Effect on Pressor and Vascular Responsiveness in Rabbits of Drugs That Decrease Norepinephrine Uptake (43774)

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Abstract. **The purpose of this study was to determine if decreases in norepinephrine (NE) uptake would result in pressor and vascular hyperresponsiveness to vasoconstrictor substances. These experiments examined the effects of cocaine and imipramine, drugs known to decrease NE uptake, on the changes in arterial pressure and total peripheral resistance (TPR) in response to NE and arginine vasopressin (AVP) in conscious rabbits. The infusion of graded doses of NE resulted in significantly greater increases in mean arterial pressure at all dose levels following the administration of cocaine (0.6 mg/kg iv) or imipramine (0.5 mg/kg) than following the administration of the vehicle alone. The infusion of NE also resulted in greater increases in TPR as well as blood pressure following cocaine or imipramine administration than occurred prior to the administration of these drugs. The infusion of AVP caused significantly larger increases in arterial pressure and in TPR following cocaine or imipramine administration than was seen after the administration of AVP to control rabbits not treated with these drugs. These studies demonstrated that cocaine and imipramine, substances known to decrease NE uptake by the sympathetic nerve terminals, will induce pressor and vascular hyperresponsiveness to NE and AVP in rabbits. These results are in keeping with the concept that pressor and vascular hyperresponsiveness in renal prehypertensive rabbits may be the result of decreases in NE uptake by sympathetic fibers supplying vascular smooth muscle cells.** [P.S.E.B.M. 1994, Vol 206]

Patients with hypertension (1–3), as well as animals with experimental hypertension (4–7), have exaggerated increases in arterial blood pressure in response to the infusion of standard doses of a variety of pressor substances. We have demonstrated that this occurs in rabbits with renal artery stenosis before they develop hypertension (5–7). We have hypothesized that this pressor and vascular hyperresponsiveness may be caused by a decrease in norepinephrine (NE) uptake by the sympathetic nerves supplying arteriolar vascular smooth muscle cells. This could result in increased concentrations of NE in the synaptic cleft, causing a partial depolarization of the cell membrane of the vascular smooth muscle cells, thus making them more responsive to vasoconstrictor substances. The present study tested this hypothesis by examining the effects of cocaine and imipramine, drugs known to decrease NE uptake (8–11), on the changes in mean arterial pressure and in total peripheral resistance (TPR) in response to infusions of NE and arginine vasopressin (AVP) in rabbits.

Materials and Methods

Male, New Zealand white rabbits, ranging from 2.8 to 3.2 kg in body weight, were used in these experiments. All rabbits were fed a commercial diet (Purina Lab Rabbit Chow HF5326) containing 0.167 mEq Na^+ and 0.467 mEq K^+ per gram. The rabbits were caged individually in a constant environmental temperature of 27°C. Illumination of the room was controlled by an automatic time switch that provided light from 7:00 AM to 7:00 PM daily. All rabbits were housed

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for at least 1 week after shipping before being used in experiments.

All rabbits were anesthetized with halothane (3%–5%) in nitrous oxide and oxygen, which was administered with a face mask, as described by Sartick *et al.* (12). With sterile surgical procedures, polyvinyl catheters (Fr 5 infant feeding tubes) were placed in the lower aorta and inferior vena cava via the femoral artery and vein. For the rabbits in which cardiac output was to be determined, an additional catheter was placed in the jugular vein so that the catheter tip lay near the right atrium. All catheters were filled with heparinized saline. The skin incisions were closed, and each rabbit was removed from the anesthesia and placed in a rectangular box (32 × 13 × 18.5 cm) to limit its movements. The rabbit remained in the box until the conclusion of the experiment. The acute experiments were performed 3 hr later on conscious rabbits. Three series of experiments were performed.

Experiment 1: Pressor Responsiveness to Norepinephrine Following Cocaine or Imipramine Administration. Eighteen rabbits were used in this experiment. At the start of the experiment an arterial blood sample of 2 ml for measurement of plasma renin activity (PRA) was collected in a chilled tube containing ethylenediamine tetraacetate (EDTA) and placed in an ice bath. Mean arterial pressure was recorded for 5 min through the arterial catheter with a pressure transducer (Statham P23Db), and arterial pressure was recorded on an oscillographic recorder (Model 7754B, Hewlett-Packard, Waltham, MA). Heart rate was measured by recording pulsatile arterial pressure at a fast paper speed (10 mm/sec). Six rabbits then received an iv injection of cocaine (0.6 mg/kg body wt, in isotonic saline); another six rabbits received an injection of imipramine (0.5 mg/kg body wt in 2 ml saline, over 2 min). A control group of six rabbits received 2.0 ml of saline alone. Mean arterial pressure was recorded continuously for an additional 10 min, then heart rate was recorded as previously. Ten minutes after the injection of the drugs or saline alone, heart rate was again measured, and a second arterial blood sample was obtained for the measurement of PRA. The gain of the recorder amplifier was then increased so that a 1 mm Hg change in mean arterial pressure would produce a 1 mm pen deflection; the recorder pen was positioned near the lower portion of the recorder channel by the use of a zero suppression control on the recorder amplifier. Solutions of NE (Levophed, Breon Laboratories) were then infused iv at dose rates of 25, 50, 100, 200, 400, and 800 ng/min/kg body wt, and the pressor response to each dose was recorded. The NE solutions were in 5% dextrose and were prepared fresh at the start of each experiment. Each NE solution was infused for 5 min, at a flow rate of either 0.34 or 0.68 ml/min; 5 min were allowed between infusions to allow the mean arterial pressure to return to normal. Blood samples for PRA were spun in a refrigerated centrifuge, and the plasma samples were stored frozen. Later, PRA was determined by the radioimmunoassay of generated angiotensin I, by a modification of the method of Cohen *et al.* (13). This assay, as used by our laboratory, has been described earlier (14). Values for PRA are expressed in ng of generated angiotensin I per ml of plasma, per hr of incubation.

