Pressor Responses to Norepinephrine During Captopril In Renal Prehypertensive Rabbits

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SUMMARY The role of angiotensin II (All) in pressor hyperresponsiveness was examined in conscious one-kidney, one clip rabbits with renal artery stenosis on 3-days' duration (renal prehypertensive rabbits). Conscious one-kidney rabbits without renal artery stenosis served as controls. Two experiments were performed. The first experiment used four groups of six rabbits each, to examine the pressor responses to intravenous (i.v.) infusions of norepinephrine (NE) at several doses, ranging from 25 to 1200 ng/min/kg body weight, in 3-day renal artery stenosis and in 3-day control rabbits, receiving NE plus the angiotensin-converting enzyme inhibitor, captopril (SQ 14,225), or receiving NE alone. The arterial pressure and values for plasma renin activity (PRA) were the same in the renal artery stenosis rabbits as in the controls. The exaggerated pressor responses to NE in the renal artery stenosis rabbits were restored to normal by captopril administration.

The second experiment investigated the pressor responses to i.v. infusions of NE at 800 ng/min/kg in six rabbits with renal artery stenosis and in six control rabbits before captopril, during captopril administration, and during the administration of captopril plus the i.v. infusion of All at 0.5, 1.0, and 2.0 ng/min/kg body weight. Plasma concentrations of All were determined at each point in this experiment. The renal artery stenosis rabbits had the same values for arterial pressure and PRA as the control rabbits. The renal artery stenosis rabbits had increased pressor responses to NE, and this pressor hyperresponsiveness was abolished by captopril. The i.v. infusion of All during captopril treatment in the renal artery stenosis rabbits increased the pressor responses to NE, and All infusion at 2.0 ng/min/kg completely restored the pressor hyperresponsiveness in these rabbits. The control rabbits had no changes in the pressor responses to NE with captopril or with captopril plus any of the All doses. Before captopril, the control and renal artery stenosis rabbits had the same plasma concentrations of All. With captopril, plasma concentrations of All in the renal artery stenosis rabbits decreased to undetectably low levels and remained so during the infusions of All at all doses. This study provided strong evidence that plasma All plays an important role in the enhanced pressor responses to NE in 3-day renal artery stenosis rabbits, and that this effect is not due to elevated plasma levels of All. (Hypertension 5: 159-165, 1983)

KEY WORDS • renal artery stenosis • pressor hyperresponsiveness • angiotensin converting enzyme inhibition • angiotensin II • plasma angiotensin II concentrations

EXAGGERATED pressor responses to vasoconstrictor agents have been observed in patients with hypertension as well as in several animal models of experimental hypertension. This pressor hyperresponsiveness occurs prior to the development of hypertension. Pressor hyperresponsiveness is associated with enhanced increases in vascular resistance in hypertensive and prehypertensive animals, suggesting that the arteriolar smooth muscle cells are more responsive to vasoconstrictor agents in these animals. Earlier studies from this laboratory have shown that i.v. infusion of the angiotensin II (All) competitive antagonist, [Sar\(^1\), Ile\(^2\)] All, abolished pressor hyperresponsiveness in renal prehypertensive rabbits.

The present study examined the effect of another antagonist of the renin-angiotensin system, the angiotensin-converting enzyme inhibitor, captopril (SQ 14,225), on pressor hyperresponsiveness in prehypertensive rabbits with renal artery stenosis. This study also investigated further the role of plasma All in pres-
sor hyperresponsiveness in this model by examining the effects of i.v. infusions of small doses of AII on pressor responsiveness in renal prehypertensive rabbits receiving captopril.

Methods

Thirty-six male New Zealand white rabbits, weighing from 2.75 to 3.15 kg, were caged individually in a constant environment of 27°C with room lights automatically controlled on a 12-hour on/off cycle. All rabbits were fed a commercial diet (Purina rabbit chow) containing 0.167 mEq of Na⁺ and 0.467 mEq of K⁺ per gram, and water ad libitum.

