Humoral Factor in Pressor Hyperresponsiveness in Renal Prehypertensive Rabbits

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SUMMARY Prehypertensive rabbits with renal artery stenosis of 3 days' duration (one-kidney, one clip) are known to have increased pressor responses to norepinephrine and vasopressin; this pressor hyperresponsiveness is restored to normal by the angiotensin II (All) antagonist, [Sar1, Ile8] All, even though plasma renin activity (PRA) and plasma AII concentrations are not elevated. In the present study, the cross-circulation of blood between conscious one-kidney, 3-day renal artery stenosis rabbits and conscious normal rabbits resulted in the transfer of pressor hyperresponsiveness to the normal rabbits, although both groups of rabbits had normal values for PRA. A similar cross-circulation of blood between one-kidney rabbits without renal artery stenosis and normal rabbits did not alter the pressor responsiveness of the normal rabbits to norepinephrine. It was concluded that a circulating humoral factor is involved in mediating pressor hyperresponsiveness in 3-day renal artery stenosis rabbits. To evaluate the interrelationship between All and the hormonal hyperresponsiveness factor, an additional experiment was performed in which blood was cross-circulated between one-kidney, 3-day renal artery stenosis rabbits and normal rabbits, with the normal rabbits receiving [Sar1, Ile8] All immediately following cross-circulation. Administration of this All antagonist to the normal rabbits prevented them from showing pressor hyperresponsiveness following the cross-circulation of blood. It is concluded that in this prehypertensive renal artery stenosis model the humoral hyperresponsiveness factor exerts its effect through All mechanisms, rather than All acting to increase the release or secretion of the hyperresponsiveness factor. (Hypertension 5: 453-459, 1983)

KEY WORDS • renal artery stenosis • angiotensin II antagonist • [Sar1, Ile8] angiotensin II • blood cross-circulation

Many studies have provided evidence that patients with hypertension1,2 and animal models with experimental hypertension3-8 have exaggerated pressor responses to vasoactive agents. There has been evidence to suggest that a humoral factor may be involved in mediating this pressor hyperresponsiveness.9-12 Previous studies from this laboratory3-4 have shown that rabbits with renal artery stenosis of only 3 days' duration are still normotensive but have enhanced pressor responses to norepinephrine and vasopressin; although they have normal values for plasma renin activity (PRA) and plasma angiotensin II (AII), the pressor hyperresponsiveness is abolished by the AII competitive antagonist, [Sar1, Ile8] AII or by the angiotensin-converting enzyme inhibitor, captopril (SQ-14,225). The purpose of the present study was to determine if a circulating humoral factor may be involved in producing the exaggerated pressor responses in one-kidney rabbits with 3-day renal artery stenosis. This was investigated by blood cross-circulation between one-kidney, 3-day renal artery stenosis rabbits and normal rabbits; for a control experiment, blood was cross-circulated between one-kidney rabbits without renal artery stenosis and normal rabbits. Since the results of these experiments indicated the presence of a blood-borne factor mediating pressor hyperresponsiveness in this model, an additional experiment was performed to evaluate the interrelationship between this humoral hyperresponsiveness factor and AII; this

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was achieved by examining pressor responsiveness in normal rabbits receiving [Sar^1, Ile^2] All after cross-circulation with 3-day renal artery stenosis rabbits.

Methods
A total of 36 male New Zealand white rabbits, weighing from 2.60 to 2.95 kg, were fed a commercial diet (Purina Lab Rabbit Chow HF5326) containing 0.167 mEq of Na⁺ and 0.467 mEq of K⁺ per gram. The rabbits were caged individually in a constant environmental temperature of 27°C. Room lights were controlled by an automatic switch that provided illumination from 7:00 a.m. to 7:00 p.m. daily. Water was available ad libitum.