Experiment 2: Vascular Responsiveness to Norepinephrine Following Cocaine or Imipramine Administration. In each of 12 rabbits, mean arterial pressure and heart rate were recorded as in Experiment 1. Cardiac output was then measured by indicator dilution. For the cardiac output measurements, each rabbit was heparinized (1000 units, iv). Blood was then pumped from the arterial catheter through a densitometer cuvette (Model DC-410, Waters Instruments, Rochester, MN) at a rate of 10.0 ml per min by a roller pump. The blood was returned to the rabbit through the femoral venous catheter. A volume of 0.150 ml of indocyanine green dye (Cardio-green; Hynson, Westcott, and Dunning, Inc.) with a concentration of 2.5 mg/ml, was placed in the jugular catheter and was flushed into the circulation with 0.8 ml of saline. The densitometer cuvette was interfaced with a densitometer (Model TD-1, Waters Instruments, Rochester, MN), and the dye concentration curves were recorded on the oscillographic recorder. All cardiac output measurements were performed in triplicate, and the average of the three determinations was accepted as the cardiac output value. Following this initial measurement of cardiac output, the gain of the recorder amplifier was increased as in Experiment 1. Each rabbit was then infused with NE iv at 800 ng/min/kg body wt for 5 min, and the pressor response was recorded as in Experiment 1. During the final minute of NE infusion, heart rate and cardiac output again were determined. After the infusion of NE, each rabbit was undisturbed for 30 min. At that time, mean arterial pressure, heart rate, and cardiac output were again measured. Each rabbit then received an iv injection of cocaine or imipramine as earlier, and mean arterial pressure was recorded continuously for the next 10 min. Heart rate and cardiac output were again determined. Each rabbit was then infused with NE (800 ng/min/kg) as before, and the pressor response was noted. Heart rate and cardiac output were determined during the 5th min of NE infusion. Cardiac output values were expressed in ml/min/kg body wt. Values for TPR were expressed in the arbitrary units that result from dividing the mean arterial pressure in mm Hg by the cardiac output in ml/min/kg body wt.

Experiment 3: Pressor and Vascular Responses to Vasopressin Following Cocaine or Imipramine Administration. This experiment used

18 rabbits. Mean arterial pressure, heart rate, and cardiac output were measured in all rabbits, as in Experiment 2. Six rabbits then received cocaine, and another six rabbits received imipramine, as in the other experiments. An additional six rabbits (controls) received the saline vehicle alone. Mean arterial pressure was recorded continuously for 10 min after the administration of cocaine, imipramine, or vehicle alone, at which time the heart rate and cardiac output again were determined. The gain of the recorder was then increased. Each rabbit then received an iv infusion of AVP (Sigma Chemical Co., St. Louis, MO) at a dose rate of 5 mU/min/kg body wt, for 5 min, and the pressor response was noted. During the final minute of AVP infusion the heart rate and cardiac output again were measured.

Statistics. Student's *t* test for paired observations (15) was used to analyze the changes in mean arterial pressure and heart rate following the administration of cocaine or imipramine for the pool of all rabbits in all three series of experiments. This statistic also was used to test for the effects of cocaine and imipramine on cardiac output and TPR for the combined rabbits in Experiment 2 and 3. For Experiment 1, the changes in PRA within each group following the administration of cocaine, imipramine, or vehicle were also analyzed by Student's *t* test for paired observations.

For Experiment 1, the initial values for heart rate, arterial pressure, and PRA were compared among the 3 groups of rabbits that were to be treated with cocaine, imipramine, or vehicle by analysis of variance (15). The pressor responses of the cocaine-treated rabbits and the imipramine-treated rabbits were compared with the responses of the control rabbits for each dose of NE by Dunnett's test (16, 17).

