Interaction of the Sympathetic Nervous System with Vasopressin and Renin in the Maintenance of Blood Pressure

Haralambos Gavras, M.D., Peter Hatzinikolaou, M.D., William G. North, Ph.D., Margaret Bresnahan, D.Sc., and Irene Gavras, M.D.

SUMMARY To evaluate the partial contributions and interaction of three vasopressor systems in blood pressure maintenance, nephrectomized rats and rats with intact kidneys were submitted sequentially to catecholamine depletion, elimination of vasopressin's vasoconstrictor action, and (for those with kidneys in situ) angiotensin blockade. Catecholamine depletion decreased blood pressure and stimulated vasopressin levels in all rats, but significantly more so in the anephric ones. Subsequent injection of an antagonist to the vasopressor effect of vasopressin produced a lasting fall of blood pressure in anephric rats, but only transient fall in those with intact kidneys. Infusion of teprotide — an angiotensin converting enzyme inhibitor — in the latter animals also produced transient blood pressure fall, but if this were followed by injection of the vasopressin antagonist, the pressure remained low for several hours. Blood pressure levels were closely correlated with those of plasma catecholamines throughout these maneuvers. Catecholamine levels were inversely correlated with those of plasma vasopressin, which were far greater in anephric rats through both stimulation and accumulation. Plasma renin activity was increasingly stimulated by falling blood pressure after each maneuver in rats with intact kidneys. Thus, it appears that in the resting state the sympathetic nervous system is more involved in the maintenance of blood pressure, whereas vasopressin and renin are important backup mechanisms.

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KEY WORDS • catecholamines • renin-angiotensin system • sympathetic nervous system • blood pressure regulation

Maintenance of blood pressure at a certain level is the end result of interplay between various vasoactive hormones. In hypertension research over the past few years, greatest emphasis has been placed on the renin-angiotensin system, probably because assays for measurement of its components and specific inhibitors for several of these components became widely available. More recently, methodology was developed for accurate measurement of plasma catecholamines and plasma vasopressin, further enhancing research in these vasopressor hormones. Interest in the cardiovascular effects of vasopressin was revived recently and was particularly stimulated by the development of chemical analogs that selectively antagonize the vasoconstrictor effects of the hormone without affecting its renal tubular actions.

The present experiments were designed to evaluate the contribution of each one of these three vasopressor systems to the maintenance of normal blood pressure. Catecholamine depletion and bilateral nephrectomy were intended to produce conditions comparable — albeit extreme — to those likely to be encountered in the therapy of human hypertension, e.g., treatment with sympatholytic agents and advanced renal failure. Under these conditions, we studied the interaction and relationships of catecholamines, vasopressin, and the renin-angiotensin system.
Methods

Fifty-two male Wistar rats (Charles River Breeding Laboratories) weighing 275–320 g were housed in a temperature- and humidity-controlled environment with automatic lighting in 12-hour cycles; they were maintained on Purina rat chow and tap water ad libitum. Of the 52 rats, 23 underwent uninephrectomy under ether anesthesia 1 week prior to the experiment. On the day of the experiment, they were again anesthetized with ether and had the remaining kidney removed. Subsequently, a PE-50 catheter was inserted in the right external iliac artery and a PE-10 catheter in the right femoral vein. Both catheters contained a heparinized dextrose 5% solution. Upon awakening, the animals were maintained in a semirestrained position on a light mesh screen for 60–90 minutes until their blood pressure gradually rose to a steady baseline.

Twenty-nine animals with intact kidneys were also catheterized in the same manner under light ether anesthesia and then maintained in the semirestrained position. In all animals, arterial pressure was continuously monitored with a Statham transducer and recorded on a Hewlett Packard recorder (model 7702B). Mean blood pressure and heart rate were recorded directly during the experiment on this recorder.

"Chemical sympathectomy" was induced by intraperitoneal injection of reserpine (Serpasil, CIBA) at a dose of 0.1 mg/100 g body weight. Four hours later, a first dose of metyrosine 2.5 mg/100 g (Merck, Sharp and Dohme) was given intraperitoneally. The animals were maintained overnight with an intravenous (i.v.) infusion of 5% dextrose administered by a Harvard pump at a rate of 0.006 ml/min for a total of approximately 5 ml. Thirteen hours later a second dose of metyrosine 2.5 mg/100 g was injected intraperitoneally. Suspension of metyrosine for injection was prepared from 25 mg metyrosine in 1.2 ml of 0.5M sodium phosphate buffer with pH of 7.4 and 0.8 ml of 5% methyl cellulose (Fisher Scientific Company).

