

Plasma Vasopressin Concentrations and Effects of Vasopressin Antiserum on Blood Pressure in Rats with Malignant Two-Kidney Goldblatt Hypertension

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SUMMARY Male Sprague-Dawley rats with unilateral renal artery stenosis and a contralateral untouched kidney develop a malignant hypertension (MH) which is characterized by high blood pressures, sodium and water depletion, and subsequent activation of the renin-angiotensin system. In the present studies we found plasma arginine vasopressin (AVP) concentrations 3-fold higher than those in rats with benign renal hypertension, and 4- to 5-fold higher than those in normotensive control rats. Analysis of individual values showed considerable scatter; about 50% of the values fell in the range of benign hypertensive or control rats. When a specific AVP antiserum was injected, iv, into eight conscious unrestrained MH rats, BP transiently fell toward control values in four; in one, BP fell by only 10 mm Hg, and three other MH rats showed no response. In the same rats, injection of a specific angiotensin II antiserum always induced a transient fall in BP. On the basis of these and previously reported observations, we conclude that, subsequent to sodium and water loss and activation of the renin-angiotensin system, vasopressin release is stimulated in a significant number of MH rats and that, in these rats, vasopressin may cause significant systemic vasoconstriction. Thereby vasopressin may contribute to the development of malignant renal hypertension in rats.

THE FOLLOWING sequence of events underlies the onset of malignant renal hypertension in rats with unilateral renal artery stenosis and an untouched contralateral kidney: blood pressure increases into a critically high range and sodium and water loss ensue, resulting in hypovolemia. High blood pressure is maintained by the subsequent activation of the renin-angiotensin system. Due to progressive vasoconstriction in the presence of high blood pressure, the chain of events which results in vascular damage is initiated.¹⁻³ Other studies have shown that during the onset of malignant deoxycorticosterone (DOC) hypertension in which the renin-angiotensin system remains markedly suppressed despite sodium and water loss,^{4,5} plasma concentrations of the antidiuretic hormone arginine vasopressin increase. Vasopressin may exert a powerful vasoconstrictor effect, and thus it may play a role similar to that which renin and angiotensin play in malignant renal hypertension.⁵ These observations indicate that both vasopressor systems, renin-angiotensin and vasopressin, may be regarded as interchangeable systems in establishing malignant hypertension.

Several findings prompted us to reinvestigate the pathogenesis of malignant renal hypertension with respect to the possible vasopressor role of ADH in this pathophysiological situation. As mentioned above, during the onset of the malignant course of renal hypertension, hypovolemia develops and plasma angiotensin II concentrations increase; both factors stimulate vasopressin release.⁶ We

have demonstrated¹⁻³ that plasma renin and angiotensin II concentrations in malignant hypertensive rats do not always exceed the range of benign hypertensive rats. This suggests that in a considerable number of animals no further activation of the renin-angiotensin system occurs during the onset of malignant hypertension despite the development of hypovolemia. Thus, additional vasopressor systems may have come into play, supporting and/or interfering with renin-angiotensin in maintaining high blood pressure levels. Since the antidiuretic hormone appears to induce systemic vasoconstriction under a variety of pathophysiological conditions,^{5, 7-9} vasopressin may be such a candidate.

Methods

Sixty male Sprague-Dawley rats (SIV-50 strain, Ivanovas), weighing 120-130 g were placed into individual cages in a room at constant temperature ($23 \pm 1^\circ\text{C}$) and humidity ($60 \pm 5\%$) which was lit from 6 a.m. to 6 p.m. The rats were fed a commercial diet (ssniff; containing 100 mEq sodium and 210 mEq potassium per kg) and were given demineralized water ad libitum.

At a body weight of 140-150 g, systolic blood pressure (BP) was measured by tail plethysmography under light ether anesthesia; in 43 rats the left renal artery then was constricted by silver clips with internal diameters of 0.21-0.23 mm. The contralateral kidney was left untouched. Seventeen rats were subjected to sham operations. Subsequently, body weight and water and food intake were measured daily at 9 a.m. BP was recorded again 1 week after the operation and at varying intervals thereafter.

