Neural Contribution to Renal Hypertension
Following Acute Renal Artery Stenosis
in Conscious Rats

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SUMMARY

To assess the hemodynamic changes during acute renal artery stenosis (RSt) and their dependence on alterations in the renin-angiotensin and sympathetic nervous systems, we studied conscious rats chronically instrumented with miniaturized pulsed-Doppler flow probes. Probes were implanted on the superior mesenteric and both renal arteries, and on the lower abdominal aorta for measurement of mesenteric (MR), renal (RR), and hindquarters (HQR) vascular resistance. Unilateral RSt, with a pneumatic cuff occluder that reduced flow by approximately 50%, increased mean arterial pressure (MAP) by 32%, reduced heart rate, and increased MR, nonstenotic (contralateral) RR and HQR. The hypertension was renin-dependent since plasma renin activity increased 6-fold and the angiotensin II (All) antagonist, saralasin, significantly reduced MAP and regional resistances. The acute hypertension was also associated with increased neurogenic vasoconstrictor tone since hexamethonium markedly reduced MAP, MR, HQR and non-stenotic RR. Hexamethonium similarly decreased MAP during hypertension induced by All infusion, whereas hypertension produced by the "pure" peripheral vasoconstrictor, phenylephrine, was unaffected by ganglionic blockade. In animals with peripheral sympathectomy produced by 6-hydroxydopamine, acute RSt produced hemodynamic changes similar in magnitude to intact animals; however, PRA increased 3-fold more than in intact rats. We conclude that hypertension induced by acute RSt in conscious rats is not only renin-dependent, but is also associated with inappropriately high neurogenic vasoconstrictor tone, presumably activated by indirect neural actions of All. (Hypertension 5 (suppl I): 1-155—1-164, 1983)

KEY WORDS • blood pressure regulation • regional vascular resistance • angiotensin II • hexamethonium • 6-hydroxydopamine • sympathetic nervous system

ALTHOUGH the etiology of renal hypertension has received intensive study, knowledge concerning both the mechanisms that maintain hypertension and produce the initial disturbances remains incomplete. There is, however, growing interest in the possibility that significant interactions may exist between the renin-angiotensin system (RAS) and sympathetic nervous system. It is clear from studies on plasma renin activity (PRA) and the effects of angiotensin (All) blockade that the RAS is activated at the onset of renal hypertension.1–4 On the other hand, during the chronic phase of renal hypertension PRA is normal or only slightly elevated and All antibodies and receptor antagonists do not substantially reduce blood pressure.4–5

Several lines of evidence suggest that sympathetic drive may be enhanced in established renal hypertension and thus contribute to the maintenance of the disease. These include elevated plasma catecholamines,6 accentuated reduction in blood pressure after ganglionic blockade,7 8 reversal or prevention of hypertension by destruction of selective regions in the anterior hypothalamus9–10 and depletion of central catecholamine stores.11 Although not confirmed,12 similar effects are produced by peripheral sympathectomy.13 It is unclear at what time in the course of renal hypertension a sympathetic contribution becomes important.

There are several mechanisms which could induce an inappropriately high level of sympathetic vasoconstrictor tone (i.e., neurogenic tone) at the very initial stage of acute renal hypertension. In addition to its direct vasoconstrictor actions, All may facilitate sympathetic transmission by an action on vascular adrenergic nerve endings.14–18 Blood-borne All is also capable of acting on receptors within the central nervous system to increase sympathetic outflow17 and elevate arterial pressure by a purely central action. Additionally,
recent studies have led to the hypothesis that renal artery stenosis may increase neurogenic tone by activating renal afferent nerve endings with mechano- and/or chemoreceptor function.18

The purpose of this study was to evaluate the involvement of the sympathetic nervous system in the onset of renal hypertension, when secondary changes such as vascular structural changes and fluid-electrolyte alterations would be absent or minimal. Specifically, we sought to determine in conscious animals with hypertension induced acutely by RSt: 1) how resistance is affected in different vascular beds (during acute RSt); 2) the degree to which the changes are dependent on a neurogenic mechanism; and 3) the effect of peripheral adrenergic sympathetomy with the neurotoxin, 6-hydroxydopamine. The results suggest that at the onset of renal hypertension, in addition to activation of the RAS, sympathetic vasoconstrictor tone is maintained at an inappropriately high level.

