The Adrenergic System and the Release and Pressor Action of Vasopressin
IRENE GAVRAS, SIMON HATINOGLOU, AND HARALAMBOS GAVRAS

SUMMARY We studied the effect of various adrenergic components on vasopressin in groups of anephric rats. Pharmacological interventions included $\alpha_1$, $\alpha_2$, and $\beta$-adrenergic receptor blockade and infusions of sodium nitroprusside to achieve a baseline blood pressure fall similar to that obtained by $\alpha_1$-blockade, followed by hypertonic saline infusion to stimulate vasopressin release and administration of a specific $V_1$ vascular vasopressin inhibitor to test the degree of blood pressure dependency on vasopressin. The combined hypotensive and osmolar stimuli of nitroprusside followed by hypertonic saline led to the highest level of plasma vasopressin (104 ± 17 pg/ml, p < 0.01) but only a 7 ± 1 mm Hg fall in blood pressure in response to the vasopressin inhibitor. Rats subjected to $\alpha_1$-blockade and saline infusion had the largest blood pressure reduction in response to the vasopressin inhibitor (43 ± 5 mm Hg, p < 0.001), despite a modest rise in vasopressin levels (18 ± 2 pg/ml). Other pharmacological maneuvers produced intermediate responses in terms of vasopressin release and blood pressure response to the vasopressin inhibitor. There was no correlation between vasopressin levels achieved by each maneuver and the magnitude of blood pressure reduction in response to the vasopressin inhibitor. We conclude that 1) plasma levels of vasopressin under these conditions do not permit an accurate estimate of the magnitude of its pressor contribution to the maintenance of a given blood pressure level, which can be demonstrated only by the depressor response to a vasopressin inhibitor, and 2) the maximal vasopressor potential of vasopressin can be expressed only under conditions of impaired $\alpha_1$-adrenergic function. (Hypertension 8 [Suppl II]: 11-163—11-167, 1986)

KEY WORDS • $\alpha_1$-blockade • $\alpha_2$-blockade • $\beta$-blockade • sodium nitroprusside • hypotensive stimuli • osmotic stimuli • vasopressin $V_1$ inhibitor

STUDIES performed in the last few years provide ample evidence of the interaction between various components of the sympathetic nervous system and the pressor effect of vasopressin. Earlier studies reported a pronounced pressor effect of vasopressin in patients with autonomic insufficiency. More recent experimental work has indicated that baroreceptor denervation intensifies the pressor action of endogenous physiological levels, as well as exogenous pharmacological doses, of vasopressin. Furthermore, after impairment of sympathetic function by chemical sympathectomy or ganglionic blockade, maintenance of blood pressure depends to a great extent on vasopressin-induced vasoconstriction.

However, the effects of various components of the sympathetic function remain controversial. On the one hand, there is convincing evidence that dopamine inhibits and that dopaminergic or combined $\alpha$- and $\beta$-adrenergic blockade enhances both the release and the pressor effectiveness of vasopressin. On the other hand, equally convincing studies suggest that dopamine enhances vasopressin secretion and that an intact $\alpha_1$-adrenergic system is a prerequisite for the release of pressor amounts of vasopressin.

The present studies were designed to clarify the roles of various adrenergic components in the secretion and the vasoconstrictor potency of vasopressin. We chose to study anephric rats in order to eliminate interference from compensatory changes of the renin-angiotensin system and to maximize changes in vasopressin levels. Secretion of vasopressin was maximally stimulated by infusion of hypertonic saline, and the effects of specific adrenergic functions were studied by selective pharmacological blockade. Our results indicate that the degree of blood pressure dependence

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on vasopressin is mostly unrelated to the plasma levels of the hormone and that the most important factor influencing the pressor action of vasopressin is α₁-adrenergic activity.

Methods

Male Wistar rats (Charles River Breeding Laboratories, Wilmington, MA, USA) weighing 200 to 240 g were housed in a temperature- and humidity-controlled environment with automatic lighting in 12-hour cycles; they were maintained on Purina rat chow (St. Louis, MO, USA) and tap water ad libitum. They underwent right uninephrectomy under ether anesthesia 1 week before the experiment. On the day before the experiment, a PE-50 catheter was inserted in the right external iliac artery, and another one in the right femoral vein. Both catheters contained a heparinized 5% dextrose solution. On the day of the experiment, the animals were again anesthetized with ether, and the remaining kidney was removed. Upon awakening, they were maintained, unrestrained, in plastic cages and observed for 60 to 90 minutes until their blood pressure gradually rose to a steady baseline value. Their arterial pressure was continuously monitored with a Statham transducer (Oxnard, CA, USA) and recorded on a Hewlett Packard recorder (Model 7702B; Lexington, MA, USA). Mean blood pressure and heart rate were recorded directly on this machine during the experiment.