Initial values for mean arterial pressure, heart rate, cardiac output, and TPR between the rabbits to be treated with cocaine and those to be treated with imipramine in Experiment 2 were compared by Student's *t* test for group observations; this test statistic was also used to compare the changes in mean arterial pressure, heart rate, cardiac output, and TPR between these two groups prior to the administration of cocaine or imipramine. The effect of NE infusion on these factors within each group, both before and after the administration of cocaine or imipramine, were tested by Student's *t* test for paired observations. Within the cocaine- and the imipramine-treated groups, the magnitudes of the changes in mean arterial pressure, heart rate, cardiac output, and TPR, during NE infusion before versus after the administration of these drugs, were tested by Student's *t* test for paired observations.

In the third experiment, initial values for heart rate, mean arterial pressure, cardiac output, and TPR between the three groups of rabbits were compared by analysis of variance. The changes in these values within each rabbit group with the administration of AVP within each group were evaluated by Student's *t* test for paired observations. Dunnett's test was the statistic used to determine if the magnitudes of the changes in heart rate, mean arterial pressure, cardiac output, and TPR that occurred during the infusion of AVP in the cocaine- and the imipramine-treated groups were different from the magnitude of the changes in these factors that occurred during AVP infusion in the control group.

Results

Effect of Cocaine and Imipramine on the Cardiovascular System. The effects of cocaine and imipramine alone on the cardiovascular system of all rabbits in this study are summarized in Table I. The administration of cocaine resulted in a rapid rise in blood pressure (average 15 ± 2 mm Hg), which lasted less than 1 min before decreasing. Ten minutes after cocaine administration, mean arterial pressure had fallen to a level significantly below the initial values. Heart rate was increased significantly ($P < 0.01$) following cocaine. Cardiac output was unaltered by cocaine, but TPR decreased ($P < 0.05$). PRA showed a significant ($P < 0.01$) decrease with cocaine, despite a fall in arterial pressure. Imipramine administration had no effect on mean arterial pressure or heart rate, but

Table I. Cardiovascular Values Before and After Cocaine or Imipramine Administration

	Mean arterial pressure	Heart rate	Cardiac output	TPR	PRA
Before cocaine	100 ± 2	267 ± 8	171 ± 9	0.59 ± 0.03	5.3 ± 0.7
After cocaine	88 ± 2[a]	288 ± 10[a]	166 ± 11	0.53 ± 0.04[b]	2.9 ± 0.7[a]
No. of rabbits	18	18	12	12	6
Before imipramine	101 ± 1	252 ± 7	173 ± 5	0.59 ± 0.02	4.6 ± 0.8
After imipramine	99 ± 1	258 ± 6	163 ± 4[a]	0.60 ± 0.02	5.0 ± 1.1
No. of rabbits	18	18	12	12	6

Note. Values are means ± SEM. Mean arterial pressure values are in mm Hg; heart rates are in bpm; cardiac output values are in ml/min/kg body wt; TPR = total peripheral resistance (mean arterial pressure/cardiac output); PRA = plasma renin activity, in ng of generated angiotensin I/ml of plasma, per hr of incubation. [a] $P < 0.01$ and [b] $P < 0.05$ that the value is different from the value before administration of the drug.

there was a slight but consistent decrease in cardiac output ($P < 0.01$); TPR and renin levels were unaffected by imipramine.

Experiment 1: Pressor Responsiveness to Norepinephrine Following Cocaine or Imipramine Administration. There were no significant differences in the initial values for mean arterial pressure, heart rate, and PRA among the three groups in this experiment. Figure 1 gives the pressor responses to NE, with the doses of NE plotted on a logarithmic scale on the abscissa and the increases in mean arterial pressure which resulted from each dose on the ordinate, for the control rabbits, those given cocaine, and those given imipramine. The equation $y = a(\log x)^n$ best describes those dose-response relationships, where y is the increase in mean arterial pressure, x is the dose of NE, while a and n are derived constants. The cocaine- and the imipramine-treated groups had significantly greater increases in mean arterial pressure in response to each dose of NE than did the control rabbits.

Experiment 2: Vascular Responsiveness to Norepinephrine Following Cocaine or Imipramine Administration. The values for mean arterial pressure, cardiac output, and TPR for the cocaine- and the imipramine-treated groups in this experiment are summarized in Figure 2 and 3, respectively. Infusion of NE prior to the administration of cocaine produced significant ($P < 0.01$) increases in mean arterial pressure and in TPR without significant changes in cardiac output. Heart rate decreased significantly ($P < 0.01$) from 265 ± 5 (SEM) to 182 ± 11 bpm during NE infusion prior to the cocaine administration. Infusion of NE after cocaine administration again produced significant ($P < 0.01$) increases in mean arterial pressure and TPR, while cardiac output was unaltered. Heart rate again decreased ($P < 0.01$) from 303 ± 14 to 176 ± 16 bpm with NE infusion.