During the 3rd and 4th weeks after renal artery constriction, signs of malignant hypertension (MH) were

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observed for at least 2 to 3 days (BP 170–190 mm Hg or above, retardation of daily weight gain or weight loss, and increase in water intake^{1,2}). In the MH rats and in benign hypertensive (BH) rats (i.e., in rats that did not exhibit signs of malignant hypertension) and in sham-operated control rats, BP was recorded again. The next day between 9 and 10 a.m. these rats were decapitated. Blood was collected into heparinized glass capillaries and heparinized plastic tubes. The collected blood was centrifuged and hematocrits and plasma sodium and urea concentrations were determined. The hematocrits, determined in blood obtained by decapitation, are central, and not peripheral hematocrits. Osmolality was measured by freezing point depression (osmometer Knauer). Plasma arginine vasopressin (AVP) concentrations were estimated by a radioimmunoassay.¹⁰ After blood collection, the right, contralateral kidneys were excised, fixed in 10% formalin, and thin paraffin sections were stained with periodic acid-Schiff and examined.

In eight hypertensive rats exhibiting signs of malignant hypertension, PE 10 catheters were placed into the femoral artery and vein under ether anesthesia. Three to 4 hours after surgery, the arterial catheter was connected to a Statham P23Db transducer. Twenty minutes later, the experiment was started by injecting various rabbit sera into the conscious unrestrained rats; 0.4 ml of an AVP antiserum, which recently has been shown to be "biologically active" (see below) was injected within 1 minute via the venous catheter; about 30–60 minutes later, 0.2 ml of a "biologically active" angiotensin II antiserum (see Ref. 5) was injected into seven of the eight MH rats. Finally, 0.4 ml of serum obtained from a normal rabbit was injected into five of the eight MH rats tested. Since it has been shown⁵ that the AVP antiserum as well as the angiotensin II antiserum used in the present studies do not affect BP of normotensive control rats, no control rats were tested in the present studies in order not to waste the antisera. At the end of the experiments, the rats were anesthetized with ether and the right kidneys were excised, fixed, and stained as described above.

Biological activity of the AVP antiserum has been assessed in previous studies⁵ by the following criteria: this antiserum does not lower BP in rats with hypothalamic

diabetes insipidus; when BP in such rats is raised by the infusion of vasopressin, the antiserum lowers BP transiently; when BP is raised by the infusion of angiotensin II, the antiserum does not affect BP (whereas an angiotensin II antiserum lowers BP transiently); finally, the antiserum effectively blocks the blood pressure increase subsequent to a sudden increase in plasma vasopressin concentration due to intravenous injection or due to injection of angiotensin II into the third ventricle.⁸

All values in the text and in the tables are means \pm SEM. To evaluate the significance of a difference between mean values, either the Student's *t*-test or the Wilcoxon test was used. Linear regression equations were calculated by the method of least squares.

Results

The MH rats had the highest BP values; they lost weight, drank more water, and took less food during the 3 days preceding blood collection (Table 1). Hematocrits were increased substantially in the MH rats (Table 2); plasma sodium concentrations were reduced, and plasma urea concentrations showed a marked increase; plasma osmolality was reduced (Table 2). In the BH rats, BP was higher than in the sham-operated control rats, but lower than in the MH rats (Table 1). Water intake was increased, and except for the slight increase of plasma urea concentration, all the other parameters in Tables 1 and 2 were not different from those of the control rats. In 20 of the 24 MH rats (the MH rats described below are included), signs of malignant nephrosclerosis were found in the contralateral kidney, i.e., arteriolosclerosis and fibrinoid deposits and necrosis of the vascular wall of arterioles. However, as previously described, the degree of alterations varied markedly. In five of those rats, signs of a cerebral vascular crisis² became apparent. Signs of malignant nephrosclerosis were not detected in the BH rats.