Surgical Procedures

Eighteen rabbits received a unilateral nephrectomy and served as controls; the remaining 18 rabbits received renal artery stenosis plus a contralateral nephrectomy (one-kidney, one clip). Renal artery stenosis was produced by the method of Brooks and Muirhead by placing a silver clip with an internal gap size of 0.6 mm on the left renal artery. These surgical procedures were performed through a ventral midline laparotomy incision under sterile conditions on rabbits anesthetized with 3% to 5% halothane in nitrous oxide and oxygen, administered with a mask. Afterward the rabbits were allowed to recover and were returned to their cages. The acute experiments were performed 3 days later.

On the morning of the 3rd postoperative day, each rabbit again was anesthetized with halothane plus nitrous oxide as before, and polyvinyl catheters (Fr 5 infant feeding tubes) were placed in the lower abdominal aorta and inferior vena cava via the femoral artery and vein. In experiments in which an additional intravenous line was required, a marginal ear vein was cannulated percutaneously with polyethylene (PE 50) tubing. After insertion of the catheters, each rabbit was placed in a rectangular box to restrict its movements and was allowed 5 hours to recover. The acute experiments were performed on conscious rabbits in these boxes, unrestrained except by the size of the box. Two separate experiments were performed.

Experiment 1: Pressor Responses to Norepinephrine During Captopril

Four groups of six rabbits each were used in these experiments. The first and second groups consisted of one-kidney control rabbits, and the third and fourth groups were one-kidney rabbits with renal artery stenosis of 3 days' duration. In each group, an arterial blood sample (2 ml) was obtained and placed in a chilled tube containing ethylenediaminetetraacetate (EDTA); this sample was used for the determination of plasma renin activity (PRA). Mean arterial pressure (MAP) was measured through the femoral arterial catheter by a pressure transducer (Statham model P23Db, Oxnard, California) and was recorded on an oscillographic recorder (Hewlett-Packard, model 7754B, Palo Alto, California). After MAP had been recorded for 5 minutes, heart rate was determined by recording pulsatile blood pressure at a fast paper speed (10 mm/sec). The gain of the preamplifier of the recorder was then increased so that a 1 mm pen deflection represented a 1 mm Hg change in arterial pressure, and the pen was positioned near the lower portion of the recording channel by the use of a zero-suppression control; this allowed the accurate recording of small changes in MAP. Each rabbit then received a 5-minute infusion of norepinephrine (NE) (800 ng/min/kg body weight) in 5% dextrose-water, and the pressor response was recorded. The solutions of NE were prepared by diluting a fresh ampule of a commercial solution (Levophed, Winthrop Laboratories, New York, New York) in 5% dextrose-water. Rabbits in Groups 2 and 4 received an i.v. injection of 300 ng of synthetic angiotensin I (Al) in saline (0.30 ml), the pressor responses noted, and a solution of captopril was then infused i.v. through the femoral venous catheter. For the remainder of the experiment, captopril dissolved in 5% dextrose-water was infused at a dose rate of 0.3 mg/min/kg of body weight 5 minutes and then at 0.1 mg/min/kg. In Groups 1 and 3, the solution of 5% dextrose-water was infused without captopril.

In Groups 2 and 4, after 10 minutes of captopril infusion, the pressor response to the i.v. injection of 300 ng of AI again was determined in each rabbit to evaluate the adequacy of the inhibition of the angiotensin-converting enzyme. Then, in each group of rabbits, NE was infused at doses of 25, 50, 100, 200, 400, 800, and 1200 ng/min/kg body weight, and the pressor responses recorded. The MAP during the 1-minute period prior to NE infusion was taken as the control pressure, and the increase in MAP that occurred during 5 minutes of NE infusion was taken as the pressor response. An interval of at least 5 minutes was allowed between infusions, and the next dose of NE was not infused until the MAP had returned to the preinfusion level and stabilized. After infusion of the last NE dose, the pressor response to 300 ng of AI was again determined.