Methods

Chronic Instrumentation

Experiments were performed on male Sprague-Dawley rats (275–350 g), which were individually housed in 25 × 17 × 18 cm opaque plastic cages. Each rat was anesthetized with pentobarbital (50 mg/kg, i.p.), which was supplemented as required, and was treated with atropine (1.3 mg/kg, i.p.). Through a midline laparotomy, the right and left renal arteries, superior mesenteric artery, and abdominal aorta below their length. Miniaturized pulsed-Doppler flow probes were placed around one or more of these vessels, depending on the experimental group. A complete description of these flow probes, their construction and implantation is provided elsewhere. A miniaturized (2.5 mm wide) perivascular pneumatic balloon occluder was implanted around one of the renal arteries either distal or proximal to the flow probe. Occluders were constructed from thin-wall vinyl tubing (No. 222224 "Inkwell tubing," Beckman). One end of a 24 cm length of tubing was occluded with a Halsted mosquito hemostat and submerged for several seconds in mineral oil heated to approximately 160°C to heat-seal the end of the tubing. A blunt-end 20 gauge needle was then attached to the open end of the tubing and the needle was fitted to a 1.0 cc syringe. The sealed end of the tubing held with the hemostat was again submerged into the hot oil for several seconds, removed, and slight pressure was applied to the tubing with the syringe until a small balloon formed adjacent to the heat-sealed end. During implantation, the flattened balloon was folded around the vessel and a 3-0 silk ligature was used to prevent the balloon from unfolding when inflated.

The wire leads from the flow probes and the occluder catheter were tunnelled underneath the skin to the back of the neck and the wires were soldered to a connector plug which was attached to the skull. A catheter (PE-50 to PE-10) was positioned in the descending thoracic aorta via the left carotid artery for measurement of arterial pressure. A similar catheter was placed in the lower abdominal vena cava via the left femoral vein. The catheters were filled with heparinized saline (50 units/ml) and led subcutaneously to exit at the back of the neck. Each rat received 3.0 cc sterile saline ip, 80,000 units penicillin im (Flo-cillin, Bristol) and was allowed to recover for at least three days from the surgery. Only animals that were gaining weight and exhibiting normal water intake after the recovery period were used in the study.

Each rat was connected to a light-weight, flexible spring which contained the flow probe wire connectors and the catheter and occluder lines, and which was suspended from the top of the animal's home cage so as to permit freedom of movement. The wire leads from the flow probes were connected to a pulsed-Doppler flowmeter (Univ. of Iowa Bioengineering Facility). Changes in blood flow velocity, measured as the Doppler shift in kHz, were recorded on a Beckman RM Dynograph. These changes in blood flow velocity have been shown to be directly and linearly related to volume flow. Mean arterial pressure (MAP) was electronically derived with a Century CP-01 low volume pressure transducer. Heart rate was derived with a Beckman 9857B tachometer which was triggered from the arterial pressure pulse. A period of 30–60 minutes was allowed to pass for stabilization of hemodynamics before beginning the protocols.

