Effects of Arginine Vasopressin on Blood Pressure and Renal Prostaglandin E₂ in Rabbits

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Abstract. The role of arginine vasopressin (AVP) in blood pressure regulation in humans and animals is still controversial. The present study was designed to investigate the effects of AVP on blood pressure and the excretion of sodium and prostaglandin (PG) E₂ in rabbits. AVP dissolved in 0.01 M acetic acid was infused subcutaneously at a rate of 0.86 ng/kg/min with a miniosmotic pump into 12 New Zealand white rabbits (2.7–3.4 kg), while 10 controls were given vehicle alone. AVP infusion resulted in a 3.5-fold rise in the level of plasma AVP (21.8±4.4 (SEM) pg/ml) as compared with controls, associated with a significant decrease in the urine volume and urinary excretion of sodium. The PGE₂ excretion was increased 1.8-fold after AVP infusion. In the chronic AVP-infused group, blood pressure was not significantly increased, but the acute vascular response to AVP was significantly attenuated without any changes in the vasopressor response to angiotensin II. Preadministration of V₁-antagonist completely abolished the vasopressor action of AVP, but not that of angiotensin II, in either group. These results suggest that circulating AVP within physiological range of concentrations may stimulate renal PGE₂ synthesis and attenuate the vascular response through vascular V₁ receptors without affecting the baroreflex, which may be attenuated through V₂ receptors.

Keywords: Vasopressin, Blood pressure, Baroreflex, Prostaglandin E₂, V₁-receptors.

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NUMEROUS STUDIES in recent years have suggested that arginine vasopressin (AVP) may be involved in the development and/or maintenance of experimental hypertension such as that in spontaneously hypertensive rats [1, 2], and rats made hypertensive by the administration of deoxycorticosterone acetate and salt [3] or by renovascular clipping [4]. However, many investigators have argued against a role of AVP in the maintenance of high blood pressure in spontaneously hypertensive rats [5], experimental animals with renovascular hypertension [6] or salt-sensitive Dahl rats [7]. Circulating AVP could raise arterial blood pressure by acting on V₁-type receptors in vascular vessels, causing vasoconstriction, and/or on V₂-type receptors in the renal collecting tubules, causing water retention. However, AVP has been shown to inhibit sympathetic nervous system activity and enhance baroreflex-mediated sympathoinhibition [8, 9]. Furthermore, depressor actions of AVP mediated through V₂-type receptors [10] or reduction of cardiac output by V₁-type receptors [11] have also been demonstrated.

The present study was therefore designed to clarify the physiological roles of AVP in both blood pressure regulation and water and sodium metabolism in rabbits receiving continuous infusion of a subpressor dose of AVP.

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Materials and Methods

New Zealand white male rabbits (body weight 2.7–3.4 kg) were housed in metabolic cages with free access to food and water. Twenty-four-hour urine samples were collected for two consecutive days with 1 ml of 1 N HCl. Blood samples were also collected into chilled glass tubes containing EDTA (5 mg/ml). After sample collection, AVP (0.86 ng/kg/min) or 0.01 M acetic acid as a vehicle (1 μl/h) was continuously infused for one week with a mini-osmotic pump (Alzet) implanted subcutaneously into 6 and 5 animals, respectively. During the final two days, i.e. on days 6 and 7, two 24-h urine specimens were obtained. Blood samples were also collected immediately after urine sampling.

Following urine and blood collection, catheters were implanted into the femoral artery and vein under anesthesia with pentobarbital and ketalar. Twenty-four hours later, basal blood pressure, heart rate and the vasopressor response to 200 ng of AVP followed by 200 ng angiotensin II were recorded on a polygraph (RM 6100, Nihon-Koden, Tokyo Japan) through a transducer (T4812AD, Gould Inc., Medical Division Products, Oxnard, Calif) connected to the femoral artery without anesthesia. The same parameters were determined 10 min after intravenous administration of 30 μg of a V1-antagonist, d(CH2)5, O-Me-Tyr2-Arg8-vasopressin (Manning compound; Bachem, Torrance, Calif). Before and after V1-blockade, blood pressure was allowed to return to the baseline between a bolus iv injection of 200 ng of AVP and angiotensin II. In the experiments when 200 ng of AVP was administered intravenously before and after V1-blockade, baroreflex sensitivity was calculated as the change in heart rate divided by the change in systolic blood pressure.