For the rabbits to be given imipramine, the initial infusion of NE resulted in significant ($P < 0.01$) in-

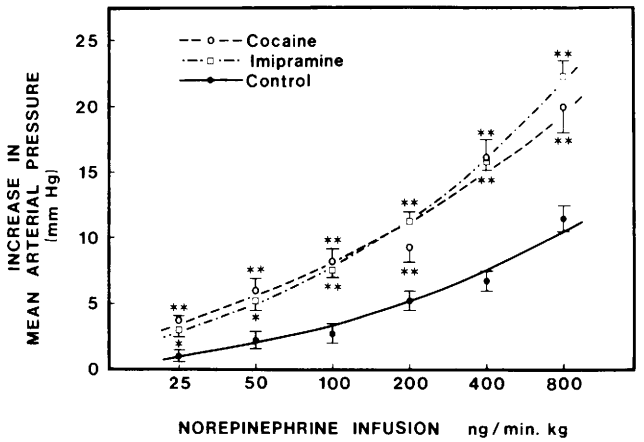

Figure 1. Increases in mean arterial pressure (mm Hg) in response to infusions of norepinephrine (ng/min/kg body wt, logarithmic scale) for the rabbits in Experiment 1. Closed circles and solid line = control rabbits. Open circles and dashed line = rabbits given cocaine (0.6 mg/kg body wt). Open squares and dot-dashed line = rabbits given imipramine (0.5 mg/kg body wt). Values are means ± SEM for six rabbits per group. Lines represent best fit of the data for each group to the equation $y = a(\log x)^n$. $^{**}P < 0.01$ that the value is greater for the cocaine-treated group or the imipramine-treated group than for the control group, by Dunnett's test.

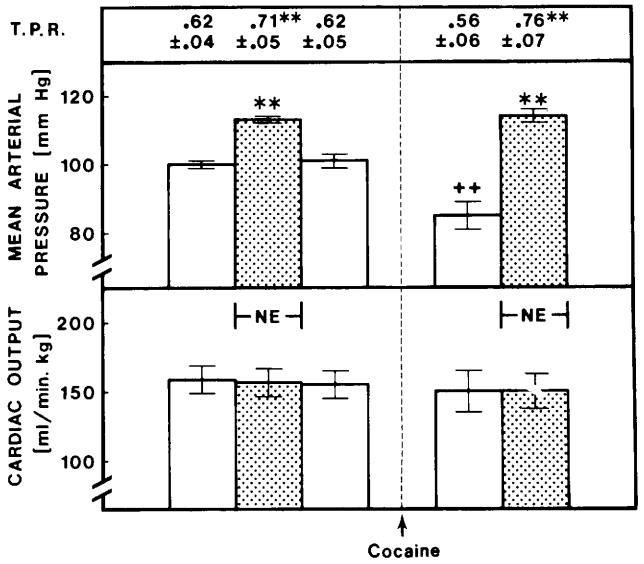

Figure 2. Effect of iv infusion of norepinephrine (NE, 800 ng/min/kg body wt; shaded bars) on mean arterial pressure, cardiac output, and total peripheral resistance (TPR) in rabbits before and after administration of cocaine (0.6 mg/kg body wt; dotted line). Values are means ± SEM for six rabbits per group. $^{**}P < 0.01$ that an increase occurred (paired Student's t) during norepinephrine infusion; $\dagger\dagger P < 0.01$ that a change occurred (paired Student's t) after cocaine administration.

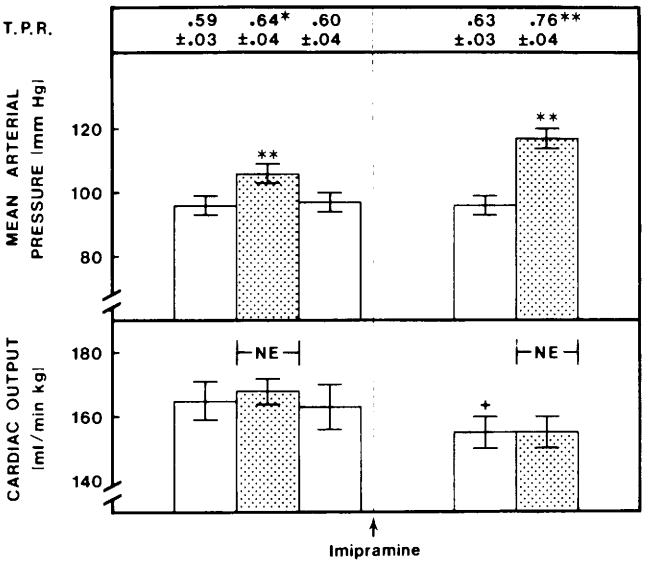

Figure 3. Effect of iv infusion of norepinephrine (NE, 800 ng/min/kg body wt; shaded bars) on mean arterial pressure, cardiac output, and total peripheral resistance (TPR) in rabbits before and after administration of imipramine (0.5 mg/kg body wt; dotted line). Values are means ± SEM for six rabbits per group. $^{**}P < 0.01$ that an increase occurred (paired Student's t) during norepinephrine infusion; $\dagger P < 0.05$ that a change occurred (paired Student's t) after imipramine administration.

creases in mean arterial pressure and in TPR, but with no changes in cardiac output. Heart rate decreased ($P < 0.05$) from 214 ± 7 (SEM) to 185 ± 6 bpm during this infusion of NE. Infusion of NE after the administration of imipramine again resulted in significant ($P < 0.01$) increases in mean arterial pressure and TPR, with significant ($P < 0.01$) decreases in heart rate from 235 ± 13 to 166 ± 11 bpm; cardiac output was unchanged by NE infusion.

