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Pressor Responsiveness in Renal Prehypertensive Rabbits with a Denervated Kidney (42178)

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Abstract. Norepinephrine was infused iv at several doses into four groups of conscious rabbits (six per group), and the pressor responses were recorded. The groups were 3-day sham-operated rabbits; 3-day, two-kidney rabbits with unilateral renal artery stenosis (RAS); 3-day, two-kidney rabbits with unilateral renal denervation; and 3-day, two-kidney rabbits with unilateral renal denervation plus RAS of the denervated kidney. The rabbits with RAS of an innervated kidney and those with RAS of a denervated kidney had the same pressor responses to norepinephrine, which were greater than the pressor responses in the sham-operated rabbits or in the rabbits with a denervated kidney but without RAS. Four additional groups of similarly prepared rabbits were infused with norepinephrine at 800 ng/min/kg body wt, and mean arterial pressure and cardiac output were determined before and during norepinephrine infusion. The rabbits with RAS of an innervated or of a denervated kidney had greater increases in total peripheral resistance as well as in mean arterial pressure during norepinephrine infusion than did the two groups of rabbits without RAS. This indicated that the rabbits with RAS also had increased vascular responses to norepinephrine. The concentration of norepinephrine in six denervated kidneys was extremely low as compared to that of six innervated kidneys. Because renal denervation did not diminish pressor and vascular hyperresponsiveness in 3-day RAS rabbits, the signal that originates in the kidney following RAS and that results ultimately in pressor and vascular hyperresponsiveness is not mediated by renal nerves.

Many investigators have observed that patients with high blood pressure (1, 2), as well as animals with experimental hypertension (3, 4) have exaggerated increases in arterial pressure in response to pressor agents. Previous studies have found that rabbits with renal artery stenosis exhibit pressor hyperresponsiveness to norepinephrine (5, 6) and to vasopressin (7) prior to the development of hypertension. Similar results have also been reported in dogs (8, 9). The perturbations that occur within the kidney following renal artery stenosis must be detected by receptors or sensors within the kidney; the resulting signal must then leave the kidney to be expressed ultimately as increased responsiveness of the smooth muscle cells of the arterioles. The present study examined the possibility that this signal created by renal artery stenosis and which results in pressor and vascular hyperresponsiveness, leaves the kidney as a neuronal signal. This was tested by determining the pressor and vascular responses to norepinephrine in rabbits with renal artery stenosis of a denervated kidney.

Methods. Fifty-four male New Zealand white rabbits, weighing 2.90 to 3.15 kg, were caged individually in a constant environment of 27°C, with room lights controlled on a 12-h on/off cycle. All rabbits were fed a commercial diet (Purina Lab Rabbit Chow HF5326), which provided 167 meq of Na^+ and 467 meq of K^+/kg of feed. Water was available *ad libitum*. Three series of experiments were performed.

Surgical procedures. Each rabbit was anesthetized with halothane (2–5%) plus nitrous oxide, as described by Sartick *et al.* (10). With sterile procedures, the left kidney was exposed

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through a ventral midline laparotomy. In 30 rabbits the left kidney was denervated surgically, severing all visible nerve tissue that coursed with the renal artery and vein and then applying a 2% phenol solution to the area to destroy any remaining nerve tissue. In 12 of these renal denervated rabbits, a unilateral renal artery stenosis of the denervated kidney was produced by placing a silver clip with an internal gap size of 0.6 mm around the left renal artery, as described by Brooks and Muirhead (11). An additional 12 rabbits with innervated kidneys also received unilateral renal artery stenosis of the left kidney. Twelve rabbits were sham operated by a laparotomy without receiving renal denervation or renal artery stenosis. In all rabbits the right kidney was not disturbed. Following these surgical procedures, all rabbits were allowed to recover and were returned to their cages. An acute experiment was performed 3 days later in each rabbit.

On the morning of the acute experiment, the 48 rabbits used in experiments 1 and 2 were again anesthetized as before, and polyvinyl catheters (Fr 5 infant feeding tubes) were inserted into the aorta and inferior vena cava via the femoral artery and vein. In the 24 rabbits for experiment 2, an additional catheter of this type was placed in the jugular vein so that the tip of the catheter would lie near the right atrium. A small polyethylene catheter (PE 50 tubing) also was inserted percutaneously into a marginal ear vein. Each rabbit was allowed to recover and was placed in a rectangular box to limit its movements; while in this box the rabbits were unrestrained and were restricted only by the size of the box. The acute experiments were performed 6 hr later on conscious rabbits, while in the box.