Groups 1 and 2: Renal Artery Stenosis

Animals in Group 1 were prepared with flow probes on the superior mesenteric artery, lower abdominal aorta, and one renal artery which also received a vascular occluder. Responses in the contralateral kidney were not evaluated in this group. Rats in Group 2 received flow probes on both renal arteries with an occluder on one of the vessels. In all groups after stabilization, renal blood flow (RBF) to one kidney was reduced to zero by complete occlusion to verify that electronic zero, achieved when excitation current to the flow probe piezoelectric crystal is interrupted, was identical to actual flow zero. Thirty minutes later control values for hemodynamic parameters were obtained and RBF was reduced by approximately 50% over a 30-second interval by inflating the vascular occluder with a pressure regulating circuit. This circuit, which consisted of a compressed air source and an anaeroid pressure regulator with several valves, when connected to the perivascular occluder allowed sudden stepwise increases in pressure in the occluder to be continuously monitored and maintained constant. The occluder pressure was held constant at this value for a 10-minute interval. After 10 minutes of stenosis and again at the 20- and 30-minute points, RBF was reset to approximately 50% of control by increasing the occluder pressure if RBF had increased above 50% in the preceding 10 min interval. Following this 30-minute stenosis protocol the pressure in the occluder circuit was held constant throughout the duration of the experiment at the last resetting value.
Hemodynamic parameters were recorded at 30-minute intervals for up to 9 hours of renal artery stenosis (RSt). After 5.5 hours, a bolus injection of angiotensin (All, Ciba, 150 ng/kg) was administered. All bolus drugs were administered intravenously in 5 to 60 μl volumes, followed by a 0.2 cc saline flush, and time (10–15 minutes) was allowed for reestablishment of control values. The competitive All receptor antagonist [Sar1-Ala8] All (saralasin, Beckman) was then given as a 10 μg/kg bolus followed by a 10 μg/kg · min⁻¹ (3.9 μl/min) infusion for 20 minutes. After termination of the infusion All (150 ng/kg) was administered to test the efficacy of angiotensin receptor blockade by saralasin, and was again tested 45 minutes later at a time when hemodynamic parameters had returned to pre-saralasin values. In some rats responses to norepinephrine (NE, Sigma, 150 ng/kg) and nitroglycerin (NG, Parke-Davis, 120 μg/kg) were then determined, followed by hexamethionium (30 mg/kg). In these same animals responses to NE and NG were again determined 5 minutes after hexamethionium to assess the adequacy of ganglionic blockade. Neurogenic vascular tone was estimated by the magnitude of the drop in MAP and regional resistance produced by ganglionic blockade. The renal stenosis was then reversed and the animal disconnected from the transducers. The vehicle for each pharmacological intervention (saline) had no significant effect on any parameter. Two days later the protocol was repeated after sham-RSt, i.e., without inflation of the renal artery occluder. The order for RSt or sham-RSt was randomized.

Group 3: Angiotensin and Phenylephrine Infusion

Rats received arterial and venous catheters 1 to 2 days prior to the experimental procedure. After a 30- to 60-minute stabilization period, animals received an infusion of either All (102 ng/kg · min⁻¹) or phenylephrine (30 μg/kg · min⁻¹). The two infusions were conducted in the same animal with one day intervening, and the order of infusion was randomized among animals. Sixty minutes later hexamethionium (30 mg/kg, i.a.) was administered during continuous infusion of phenylephrine or All.

Group 4: Sympathectomy

Each rat was chronically instrumented with flow probes on the superior mesenteric and both renal arteries and the abdominal aorta, with a right renal artery occluder, and with intravascular catheters as described for Group 1. Two days later animals were anesthetized with ether and the adrenal glands were demedullated through retroperitoneal incisions. After 2 additional days each conscious rat received phentolamine (Regitine mesylate, Ciba, 2.5 mg/kg, iv) following by 6-hydroxydopamine (6-OHDA, Sigma, 100 mg/kg, iv). Six-hydroxydopamine was dissolved in 1.0% ascorbic acid in saline and administered by a slow, 5-minute infusion while monitoring blood pressure. Phentolamine pretreatment limited MAP increases to approximately 25 mm Hg during 6-OHDA infusion. The administration of the vehicle for 6-OHDA, alone, has been shown to have no effect on the response to tyramine, norepinephrine, or other interventions.[21, 22]

Two days later conscious animals were connected to the appropriate transducers, 30–60 minutes was allowed for stabilization of hemodynamics, and responses to NE (150 ng/kg, i.v.) and tyramine (Sigma, 250 μg/kg, i.v.) were obtained (the order of administration was randomized). Animals were then subjected to the 30 minute RSt protocol described above and monitored for an additional 30 minutes, after which a plasma sample was collected for determination of PRA. After an additional 2 days, the protocol was repeated with sham-RSt. The order of the protocol (RSt or sham-RSt) was randomized.