The most important data for this experiment are comparisons of the magnitudes of the changes in the mean arterial pressure and TPR resulting from NE infusion before and after the administration of cocaine or imipramine. These comparisons are summarized in Table II. Treatment with each of these drugs resulted in significant ($P < 0.01$) enhancements of the pressor responses to NE, as well as significantly greater increases in TPR with NE infusion.

Experiment 3: Pressor and Vascular Responses to Vasopressin Following Cocaine or Imipramine Administration. The initial values for heart rate, mean arterial pressure, cardiac output, and TPR did not vary among the three groups of rabbits in this experiment. The infusion of AVP caused significant ($P < 0.01$) increases in mean arterial pressure and TPR, with significant ($P < 0.01$) decreases in cardiac output and heart rate in all three groups (Fig. 4–6). Table III summarizes the magnitudes of these changes with AVP infusion for all three groups. The decreases in cardiac output with AVP for the cocaine- and the imipramine-treated rabbits were not significantly different from the decreases seen in the control rabbits. However, the rabbits that had received cocaine or imipramine had significantly greater increases in both arterial pressure and TPR during AVP infusion than did the nontreated control group.

Discussion

In this study, the administration of cocaine to conscious rabbits resulted in a transient increase in mean arterial pressure, followed by a prolonged decrease in arterial pressure. This decrease in mean arterial pressure was accompanied by a decrease in TPR, while cardiac output was not greatly altered (Fig. 2 and 4). Pitts *et al.* (18) studied the effect of a similar dose of cocaine on arterial pressure in conscious rats and also found an immediate but transitory increase in arterial pressure, but they observed that the arterial pressure subsequently returned to the precocaine levels rather than decreasing to subnormal values. Studies in conscious dogs (19) and in humans (20) have found that cocaine produced large and prolonged increases in arterial pressure. It is not clear why cocaine produced decreases in arterial pressure and TPR in the conscious rabbits in the present study instead of the elevations in blood pressure seen by others in other animal species. Imipramine, on the other hand, in the dose used in this study, did not produce significant reductions in arterial pressure but did cause slight yet consistent decreases in cardiac output (Fig. 3 and 5). Sigg *et al.* (21) observed that this dose of imipramine resulted in variable changes in arterial pressure in anesthetized dogs, but that a much larger dose (5 mg/kg) decreased the blood pressure and cardiac output, with increases in TPR.

The purpose of the present study was to determine

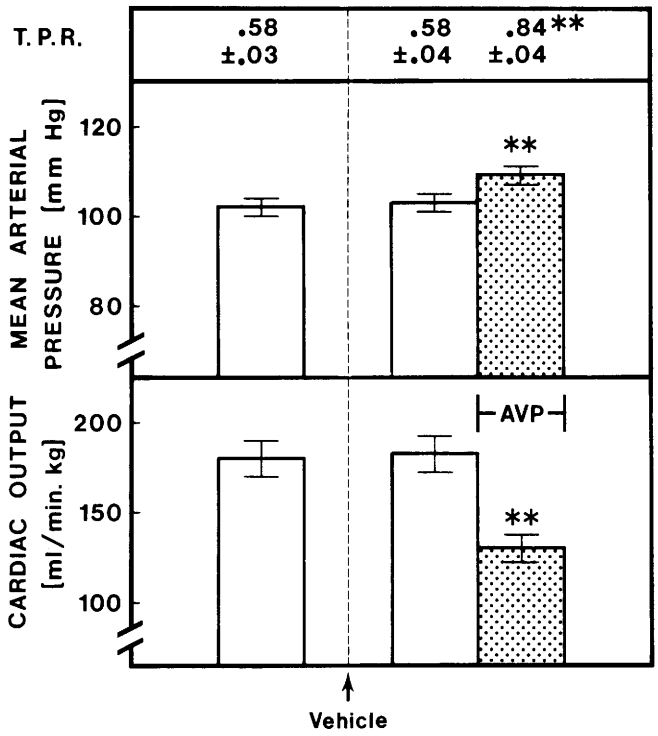

Figure 4. Effect of iv infusion of vasopressin (AVP, 5 mU/min/kg body wt; shaded bars) on mean arterial pressure, cardiac output, and total peripheral resistance (TPR) in rabbits after the iv administration of cocaine (0.6 mg/kg body wt; dotted line). Values are means ± SEM for six rabbits. †$P < 0.05$ and ††$P < 0.01$ that a change occurred after cocaine administration (paired Student's *t*). **$P < 0.01$ that an increase in blood pressure and TPR and a decrease in cardiac output occurred during AVP infusion (paired Student's *t*).