Experiment 1: Pressor responses to norepinephrine. This experiment used six sham-operated rabbits, six rabbits with unilateral renal artery stenosis (two-kidney one-clip), six rabbits with a denervated kidney, and six rabbits with a denervated kidney plus renal artery stenosis of the denervated kidney. At the start of the experiment an arterial blood sample (2 ml) was obtained for plasma renin activity. The blood sample was added to a chilled tube containing ethylenediaminetetraacetate (EDTA); the sample was spun in a refrigerated centrifuge, and the plasma was stored at −14°C until a later time, when it was processed and assayed. Mean arterial pressure was measured with a pressure transducer and was recorded on an oscillographic recorder (Hewlett-Packard, Model 7754B). After a 5-min initial control measurement of mean arterial pressure was obtained, the gain of the recorder amplifier was increased so that a 1 mm Hg change in mean arterial pressure would produce a 1 mm pen deflection on the recorder, and the pen was positioned near the lower portion of the recording channel by means of a zero-suppression control; this allowed the recording of small changes in mean arterial pressure. Solutions of norepinephrine were prepared in 5% dextrose in water. While mean arterial pressure was being recorded continuously, norepinephrine was infused iv at doses of 25, 50, 100, 200, 400, 800, and 1200 ng/min/kg of body wt, with a syringe infusion pump. Each norepinephrine solution was infused for 5 min, and at least 5 min were allowed between infusions for the mean arterial pressure to return to the preinfusion level and to stabilize. The mean arterial pressure during the 1-min period prior to norepinephrine infusion was taken as the control pressure, and the increase in mean arterial pressure that occurred by the fifth min of infusion was taken as the pressor response.

Experiment 2: Vascular responses to norepinephrine. As in experiment 1, this experiment also used six sham-operated rabbits, six rabbits with unilateral renal artery stenosis, six rabbits with a denervated left kidney, and six rabbits with a denervated left kidney plus renal artery stenosis of the denervated kidney. At the start of the experiment an arterial blood sample (2 ml) was collected for plasma renin activity. Each rabbit was then given 1000 units of heparin iv. Control measurements were obtained for mean arterial pressure and cardiac output. Cardiac output was determined by dye dilution, as described previously (12). Blood was pumped from the arterial catheter and through a densitometer cuvette (Waters Instruments, Model DC-410), at a rate of 10.0 ml/min, by a roller pump; the blood was returned to the rabbit through the femoral catheter. A volume of 0.15 ml of indocyanine green dye (Cardio-Green; Hynson, Westcott, and Dunning, Inc.), with a dye concentration of 2.5 mg/ml, was placed in the jugular catheter

and was flushed into the circulation with 0.8 ml of sterile saline. The densitometer cuvette was interfaced with a densitometer (Waters Instruments, Model TD-1), and the dye concentration curves were recorded on the oscillographic recorder. All cardiac output determinations were performed in triplicate, and the average of the three determinations was accepted as the cardiac output value.

Following these control measurements, the gain of the recorder amplifier was increased, as in experiment 1. A solution of norepinephrine, prepared as in experiment 1, was infused iv at a dose rate of 800 ng/min/kg of body wt, for 5 min, and the pressor response was recorded. During the final minute of norepinephrine infusion, cardiac output again was determined.

Cardiac output values were expressed in milliliters per minute per kilogram of body weight. Values for total peripheral resistance (TPR) were expressed in the arbitrary units that result from dividing the mean arterial pressure in mm Hg, by the cardiac output in milliliters per minute per kilogram of body weight.

Experiment 3: Norepinephrine concentrations in denervated kidneys. To evaluate the effectiveness of the renal denervation procedures, six rabbits received only a left renal denervation. Three days later these rabbits were killed, both kidneys were quickly removed, and tissue sections of 200–400 mg each were obtained from the cortex of each kidney. These kidney sections were weighed, frozen at −70°C, and were assayed later for norepinephrine content.