Measurement of Plasma Renin activity (PRA)

In a separate group of animals PRA was determined in blood samples obtained from chronically instrumented conscious rats after 60 minutes of RSt and sham-stenosis which were separated in time by at least 2 days. A 2.0 ml blood sample was withdrawn within 45–60 seconds from the arterial catheter into a chilled heparinized syringe, transferred into a chilled centrifuge tube, and two hematocrit capillary tube samples were taken. The blood sample was then centrifuged (1200 x g, 15 min, 4°C) and the plasma collected and stored at −80°C until assay. The blood cells were resuspended in warmed saline and returned to the animal. Plasma renin activity was determined by radioimmunoassay (New England Nuclear Al Radioimmunoassay Kit).

Data Analysis

The maximal response was determined for each pharmacological intervention and was compared with the control value determined for the 1-minute interval immediately preceding drug administration. Comparisons were made of the peak response to hexamethionium that occurs approximately 1 minute after administration, since arterial pressure and vascular resistance tend to increase after this peak response possibly in association with hypotension-induced release of humoral factors (e.g., renin and vasopressin)[19] or autoregulatory changes. Responses of each vascular bed are expressed as changes in relative vascular resistance as a percent of control resistance, where resistance for a given bed is calculated: MAP/Doppler shift in kHz. This is a valid determination of vascular resistance since percentage changes in Doppler shift (blood velocity) are equivalent to true percentage changes in volume flow.[19]

Average values for hemodynamic parameters were determined for the 2.0- to 5.5-hour interval after RSt and sham-RSt, and were compared by paired or unpaired t-tests. Responses to drugs were compared by i tests or by analysis of variance when comparisons were made between more than two groups. Significant F tests were followed by Duncans multiple range test. All values are expressed as the mean, ± 1 se, unless otherwise indicated.


**Results**

**Response to Acute Renal Artery Stenosis**

Control values for the different hemodynamic parameters prior to RSt or sham-RSt, which were separated by 2 days, were not significantly different. Mean arterial pressure (mm Hg) was 120 ± 2 prior to RSt and 121 ± 2 prior to sham RSt. Heart rate (beats/min) averaged 364 ± 7 prior to RSt and 360 ± 5 prior to sham RSt. Renal flow (kHz) in the stenotic kidney was 5.1 ± 0.5 prior to stenosis and 5.2 ± 0.4 prior to the sham procedure. Flow in the superior mesenteric and hindquarters beds were respectively 5.9 ± 0.3 and 4.4 ± 0.4 prior to stenosis, and 5.9 ± 0.3 and 4.0 ± 0.2 prior to sham-RSt. These data indicate that the probe itself, which is implanted loosely around the particular vessel, has no effect on flow and resistance with time, and that its acoustic coupling to the vessel remains constant.

The hemodynamic pattern that occurred over the first 5.5 hours of acute renal hypertension is summarized in figure 1. Sham stenosis had no effect on any parameters indicating the absence of any time effects on hemodynamics. Following RSt blood pressure increased to a stable value within 30 to 60 minutes, as did mesenteric resistance. However, hindquarters resistance increased gradually, requiring approximately 4 hours to stabilize. Unlike the other vascular beds, flow to the hindquarters increased initially and then gradually declined toward control between 2 to 5.5 hours after RSt. Heart rate declined during the onset of acute renal hypertension (RH) with persistent bradycardia evident throughout the period of observation (fig. 1).