α₁-Adrenergic receptor blockade was induced by subcutaneous injections of prazosin, 0.2 mg/kg, at 2-hour intervals (total of two doses). α₂-Adrenergic receptor blockade was induced by intravenous injection of yohimbine, 0.125 mg/kg, repeated at 30-minute intervals (total of six doses). β-Adrenergic receptor blockade was induced by an intravenous injection of propranolol, 2.0 mg/kg. In previous studies, we have determined that these dosage schedules ensure adequate blockade for the 3-hour duration of each experiment. A sodium nitroprusside solution of 50 mg/100 ml was infused at the rate of 2.5 μg/min (approximately 1 ml/hr).

The peptide [1-(β-mercaptopo-β,β-cyclopentamethyl-ene propionic acid), 2-(O-methyl)tyrosine] arginine vasopressin, which is an analogue and competitive antagonist of arginine vasopressin at the vascular receptor level, was used as an inhibitor of the vasoconstrictor effects of vasopressin. A 1-ng amount of this compound was dissolved in 10 ml of a 5% dextrose solution. A dose of 0.3 ml containing 30 μg of the vasopressin antagonist was administered intravenously.

A hypertonic saline infusion consisting of 4% NaCl was given at the rate of 0.018 ml/min for a total of 2 ml over a period of 2 hours.

Eight groups of rats were studied. Group 1 (n = 14) was submitted to α₁-blockade, followed by hypertonic saline infusion for 2 hours. At the end of this period seven rats received an injection of the vasopressin antagonist, and the other seven had 2 ml of blood drawn for measurement of vasopressin levels.

Group 2 (n = 14) was also submitted to α₁-blockade with prazosin but received no saline infusion. After 2 hours, seven rats received an injection of the vasopressin antagonist, and seven had 2 ml of blood drawn for measurement of plasma vasopressin levels.

Group 3 (n = 14) was submitted to α₁-blockade with yohimbine, followed by a 2-hour infusion of hypertonic saline. Seven rats then received the vasopressin antagonist, and the other seven had blood drawn for measurement of vasopressin levels.

Group 4 (n = 7) was also submitted to α₁-blockade with yohimbine but was observed for 2 hours without other intervention and then had blood drawn for vasopressin measurement.

Group 5 (n = 14) was submitted to β-blockade with propranolol, followed by a 2-hour saline infusion. Seven rats then received an intravenous injection of the vasopressin antagonist, and the other seven had blood drawn for vasopressin measurement.

Group 6 (n = 7) was also submitted to β-blockade with prazosin but was observed without other intervention over the next 2 hours and then had blood drawn for AVP measurement.

Since α₁-blockade caused an immediate, sharp drop in blood pressure, a control was needed to separate the effect of α₁-adrenergic receptor inhibition from the nonspecific effect of abrupt hypotension. For this reason, infusion of sodium nitroprusside was used in the last two groups. Group 7 (n = 13) received an infusion of sodium nitroprusside calculated to reduce blood pressure to the level achieved by α₁-blockade (i.e., approximately 70 mm Hg). The 2-hour saline infusion was then given, followed by either the vasopressin inhibitor (in 7 rats) or blood sampling for measurement of vasopressin levels (in 6 rats).

Group 8 (n = 7) received the infusion of nitroprusside for 2 hours, at the end of which blood was drawn for measurement of vasopressin levels.

Plasma vasopressin levels were determined by radioimmunoassay. The minimum detectable level is 0.2 pg/ml with this method, and a 50% displacement of iodinated vasopressin is regularly produced by 2 pg of the peptide. In anephric conscious rats that do not undergo further manipulation, the mean ± SEM plasma level is 10.7 ± 1.1 pg/ml.