Analytical procedures. Plasma renin activity was determined by radioimmunoassay of generated angiotensin I, by a modification of the method of Cohen *et al.* (13). This procedure, as used in our laboratory, has been described previously in detail (12). Values for plasma renin activity were expressed as nanogram of generated angiotensin I per milliliter of plasma, per hour of incubation. Norepinephrine was extracted from the kidney samples by the procedures described by Anton and Sayres (14). The kidney samples were homogenized in a tissue grinder with 1.5 *M* Tris buffer, pH 8.7. The homogenate was centrifuged and filtered, and the norepinephrine was extracted from the filtrate by adsorbing it to acid-washed alumina. The norepinephrine was eluted from the alumina with 0.1 *M* perchloric acid. The recovery of dihydrobenzylamine, added to the filtrate prior to the extraction with alumina, permitted the determination of the recovery of norepinephrine from the sample. Concentrations of norepinephrine and dihydrobenzylamine in the final solution were assayed by high-performance liquid chromatography, with a reverse-phase C-18 column, 25 cm in length (Rainin Instrument Co.), and an electrochemical detection system. Norepinephrine concentrations were expressed as nanogram per gram of renal cortex.

Statistics. Values for body weight, plasma renin activity, mean arterial pressure, and the increases in mean arterial pressure in response to infusions of the various doses of norepinephrine were tested for differences among the four groups of rabbits in experiment 1 by analysis of variance (15); when significant ($P < 0.05$) values were obtained the data were tested further by Duncan's new multiple range test (15). In experiment 2, the values for body weight and plasma renin activity, and the initial values for mean arterial pressure, cardiac output, and TPR also were tested by analysis of variance and Duncan's new multiple range test. The changes in mean arterial pressure, cardiac output, and TPR that occurred during norepinephrine infusion were tested by the *u* test (15) to determine if the change was significant; when significant ($P < 0.05$) changes were found, the magnitudes of the changes among the four groups of rabbits were tested by analysis of variance plus Duncan's new multiple range test.

Results. *Experiment 1: Pressor responses to norepinephrine.* As indicated in Table I, there were no significant differences among the four groups of rabbits in the initial values for body weight, plasma renin activity, or mean arterial pressure. Figure 1 gives the dose–response curves for the pressor responses to the various doses of norepinephrine for all four groups of rabbits. These curves represent the best-fit of the data for each group to the equation $y = a(\log x)^n$, where y is the pressor response, x is the norepinephrine dose, and a and n are constants. The pressor responses for the rabbits with renal artery stenosis, both with innervated and with denervated kidneys, were significantly greater than for the rabbit groups with-

TABLE I. VALUES FOR BODY WEIGHT, MEAN ARTERIAL PRESSURE, AND PLASMA RENIN ACTIVITY (EXPERIMENT 1)

	Body weight (kg)	Mean arterial pressure (mm Hg)	Plasma renin activity
3-Day sham (renal innervated)	3.10 ± 0.05	94 ± 4	3.0 ± 0.6
3-Day RAS (renal innervated)	3.06 ± 0.06	97 ± 3	3.2 ± 0.5
3-Day sham (renal denervated)	3.11 ± 0.04	99 ± 2	3.4 ± 0.8
3-Day RAS (renal denervated)	3.04 ± 0.02	97 ± 5	2.7 ± 0.4

Note. Values are means ± SEM for six rabbits per group. Sham = two-kidney sham-operated rabbits; RAS = two-kidney rabbits with unilateral renal artery stenosis. Values for plasma renin activity are ng of generated angiotensin I per ml of plasma per hr of incubation. There were no significant differences among the four groups for any of the values.

out renal artery stenosis, at all doses of norepinephrine except the lowest dose. The rabbits without renal artery stenosis and with denervated left kidneys had the same pressor responses to norepinephrine at all doses as did the rabbits without renal artery stenosis and with innervated left kidneys. Also, no significant differences were observed for the pressor responses to any norepinephrine dose between the renal artery stenosis rabbit group with denervated left kidneys and the renal artery stenosis rabbits with innervated left kidneys.

Experiment 2: Vascular responses to norepinephrine. The initial values for the rabbits in experiment 2 are summarized in Table II. There were no significant differences in these