In Group 2 animals (n = 9) with flow probes on both renal arteries, sham-RSt had no effect. Unilateral RSt produced a maintained reduction in RBF (-22% ± 5%; p < 0.01) and increase (+65% ± 8%; p < 0.001) in resistance in the non-stenotic kidney, with a time course similar to that of the mesenteric bed and the rise in arterial pressure. Several animals from both experimental groups were observed for up to 9 hours after RSt with no further significant change occurring in any parameter.

**Dependency on Renin-Angiotensin System**

To assess the extent to which the changes in hemodynamics after renal artery constriction were dependent on activation of the renin-angiotensin system, saralasin was infused between 5.5 and 6 hours after RSt or the sham procedure. In the normotensive (NT) and hypertensive (HT) states prior to saralasin, All (150 ng/kg) produced a 25 ± 5 mm Hg (n = 10) and 11 ± 3 mm Hg (n = 7) increase in arterial pressure. Immediately after the 20 minute saralasin infusion the response to All was abolished. Saralasin infusion had no effect on MAP, HR, or regional resistance in NT animals (fig. 2). However, during acute RH, saralasin produced a marked reduction in arterial pressure. Heart rate increased significantly in response to saralasin, and regional resistance decreased significantly in all vascular beds. After termination of the saralasin infusion, all parameters including pressor responses to All returned to control values by 45 minutes.

In a separate group of conscious instrumented rats (n = 5), PRA, which was 1.7 ± 0.4 (ng Al/ml/hr) prior to RSt, increased 6-fold to 10.0 ± 2.6 after 1 hour of acute RSt (p < 0.025). Hematocrit, which averaged 36 ± 1 in the normotensive state (n = 5), increased to 39 ± 1 in these same animals after 60 minutes of acute RSt (p < 0.005).
Dependency on the Sympathetic Nervous System

To determine whether hemodynamic changes during acute RSt were dependent on an interaction between All and the sympathetic nervous system, hexamethonium was administered after time was allowed for reversal of All receptor blockade. Hexamethonium significantly reduced MAP in the NT state and during acute RH by similar percentages (fig. 3). The blood pressure of the HT animals remained significantly elevated after ganglionic blockade when compared to hexamethonium-treated NT animals. Regional resistances were decreased by similar amounts in both the NT and HT states, except for the significantly greater fall in hindquarters resistance during acute RH (fig. 3). As shown in table 1, the efficacy of ganglionic blockade was confirmed by the absence of reflex changes in heart rate with administration of NE and NG.

The level of neurogenic tone, estimated by the reduction in MAP produced by ganglionic blockade, was compared during hypertension induced by either RSt or by infusion of All or phenylephrine (fig. 4). Like hypertension produced by RSt, MAP during All infusion was markedly reduced by hexamethonium. In contrast, phenylephrine-dependent hypertension was unaffected by ganglionic blockade, indicating complete withdrawal of peripheral neurogenic tone. As with acute RH, bradycardia persisted in both All- (−52 ± 15 bpm) and phenylephrine- (−63 ± 19 bpm) induced hypertension.

Effect of Peripheral Sympathectomy

In a group of conscious, instrumented rats that had not received 6-OHDA and adrenal demedullation, tyramine (250 μg/kg, i.v.) increased MAP by 52 ± 9 mm Hg (n = 6), hindquarters resistance by 51% ± 24% (n = 4), mesenteric resistance by 272% ± 70% (n = 3), and renal resistance by 65% ± 15% (n = 4). By comparison, 2 days after 6-OHDA tyramine-induced increases in blood pressure (11 ± 4 mm Hg) and