Table II. Comparison of the Increases in Mean Arterial Pressure and Total Peripheral Resistance (TPR) in Response to Norepinephrine Before and After Cocaine or Imipramine in Experiment 2

	Increases in mean arterial pressure	Increases in TPR
Before cocaine	+13 ± 1	+0.09 ± 0.02
After cocaine	+29 ± 6[a]	+0.20 ± 0.05[b]
Before imipramine	+10 ± 1	+0.05 ± 0.02
After imipramine	+21 ± 1[a]	+0.13 ± 0.01[a]

Note. Values are means ± SEM for six rabbits per group. Mean arterial pressure values are in mm Hg; TPR = total peripheral resistance. [a]$P < 0.01$ and [b]$P < 0.05$ that the magnitude of the response to norepinephrine after treatment with the drug was greater than the magnitude of the response before treatment.

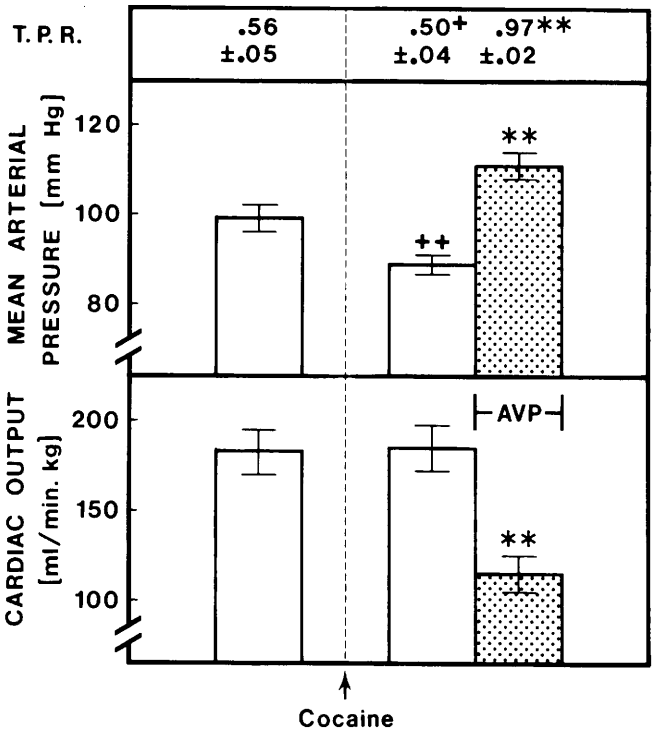

Figure 5. Effect of iv infusion of vasopressin (AVP, 5 mU/min/kg body wt; shaded bars) on mean arterial pressure, cardiac output, and total peripheral resistance (TPR) in rabbits after the iv administration of imipramine (0.5 mg/kg body wt; dotted line). Values are means ± SEM for six rabbits. $^{**}P < 0.01$ that an increase in blood pressure and TPR and a decrease in cardiac output occurred during AVP infusion (paired Student's *t*).

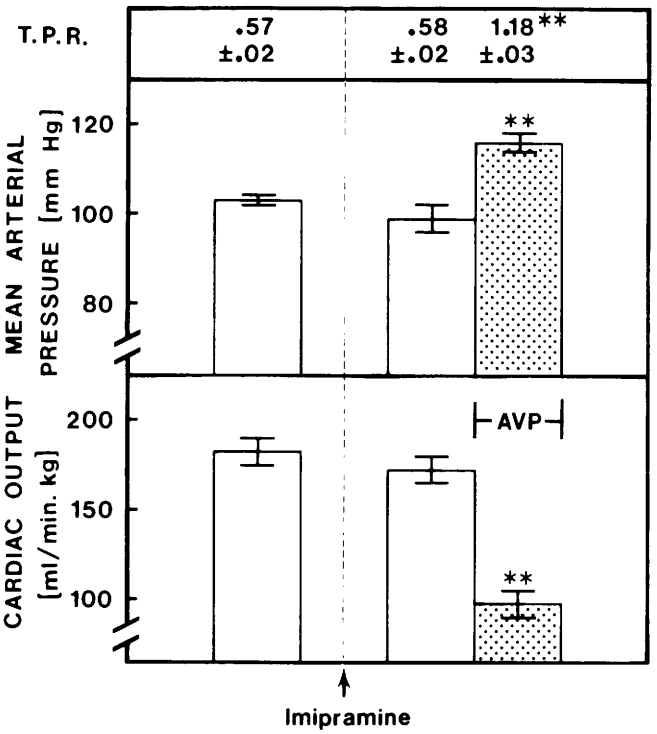

Figure 6. Effect of iv infusion of vasopressin (AVP, 5 mU/min/kg body wt; shaded bars) on mean arterial pressure, cardiac output, and total peripheral resistance (TPR) in rabbits after the iv administration of vehicle without cocaine or imipramine (dotted line). Values are means ± SEM for six rabbits. $^{**}P < 0.01$ that an increase in blood pressure and TPR and a decrease in cardiac output occurred during AVP infusion (paired Student's *t*).

