Vasopressin-induced increase in total peripheral resistance in deoxycorticosterone acetate hypertensive rats is buffered by the baroreceptor reflex

W. RASCHER, R. E. LANG, M. TAUBITZ, H. MEFFLE, TH. UNGER, D. GANTEN AND F. GROSS

Department of Pharmacology, University of Heidelberg, and German Institute for High Blood Pressure Research, Heidelberg, F.R.G.

Summary

1. The role of arginine-vasopressin (AVP) in the maintenance of high blood pressure in rats with deoxycorticosterone acetate (DOCA) hypertension was investigated.

2. Plasma concentrations of AVP were significantly elevated in DOCA hypertensive rats compared with normotensive control rats, whether or not they received 1% sodium chloride solution or demineralized water to drink.

3. The specific antagonist of the vasopressor response to AVP, d(CH₃)VDAVP (100 µg/kg intravenously), significantly increased cardiac output and decreased total peripheral resistance, but had no effect on mean arterial pressure in DOCA hypertensive rats. No changes of mean arterial pressure, cardiac output and total peripheral resistance were observed in the normotensive control groups after d(CH₃)VDAVP.

4. After sino-aortic baroreceptor deafferentation, d(CH₃)VDAVP decreased mean arterial pressure in DOCA–salt hypertensive rats, but not in the control groups.

5. It is concluded that elevated circulating AVP causes vasoconstriction in DOCA hypertensive rats. The AVP-induced increase in total peripheral resistance is counter-regulated by an activation of the baroreceptor reflex and subsequent reduction in cardiac output.

Key words: arginine-vasopressin, deoxycorticosterone acetate hypertension, haemodynamics, vasopressin antagonist.

Abbreviations: AVP, arginine-vasopressin; d(CH₃)VDAVP, [1-(β-mercaptop-ββ-cyclopentamethylenepropionic acid), 4-valine, 8-D-arginine]-vasopressin; DOCA, deoxycorticosterone acetate; SAD, sino-aortic deafferentation.

Introduction

It has been suggested that arginine-vasopressin (AVP) plays an important role in the maintenance of high blood pressure in DOCA–salt hypertensive rats [1, 2]. In the present study, the pathophysiological role of AVP in DOCA hypertension was further investigated using [1-(β-mercapto-ββ-cyclopentamethylene-propionic acid),4-valine,8-D-arginine]vasopressin [d(CH₃)VDAVP], a specific antagonist of the vasopressor response to AVP [3]. The effect of the vasopressin antagonist on mean arterial pressure, cardiac output and total peripheral resistance was determined in conscious unrestrained DOCA-treated rats. Since vasopressin has also been shown to interfere with the baroreceptor reflex [4, 5] additional experiments were performed in DOCA-treated rats after sino-aortic baroreceptor deafferentation (SAD).

Materials and methods

Male Wistar rats (150–200 g) received deoxycorticosterone acetate (DOCA) subcutaneously as an oily solution (sesame oil) in a dose of 2 x 5 mg/kg daily for 7 days. In addition, a microcrystalline suspension of deoxycorticosterone trimethylacetate (Percorten M, CIBA AG, Basle, Switzerland) was injected subcutaneously, 15 mg/kg, three times a week until the end of the experiment at 4 weeks. Rats were fed on a standard diet (Altromin) containing 100 mmol of
sodium/kg. Four groups of rats were studied: (1) DOCA + 1% sodium chloride solution (saline) as drinking fluid \((n = 18)\); (2) sham treatment + saline \((n = 17)\); (3) DOCA + demineralized water as drinking fluid \((n = 18)\); (4) sham treatment + demineralized water \((n = 18)\) [6]. Plasma concentrations of AVP were measured after 4 weeks of treatment in 10 animals from each group by a radioimmunoassay which was recently developed in our laboratory and is described in detail elsewhere [7]. In eight animals from each group haemodynamic measurements were performed.

Catheters were implanted 1 day before the experiment into the femoral artery and into the femoral vein. The next morning rats were again anaesthetized with ether and a catheter (PE 10) was introduced into the right jugular vein with the tip placed in front of the right atrium. The left carotid artery was also cannulated and a thermistor probe with an external diameter of 0.6 mm was introduced into the aorta so that the tip lay in the main blood stream of the aortic arch. At least 4 h after completion of surgery, arterial blood pressure and cardiac output were measured in the conscious unrestrained rats. Cardiac output was determined by the thermodilution method [8, 9], a computer with an automatic calculation of the dilution curve (HMV 7905, Hoyer Co., Bremen, F.R.G.) being used. A bolus of 0.2 ml of 0.9% sodium chloride solution at room temperature (20–22°C) was injected into the right atrium. Control values of cardiac output were determined twice within 5 min; 10 min later the vasopressin antagonist \(d(CH_2)_3VDAVP\) was injected \((100 \mu g/kg)\) into the femoral vein, 0.5 and 5 min after which cardiac output measurements were repeated.