<table>
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<th>Table 1. Effect of Hexamethonium (30 mg/kg) on Baroreflex Ratio</th>
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<td>ΔHR/ΔBP (beats/min mm Hg⁻¹)</td>
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| No.               Control                          Hexameth.
|                   |       |                           |
| Norepinephrine    |       |                           |
| (150 ng/kg)       |       |                           |
| Normotensive      | 4     | 2.73 ± 0.58               | 0.02 ± 0.45 | <0.050 |
| Hypertensive      | 4     | 2.47 ± 0.80               | 0.04 ± 0.22 | <0.025 |
| Nitroglycerin     |       |                           |
| (120 μg/kg)       |       |                           |
| Normotensive      | 10    | 3.60 ± 0.41               | 0.48 ± 0.12 | <0.0005 |
| Hypertensive      | 7     | 2.57 ± 0.19               | 0.49 ± 0.15 | <0.0005 |

Values are means ± SE. ΔHR = change in heart rate; ΔBP = change in mean arterial pressure; No. = number of animals.
mesenteric (16% ± 7%) and renal (11% ± 6%) resistances were reduced significantly. The smaller increase in hindquarters resistance (23 ± 8) was not statistically significant. Evidence for peripheral sympathectomy was also indicated by arterial pressure and regional vascular hyperresponsiveness to exogenous norepinephrine (NE). Baseline values for MAP, heart rate, mesenteric resistance and hindquarters resistance were significantly lower in 6-OHDA treated animals when compared to normotensive animals from Groups 1 and 2 that did not receive 6-OHDA (fig. 5). Baseline resistance in both kidneys was unaffected. In 6-OHDA treated animals, 1 hour of acute RSt, which reduced blood flow to the affected kidney by an amount similar to that of Group 1 animals, produced hemodynamic changes that were not significantly different from responses in Group 1 and 2 animals after 1 hour of RSt (fig. 5). However, hindquarters resistance showed a significantly greater increase in the 6-OHDA treated group. Plasma renin activity (ng Al/ml/hr) prior to RSt was significantly higher (10.1 ± 0.6, p < 0.001) in 6-OHDA treated animals relative to normotensive animals that had not received 6-OHDA (1.7 ± 0.4). Moreover, after 1 hour of stenosis in 6-OHDA treated rats PRA increased to levels 3-fold greater (30.1 ± 1.8, p < 0.01) than that of nonsympathectomized animals after 1 hour of RSt (10.0 ± 2.6).

**Discussion**

The overall objective of this study was to quantitate the relative changes in regional vascular resistance and the neurogenic contribution to these changes during the onset of renal hypertension produced by acute RSt. We employed techniques that permitted the use of conscious, freely-moving rats, since it is well recognized that anesthetics can significantly alter humoral and sympathetic mechanisms and, in particular, markedly attenuate or abolish the centrally mediated cardiovascular actions of AII.21 Following acute RSt arterial
pressure and PRA increased immediately and saralasin markedly lowered arterial pressure. These data clearly demonstrate the primary contribution of the renin-angiotensin system and confirm earlier studies employing acute RSt in conscious dogs.14-26

While microsphere techniques have been employed to study regional resistance in chronic renal hypertension, little information exists concerning the changes in regional resistance during hypertension following acute RSt. Recently, Gavras and Liang23 examined changes in organ resistance with microspheres during acute RSt in conscious dogs. After 30 minutes of almost complete occlusion of blood flow to one kidney, resistance was increased in splanchnic organs, but was unchanged in skin and skeletal muscle which contrasts with the present observations in rats. The present study provides new information on continuous changes in regional resistance during the first several hours of acute renal hypertension. The mesenteric circulation exhibited the greatest increase in vascular resistance, which may partially result from the greater sensitivity of the mesenteric bed to norepinephrine and angiotensin relative to the hindquarters bed20 which predominately consists of skeletal muscle. The magnitude of the decrease in renal flow which was intermediate compared with the other two beds, would be expected to depend on an interaction between active vasoconstriction and the strong autoregulatory capacity of the kidney. In contrast to the mesenteric and renal vasculatures, hindquarters resistance showed a protracted increase over the first 4 hours after RSt (fig. 1). A major finding of this study is that after several hours of acute renal hypertension neurogenic vascular tone is not reduced, as might be expected by the persistent bradycardia presumably of reflex origin, but rather is maintained or slightly elevated above levels present under normotensive conditions. That baroreflex activation underlies the bradycardia during acute renal hypertension is supported by the observation that heart rate does not decrease in conscious rats (unpublished results) or dogs subjected to sinoaortic deafferentation during acute RSt-induced hypertension. Hence despite evidence for persistent baroreflex activation, neurogenic vascular tone remains high during acute renal hypertension.