if cocaine and imipramine, two drugs known to decrease NE uptake by the sympathetic nerve terminals, would induce pressor and vascular hyperresponsiveness in conscious rabbits. The results of Experiment 1 clearly show that rabbits given cocaine or imipramine have exaggerated increases in blood pressure in response to infusions of NE, and Experiment 2 demonstrates that both cocaine and imipramine enhance the ability of NE to increase the TPR. Because changes in TPR are the result of changes in the contraction of arteriolar smooth muscle cells, the exaggerated increases in TPR indicate that the pressor hyperresponsiveness seen following cocaine or imipramine administration in these animals is a reflection of vascular hyperresponsiveness. The results of Experiment 3 show that cocaine and imipramine produce vascular hyperresponsiveness not only to NE, but also to AVP, a substance which acts through an entirely different receptor system from NE (22). These results are in keeping with the findings of others on the potentiation of the cardiovascular effects of vasoconstrictor substances by cocaine and imipramine. Graham *et al.* (23) reported that the administration of a large dose of cocaine (5 mg/kg) to anesthetized dogs did not alter mean arterial pressure or cardiac output, but did enhance the effects of NE on blood pressure and TPR. Also, Masuda *et al.* (24) found that the inotropic and chronotropic responses to NE in anesthetized dogs were enhanced by cocaine, whereas metanephrine, an extraneuronal uptake blocking agent, did not alter these responses. Furthermore, Jones and Tackett (25) observed that isolated coronary and femoral arteries from dogs chronically treated with cocaine gave greater contractile responses to NE, serotonin, and to a thromboxane A_2 analog. Imipramine also has been shown to potentiate the pressor responses to NE (26, 27) and to angiotensin II (Ang II) (27) in anesthetized dogs and to enhance the contractile responses to NE in the isolated rat vas deferens (28). Gumulka and Kostowski (29) observed that the addition of imipramine to the bathing solution of *in vitro* rabbit atria enhanced the inotropic effect of NE.

We previously have shown that rabbits with hypertension induced by renal artery stenosis (5, 7), like patients with hypertension (1–3), have exaggerated pressor and vascular responses to vasoconstrictor substances. The pressor and vascular hyperresponsiveness occurs at 3 days following renal artery stenosis, before the animals develop hypertension (5–7). Ang II plays a role in mediating the pressor hyperresponsiveness in this rabbit model, as treatment of these animals with the Ang II antagonist [Sar^1, Ile^8] Ang II (5–7), or with captopril, an angiotensin converting enzyme inhibitor (30), abolished the hyperresponsiveness, de-

Table III. Initial Values for Rabbits in Experiment 3

	Mean arterial pressure	Heart rate	Cardiac output	TPR
To receive cocaine	100 ± 3	263 ± 13	179 ± 16	0.56 ± 0.05
To receive imipramine	102 ± 1	245 ± 6	180 ± 10	0.57 ± 0.02
To receive vehicle	102 ± 2	253 ± 9	179 ± 10	0.58 ± 0.03

Note. Values are means ± SEM for six rabbits per group. Values for mean arterial pressure are in mm Hg; heart rates are bpm; cardiac output values are ml/min/kg body wt. TPR = total peripheral resistance. There were no differences among these three groups for any of these measurements, by analysis of variance.

Table IV. Comparison of the Changes in Mean Arterial Pressure, Heart Rate, Cardiac Output, and Total Peripheral Resistance (TPR) in Response to Arginine Vasopressin in Rabbits Receiving Vehicle Only, Cocaine, or Imipramine for Experiment 3

	Mean arterial pressure	Heart rate	Cardiac output	TPR
Treated with vehicle	+6 ± 1	−57 ± 2	−46 ± 6	+0.26 ± 0.05
Treated with cocaine	+22 ± 3[a]	−71 ± 10	−61 ± 13	+0.47 ± 0.07[a]
Treated with imipramine	+15 ± 2[b]	−64 ± 18	−73 ± 7	+0.60 ± 0.05[a]

Note. Values are means ± SEM for six rabbits per group. Mean arterial pressure values are in mm Hg; heart rates are bpm; cardiac output values are ml/min/kg body wt; TPR = total peripheral resistance. [a] $P < 0.01$ and [b] $P < 0.05$ that the value is significantly greater than the value for the control (vehicle-treated) group, by Dunnett's test.

spite PRA and plasma Ang II values being normal. Furthermore, the iv infusion of Ang II into captopril-treated renal artery stenosis rabbits restored pressor hyperresponsiveness before plasma Ang II levels had reached normal values (30). These findings suggested that the role of Ang II in mediating pressor hyperresponsiveness in this model may be through increasing the number or activity of Ang II receptors rather than by increasing the amount of Ang II. It is of interest that another Ang II antagonist, [Sar^1, Ala^8] Ang II, in doses that completely block the pressor effects of Ang II, will not block the pressor hyperresponsiveness of renal prehypertensive rabbits (31), indicating that the Ang II receptors involved in mediating pressor hyperresponsiveness in this model are not the same Ang II receptors as those mediating the direct pressor effects of Ang II.

