed decrease in plasma renin activity and kidney renin activity following denervation is best explained by renal baroreceptor-mediated stimulation of renin synthesis and/or release by the lower blood pressure in clipped-kidney denervated rats.24 These effects would tend to oppose any decrease in renin produced by interruption of the renal efferent nerves or the observed sodium retention.25

Although increased activity of the sympathetic nervous system has been shown to contribute to the maintenance of established hypertension in the two-kidney, one clip rat, and increased efferent renal sympathetic nerve activity facilitates the retention of sodium, nonclipped kidney denervation was not accompanied by a natriuresis and resultant decrease in blood pressure. This finding is consistent with the work of others suggesting that there is an attenuation of efferent sympathetic control of renal vascular resistance in the untouched kidney of two-kidney Grollman hypertension.26 In addition, at this stage in the hypertensive process the nonclipped kidney's ability to excrete sodium is likely decreased due to an increase in renal vascular reactivity to angiotensin II and pressure-induced vascular changes.27-29

The observation that renal denervation lowered but did not normalize blood pressure supports the work of others demonstrating that factors other than enhanced peripheral sympathetic activity contribute to the maintenance of two-kidney, one clip Goldblatt hypertension in the rat.30,31 For example, unclipping which restored blood pressure to normal levels was accompanied by decreased activity of the renal-angiotensin system as well as a decrease in peripheral sympathetic activity. The response to SQ 20,881 provides further evidence that the renin-angiotensin system is partially responsible for the maintenance of the hypertension. In contrast, our findings confirm those of other investigators that sodium-volume factors do not contribute to the increase in blood pressure.32 The finding that after SQ 20,881 administration the blood pressure of clipped-kidney denervated rats did not fall to the level seen in unclipped or control rats suggests that additional factors may be responsible for the maintenance of the hypertension. Possibilities include the presence of vascular changes in hypertensive animals or the inhibition of the release of renal vasodepressor substances due to the presence of a clip.33,34

The mechanism responsible for activation of the sympathetic nervous system in the two-kidney, one clip Goldblatt hypertensive rat is being investigated in a number of laboratories. It has been suggested that the increase in peripheral sympathetic activity present in two-kidney, one clip hypertensive rats could be due to changes in the central nervous system triggered by an increase in circulating angiotensin II.35-37 Although this mechanism could be used to explain the decrease in sympathetic activity following unclipping, clipped kidney denervation lowered blood pressure in the absence of changes in renin-angiotensin system activity. Another possible explanation of our data is that clipped kidney denervation might facilitate the release of a circulating renal factor that down-regulates sympathetic nervous system activity. If this was the case, one would have to postulate that unclipping a kidney with intact renal nerves also resulted in the release of a renal factor.
A more attractive explanation for our findings is that clipped kidney denervation or unclipping in this model decreased afferent renal nerve activity and thereby attenuated peripheral sympathetic tone. Consistent with this hypothesis is the increasing evidence demonstrating that afferent sympathetic signals from various organs, including the kidney, play an important role in modulating peripheral efferent sympathetic responses. If clipping the renal artery in a two-kidney rat resulted in an increase in afferent renal nerve signals which triggered increased central sympathetic outflow, then decreasing afferent renal nerve signals, whether by interrupting the renal nerves (denervation) or removing the stimulus to increased afferent renal signals (unclipping), should result in a lowering of sympathetic activity and a prompt lowering of blood pressure. Consistent with this hypothesis are our observations that clipping the renal artery resulted in increased plasma norepinephrine and enhanced responses to hexamethonium while clipped kidney denervation and unclipping resulted in a lowering of plasma norepinephrine and a diminution of blood pressure response to ganglionic blockade.

In support of the hypothesis that the afferent renal nerves contribute to the pathogenesis of hypertension in the two-kidney, one clip model via an effect on the central and thereby the peripheral sympathetic nervous system are a number of lines of evidence indicating that afferent renal nerve signals participate in cardiovascular regulation. Both mechanoreceptors and chemoreceptors have been demonstrated in the kidney, and a variety of stimuli, including alterations in renal artery pressure, renal venous occlusion, ureteral occlusion, compression of the kidney, ischemia, and changes in the ionic composition of the pelvic urine, have been shown to produce alterations in renal afferent nerve activity. Stimulation of afferent renal fibers alters the electrical activity in hypothalamic structures implicated in central cardiovascular regulation. Further evidence that the changes produced by afferent renal nerve stimulation may be mediated via supraspinal neurons comes from studies demonstrating that stimulation of afferent renal fibers elicits efferent sympathetic responses with a reflex latency period comparable to known somatosympathetic reflexes which are modulated at a central level. These efferent sympathetic responses to afferent renal fiber stimulation can be abolished by spinal cord sectioning and by lesioning of the anteroventral third ventricle (AV3V) region. In summary, this study provides evidence that the afferent renal nerves contribute to the maintenance of hypertension in the two-kidney, one clip Goldblatt hypertensive rat by modulating sympathetic nervous system activity. The relationship of the afferent renal nerves to the development of hypertension in this model merits further study.

Acknowledgments

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References

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