Plasma AVP concentrations were higher in BH rats than in normotensive control rats (1.6 ± 0.2 pg/ml, $n = 19$, vs. 1.0 ± 0.1 pg/ml, $n = 17$; $P < 0.01$). In the MH rats, plasma AVP was further increased to a mean value of 4.7 ± 1.3 pg/ml ($n = 15$; $P < 0.01$ as compared with BH rats). One value of 40.2 pg/ml measured in an MH

TABLE 1 Blood Pressure, Weight Gain, and Water and Food Intake in Renal Hypertensive Rats

	Sham-operated controls	Benign hypertensives	Malignant hypertensives
<i>n</i>	17	19	16
Blood pressure (mm Hg)	106 ± 1	$158 \pm 3^*$	$185 \pm 3^*$
Weight gain (g/day)	4.3 ± 0.3	4.5 ± 0.4	$-5.9 \pm 1.3^*$
Water intake (ml/day)	30.0 ± 0.9	$34.8 \pm 1.1^*$	$53.9 \pm 3.6^*$
Food intake (g/day)	22.1 ± 0.5	22.8 ± 0.4	$15.3 \pm 1.3^*$

Values are means \pm SEM.

Systolic blood pressures were measured the day before the end of an experiment. Values of weight gain and of water and food intake are means of daily values measured during the last 3 days of the studies. Values for the eight malignant hypertensive rats in which the antiserum experiments were performed (Table 3) are not included.

* $P < 0.01$, compared with controls or benign hypertensive rats.

TABLE 2 Hematocrit, Plasma Osmolality, and Plasma Sodium and Urea Concentrations in Renal Hypertensive Rats

	Sham-operated controls	Benign hypertensives	Malignant hypertensives
<i>n</i>	17	19	16
Hematocrit (%)	42.1 ± 0.4	42.9 ± 0.6	49.3 ± 0.7*
Osmolality (mOsmol/kg)	296.2 ± 1.2	296.2 ± 1.3	291.1 ± 2.0†
Sodium (mEq/liter)	139.4 ± 0.4	138.4 ± 0.7	130.2 ± 1.5*
Urea (mmol/liter)	6.3 ± 0.2	7.2 ± 0.2*	15.1 ± 0.9*

Values are means ± SEM.

* $P < 0.01$, compared with controls or benign hypertensive rats.

† $P < 0.05$, compared with controls or benign hypertensive rats.

rat, which exhibited most severe signs of a cerebral vascular crisis and which was moribund before blood collection, has not been included in the above mean value of MH rats. There was a remarkable scatter of individual values (Fig. 1). In fact, in only half of the MH rats, plasma AVP was significantly raised; the other values fell into the range of the BH animals, and four values were even "normal." Also in the BH rats, only half of the values fell above the upper limit of the values measured in the normotensive control rats.

When values of plasma AVP were plotted against the respective values of either hematocrit, plasma osmolality, or plasma sodium concentration, no correlations were obtained for any of these parameters within each experimental group (controls, BH, and MH rats) or for all rats studied ($P > 0.3$). Only when BP was plotted against the logarithm of plasma AVP concentration was a significant positive correlation obtained for all rats studied ($r = 0.46$, $P < 0.001$). Within each experimental group no significant correlation was found.

The effects of a biologically active AVP antiserum, of a

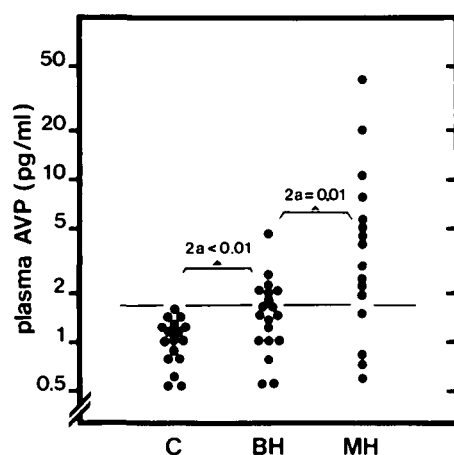


FIGURE 1 Plasma concentrations of arginine vasopressin in normotensive control rats (C) and in rats exhibiting a benign (BH) or a malignant course (MH) of renal hypertension. Values are presented on a logarithmic scale. The horizontal line indicates the upper limit of normal values. The significance of differences between groups were evaluated by the Wilcoxon test.

biologically active angiotensin II antiserum, and of a serum from a normal rabbit on the BP of two rats with malignant renal hypertension are shown in Figure 2. In one MH rat (rat 20), the AVP antiserum did not affect BP, while in the other animal (rat 30) it induced a transient fall. The injection of the angiotensin II antiserum induced a transient fall of BP in both MH rats. The injection of serum from a normal rabbit ("control serum") into one of these MH rats did not affect BP (Fig. 2).