Experiment 2: Pressor Responses to Norepinephrine During Captopril Plus AII

This experiment required six one-kidney control rabbits and six one-kidney, 3-day renal artery stenosis rabbits. At the start of Experiment 2, a 5 ml sample of arterial blood was collected for PRA and plasma AII determinations. The 3 ml blood sample for plasma AII concentration was placed in a chilled tube containing EDTA plus 50 μg of captopril. Control measurements of MAP were obtained for 5 minutes, and heart rate was measured in each rabbit as previously described. The gain of the recorder was increased, and the pressor response to NE, infused at 800 ng/min/kg body weight, was determined as in Experiment 1. After cessation of the NE infusion and after the MAP had returned to the control level, the pressor response to an i.v. injection of 300 ng of AI was recorded. Each rabbit then was infused with captopril as in Experiment
1. After 10 minutes of infusion of the angiotensin-converting enzyme inhibitor, a 3-ml blood sample was collected for plasma AI concentration. Again, 300 ng of AI was injected i.v. while MAP was recorded, to test the adequacy of the inhibition of the angiotensin-converting enzyme. While infusion of captopril was continued, the pressor response to NE at 800 ng/min/kg was determined. A solution of AI in 5% dextrose-water was then infused i.v. at 0.5 ng/min/kg body weight, concurrent with the captopril infusion. After 5 minutes of AI infusion at this dose, an arterial blood sample (3 ml) again was obtained for plasma AI concentration, and the pressor response to NE at 800 ng/min/kg was determined, as previously. The AI solution was then changed so as to infuse AI at 1.0 ng/min/kg, and 5 minutes later another arterial blood sample was collected for plasma AI concentration. Again, the pressor response to an infusion of NE at 800 ng/min/kg was recorded. The AI infusion was increased further to 2.0 ng/min/kg, and after 5 minutes of infusion at this dose, an arterial blood sample was collected for determination of plasma AI concentration, and again the pressor response to NE (800 ng/min/kg) was obtained. To verify the continued inhibition of angiotensin-converting enzyme, the pressor was obtained for a final i.v. injection of 300 ng of AI. In these experiments, all blood removed was replaced immediately with the same volume of blood from a normal donor rabbit.

Analytical Procedures

Determinations of PRA were by radioimmunoassay (RIA) of generated AI, by a modification of the method of Cohen et al.,10 this modification, as performed in our laboratory, has been described previously.11 Plasma concentrations of AI were determined by RIA by a modification of the method described by Gocke et al.12 Blood samples, collected in chilled tubes containing EDTA plus captopril (20 µg/ml blood), were placed in ice, spun in a refrigerated centrifuge, and the plasma samples were stored frozen at −20°C. Before assay, the samples were thawed in an ice bath, and 0.75 ml of each plasma sample was placed in a small plastic tube. To each tube was added 1.50 ml of absolute ethanol to precipitate the proteins. The tubes were spun, and 200 µl aliquots of the supernatant were pipetted into a series of small plastic tubes, for the assay both of endogenous AI and AI. The tubes were evaporated to dryness with filtered air and stored at −20°C until assayed. At the time of assay, 125I-AI (New England Nuclear) was diluted in a Tris buffer (0.1 M Tris, pH adjusted to 7.4, plus bovine serum albumin, 2.5 mg/ml). Synthetic asp-1, Ile-5 AI (Vega Biochemicals) was dried in vacuum for 24 hours, and a stock solution of 10,000 ng/ml was prepared in the Tris buffer; dilutions were prepared in a series of tubes to provide a range of standards from 3.9 to 250 pg. The diluted AI trace (0.5 ml) was added to each sample and standard tube. Each tube also received 0.5 ml of AI antiserum, diluted 1/160,000 in Tris buffer. The AI antiserum was produced by the periodic injection of rabbits with AI conjugated to serum albumin, together with Freund’s adjuvant. The tubes for the assay of AI likewise received 125I-AI and AI antiserum, as in the assay of PRA. Each tube was incubated in an ice bath for 18 hours, and then 1 ml of a solution of dextran-coated charcoal in barbital buffer (pH 7.4) was added to separate the free from the antibody-bound angiotensin. The samples were centrifuged and decanted, and the charcoal pellets (free angiotensin) were counted in a well-type automated gamma counter. The results were calculated from a log-logit transformation of the angiotensin standards vs the ratio of the bound counts of angiotensin for each standard to the bound counts of angiotensin for the zero angiotensin standard. Because AI has approximately a 20% cross-reactivity with the AI antiserum, plasma AI concentrations were corrected for this. With this method, the recovery of AI added to human plasma samples averaged 102% (n = 9) over a range of 75 to 600 pg/ml. Intraassay variation averaged 2.4% (n = 10), based on an average AI concentration of 79 ± 5.6 (SD) pg/ml; interassay variation averaged 10.7% (n = 25).