Urinary and plasma sodium or potassium were determined by flame photometry. Urinary PGE2 was determined by a specific radioimmunoassay following purification of 2 ml of urine by column chromatography with a Sep-Pak C18 cartridge (Waters Associates, Milford, Mass) as reported previously [12]. Cross-reactivity of antibody with PGE2 (Pasteur Institute, Paris, France) was as follows: 6.5% with PGE1, 2.3% with dihydro-PGE2, 13.2% with dihydroketo-PGE2, 0.3% with PGA2 and 0.11% with PGF2α. Plasma renin activity and plasma AVP levels were determined by a specific radioimmunoassay as reported previously [13, 14].

The data were expressed as the means ± SEM. Statistical difference was evaluated by paired or unpaired Student’s t test and considered to be significant at p values of less than 0.05.

Results

Plasma AVP levels achieved by continuous infusion with a mini-osmotic pump reached 21.8±4.4 pg/ml, significantly higher than in controls, as shown in Table 1. AVP infusion did not increase body weight. Both daily water intake and urine volume were significantly decreased by AVP infusion. However, after AVP s.c. administration, blood pressure and heart rate tended to increase, but not significantly. AVP infusion resulted in a decrease in urinary sodium excretion and a 1.8-fold increase in urinary PGE2 excretion. Plasma sodium concentrations and PRA levels were similar in both groups.

Angiotensin II injection caused a significant increase in systolic blood pressure to the same extent in both groups, as shown in Fig. 1. However, the vasopressor response to 200 ng of AVP was attenuated in the AVP-infused group in comparison with the controls. After the administration of V1 antagonist, the vasopressor response to AVP was significantly decreased in both the controls and the AVP-infused group. However, V1 blockade did not affect blood pressure after angiotensin II injection. A bolus injection of AVP reduced the heart rate in both groups. V1-blockade completely abolished the bradycardia induced by AVP injection. On the other hand, angiotensin II did not affect the heart rate in either group.

When baroreflex sensitivity was analyzed, it was found not to be affected by AVP infusion (−2.8±0.5 in controls vs. −1.9±0.4 in the AVP-infused group). As a result, a significant negative correlation between the change in the heart rate and the change in systolic blood pressure was obtained (Fig. 2).

Discussion

Chronic infusion of AVP resulted in a 3.5-fold
Table 1. Effects of AVP-infusion on body weight, water intake, urine volume, plasma hormonal levels, blood pressure, and urinary excretion of sodium and PGE$_2$

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=5)</th>
<th>AVP-infused (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>3.21±0.20</td>
<td>3.10±0.14</td>
</tr>
<tr>
<td>Water intake (ml/day)</td>
<td>240±24.5</td>
<td>228±14.3</td>
</tr>
<tr>
<td>Urine volume (ml/day)</td>
<td>139±16.8</td>
<td>127±17.0</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123.7±8.4</td>
<td>132.5±12.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.5±7.4</td>
<td>94.8±13.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>237±17.7</td>
<td>260±36.1</td>
</tr>
<tr>
<td>Plasma Na level (mEq/l)</td>
<td>144.6±0.96</td>
<td>145.4±4.6</td>
</tr>
<tr>
<td>Plasma AVP level (pg/ml)</td>
<td>5.0±0.4</td>
<td>5.7±0.8</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>8.7±1.9</td>
<td>8.9±3.9</td>
</tr>
<tr>
<td>$U_{Na}$V (mEq/day)</td>
<td>5.2±0.7</td>
<td>4.5±0.6</td>
</tr>
<tr>
<td>$U_K$V (mEq/day)</td>
<td>39.8±5.6</td>
<td>40.0±5.1</td>
</tr>
<tr>
<td>$U_{con}$V (μg/day)</td>
<td>1.8±0.3</td>
<td>2.3±0.7</td>
</tr>
</tbody>
</table>

Each value indicates the mean±SEM.
* p<0.05 vs. own controls; ** p<0.01 vs. own controls; *** p<0.01 vs. controls after vehicle administration.