Antiserum experiments were performed in six additional MH rats (Table 3). The initial BP of all eight rats tested was 183 ± 5 mm Hg. In four of the animals, BP fell by 60–75 mm Hg (mean: 65 ± 4 mm Hg) after injection of the AVP antiserum. In these rats, BP started to decline within 1–2 minutes after the start of antiserum injection; it reached a minimum within 6–8 minutes and

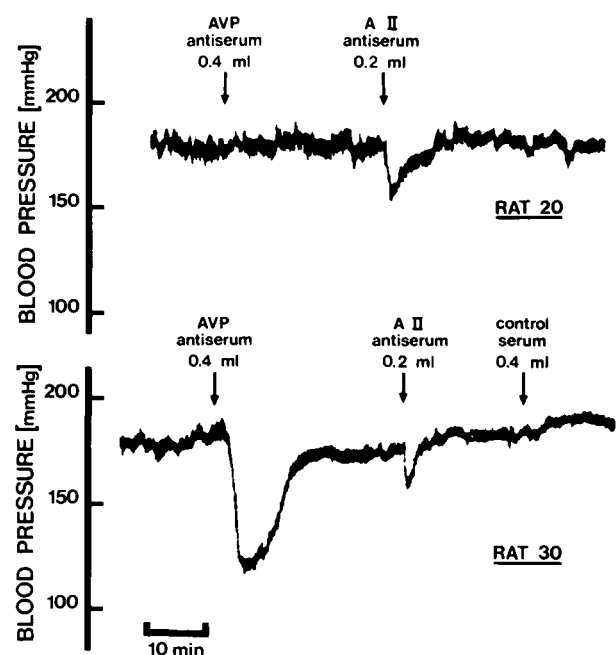


FIGURE 2 Effects of a vasopressin (AVP) antiserum, of an angiotensin II (A II) antiserum, and of a serum from a normal control rabbit (control serum) on blood pressure in two conscious unrestrained rats with malignant renal hypertension.

then increased again. This second increase of BP was rapid initially, but then slowed to reach the preinjection level (or a plateau slightly below that level; see Figure 2) within 28 to 56 minutes. In another MH rat, BP fell by only 10 mm Hg. In the remaining three MH rats there was no response to the injection of the AVP antiserum (Table 3). After the injection of 0.2 ml of angiotensin II antiserum into seven of the eight MH rats (Table 3), BP fell. The mean decrease was 23 ± 5 mm Hg (range, 10–50 mm Hg). Within 20–30 seconds after the start of antiserum injection, BP started to decline, reached a minimum within 1–2 minutes, and returned to the preinjection level within 4–14 minutes. In all but one rat, BP leveled off at BP levels 10–15 mm Hg higher than before the injection of the angiotensin II antiserum (Table 3). The administration of 0.4 ml of the control serum did not affect BP in the five MH rats tested.

Discussion

Ellis and Grollman¹¹ were the first to suggest that the secretion of antidiuretic hormone is enhanced in hypertension. They found that urinary excretion of antidiuretic activity is increased in hypertensive humans and in rats and dogs with renal hypertension. They also stated that this could be a "secondary response to the primary disturbance in kidney and liver which is responsible for the altered salt and water metabolism." Recently, these suggestions have been demonstrated experimentally in the benign and malignant phase of deoxycorticosterone (DOC) hypertension in rats.⁵ Moreover, increased plasma vasopressin concentrations have been found during the developmental phase of renal hypertension in rats, that had one renal artery constricted and the contralateral kidney left untouched.¹² The present studies demonstrate that in this latter model of experimental renal hypertension, plasma vasopressin concentrations remain elevated during the benign course and increase further during the malignant course.