Results

Table 1 presents the effects of each intervention on blood pressure and plasma levels of vasopressin. Both the α₁-adrenergic receptor blockade with prazosin and the infusion of sodium nitroprusside produced a profound drop in blood pressure, from original baseline values of 104 to 114 mm Hg to new baseline values
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**Discussion**

In this study we attempted to clarify the influence of various components of the adrenergic system on the release of vasopressin after an osmotic stimulus and on its pressor effectiveness and to separate that specific influence from the nonspecific effect of profound hypotension. Baseline vasopressin levels in anephric animals are already somewhat elevated (average value, 10 pg/ml), but in the absence of any other manipulation, the vasopressin inhibitor produces no depressor effect ranging from 68 to 74 mm Hg. The new blood pressure level obtained after each pharmacological intervention was taken as the baseline for subsequent calculations of blood pressure changes. Unlike $\alpha_1$-blockade, $\alpha_2$- and $\beta$-adrenergic receptor blockade produced no change or a minor rise in blood pressure, respectively. After hypertonic saline infusion for 2 hours, blood pressure rose by 22 to 35 mm Hg in all four groups receiving the infusion ($p < 0.001$). At that point, the vasopressin antagonist was injected to determine to what extent vasopressin contributed to the new blood pressure level. The degree of blood pressure reduction after injection of the vasopressin antagonist was considered to be the vasopressin-dependent component, whereas the remaining difference in blood pressure between the baseline value and the value after injection of the vasopressin antagonist was considered to be the "residual" pressure (i.e., residual blood pressure equals blood pressure after vasopressin inhibition minus blood pressure before saline infusion). There was no correlation whatsoever between the plasma levels of vasopressin induced by each maneuver and the magnitude of the vasopressin-dependent component of the blood pressure resulting from the same maneuver ($r = 0.232, p = 0.15$). Animals treated with sodium nitroprusside plus hypertonic saline had the highest plasma vasopressin levels ($p < 0.01$, compared with all groups) but the smallest contribution of vasopressin to the maintenance of blood pressure ($p < 0.001$, compared with all groups except Group 2). In contrast, animals submitted to $\alpha_1$-blockade had the largest vasopressin-dependent blood pressure component ($p < 0.001$, compared with all other groups), even though they had only a modest rise in plasma vasopressin levels.

Figure 1 illustrates the blood pressure changes observed after each pharmacological intervention followed by a 2-hour hypertonic saline infusion and injection of the vasopressin antagonist. Clearly, the magnitude of blood pressure reduction in response to the vasopressin antagonist was unrelated to either the baseline blood pressure observed after the initial pharmacological intervention or the level attained at the end of the hypertonic saline infusion.

**Table 1. Effects of Various Pharmacological Interventions on Blood Pressure and Plasma Vasopressin Levels in Anephric Rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pharmacological intervention</th>
<th>Immediate $\Delta$BP (mm Hg)</th>
<th>NaCl 4% infusion</th>
<th>Postsaline $\Delta$BP (mm Hg)</th>
<th>AVP level (pg/ml)</th>
<th>AVP-dependent BP component (mm Hg) $^*$</th>
<th>Residual BP (mm Hg) $^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\alpha_1$-Blockade</td>
<td>$-34 \pm 3$</td>
<td>Yes</td>
<td>$34 \pm 5$</td>
<td>$18.2 \pm 2.5$</td>
<td>$43 \pm 5$</td>
<td>$-9 \pm 5$</td>
</tr>
<tr>
<td>2</td>
<td>$\alpha_2$-Blockade</td>
<td>$-40 \pm 3$</td>
<td>No</td>
<td>$30.4 \pm 8.2$</td>
<td>$-6 \pm 3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$\beta$-Blockade</td>
<td>$0 \pm 1$</td>
<td>Yes</td>
<td>$29 \pm 2$</td>
<td>$34.0 \pm 4.6$</td>
<td>$15 \pm 2$</td>
<td>$14 \pm 2$</td>
</tr>
<tr>
<td>4</td>
<td>$\alpha_2$-Blockade</td>
<td>$-6 \pm 2$</td>
<td>No</td>
<td>$68.0 \pm 9.0$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$\beta$-Blockade</td>
<td>$8 \pm 2$</td>
<td>Yes</td>
<td>$29 \pm 4$</td>
<td>$20.4 \pm 3.6$</td>
<td>$22 \pm 3$</td>
<td>$7 \pm 3$</td>
</tr>
<tr>
<td>6</td>
<td>$\beta$-Blockade</td>
<td>$6 \pm 2$</td>
<td>No</td>
<td>$26.0 \pm 4.9$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NTP</td>
<td>$-36 \pm 2$</td>
<td>Yes</td>
<td>$22 \pm 2$</td>
<td>$104.5 \pm 17.6$</td>
<td>$7 \pm 1$</td>
<td>$15 \pm 2$</td>
</tr>
<tr>
<td>8</td>
<td>NTP</td>
<td>$-38 \pm 4$</td>
<td>No</td>
<td>$65.6 \pm 15.9$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM. BP = blood pressure; AVP = arginine vasopressin; NTP = sodium nitroprusside.