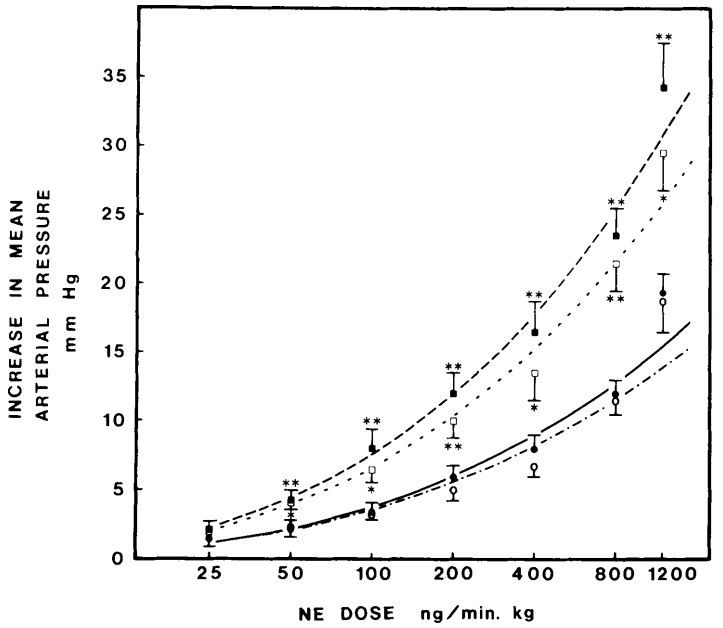

FIG. 1. Increases in mean arterial pressure (mm Hg) in response to infusions of norepinephrine (ng/min/kg body wt; logarithmic scale) in four groups of rabbits in experiment 1. Black squares and dashed line = 3-day renal artery stenosis rabbits with innervated kidney. Open squares and dotted line = 3-day renal artery stenosis rabbits with denervated kidney. Black circles and solid line = sham-operated rabbits with innervated kidney. Open circles and dot-dashed line = sham-operated rabbits (without renal artery stenosis) with denervated kidney. Values are means ± SEM for six rabbits per group. Lines represent best fit of the data for each group to the equation: $y = a(\log x)^n$. *$P < 0.05$ and **$P < 0.01$ that the value is greater than the corresponding value for the sham-operated group with innervated kidney.

TABLE II. INITIAL VALUES FOR BODY WEIGHT, MEAN ARTERIAL PRESSURE, CARDIAC OUTPUT, TOTAL PERIPHERAL RESISTANCE, AND PLASMA RENIN ACTIVITY (EXPERIMENT 2)

	Body weight (kg)	Mean arterial pressure (mm Hg)	Cardiac output (ml/min kg)	TPR	Plasma renin activity
3-Day sham (renal innervated)	3.10 ± 0.05	95 ± 4	222 ± 19	0.44 ± 0.04	3.5 ± 0.8
3-Day RAS (renal innervated)	3.08 ± 0.06	96 ± 4	219 ± 17	0.45 ± 0.04	3.2 ± 0.9
3-Day sham (renal denervated)	3.09 ± 0.05	96 ± 3	237 ± 22	0.42 ± 0.03	3.3 ± 1.0
3-Day RAS (renal denervated)	3.11 ± 0.07	99 ± 3	236 ± 19	0.43 ± 0.03	2.7 ± 0.5

Note. Values are means ± SEM for six rabbits per group. Sham = two-kidney sham-operated rabbits; RAS = two-kidney rabbits with unilateral renal artery stenosis. Values for total peripheral resistance (TPR) determined by dividing mean arterial pressure (mm Hg) by cardiac output (ml/min/kg body wt). Values for plasma renin activity are ng of generated angiotensin I per ml of plasma per hr of incubation. There were no significant differences among the four groups for any of the values.

initial values among the four groups of rabbits. The changes in mean arterial pressure, cardiac output, and TPR in response to norepinephrine infused at 800 ng/min/kg body weight are given in Table III. Norepinephrine infusion resulted in significant ($P < 0.01$) increases in mean arterial pressure and in TPR in each group of rabbits, while no significant changes in cardiac output were observed. The magnitudes of the increases in mean arterial pressure and TPR were significantly ($P < 0.01$) greater in the two groups of rabbits with renal artery stenosis, both with denervated and with innervated kidneys, than in the two groups of rabbits without renal artery stenosis.

Experiment 3: Norepinephrine concentrations in denervated kidneys. The concentrations of norepinephrine in the cortex of the innervated kidneys averaged 134 ± 8 (SEM) ng/g of kidney, while the denervated kidneys had an average norepinephrine concentration of only 6.5 ± 1.6 ng/g. These very low amounts of norepinephrine in the denervated kidneys provided evidence for the completeness of the denervation.