It has been shown that Ang II will promote decreases in NE uptake (32–34) and that animals with experimental hypertension have decreased NE uptake (34). Also, Ang II in subpressor doses will enhance the vasoconstrictor effects of NE in normal conscious rabbits (5), cat mesenteric blood vessels (34), perfused rabbit ears (36), perfused rat hindlimbs (37), and in isolated rat caudal arteries (38). We have suggested previously (5–7) that the role of Ang II in mediating pressor hyperresponsiveness in our renal artery stenosis rabbit model may be by increased activity of Ang II promoting a decrease in NE uptake by the sympathetic nerve terminals. In this case, the increased concentrations of NE in the synaptic cleft of the sympathetic nerve fibers supplying vascular smooth muscle cells could produce a partial depolarization of the muscle fibers and thus make them more responsive to infused vasoconstrictor agents.

Earlier studies from this laboratory (39) found that a circulating hormonal factor other than Ang II is involved in mediating pressor hyperresponsiveness in renal prehypertensive rabbits. The short-term cross-circulation of blood between 3-day renal artery stenosis (donor) rabbits and normal (recipient) rabbits resulted in the transfer of pressor hyperresponsiveness to the normal recipient rabbits. The administration of [Sar^1, Ile^8] Ang II to the recipient rabbits following the blood cross-circulation served to block the pressor hyperresponsiveness in the recipient rabbits, indicating that the role of Ang II was in mediating the effects of the hormonal factor and not in promoting its release.

Further evidence for a hormonal factor in mediating vascular hyperresponsiveness in renal prehypertensive rabbits was provided by a recent series of experiments from this laboratory (40) in which it was found that isolated vascular rings from the renal arteries of normal rabbits, when bathed in extracts of plasma from renal prehypertensive rabbits, exhibited greater contractile responses to NE than did matched rings bathed in extracts of plasma from sham-operated control rabbits. Furthermore, the addition of [Sar^1, Ile^8] Ang II to the bathing solution abolished the ability of the prehypertensive plasma extract to promote vascular hyperresponsiveness, whereas the addition of [Sar^1, Ala^8] Ang II to the bath, in doses that blocked the contractile effects of Ang II, failed to block the ability of the prehypertensive plasma extract to promote vascular hyperresponsiveness. Because these isolated vascular rings behaved in the same manner as

the whole animal model, probably the same mechanisms are involved in mediating vascular hyperresponsiveness in the renal prehypertensive animal model. A role for the sympathetic nerves in mediating vascular hyperresponsiveness is suggested by the recent findings (unpublished) that chemical denervation of these vascular rings by 6-hydroxydopamine abolished the effect of prehypertensive plasma extracts to elucidate exaggerated contractile responses to NE in these isolated vascular rings.

In the present study, the administration of cocaine to conscious rabbits produced a fall in arterial pressure. Because decreases in arterial pressure are usually associated with increases in renin release (41), it might be thought that the pressor and vascular hyperresponsiveness following cocaine administration could be due to increased activity of the renin-angiotensin system. However, the administration of cocaine in this study consistently resulted in decreases in PRA, suggesting that the pressor hyperresponsiveness resulting from cocaine was not due to elevations in plasma Ang II. The mean arterial pressure did not decrease following the injection of imipramine, and PRA was not altered by the administration of this drug. Thus, the changes in pressor and vascular responsiveness induced by cocaine and by imipramine were not due to increased activity of the renin-angiotensin system.

The decreases in cardiac output observed with the infusion of AVP have been reported previously for several species, including rabbits (6), dogs (42), and humans (43). The reduction in cardiac output with AVP is probably due to its effect to decrease coronary blood flow. Hanson and Johnson (44) found marked increases in resistance in isolated perfused rabbit hearts in response to AVP, whereas Nakano and Shackford (45) observed that AVP did not decrease the myocardial contractility of isolated atria from guinea pigs.

The present studies have revealed that normal rabbits have pressor and vascular hyperresponsiveness to two different vasoconstrictor substances, NE and AVP, following the administration of cocaine or imipramine, two different classes of drugs that share the common feature of decreasing NE uptake by the sympathetic nerve terminals (8–11). Thus, the results of the present studies are in keeping with the concept that decreased NE uptake will promote pressor and vascular hyperresponsiveness.

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