Statistics

In Experiment 1, the control values for MAP, heart rate, PRA and the pressor responses to each dose of NE were compared among the four groups of rabbits by analysis of variance; when significant values were observed, the data were analyzed further by Duncan’s new multiple range test.13 In Experiment 2, the values obtained during the control period for MAP heart rate, PRA, plasma AI concentration, and the pressor response to NE were compared between the control and 3-day renal artery stenosis groups by Student’s t test for group observations. Changes in MAP, NE pressor responses, and plasma AI concentrations with captopril alone and with each AI infusion were evaluated within each group by Student’s t test for paired observations.13

Results

Experiment 1: Pressor Responses to Norepinephrine During Captopril

The initial values for MAP, heart rate, PRA, and the pressor responses to NE at 800 ng/min/kg are summarized in Table 1. There were no significant differences in MAP, heart rate, and PRA among the four groups. The pressor responses to NE prior to infusion of captopril were significantly (p < 0.01) greater in Groups 3 and 4 (renal artery stenosis groups) than in Groups 1 and 2 (control groups). Figure 1 gives the log-dose response curves for the pressor responses to the various doses of NE for all four groups. The 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 NE dose, and a and n are constants. The pressor responses for the 3-day renal artery stenosis rabbits not receiving captopril (Group 3) were significantly greater than the pressor responses for the other three groups.
TABLE 1. Initial Values for Rabbits in Experiment 1

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (controls)</th>
<th>Group 2 (controls)</th>
<th>Group 3 (RAS)</th>
<th>Group 4 (RAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>93 ± 2</td>
<td>100 ± 3</td>
<td>92 ± 5</td>
<td>98 ± 3</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>261 ± 10</td>
<td>229 ± 14</td>
<td>238 ± 9</td>
<td>219 ± 9</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>6.3 ± 1.0</td>
<td>5.2 ± 0.6</td>
<td>4.8 ± 0.7</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>Pressor response to norepinephrine (800 ng/min/kg)</td>
<td>+12 ± 1</td>
<td>+14 ± 2</td>
<td>+22* ± 2</td>
<td>+23* ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SEM for six rabbits per group. Controls are one-kidney (3-day) rabbits; RAS are one-kidney, one clip (3-day) rabbits. Groups 1 and 3 did not receive captopril; Groups 2 and 4 received captopril subsequent to these measurements.

*p < 0.01, compared with values obtained for the other groups.

Experiment 2: Pressor Responses to Norepinephrine During Captopril Plus AlI

Table 2 gives the initial values for MAP, heart rate, and PRA for the one-kidney (3-day) control and for the one-kidney, one clip (3-day) experimental groups of rabbits. There were no significant differences between these two groups for any of these factors except for pressor responses to NE, which were significantly (p < 0.01) greater in the renal artery stenosis group than in the control group.

Values for the pressor responses to NE in the control and renal artery stenosis groups are summarized in figures 2 and 3, respectively. In the control group (fig. 2), the pressor responses to NE were not altered by captopril nor by infusion of AlI at the three dose levels during captopril infusion. In the 3-day renal artery stenosis rabbits (fig. 3), however, captopril infusion resulted in a marked and significant (p < 0.01) reduction in the pressor responses to NE. Furthermore, infusion of AlI during captopril administration increased the pressor responses to NE in a progressive manner with increasing AlI dose infusion rates until the initial pressor responses to NE were reestablished with AlI infusions of 2.0 ng/min/kg of body weight.

Plasma AlI concentrations were successfully determined for five control and five renal artery stenosis rabbits, and are summarized in table 3. Prior to captopril administration, the plasma concentrations of AlI were very similar between the two groups. Following administration of captopril, the plasma AlI concentrations in the control rabbits showed a slight decrease, although not statistically significant, and the infusion of AlI produced slight rises in plasma AlI levels. In the renal artery stenosis rabbits, however, the administration of captopril resulted in a decrease in plasma AlI concentrations to undetectably low levels in four of the five rabbits, and plasma AlI concentrations remained undetectably low during the subsequent infusion of AlI.