Twelve rabbits were subjected to renal artery stenosis and contralateral nephrectomy (one-kidney, one clip), and in six other rabbits unilateral nephrectomy only was done. Renal artery stenosis was produced by the method of Brooks and Muirhead. Rabbits were anesthetized with 3% to 5% halothane in nitrous oxide and oxygen, administered with a face mask, as described by Sartick et al. With sterile surgical procedures, a ventral midline laparotomy was performed. A silver clip with an internal gap size of 0.6 mm was used because earlier studies revealed that it produces a pressor response that is on the steep portion of the dose-response curve, but is not large enough to produce stroke in the animal. After the norepinephrine infusions, the solutions were cleared from the venous catheters of each rabbit in the pair. The femoral catheters of the donor and recipient rabbit of each pair were then connected to the tubing of a single-roller, dual-chamber infusion pump in a manner so that in one chamber the blood would be pumped from the femoral artery of the donor rabbit into the femoral vein of the recipient and in the other chamber the blood would be pumped from the femoral artery of the recipient rabbit into the femoral vein of the donor. The tubing of each chamber had a volume capacity of approximately 3 ml and was filled with isotonic saline prior to being connected to the catheters of the rabbits. The pump was then started, and the pump speed was adjusted so that the rate of blood exchange between the pair of rabbits would be 10 ml/min. Because both pump chambers were connected to the same roller, the rate of exchange of blood between the two rabbits in each pair was the same. After cross-circulation of blood for 5 minutes, the pump was stopped, the arterial catheter of the recipient rabbit was connected again to the pressure transducer, and mean arterial pressure was recorded. Pressor responses to norepinephrine infused again at 800 ng/min per kg of body weight were determined in the recipient rabbits at 5, 30, and 60 minutes after the termination of the cross-circulation.

Experiment 1: Cross-Circulation with One-Kidney, 3-Day Renal Artery Stenosis Donors
This experiment used six one-kidney rabbits with renal artery stenosis of 3 days' duration as donors and six normal rabbits as recipients. Each donor rabbit was paired with a recipient rabbit. After the 6-hour waiting period, an arterial blood sample (2 ml) was collected from each pair of donors and recipients. This blood sample was added to a chilled tube containing ethylenediaminetetraacetate (EDTA) and was used for the determination of PRA. Each rabbit then was given an i.v. injection of 1000 units of heparin. Mean arterial pressure was measured by attaching the femoral arterial catheter to a pressure transducer (model P23Db, Gould, Oxnard, California); blood pressure was recorded on an oscillographic recorder (model 7754A, Hewlett-Packard Company, Palo Alto, California). Heart rate was determined by recording pulsatile arterial pressure at a fast paper speed (10 mm/sec). After mean arterial pressure had been recorded for 15 minutes, the gain of the recorder amplifier was increased so that a 1 mm change in mean arterial pressure would produce a 1 mm pen deflection; by the use of the zero-suppression control of the amplifier, the pen was positioned near the lower portion of the channel. This change in the gain of the recorder allowed the accurate recording of small changes in mean arterial pressure. Each donor and recipient rabbit then received an i.v. infusion of norepinephrine (Levophed; Breon Laboratories Inc., New York, New York) in 5% dextrose-water, at a rate of 800 ng/min per kg of body weight, for 5 minutes. This dose of norepinephrine was selected to produce a pressor response that is on the steep portion of the dose-response curve, but is not large enough to produce stroke in the animal. After the norepinephrine infusions, the solutions were cleared from the venous catheters of each rabbit in the pair. The femoral catheters of the donor and recipient rabbit of each pair were then connected to the tubing of a single-roller, dual-chamber infusion pump in a manner so that in one chamber the blood would be pumped from the femoral artery of the donor rabbit into the femoral vein of the recipient and in the other chamber the blood would be pumped from the femoral artery of the recipient rabbit into the femoral vein of the donor. The tubing of each chamber had a volume capacity of approximately 3 ml and was filled with isotonic saline prior to being connected to the catheters of the rabbits. The pump was then started, and the pump speed was adjusted so that the rate of blood exchange between the pair of rabbits would be 10 ml/min. Because both pump chambers were connected to the same roller, the rate of exchange of blood between the two rabbits in each pair was the same. After cross-circulation of blood for 5 minutes, the pump was stopped, the arterial catheter of the recipient rabbit was connected again to the pressure transducer, and mean arterial pressure was recorded. Pressor responses to norepinephrine infused again at 800 ng/min per kg of body weight were determined in the recipient rabbits at 5, 30, and 60 minutes after the termination of the cross-circulation.