Fig. 1. Changes in systolic blood pressure (SBP) and heart rate (HR) in response to a bolus i.v. injection of 200 ng of AVP (left panel) or angiotensin II (right panel) in control animals (CONTROL) and AVP-infused animals (AVP) before and 10 min after 30 μg i.v. administration of V$_1$-antagonist.
increase in plasma AVP levels with water and sodium retention, as well as a 1.8-fold increase in PGE2 excretion. However, arterial blood pressure was not increased significantly. It is generally known that AVP plays an important role in the maintenance of arterial blood pressure under conditions such as hemorrhage and water deprivation. However, its precise role in the chronic regulation of arterial blood pressure and in the pathogenesis of hypertension is much more controversial. In the present study, AVP-infused animals did show a blunted vasopressor response to a bolus injection of 200 ng of AVP, but not to angiotensin II injection. Since V1-antagonist completely abolished the pressor response to a bolus injection of AVP, these results indicate that V1-type receptor-mediated vasoconstriction may be attenuated after one-week AVP infusion. This might be due to prior occupancy of circulating AVP on vascular V1-receptors or down-regulation of V1-receptors in vascular walls. However, the former possibility seems unlikely, because plasma AVP levels achieved by continuous infusion were far lower than the dissociation constant (2 nM) for in vitro binding of AVP to its receptors [15]. The renal V2-receptor has been reported to undergo down-regulation in response to acute increases in AVP [16], but little is known about modulation of the vascular V1 receptor by AVP. In AVP-deficient diabetes insipidus rats, the V1 binding site concentration in the liver has been shown to be greater than in Long-Evans control rats, whereas the V2 binding site concentration has been shown to be similar in both strains [17]. Enhanced response of isolated mesenteric arteries to AVP, but not to norepinephrine or angiotensin II, has been reported in dexamethasone-induced hypertension [18], indicating increased sensitivity or number of V1-receptors.

One further point to be noted is baroreceptor-mediated blood pressure regulation. When changes in heart rate were analyzed in relation to blood pressure changes, the reduction in the heart rate relative to the increase in systolic blood pressure was not significantly attenuated in the group given AVP infusion, implying that the baroreflex was not depressed by continuous AVP infusion in the present study. This is consistent with the results of a previous study demonstrating that the baroreflex was sensitized through V2 receptors accessible from the blood [19]. Taken together, circulating AVP within a physiological range may regulate blood pressure mainly through vascular V1 receptors, possibly through down-regulation of V1 receptors.

It has been reported that AVP stimulates renal PGE2 biosynthesis by enhancing the conversion of phospholipids to arachidonic acid [20]. On the other hand, urinary PGE2 excretion rates have been reported to be dependent on the urine flow rate [21]. Increased urinary PGE2 excretion in AVP-infused rabbits in spite of antidiuresis observed in the present study suggests a stimulatory effect of AVP on renal PGE2. PGE1 has been demonstrated to inhibit AVP- but not cAMP-induced water movement in the toad bladder and isolated collecting duct cells [22, 23], suggesting an inhibitory effect of PGE1 on AVP-stimulatory adenylate cyclase. In this context, there exists a negative feedback between AVP and renal PGE2. PGE2 has been demonstrated to be a potent vasodilator. AVP-stimulated renal PGE2 synthesis may attenuate the vasoconstriction induced by AVP.

In summary, circulating AVP within physiological ranges may stimulate renal PGE2 synthesis and attenuate the vasopressor action of AVP by blunting vasoconstriction, but not attenuate the baroreflex.
EFFECTS OF AVP ON BLOOD PRESSURE AND PGE2

Acknowledgments

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References