The peptide [1-(/8-mercapto-/3, ^-cyclopentamethylene propionic acid, 2-(0-methyl) tyrosine] arginine vasopressin, which is an analog and competitive antagonist of arginine vasopressin (AVP) at the vascular receptor level[4, 5] was used as an inhibitor of the vasoconstrictor effects of AVP. A 2 mg amount of this compound was dissolved in a solution made from 10 ml 0.9% NaCl, 10 mg bovine serum albumin, 3 ml acetic acid, brought to a pH of 6.4 with NaOH. A dose of 0.15 ml of this solution containing 30 μg of the AVP antagonist was administered i.v.

The angiotensin converting enzyme inhibitor teprotide (SQ20,881, Squibb) was used as inhibitor of the renin-angiotensin system. A dose of 0.2 mg/100 g was dissolved in 0.9% NaCl and infused intravenously by a Harvard pump over a 90-minute period at a rate of 0.018 ml/min for a total of 1.6 ml.

The animals were divided in seven groups: Group 1 (n = 8) included nephrectomized animals submitted to chemical sympathectomy. Three hours after the second dose of metyrosine they received injection of the AVP antagonist and 1 hour later they had 0.4 ml of blood drawn for measurement of plasma catecholamine levels.

Group 2 (n = 7) consisted of nephrectomized and chemically sympathectomized animals. Three hours after the second metyrosine injection they had two samples of blood (2 and 0.4 ml) drawn for determination of plasma AVP and plasma catecholamine levels respectively.

Group 3 (n = 7) consisted of nephrectomized animals with sympathetic system intact. They were catheterized and maintained overnight with a dextrose 5% infusion and at approximately 20 hours after the nephrectomy they had blood samples drawn as above for determination of plasma catecholamines and AVP to be used as controls in the anephric state.

Group 4 (n = 7) consisted of rats with intact kidneys, submitted to chemical sympathectomy. Three hours after the second dose of metyrosine the teprotide infusion was started. One half hour later, when blood pressure had reached approximately pre-teprotide levels, the AVP antagonist was injected i.v. At 1 hour later, a 0.4 ml blood sample was drawn for catecholamine determination.

Group 6 (n = 9) consisted of rats with intact kidneys submitted to chemical sympathectomy. Three hours after the second dose of metyrosine the teprotide infusion was started. One half hour later, when blood pressure had reached approximately pre-teprotide levels, the AVP antagonist was injected i.v. At 1 hour later, a 0.4 ml blood sample was drawn for catecholamine determination.

PRA levels were also determined by radioimmunoassay, and plasma catecholamines were measured by radioenzymatic assay. Results are reported as means ± SEM. Statistical evaluation was made with Student's t test for paired or nonpaired comparisons as appropriate. Correlations were calculated by the Spearman rank correlation method. Results were considered to be significant if p < 0.05.
Results

Changes in blood pressure during the various manipulations in anephric rats and rats with intact kidneys are illustrated in figure 1. Reserpine alone produced a small but significant fall in pressure in all animals, and metyrosine caused a further drop in pressure. At 20 hours after the beginning of the experiment, injection of the AVP antagonist produced an abrupt major fall in blood pressure of both nephrectomized animals (Panel A) and those with intact kidneys (Panel B), indicating that AVP contributed to a major extent to the maintenance of blood pressure in these chemically sympathectomized animals. However, rats with intact kidneys showed a rapid gradual increase in pressure toward levels similar to those preceding the injection of AVP antagonist, whereas blood pressure of anephric rats remained depressed for the next 4 hours of observation. In rats with intact kidneys who at 3 hours after the second metyrosine injection received infusion of the converting enzyme inhibitor teprotide (Panel C), blood pressure decreased abruptly, but transiently, despite continuing teprotide infusion. When blood pressure in these animals again reached the pre-teprotide levels, injection of AVP antagonist caused the blood pressure to fall further and stay at that level for the remaining period of observation (at least 1 hour and as long as 4 hours).

Blood pressures and hormone levels for each group of animals are shown in table 1. Groups 3 and 7 are nonmanipulated animals used to provide baseline hormone values for anephric and intact animals respectively. It is apparent that levels of AVP and epinephrine were significantly higher (p < 0.001 and p < 0.05 respectively) in anephric animals, whereas norepinephrine also tended to be higher but not significantly so. After reserpine and metyrosine injections, catecholamines were markedly depleted in all groups so treated: both norepinephrine and epinephrine were significantly lower (p < 0.01 and p < 0.001 respectively) from control values in the anephric animals and in the animals with intact kidneys (p < 0.001 for both), compared with the control values of each group. Although norepinephrine tended to be somewhat higher in the chemically sympathectomized anephric rats (Groups 1 and 2) than their counterparts with kidneys in situ (Groups 4, 5, and 6), the differences were not significant.