Experiment 2: Cross-Circulation with One-Kidney Donors without Renal Artery Stenosis
The procedures in this experiment were identical to those in Experiment 1, except that six one-kidney rabbits without renal artery stenosis were used as donor rabbits. As before, six normal rabbits served as the recipients.

Experiment 3: Cross-Circulation with One-Kidney, 3-Day Renal Artery Stenosis Donors, and Normal Recipients Receiving an Angiotensin II Antagonist
In this experiment the donors were six one-kidney rabbits with 3-day renal artery stenosis, and the recip-
ents were six normal rabbits, as in Experiment 1. After the arterial blood sample for PRA was obtained and after mean arterial pressure and heart rate were recorded, each recipient rabbit received a single i.v. injection of 300 ng of All, and the pressor response was recorded. When the pressor response to All had subsided, the pressor response to the i.v. infusion of norepinephrine was obtained for each donor and recipient rabbit, as in the other experiments. Blood was then cross-circulated between each donor and recipient pair, as in the other experiments, at 10 ml/min for 5 minutes. Immediately upon completion of the cross-circulation of blood, each recipient rabbit received a single i.v. injection of the All antagonist, [Sar1, Ile8] All, 1 μg per kg of body weight, in 1 ml of isotonic saline; this All antagonist was then infused continuously at 300 ng/min per kg body weight (0.14 ml/min) for the remainder of the experiment. The pressor responses to norepinephrine, were obtained at 5, 30, and 60 minutes, as in the previous experiments. At 10 minutes and at 65 minutes, after the pressor responses to norepinephrine had subsided, All (300 ng) again was injected i.v. while arterial pressure was recorded continuously; this was to verify the adequacy of the pressor blockade to All.

Plasma Renin Activity Determination

Blood samples collected for PRA were placed immediately in ice and were spun in a refrigerated centrifuge to obtain plasma. These plasma samples were stored frozen at −14°C until processed and assayed. PRA was determined by radioimmunoassay of generated angiotensin I by a modification of the method of Cohen et al.16 This assay, as used by our laboratory, has been described in detail previously.17

Statistics

Values for mean arterial pressure, heart rate, PRA, and changes in mean arterial pressure in response to norepinephrine before cross-circulation were compared between the donor and recipient groups for each experiment by Student’s t test. In each of the three experiments, the pressor responses to norepinephrine in the recipient rabbits at 5, 30, and 60 minutes after cross-circulation were compared to the pressor response to norepinephrine in each rabbit prior to cross-circulation by testing whether the changes in the pressor responses were significantly different from zero, by use of the u-test.18

Results

Values for mean arterial pressure, heart rate, and PRA in the donor and recipient rabbits for all three experiments are given in Table 1. There were no sig-
FIGURE 2. Pressor responses to i.v. infusions of norepinephrine at 800 ng/min per kg body wt in one-kidney control donor rabbits (shaded bar) and in normal recipient rabbits (clear bar) before cross-circulation (X-Circ.) and in normal recipient rabbits at 5, 30, and 60 minutes after cross-circulation of blood with donors. Values are means ± SEM for six rabbits in each group. There were no significant differences in the pressor responses between the donors and recipients prior to cross-circulation, and the pressor responses were not altered in the recipient rabbits after cross-circulation.

<table>
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<th>1-Kidney Control</th>
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<td>30</td>
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Significant differences in any of these values between the donors and recipients for any experiment.