Discussion. Previous studies from this laboratory have found that both one-kidney rabbits and two-kidney rabbits with unilateral renal artery stenosis of 3-days duration have exaggerated pressor responses to norepineph-

TABLE III. CHANGES IN MEAN ARTERIAL PRESSURE, CARDIAC OUTPUT, AND TPR DURING INFUSION OF NOREPINEPHRINE (EXPERIMENT 2)

	Δ Mean arterial pressure (mm Hg)	Δ Cardiac output (ml/min kg)	Δ TPR
3-Day sham (renal innervated)	+14 ± 1[a]	0 ± 6	+0.06 ± 0.01[a]
3-Day RAS (renal innervated)	+24 ± 2[a,b]	−14 ± 6	+0.14 ± 0.02[a,b]
3-Day sham (renal denervated)	+14 ± 1[a]	+2 ± 3	+0.06 ± 0.01[a]
3-Day RAS (renal denervated)	+24 ± 4[a,b]	−26 ± 15	+0.19 ± 0.05[a,b]

Note. Values are means ± SEM for six rabbits per group. Sham = two kidney sham-operated rabbits; RAS = two-kidney rabbits with unilateral renal artery stenosis. Values for total peripheral resistance (TPR) determined by dividing mean aterial pressure (mm Hg) by cardiac output (ml/min/kg body wt). Norepinephrine infusion dose was 800 ng/min/kg body wt.

[a] $P < 0.01$ that a change occurred during norepinephrine infusion.

[b] $P < 0.01$ that the magnitude of the change is greater than for the corresponding sham-operated rabbit group.

rine to the same extent as do rabbits with renal artery stenosis of 30-days duration and hypertension (5, 6). However, 3-day renal artery stenosis rabbits have normal values for mean arterial pressure and plasma renin activity. Thus, the changes in mean arterial pressure that result from norepinephrine infusions occur from the same basal value in both the clipped and the control rabbits. Likewise, in the present study the values for mean arterial pressure and plasma renin activity in experiment 1, plus the values for cardiac output and TPR in experiment 2 were approximately the same among the four groups of rabbits in each experiment.

The results of experiment 1 indicate that rabbits with renal artery stenosis of a denervated kidney have enhanced pressor responses to norepinephrine to the same extent as rabbits with renal artery stenosis of an innervated kidney. Thus, renal denervation does not attenuate the pressor hyperresponsiveness to norepinephrine in two-kidney rabbits with 3-day renal artery stenosis. The results of experiment 2 reveal that the pressor hyperresponsiveness to norepinephrine in the two groups of rabbits with renal artery stenosis was accompanied by greater increases in TPR than in the sham-operated rabbits or the rabbits with renal denervation without renal artery stenosis. Because these greater increases in TPR are presumed to be due to exaggerated contractions of arteriolar smooth muscle cells in response to norepinephrine, the pressor hyperresponsiveness is a reflection of vascular hyperresponsiveness in these rabbits.

Expansion of extracellular fluid volume by the infusion of saline (16) or by the administration of deoxycorticosterone acetate plus the ingestion of isotonic saline for a drinking fluid (17) has been seen to result in pressor and vascular hyperresponsiveness in rabbits. It may be conjectured that pressor and vascular hyperresponsiveness following renal artery stenosis could be due to diminished ability of the kidneys to maintain a normal fluid balance, with an increase in extracellular fluid volume. However, measurements of plasma volume, extracellular fluid volume, and total body water in two-kidney rabbits with 3-day unilateral renal artery stenosis have shown that these fluid volumes are not altered (6).

Renal artery stenosis causes perturbations in the kidney which are sensed by some detecting system within the kidney. After detection, the resulting signal must pass from the kidney by some means, to be expressed eventually as increased responsiveness of the arteriolar smooth muscle cells. The two most likely ways for a signal from one organ to be transmitted to a distant organ or tissue are by neuronal mechanisms or by hormonal mechanisms. There is evidence for afferent neuronal fibers from the kidney (18, 19), and renal denervation has been reported to reduce the arterial pressure in animals with renal hypertension (20–23). However, in the present study, renal denervation did not alter the pressor and vascular hyperresponsiveness in 3-day renal artery stenosis rabbits. These findings indicate that neuronal mechanisms are not involved in transmitting the signal from the kidney for pressor and vascular hyperresponsiveness. This suggests that a hormonal signal from the kidney mediates pressor and vascular hyperresponsiveness following renal artery stenosis.

Previous studies (24) have provided evidence for a hormonal mechanism being involved in mediating pressor hyperresponsiveness in 3-day renal artery stenosis rabbits; the cross-circulation of blood between rabbits with 3-day renal artery stenosis and normal rabbits resulted in the transfer of pressor hyperresponsiveness to the normal rabbits. These earlier studies, however, did not eliminate the possibility that following renal artery stenosis a neuronal signal from the kidney could elicit the release of a hormonal hyperresponsiveness factor from some other organ. The findings of the present study suggest that the hormonal factor responsible for mediating pressor hyperresponsiveness may be of renal origin, although the possibility of a multiple hormonal system being involved in relaying pressor hyperresponsiveness cannot be excluded.

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