Chemical sympathectomy produced variable but in all cases concomitant degrees of depletion of plasma levels of both norepinephrine and epinephrine. The levels of the two catecholamines were always closely correlated. In anephric rats (Groups 1, 2 and 3) the correlation coefficient between them was $r = 0.818$, p < 0.001; in rats with intact kidneys it was $r = 0.928$, p < 0.001.

Plasma levels of AVP were already higher in anephric controls than in normal rats (p < 0.001). They were greatly stimulated after catecholamine depletion in both the anephric rats and the ones with in-

![Figure 1. Time sequence and blood pressure effects of catecholamine depletion, injection of the vasopressin antagonist, and infusion of the angiotensin converting enzyme inhibitor in anephric rats and rats with intact kidneys.](image1)

![Figure 2. Correlation between blood pressure levels and plasma levels of norepinephrine and epinephrine in anephric rats and rats with kidneys in situ, with intact sympathetic system, or catecholamine-depleted.](image2)
TABLE 1. Blood Pressure and Hormone Levels in Seven Groups of Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressures (mm Hg)</th>
<th>Hormone levels (pg/ml)</th>
<th>PRA (ng/ml/hr)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Reserpine</td>
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<td>1 (n = 8)</td>
<td>109 ± 1.5</td>
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</tr>
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<td>5 (n = 7)</td>
<td>110 ± 1.4</td>
<td>92 ± 1.6</td>
<td>74 ± 4.0</td>
</tr>
<tr>
<td>6 (n = 9)</td>
<td>114 ± 2.3</td>
<td>98 ± 3.2</td>
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<td>7 (n = 6)</td>
<td>111 ± 3.1</td>
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There was a highly significant correlation between blood pressure levels and those of norepinephrine ($r = 0.925, p < 0.001$) and epinephrine ($r = 0.810, p < 0.001$) when data from animals of the four groups who received no AVP antagonist or teprotide were pooled together (Groups 2, 3, 6, and 7), as shown in figure 2. There was also a significant inverse correlation between levels of AVP and those of norepinephrine ($r = -0.724, p < 0.001$) and epinephrine ($r = -0.748, p < 0.001$) in the same four groups, as shown in figure 3.

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When all the anephric animals and all those with kidneys in situ were analyzed as two separate groups, the correlations between blood pressure and plasma catecholamines and vasopressin remained the same. In anephric rats, the blood pressure was highly correlated with norepinephrine ($r = 0.932, p < 0.001$) and epinephrine ($r = 0.904, p < 0.001$). In those with intact kidneys blood pressure was also highly correlated with norepinephrine ($r = 0.822, p < 0.001$) and epinephrine ($r = 0.818, p < 0.001$). Blood pressure was also significantly correlated with AVP levels in the two groups of anephric rats (Groups 2 and 3; $r = 0.715, p < 0.001$) as well as those with intact kidneys (Groups 6 and 7; $r = 0.776, p < 0.001$). The plasma AVP levels were also inversely correlated with the plasma levels of norepinephrine and epinephrine ($r = 0.653, p < 0.001$ and $r = -0.679, p < 0.01$ respectively) in the anephric rats of Groups 3 and 4; in rats with intact kidneys (Groups 6 and 7) these correlations were even closer ($r = -0.825, p < 0.001$ and $r = -0.795, p < 0.001$ respectively).

Plasma renin activity was measured in all rats with intact kidneys except for those of Group 5 who received teprotide. It was significantly higher than normal in those who had chemical sympathectomy only and even more in those who received in addition the AVP antagonist ($p < 0.001$ for both). In fact, there was a significant negative correlation between blood pressure levels obtained after removal of the sympathetic system and vasopressin sequentially and corresponding PRA levels ($r = -0.667, p < 0.02$), indicating an attempt of the renin system to maintain normal blood pressure, which was decreasing after each maneuver.

Discussion

These experiments attempt to define the participation and interrelation of three vasopressor systems: the sympathetic nervous system, renin-angiotensin system, and arginine vasopressin (AVP) in blood pressure maintenance. We chose two rat models, one anephric, because in previous experiments we found that the plasma levels and pressor effects of catecholamines and AVP seemed to be very pronounced in nephrectomized animals, and one with intact kidneys for comparison. Indeed, our present data indicate that levels of AVP were significantly higher in the anephric rats than in those with kidneys in situ (Groups 2 and 3 vs Groups 6 and 7 in table 1), which is compatible with knowledge of the kidney's participation in the clearance of AVP. Catecholamines also tended to be higher in anephric rats than in their counterparts with intact kidneys, but only the levels of epinephrine were significantly higher in the anephric model with intact sympathetic system.