The level of neurogenic vascular tone during acute renal hypertension may be viewed as "inappropriately" elevated for the attendant level of arterial pressure. This becomes particularly apparent when compared with phenylephrine induced hypertension of similar magnitude (fig. 4) wherein ganglionic blockade had no effect on arterial pressure. It is unlikely that this lack of effect of ganglionic blockade can be ascribed to maximal alpha-receptor stimulation by phenylephrine. The
dose of phenylephrine which we employed was well below that required to produce a maximal increase in arterial pressure mediated by alpha-receptor stimulation. Accordingly, if significant peripheral adrenergic nerve activity was present during phenylephrine hypertension, we would have expected binding of the released norepinephrine and the resultant additional vasoconstriction to be uncovered by a drop in arterial pressure after ganglionic blockade. Thus, since ganglionic blockade had no effect during phenylephrine hypertension, the data are best explained by a reflex withdrawal of neurogenic tone during phenylephrine but not All-dependent hypertension. Support for this interpretation comes from a recent study demonstrating that step-wise increases in arterial pressure with infusions of All into the vertebral artery of anesthetized rabbits produced significantly smaller reductions in lumbar sympathetic nerve activity and heart rate than for similar pressure elevations with phenylephrine infusion.

In the present study the dependency of vascular resistance and blood pressure on neurally mediated vasoconstrictor tone was estimated by the magnitude of the drop in these parameters after interruption of sympathetic transmission with a ganglionic blocking agent. This approach has been used by our laboratory to estimate sympathetic vascular tone in rats made hypertensive by baroreceptor deafferentation. It was found that ganglionic blockade reduced arterial pressure and vascular resistance in these hypertensive animals to the same plateau values as in normotensive animals, indicating that in a "purely" neurogenic model of hypertension the expected exaggeration in neural constrictor tone could be unmasked with this experimental approach. In the present study, ganglionic blockade markedly reduced arterial pressure and regional resistances during acute RH to plateau values which, however, were significantly higher than for normotensive animals after ganglionic blockade. This residual vasoconstriction probably largely reflects the direct vasoconstrictor actions of All. Thus, unlike hypertension produced by sinoaortic deafferentation, acute renal hypertension is not "purely" neurogenic in origin but involves both the renin-angiotensin and sympathetic nervous systems.

As evidenced by the lack of effect of ganglionic blockade on blood pressure during phenylephrine-induced hypertension, the hypotensive action of hexamethonium does not result from a direct effect on vascular smooth muscle, but rather evidence strongly supports its dependence on the existing level of sympathetically-derived vasoconstrictor tone. It is possible however, that vasodilation and hypotension produced by ganglionic blockade could induce autoregulatory changes to a variable degree depending on the particular vascular bed. Under the conditions of the present study, i.e., conscious instrumented animals, it is difficult to estimate the contribution that autoregulatory factors might make to the level of vascular resistance observed after ganglionic blockade. However, we feel that by obtaining the peak response to hexamethonium within one minute after administration, any autoregulatory effects would be minimized in our study.