The administration of captopril in this experiment resulted in a slight decrease in MAP, averaging 4 mm Hg for both the control and renal artery stenosis groups of rabbits; these declines were not statistically signifi-
TABLE 2. Initial Values for Rabbits in Experiment 2

<table>
<thead>
<tr>
<th></th>
<th>One-kidney (3-day) rabbits</th>
<th>One-kidney, one clip (3-day) rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>97 ± 2</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>240 ± 11</td>
<td>226 ± 11</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>4.0 ± 0.5</td>
<td>5.2 ± 1.9</td>
</tr>
<tr>
<td>Pressor response to norepinephrine (800 ng/min/kg)</td>
<td>+12 ± 2</td>
<td>+24* ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SEM for six rabbits per group. *p < 0.01, compared to the control group.

Discussion

These experiments were performed in conscious rabbits; however, 5 hours prior to an experiment each rabbit was anesthetized with halothane plus nitrous oxide in order to place catheters in the blood vessels. Because halothane is known to produce changes in the circulatory system, the question arises as to whether the 5-hour recovery time allotted was adequate for complete recovery from the effects of this anesthetic agent. Previous studies from this laboratory have shown that rabbits anesthetized with halothane plus nitrous oxide to surgical levels had decreases in arterial pressure and cardiac output, with elevated values for PRA. These studies also demonstrated, however, that after removing the animals from the anesthesia the MAP and cardiac output recovered to preanesthetic values by 15 minutes, and PRA returned to control levels within 210 minutes. Therefore, the 5-hour time allowed following removal from anesthesia until the beginning of the experimental procedures in the present study should have been adequate for the rabbits to recover fully from the effects of the short-term anesthetization with halothane.

There is considerable evidence that All in subpressor doses in normal animals will enhance the vasoconstrictor effects of NE or of sympathetic nerve stimulations. Studies by Khairallah et al. and by Sakurai and Hashimoto have demonstrated that in isolated perfused rabbit ears the addition of All to the...
perfusing solution potentiated the vasoconstrictor effects of NE. Similar potentiating effects of All on the constrictor action of NE and of sympathetic nerve stimulation have been observed in perfused mesenteric blood vessels of cats\textsuperscript{11} and in perfused hindlimbs\textsuperscript{19} and caudal arteries\textsuperscript{16} of rats. Earlier studies from this laboratory\textsuperscript{2} found that the i.v. infusion of All in subpressor doses into normal conscious rabbits resulted in exaggerated pressor responses to infusions of NE. The mechanisms whereby All administration in subpressor amounts enhances the vasoconstrictor effects of NE are not completely understood. However, studies have provided evidence that All will increase the rate of NE release\textsuperscript{26-22} and decrease the rate of NE uptake\textsuperscript{15, 17, 23} by the sympathetic nerve terminals. Increased NE release and/or decreased uptake would result in an accumulation of NE in the synaptic cleft; the resulting increases in NE in the synaptic cleft of sympathetic fibers terminating on arteriolar smooth muscle cells could act to depolarize partially these cells and thus make them more responsive to the vasoconstrictor action of pressor substances.

Previous studies from this laboratory\textsuperscript{5-8} have found that one-kidney and two-kidney rabbits with unilateral renal artery stenosis of 3 days' (prehypertensive rabbits) and 30 days' (hypertensive rabbits) duration had exaggerated pressor responses to NE that were abolished or attenuated by the All competitive antagonist, [Sar\textsuperscript{1}, Ile\textsuperscript{8}] All. The ability of this All analog to block hyperresponsiveness is not confined to the pressor effects of only NE since one-kidney rabbits with 3-day renal artery stenosis also exhibited pressor and vascular hyperresponsiveness to vasopressin, a pressor substance that acts on different receptors than does NE, and the heightened pressor and vascular responses to vasopressin in these rabbits were alleviated by [Sar\textsuperscript{1}, Ile\textsuperscript{8}] All.\textsuperscript{9} In these rabbit models with renal artery stenosis, the PRA values and presumably the plasma All concentrations were normal or subnormal. From these findings we hypothesized that in rabbits with renal artery stenosis there is increased interaction of All with its "hyperresponsive" receptors due either to an increased number of these receptors or to an increased affinity of these receptors for All.