Treatment with combination of reserpine and metyrosine was chosen as an effective and rapid way to eliminate catecholamines. The former interferes with uptake and storage of catecholamines by adrenergic neurons, thus inducing catecholamine depletion which is maximal by 24 hours after administration. The latter inhibits tyrosine hydroxylase, the enzyme catalyzing the conversion of tyrosine to dihydroxyphenyl alanine (DOPA), which is the first step in catecholamine biosynthesis. Effectiveness of this treatment was shown by significant depletion of all catecholamines in all groups so treated.

This "chemical sympathectomy" was accompanied by gradual fall of blood pressure and corresponding levels of catecholamines in all groups, as shown by figure 2, indicating the degree of contribution of the sympathetic system to maintenance of blood pressure levels. Depletion of catecholamines was associated with a marked stimulation of AVP levels in an effort to maintain blood pressure. There was a significant inverse correlation between AVP levels and those of epinephrine and norepinephrine (figure 3), indicating that the more pronounced the depletion of catecholamines, the more the release of AVP was stimulated. This could partly be attributed to hypotension per se acting as a stimulus for secretion of AVP and partly to removal of the attenuating or inhibitory influence of catecholamines on the secretion of AVP.

In the anephric model, the participation of AVP in maintaining blood pressure after chemical sympathectomy was far more important, as shown by both the excessively high plasma AVP levels and the magnitude of blood pressure fall (average 40 mm Hg) after injection of the AVP antagonist (fig. 1 A and table 1, Group 1). Moreover, blood pressure remained at that low level for several hours. Remarkably, these animals tolerated pressures ranging between 35–55 mm Hg very well, since they appeared to be alert and in no distress during the period of observation.

On the contrary, rats with intact kidneys seemed to have at least two more backup mechanisms to maintain blood pressure after catecholamine depletion. Both PRA and AVP release were significantly stimulated by this maneuver (as shown in Group 6 of table 1). The AVP antagonist produced a blood pressure fall of only 15 mm Hg, on the average, which within minutes started increasing again toward preinjection levels. The high PRA levels at that point suggest that stimulation of the renin-angiotensin system tended to offset the hypotensive action of the AVP analog in these animals (as shown in fig. 1 B and table 1, Group 4). When the catecholamine-depleted model with intact kidneys was submitted to infusion of teprotide, which eliminated the formation of angiotensin II, blood pressure again fell temporarily, but soon returned to preinjection levels despite continuing infusion of teprotide (fig. 1 C and table 1, Group 5). At that point, additional administration of AVP antagonist had a marked depressor effect which remained unchanged for up to 4 hours of observation, indicating that the blood-pressure-maintaining reserves were now neutralized.

Arginine vasopressin does not seem to play an important role in blood pressure maintenance under normal conditions, unless the subject has suffered dehydration or hemorrhage which has compromised effective arterial pressure and volume and increased plasma osmolality. The renin-angiotensin system...
also does not contribute to the blood pressure maintenance unless sodium deprivation, diuretics, tilting, etc., manipulations act to decrease blood pressure, in which case a compensatory renin release tends to restore pressure to normal.

Recently, Andrews and Brenner, using the anesthetized dehydrated rat model, showed that both angiotensin II and vasopressin assume an important role in the homeostasis of blood pressure that has been compromised, but not in the normal state. Our present experiments also indicate that these two mechanisms become important when another vasopressor mechanism, the sympathetic system, has been interfered with. Particularly in the renoprivil state, stimulated vasopressin accumulates to excessive levels and assumes a major role in the maintenance of blood pressure.

In conclusion, our findings indicate that in the resting state the sympathetic system is more involved in the maintenance of normal blood pressure, whereas vasopressin and the renin-angiotensin system are important backup mechanisms. During sequential interference with, or elimination of, each one of these systems, the remaining mechanisms are stimulated to take over the task of preserving the homeostasis of blood pressure.

These findings produced in an experimental model with nephrectomy or chemical sympathectomy could be relevant to the management of clinical hypertension. It is possible that treatment with sympatholytic agents, especially in subjects with various degrees of renal insufficiency and variable capacity to stimulate renin secretion, could produce conditions similar to those observed in the present experiments. It is well known that the antihypertensive effect of diuretics may be limited by reactive hyperreninemia. It is reasonable to speculate that volume depletion by diuretics and sympathetotropic blockade by various antihypertensive agents may lead to compensatory stimulation of vasopressin as well, thus offsetting the blood-pressure-lowering effect of these agents. This would be particularly relevant to subjects with renal insufficiency in whom a sodium and fluid load is more likely to induce elevation in blood pressure through AVP release and whose AVP clearance may be impaired so that the hormone’s levels can become excessive. Therefore, AVP antagonists may have an antihypertensive potential not only in the rare cases of mineralocorticoid-induced hypertension but also as an adjunct treatment in refractory hypertension of chronic renal failure treated by sympatholytic agents.

References


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