The magnitude of the fall in arterial pressure and regional resistance in the hypertensive animals after ganglionic blockade could be enhanced due to an increase in vascular smooth muscle sensitivity to norepinephrine. Lack of consideration of this possibility could lead to false conclusions about the nature of the high neurogenic tone during acute RSt. There is evidence that increased vascular reactivity to norepinephrine occurs as early as 3 days after renal artery stenosis. Also, ganglionic blockade, which removes baroreflex buffering, may alone increase responsiveness to pressor agents. However, in the present study pressor responses and increases in vascular resistance produced by norepinephrine during ganglionic blockade were not increased during acute renal hypertension.

How is sympathetic vasoconstrictor tone maintained at an inappropriately high level during acute RSt? Clearly, elevation of plasma All is a key factor since saralasin significantly decreased arterial pressure and vascular resistance during acute renal hypertension. Several lines of evidence suggest that All can produce an increase in vasoconstrictor tone and blood pressure by actions on both central and peripheral aspects of the sympathetic nervous system. Administration of All into the brain via either the cerebral circulation or the cerebral ventricles increases arterial pressure by enhancing sympathetic outflow and vasopressin secretion. Interruption of sympathetic outflow by peripheral sympathectomy markedly reduces this response. Furthermore, pharmacological blockade of brain All receptors or surgical ablation of regions containing them abolishes the central pressor actions of bloodborne All. In addition to producing direct contraction of vascular smooth muscle, angiotension may also interact peripherally with the sympathetic nervous system through presynaptic receptors on vascular adrenergic endings to augment norepinephrine release for a given number of impulses. The present data do not allow a distinction to be made between these possibilities, since intravenous saralasin blocks All receptors at both central and peripheral sites of interaction with the sympathetic nervous system, and since ganglionic blockade interrupts all neurogenic vascular tone resulting from either existing nerve traffic or alterations in transmitter release. In recent unpublished studies however, we have demonstrated that removal of the central pressor actions of All through surgical ablation of a pathway in the anterior hypothalamus which mediates these effects significantly attenuates the development of hypertension following acute RSt. This suggests that a sympathoexcitatory action of All on the CNS underlies a portion of the rise in arterial pressure and relatively high neurogenic tone present at the onset of renal hypertension.

Since acute renal hypertension appeared to involve activation of both the renin-angiotensin and sympathetic nervous systems, we attempted to dissect the
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direct AII-mediated vasoconstrictor effects from the adrenergically mediated effects by comparing responses to acute RSt in normal rats and in animals subjected to adrenal demedullation and peripheral adrenergic sympathectomy with 6-OHDA, which does not penetrate the blood-brain barrier.44 If the presence of an inappropriately high level of neurogenic tone contributes to the onset of renal hypertension, then removal of this component should attenuate the severity of the hemodynamic changes, providing compensation by other factors does not occur. However, despite good evidence for peripheral sympathectomy, the development of acute renal hypertension was only modestly attenuated in the sympathectomized animals (fig. 5).

The failure of sympathectomy to produce a significant attenuation of the hemodynamic changes during RSt may rest in the ability of the renin-angiotensin system to compensate for loss of the adrenergic component. Sympathectomized animals exhibited lower arterial pressure and higher PRA values prior to RSt, which confirms other studies.21 25 26 During acute renal stenosis PRA increased to levels that were 3-fold higher in sympathectomized rats relative to values for PRA in intact animals during acute RSt. This suggests that a much greater degree of direct AII-mediated vasoconstriction was present during RSt in the absence of the sympathetic nervous system. Thus because of possible compensation by the renin-angiotensin system, one cannot interpret the failure to attenuate the hypertension by removal of one component, i.e., the adrenergic system, as evidence against its involvement in acute renal hypertension.

In summary, acute renal artery stenosis produced increases in arterial pressure and vascular resistance that were profoundly reduced by both angiotensin receptor antagonism and ganglionic blockade. Although the findings suggesting enhanced sympathetically mediated activity require confirmation by more direct methods, they suggest that a relatively high level of sympathetic vasoconstrictor tone, presumably dependent on indirect neural actions of AII, is present at the onset of acute renal hypertension.

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