$^*$The blood pressure fall observed immediately after AVP inhibition.

$^+$Residual BP is BP after vasopressin inhibition minus BP before saline infusion (i.e., baseline).
in these animals (personal observation, unpublished). Adrenergic α₁- or β-blockade produced modest increases in plasma vasopressin levels in anephric rats. Infusion of sodium nitroprusside brought the blood pressure down to levels similar to those attained by α₁-blockade alone (i.e., in the range of 66–70 mm Hg) but was associated with a marked surge of plasma vasopressin levels. A similar elevation in vasopressin levels was observed after α₁-blockade alone. When each of these maneuvers was followed by the hyperosmotic stimulus of hypertonic saline infusion, there was an increase in blood pressure, accompanied by an excessive stimulation of vasopressin in nitroprusside-treated rats but only modest increases in plasma vasopressin levels in the other groups. In the case of α₁- and β-blockade, however, this rise in blood pressure was only partly due to the pressor effect of vasopressin; in the case of nitroprusside, the vasopressin component was even smaller. In contrast, with α₁-blockade, despite a minor rise in vasopressin levels, the vasopressin antagonist produced a major fall in blood pressure, to levels well below baseline, indicating that in these rats vasopressin-mediated vasoconstriction was the sole factor sustaining the blood pressure. These observations are in agreement with earlier experiments in which we found that anephric rats submitted to concomitant nonelective α- and β-blockade (with phenotolamine and propranolol), followed by hypertonic saline infusion, had an average rise in blood pressure of 44 mm Hg, all of which was attributable to stimulated vasopressin, since it was totally reversible by inhibition of vasopressin. Our findings also indicate that of all the adrenergic components blocked in those experiments, it was the α₁-adrenergic blockade that allowed vasopressin to take over as the primary vasoconstricting factor. When vasopressin was inhibited in rats treated with α₁-blockade without further intervention, blood pressure decreased by only an average of 6 mm Hg, to approximately 65 mm Hg. This level probably represents the intrinsic vascular resistance when most hormonal effects are removed from the arteriolar wall.

Remarkably, there was absolutely no correlation between the plasma levels of vasopressin and the degree of blood pressure dependency on the vasoconstrictor action of vasopressin in the various groups. The release of vasopressin was maximally stimulated by the combined hypotensive and osmolar stimuli of nitroprusside and saline infusion, but the blood pressure level resulting from these maneuvers was only to a small extent — by approximately one third — sustained by vasopressin-dependent vasoconstriction. Other authors have also reported excessive stimulation of vasopressin release by nitroprusside, corroborating the conclusions of studies using other hypotensive stimuli — that vasopressin is a major defense mechanism against hypotension. However, hypotension is also a potent stimulator of the sympathetic nervous system through baroreflex activation, which in itself contributes to blood pressure maintenance but blunts the pressor effectiveness of vasopressin. In fact, α₁ and β sympathetic functions seem to contribute partly to the buffering of vasopressin’s pressor action. But it appears that the α₁-sympathetic component is mostly responsible for this blunting effect is the α₁-adrenergic function, since its blockade uncovers the maximal pressor potency of vasopressin.

In conclusion, our experiments indicate that circulating plasma levels of vasopressin do not permit an accurate estimate of the magnitude of its contribution to blood pressure maintenance, which can be demonstrated only by the blood pressure response to a receptor antagonist. A number of antivasopressor vasopressin antagonists could serve as diagnostic and therapeutic agents in appropriate situations. Moreover, our studies suggest that the maximal pressor potential of vasopressin can be expressed only under conditions of impaired α₁-adrenergic receptor function. This is especially true in the anephric state, since the renin-angiotensin system has been virtually eliminated. By extrapolation from these data, the vasoconstrictor effect of vasopressin may be clinically important in patients with hypertension, chronic renal failure, or congestive heart failure, especially those being treated with α₁-adrenergic receptor blockade and angiotensin inhibition. Initial clinical studies along these lines have shown this supposition to be true.

References


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