In rats exhibiting a benign course of renal hypertension, the mean value of plasma arginine vasopressin concentrations was increased by 60%. In rats developing a malignant course, plasma vasopressin concentrations further

increased; the mean value was 3-fold higher than in benign hypertensive rats and 4- to 5-fold higher than in normotensive control rats. However, values of individual malignant hypertensive rats showed considerable scatter; some fell into the range of control animals (Fig. 1). Thus, plasma vasopressin concentrations were higher than in the BH rats in only about 50% of the malignant hypertensive rats. These increased values were comparable to those found in rats with malignant DOC hypertension, in which plasma vasopressin concentrations always were higher than in rats with benign DOC hypertension.⁵

The factors that might have stimulated vasopressin release during the onset of the malignant course of renal hypertension, i.e., subsequent to sodium and water loss,¹ have not been evaluated in detail in the present studies. However, it is reasonable to suggest that hypovolemia played a major role,^{6, 13} and that increased plasma angiotensin II concentrations may have been important too.⁶ Stimulation of vasopressin release occurred in the presence of reduced plasma osmolality. This was clearly a consequence of the marked reduction in plasma sodium concentration. In fact, as may be derived from the mean value of plasma osmolality (Table 2), in a considerable number of malignant hypertensive rats, plasma osmolalities fell below 290 mOsmol/kg, i.e., below the threshold value at which vasopressin release generally is triggered in the rat.¹³

In the benign hypertensive rats, in which the renin-angiotensin system is activated,^{1, 2} plasma vasopressin concentrations also were increased. The increase of plasma vasopressin occurred in the absence of measurable increases of plasma osmolality or sodium concentration and presumably also in the presence of hypervolemia as previously observed in such rats.¹ This suggests that plasma vasopressin concentrations may have been raised by increased plasma angiotensin II concentrations and thus may have contributed to the maintenance of hypervolemia in benign hypertensive rats. However, other so far unknown factors may have been more important in inducing inappropriately high plasma vasopressin concentrations in rats with benign renal hypertension.

In an attempt to elucidate if increased plasma vasopres-

TABLE 3 Effects of Antisera against Arginine Vasopressin (AVP) and Angiotensin II (A II) on Mean Blood Pressure (BP) of Eight Individual Rats with Malignant Hypertension (Two-Kidney Goldblatt Hypertension)

Rat no.	BP before AVP antiserum injection (mm Hg)	Fall of BP after AVP antiserum injection (Δ mm Hg)	BP before A II antiserum injection (mm Hg)	Fall of BP after A II antiserum injection (Δ mm Hg)	Final BP (mm Hg)
8	187	60			193
7	160	65	170	12	180
32	170	10	170	50	165
13	200	75	200	10	210
4	195	0	195	25	205
5	195	0	195	30	205
20	180	0	180	20	195
30	180	60	172	12	185

Experiments are listed in chronological order. In rats no. 4, 7, 8, 13, and 30, 0.4 ml of a serum from a nonimmunized rabbit was injected at the end of the experiments, and no effect on BP was observed.

sin concentrations could contribute to the development of malignant hypertension in rats exhibiting malignant renal hypertension a "biologically active" vasopressin antiserum was used to block a possible vasopressor effect of plasma vasopressin. When the vasopressin antiserum was injected intravenously into eight rats with malignant renal hypertension, blood pressure decreased transiently toward normotensive levels in four animals; in one rat, only a small reduction of blood pressure occurred and, in the other three rats, blood pressure remained unchanged. These findings suggest that in about 50% of rats with malignant renal hypertension, the antidiuretic hormone arginine vasopressin may have exerted a significant vasoconstrictor effect. This would then correspond to the 50% of rats in which plasma vasopressin concentrations were raised to levels comparable to those found in malignant DOC hypertension; in this form of experimental hypertension, the vasopressin antiserum always reduced blood pressure markedly.⁵

The AVP antiserum experiments reported here, as well as those performed in previous studies,⁵ did not give any positive evidence for an artificial effect of the AVP antiserum on blood pressure. The data obtained in a series of control studies (see Möhring *et al.*⁵ and this paper under Materials and Methods) and in rats with benign and malignant DOC hypertension⁵ were completely consistent with the notion that the AVP antiserum lowered blood pressure only when increased plasma AVP concentrations were vasopressor and that the degree of blood pressure reduction was related to the plasma concentrations of AVP and to the volume of antiserum injected. Nonetheless, such experiments could not principally exclude that the fall of blood pressure, if it occurred after the injection of the crude AVP antiserum, was due to a mechanism other than AVP blockade. Thus, the results obtained so far should be interpreted with caution until they are controlled and confirmed by comparable experiments using specific AVP antagonists or purified AVP antibodies, neither of which is available to date.