Increases in mean arterial pressure that occurred with the i.v. infusion of norepinephrine in Experiment 1 are summarized in figure 1. The donor rabbits with 3-day renal artery stenosis had pressor responses averaging 26 ± 3 (SEM) mm Hg, which were significantly (p < 0.01) greater than the pressor responses of 11 ± 1 mm Hg seen for the normal recipient rabbits. At 5 minutes after the cross-circulation of blood, the normal recipient rabbits had pressor responses averaging 19 ± 1 mm Hg, which were significantly (p < 0.01) greater than were observed prior to cross-circulation. Pressor responses to norepinephrine in Experiment 2 were very similar between the one-kidney control rabbits that served as donors and the normal recipient rabbits, and following cross-circulation, the pressor responses were similar to those seen before the cross-circulation. The basal mean arterial pressure in the recipient rabbits was not changed following blood cross-circulation.

Figure 2 illustrates the pressor responses to norepinephrine in Experiment 3. The pressor responses to norepinephrine prior to cross-circulation were very similar between the one-kidney control rabbits that served as donors and the normal recipient rabbits, and following cross-circulation, the pressor responses to this dose of norepinephrine in the recipient rabbits were unaltered. Also, cross-circulation did not alter the basal mean arterial pressure in the recipient rabbits.

The pressor responses to norepinephrine in Experiment 3 are given in figure 3. The 3-day renal artery stenosis rabbits (donors) had pressor responses of 25 ± 2 mm Hg, which were significantly (p < 0.01) greater than the average value of 12 ± 1 mm Hg recorded in the normal recipient group in this experiment. Following the cross-circulation of blood and the administration of [Sar¹, Ile⁸] All to the recipient rabbits, the pressor responses to norepinephrine were the same at each time period as the pressor responses recorded for this group prior to cross-circulation. Immediately following the bolus injection of [Sar¹, Ile⁸] All, the mean arterial pressure increased by an average of 8 ± 2 mm Hg in the recipient rabbits; approximately 3 minutes later, however, it had returned to the basal level in each rabbit. Before cross-circulation, the pressor responses to i.v. injections of 300 ng of All in the recipient rabbits averaged 23 ± 3 mm Hg; at both 10 minutes and 65 minutes after the administration of [Sar¹, Ile⁸] All, no increases in arterial pressure were observed in response to the injections of this dose of All.

Discussion

The mechanisms producing pressor hyperresponsiveness in hypertensive patients and animal models of hypertension are not totally understood. Folkow et al.¹⁰ proposed that structural alterations in the walls of the resistance vessels that occurred as a result of the hypertension were responsible for it. This concept was supported by the experiments of Conway,³ who found pressor hyperresponsiveness in rabbits made hypertensive by renal compression only after the animals had developed hypertension. However, it has been reported that hypertensive animal models have a lowered threshold for pressor substances,⁵,²⁰ which cannot be explained by structural changes in blood vessel walls. Furthermore, several studies⁴-⁷,¹¹ in addition to the present one have found that exaggerated pressor responses in animal models of hypertension occur prior to the development of hypertension. Also, pressor hyperresponsiveness in renal hypertensive rabbits is attenuated or abolished by the All antagonist, [Sar¹, Ile⁸] All, which would not be expected if the hyperresponsiveness were due only to structural changes in the resistance vessels. Thus, the bulk of evidence indicates that mechanisms other than structural changes in blood vessel walls are responsible for the pressor hyperresponsiveness seen in hypertension.

Several studies have provided evidence for a humoral factor mediating pressor and vascular hyperrespon-
siveness in hypertension. Hinke \(^{10}\) found that the addition of serum from DOCA-salt hypertensive rats or from renal hypertensive rats to the solution perfusing isolated tail arteries of rats increased the responsiveness of the arteries to pressor substances. Bloom et al.\(^9\) reported that the addition of plasma from essential hypertensive patients to the perfusing solution of isolated femoral arteries of rabbits resulted in increased responses of the arteries to norepinephrine, whereas the addition of plasma from normotensive patients did not alter the responses. Evidence was presented by Mizukoshi and Michelakis\(^ {13}\) that the plasma of hypertensive patients contains a humoral factor that causes rats to have enhanced pressor responses to norepinephrine and AN. In later studies, Michelakis et al.\(^ {12}\) found this humoral factor also in the plasma of dogs with renal artery stenosis, and this group later reported that plasma from perinephritic hypertensive dogs and from one-kidney renal artery stenosis rats, when injected into assay rats, also produced greater arterial pressure rises in response to pressor substances.