The present study demonstrated that pressor hyperresponsiveness to NE in one-kidney rabbits with renal artery stenosis of 3 days' duration was abolished by captopril, which blocks the formation of All from AI. These results provided further evidence that All participates in the enhanced pressor responses to vasoactive agents following renal artery stenosis in rabbits. Values for plasma All concentrations in this study agreed closely with those reported by Zakheim et al.\textsuperscript{24} for normal, conscious rabbits. In the present study, the values for PRA and for plasma All concentrations were the same in the renal artery stenosis and control rabbits, which provides strong evidence that the participation of All in this hyperresponsiveness mechanism is not through increased plasma All levels. Following the administration of captopril, the plasma concentrations of All fell to undetectably low levels in the renal artery stenosis group, and with the i.v. infusion of All at 2.0 ng/min/kg by weight, a dose of All that completely restores pressor hyperresponsiveness in these rabbits, the plasma levels of All were still below the minimal detectable level of the assay. Thus, although All appears to be necessary for pressor hyperresponsiveness to occur in this renal artery stenosis model, only very small amounts of All are required to promote this phenomenon. These findings support the hypothesis that increased receptor binding of All is involved in mediating pressor hyperresponsiveness in these renal prehypertensive rabbits. The observation in this study that captopril administration resulted in a greater decrease in plasma All concentrations in the 3-day renal artery stenosis rabbits than in the normal rabbits is in keeping with this hypothesis of increased All binding in this renal artery stenosis model.

Kikta and Fregly,\textsuperscript{25} studying the contractility of aortic rings from normal rats, reported that the degree of contractility of the rings in response to NE and to phenylephrine was diminished by captopril; they conclude that captopril depresses alpha-adrenergic responsiveness in vascular smooth muscle similarly. Okuno et al.\textsuperscript{26} found that captopril decreased the contractile responses to NE in perfused mesenteric vascular beds of normal rats. From these studies it could be surmised that the decreased pressor responses to NE infusions produced by captopril in the renal artery stenosis rabbits in the present study may have been due to an effect of captopril on adrenergic receptors, independent of its effect to block angiotensin conversion. However, the present study found no effect of captopril on the pressor responses to NE in normal conscious rabbits after the administration of captopril. Furthermore, the observation that the infusion of All in low doses restored pressor hyperresponsiveness to NE in captopril-treated rabbits with renal artery stenosis provides further evidence that captopril does not diminish the pressor response to NE in this rabbit model by a direct effect on adrenergic receptors of arteriolar smooth muscle cells. This observation also indicates that the decreased pressor responses to NE that occurred following captopril administration in the renal artery stenosis rabbits did not result from the bradykinin-potentiating activity of captopril nor from any direct action of captopril on the arterioles.

It has been reported that AI may be produced in certain localized areas of the body. There is considerable evidence for the presence of a functional renin-angiotensin system in the brain.\textsuperscript{28} Also, Malik and Nasjletti\textsuperscript{29} have provided evidence that renin located within the vascular walls of isolated mesenteric arteries from normal rats has the capability of producing All in amounts sufficient to potentiate the vasoconstrictor effects of NE or of sympathetic nerve stimulation. In studies from our laboratory, because pressor hyperresponsiveness in renal prehypertensive rabbits was abolished by agents that block the renin-angiotensin system despite the consistent finding of normal
values for PRA and the finding of normal values for plasma All concentrations, it would seem plausible that All produced in some localized area, rather than All that is in the plasma, may be the All involved in mediating the pressor hyperresponsiveness in this model. However, the results of the present study demonstrated that pressor hyperresponsiveness following captopril in 3-day renal artery stenosis rabbits was restored by the i.v. infusion of a low dose of All. Because this restoration of pressor hyperresponsiveness occurred with infusion of All into the circulatory system, these results implicate plasma All and not locally-produced tissue All as the source of the All involved in mediating pressor hyperresponsiveness in this model.

Acknowledgments

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