It has been shown that the renin-angiotensin system induces systemic vasoconstriction in renal hypertension in rats,¹⁴⁻¹⁹ and the degree of vasoconstriction is closely related to the actual plasma renin activity.^{18, 19} Similar results have been obtained by using the renin inhibitor pepstatin²⁰ in rats with benign and malignant renal hypertension (unpublished observations). From these observations as well as from the present finding, that an angiotensin II antiserum always lowered blood pressure, it may be concluded that the renin-angiotensin system always played a significant vasopressor role during the onset of malignant renal hypertension. Hence, it is conceivable that the sum of the effects of the two vasopressor systems, renin-angiotensin and vasopressin, may have accounted quantitatively for the maintenance of high blood pressure levels during the development of hypovolemia in malignant renal hypertension. Consistent with such a notion is the observation that in rats with hereditary hypothalamic diabetes insipidus, which do not produce any antidiuretic hormone¹⁰ and which were submitted to unilateral renal artery constriction, plasma renin concentration increased 10-fold during the onset of malignant hypertension,²¹

whereas in the rats used in the present studies it increased only 4-fold.^{2, 3} On the other hand, in rats with malignant DOC hypertension, in which plasma renin concentrations were markedly suppressed or almost unmeasurable,^{4, 5} plasma vasopressin concentrations increased tenfold⁵ i.e., much more than in malignant renal hypertension. Accordingly malignant renal hypertension would represent a situation in which both vasopressor systems may be involved.

When rats with hypothalamic diabetes insipidus were infused with arginine vasopressin, an increase in blood pressure by 15-50 mm Hg was obtained only when plasma vasopressin concentrations were raised by 115-160 pg/ml.⁵ These values are higher than those measured in rats with malignant renal or malignant DOC hypertension. Consequently, a great increase in the sensitivity to the vasopressor effect of vasopressin would have occurred in rats with malignant renal and with malignant DOC hypertension.

Marked increases of the systemic vasopressor response to vasopressin have been reported to occur under various experimental conditions. Cowley *et al.*²² observed that, in conscious dogs, the blood pressure response to vasopressin was increased 60- to 100-fold after baroreceptor denervation, but no such increase occurred with angiotensin II or noradrenaline. This indicated that in normal dogs the feedback gain of the baroreceptor reflex system could be enhanced markedly under the influence of exogenous vasopressin. Consequently, the vasopressor effect to endogenous vasopressin could depend on concomitant modulation of the baroreceptor reflex gain. Moreover, the above authors showed that in decapitated dogs that were infused with noradrenaline in order to maintain normal blood pressure levels the dose response curve for vasopressin was shifted further to the left by a factor of 8000.²² Such an increase in the sensitivity to the vasopressor effect of neurohypophyseal hormones by catecholamines (and vice versa) has been demonstrated repeatedly by various authors.²³⁻²⁵ These findings may be relevant in explaining an enhanced sensitivity to a vasopressor effect of vasopressin, which is suggested for benign and malignant DOC hypertension,⁵ as well as for rats exhibiting malignant renal hypertension. Under these pathophysiological conditions, the baroreceptor reflex system could be damped and/or a noradrenaline-mediated increase in the sensitivity of vascular smooth muscles may have occurred. However, to our knowledge, no experimental data are at hand to date to substantiate such a notion for malignant renal hypertension.

The observations reported in this communication give further support to the notion of a vasopressor role of the antidiuretic hormone under various pathophysiological conditions in rats,^{5, 7-9} and they may be of potential interest in light of recent observations made in humans in whom urinary excretion rates and plasma concentrations of vasopressin were increased during benign or malignant hypertension.^{26, 27}

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