Earlier studies from this laboratory\(^5\) revealed that one-kidney rabbits with renal artery stenosis of 3 days' duration were normotensive, but had exaggerated pressor responses to norepinephrine. Also, the i.v. infusion of [Sar\(^1\), Ile\(^6\)] AN restored the pressor responsiveness to normal in these rabbits, despite the fact that they had normal values for PRA; this AN antagonist did not alter the pressor responses to norepinephrine in normal rabbits. Vasopressin infusion also was seen to produce abnormally large increases in mean arterial pressure and more pronounced increases in total peripheral resistance in rabbits with 3-day renal artery stenosis than in normal rabbits;\(^6\) this pressor and vascular hyperresponsiveness to vasopressin in this prehypertensive rabbit model also was blocked by [Sar\(^1\), Ile\(^6\)] AN. Thus, the pressor hyperresponsiveness in this model is not specific for only a single pressor substance, as this renal artery stenosis model exhibits increased pressor responses to at least two different vasoactive agents that act on different receptors on arteriolar smooth muscle cells; likewise, the role of AN in mediating this hyperresponsiveness phenomenon appears to be a general one.

Results of the present study provide strong evidence that a circulating humoral factor is involved in promoting pressor hyperresponsiveness in this one-kidney, 3-day renal artery stenosis rabbit model. These renal prehypertensive rabbits had greater pressor responses to norepinephrine than did the normal rabbits, as was observed in our earlier studies. The cross-circulation at an equal rate between the renal artery stenosis rabbits and the normal rabbits resulted in a transfer of the pressor hyperresponsiveness to the normal rabbits. This humoral hyperresponsiveness factor appears to have a rather short onset time, as exaggerated pressor responses were observed in the recipient rabbits by 5 minutes after the blood cross-circulation. It also has a fairly long duration of action, as the pressor hyperresponsiveness was still present in the normal rabbits at 30 minutes following cross-circulation. With the duration and rate of blood exchange in these experiments, there was a maximum net exchange of 50 ml of blood between the pairs of rabbits, and as the blood volume of rabbits this size is about 54 ml per kg of body weight,\(^7\) it can be calculated that less than 30% of the total blood volume of each recipient rabbit was replaced with blood from the donor.

It might be conjectured that the technique for cross-circulation in this study may have produced trauma to some of the cellular components of the blood and that this or other perturbations to the biological system resulting from the cross-circulation may have been responsible for the observed pressor hyperresponsive-
ness in the recipient rabbits. However, because the cross-circulation of blood between one-kidney rabbits without renal artery stenosis and normal rabbits failed to alter the pressor responses in the recipients, it is unlikely that the procedure of blood cross-circulation alone could have produced disturbances that could lead to pressor hyperresponsiveness. Thus, the pressor hyperresponsiveness that occurred in the recipient rabbits following cross-circulation with renal artery stenosis rabbits was the result of the presence of some factor in the blood of the donor rabbits.

The question is raised as to whether the circulating humoral factor from the renal artery stenosis rabbits is merely All. It is well established that the administration of All to animals or to isolated perfused vascular beds, even in subpressor doses, will potentiate the pressor and vascular responses to norepinephrine. Sakurai and Hashimoto,22 as well as Khairallah et al.,23 reported that the vasoconstrictive effect of the isolated perfused rabbit ears was enhanced by All. Also, perfused hindlimbs of rats29 and mesenteric blood vessels of cats30 have been seen to exhibit more pronounced vasoconstrictor responses to norepinephrine in the presence of added All. Studies from our laboratory8 have revealed that the i.v. infusion of All in subpressor or in slightly pressor doses into normal rabbits will result in exaggerated pressor responses to norepinephrine. However, a recent study from our laboratory5 has provided convincing evidence that the hyperresponsiveness factor is not All. This study found that one-kidney rabbits with 3-day renal artery stenosis had PRA values and plasma All concentrations that were similar to those in normal rabbits. The i.v. infusion of the angiotensin converting enzyme inhibitor, captopril, to these prehypertensive renal artery stenosis rabbits reduced plasma concentrations to undetectable levels and abolished the pressor hyperresponsiveness to norepinephrine. However, when All was infused i.v. into these captopril-blocked rabbits at 2 ng/min per kg of body weight, the pressor hyperresponsiveness to norepinephrine was completely restored, although plasma concentrations of All remained depressed below normal. The i.v. infusion of All at this dose into normal rabbits receiving captopril did not result in pressor hyperresponsiveness to norepinephrine although plasma All concentrations were restored to near normal levels. Thus, while All obviously plays an essential role in mediating pressor hyperresponsiveness in this renal prehypertensive rabbit model, it is improbable that All was the humoral factor that triggered the pressor hyperresponsiveness in the normal recipient rabbits receiving blood from the 3-day renal artery stenosis rabbits in the present study.

Because All is essential to pressor hyperresponsiveness in 3-day renal artery stenosis rabbits but PRA and plasma All concentrations are not increased in this model, we have proposed previously2-8 that probably there is an increased number of All receptors and/or an increased affinity of the All receptors in this model. Because All receptors are found in a large number of different tissues and organs, the All receptors involved in mediating pressor hyperresponsiveness may be receptors other than those located on the arteriolar smooth muscle cells. Indeed, recent investigations from this laboratory26 have found that the All analog, [Sar1, Ala8] All, in doses that totally blocked the pressor responses to All in rabbits, did not attenuate the pressor hyperresponsiveness to norepinephrine in one-kidney, 3-day renal artery stenosis rabbits; this finding indicated that the All receptors involved in pressor hyperresponsiveness in this model are not the same as the receptors mediating pressor responsiveness to All.

There are basically two ways in which All and the blood hyperresponsiveness factor may be related to bring about pressor hyperresponsiveness in the 3-day renal artery stenosis rabbits: either All is involved in the release or secretion of the hyperresponsiveness factor, or the hyperresponsiveness factor requires All to exert its effect. The third experiment of the present study, in which [Sar1, Ile8] All was administered to the normal recipient rabbits after cross-circulation with the 3-day renal artery stenosis rabbits, provides insight into these possibilities. Presumably the donor rabbits with renal artery stenosis were secreting the hyperresponsiveness factor, which then was transferred to the normal recipients during the cross-circulation of blood, but pressor hyperresponsiveness did not occur in the recipient rabbits receiving [Sar1, Ile8] All. Because this All analog prevented pressor hyperresponsiveness in these recipient rabbits in the presence of adequate amounts of the circulating hyperresponsiveness factor, these results provide strong evidence that All is required for the hyperresponsiveness factor to produce pressor hyperresponsiveness, rather than All being required for the secretion of the hyperresponsiveness factor.

The mechanisms whereby All permits the circulating hyperresponsiveness factor to produce pressor hyperresponsiveness are not understood. However, studies have shown that All will increase the rate of norepinephrine release and decrease the rate of norepinephrine reuptake by the sympathetic nerve terminals;23-25,27,28 this should result in an increased norepinephrine concentration in the synaptic cleft of sympathetic nerve fibers terminating on arteriolar smooth muscle cells, producing a partial depolarization of these cells so that they will contract more readily in response to vasoconstrictor agents. We speculate that the humoral hyperresponsiveness factor in the blood of renal artery stenosis rabbits acts to increase the number and/or affinity of the All receptors on the sympathetic nerve terminals, so that increased receptor-all interaction occurs with normal plasma levels of All. The increased receptor binding of All then would result in pressor hyperresponsiveness by the same mechanisms as occur with increased plasma All concentrations.

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