The effect of \(d(CH_2)_3VDAVP\) on blood pressure was studied in rats with bilateral SAD \((n = 20)\) performed by the procedure described by Krieger [10] and in rats submitted to a sham operation \((n = 17)\). One week after recovery from the surgical procedure treatment with DOCA + 1% sodium chloride solution or sham treatment + 1% sodium chloride solution was performed as described above. In these rats catheters were implanted into the femoral artery and vein the day before the experiment. Mean arterial pressure was measured at exactly 5 min intervals during 1 h (i.e. 12 different time points) because of the variability of blood pressure in rats with SAD [11]. An average mean arterial pressure for each rat was calculated from individual measurements.

Results are given as means ± SEM. Significance of differences was assessed by Student’s paired \(t\)-test or by analysis of variance followed by Scheffe’s test when statistical significance for the mean effect was reached.

Results

Plasma concentrations of AVP were significantly higher in rats treated for 4 weeks with DOCA than in normotensive control rats (DOCA + saline: \(8.42 ± 1.32\) fmol/ml; saline: \(4.33 ± 0.47\) fmol/ml, \(P < 0.05\); DOCA + water: \(7.88 ± 0.62\) fmol/ml; water: \(3.30 ± 0.23\) fmol/ml, \(P < 0.05\)). Intravenous administration of the antagonist of the vasopressor action of AVP [\(d(CH_2)_3VDAVP\)] in a dose of 100 \(\mu g/kg\) to both groups of DOCA-treated rats increased cardiac output and decreased total peripheral resistance, but had no effect on mean arterial blood pressure (Table 1). In the control groups, not treated with DOCA, no changes of mean arterial pressure, cardiac output and total peripheral resistance were observed after administration of \(d(CH_2)_3VDAVP\) (Table 1).

In DOCA-saline-treated rats with SAD mean arterial pressure rose to \(156 ± 3.2\) mmHg \((n = 10)\) after 4 weeks of treatment as compared with \(147 ± 6.7\) mmHg \((n = 8)\) in sham-operated DOCA-saline-treated rats \((P > 0.05)\). In the baroreceptor-denervated control group mean arterial pressure was slightly but not significantly higher \((121 ± 4.4\) mmHg, \(n = 9)\) than in the sham-operated control group \((108 ± 2.8\) mmHg, \(n = 9, P > 0.05)\). The variability of blood pressure (SD of 12 measurements) was significantly higher in rats with SAD \((DOCA: 14.6 ± 2.5; control: 10.0 ± 1.1)\) than in the sham-operated rats \((DOCA: 6.8 ± 0.7; control: 4.5 ± 0.2)\) \((P < 0.05)\) respectively.

In DOCA-saline-treated rats with SAD intravenous administration of \(d(CH_2)_3VDAVP\) elicited a fall in mean arterial pressure of \(22.4 ± 5.8\) mmHg \((P < 0.01)\); no change of blood pressure occurred in the three other groups studied (sham-operated DOCA: \(-1.0 ± 1.1\) mmHg; SAD control group: \(0.7 ± 1.1\) mmHg; sham-operated control groups: \(0.4 ± 1.8\) mmHg).

Discussion

The results of this study demonstrate that circulating AVP is elevated in DOCA hypertensive rats. An increase of plasma AVP levels in DOCA hypertensive rats which had received saline as drinking fluid has previously been reported [1]. In our experiments this finding is
confirmed and extended by the observation of a similar elevation of circulating AVP in DOCA-treated rats independently of whether the rats received demineralized water or saline as drinking fluid.

The two- to three-fold elevation of endogenous AVP in DOCA hypertension has significant vasoconstrictor effects, since the intravenous administration of a specific antagonist of the vasopressor action of arginine-vasopressin \( \text{d(CH\textsubscript{2}})\text{DAVP} \) in conscious unrestrained DOCA hypertensive rats has been confirmed and extended by the observation of a significant increase of blood pressure, in baroreceptor-denervated dogs, confirming that the role of AVP as a vasoconstrictor agent is obscured by its sensitizing effect on the counter-regulatory baroreceptor reflex mechanism. The latter effect may explain why Rabito et al. [12] did not observe a fall in blood pressure using two different AVP antagonists in DOCA and renal hypertensive rats. Our findings are in contrast to the dramatic decrease of blood pressure after intravenous administration of a specific AVP antiserum in intact DOCA-treated rats [1].

### Table 1. Mean arterial pressure, cardiac output and total peripheral resistance before (0) and 0-5 and 5 min after intravenous injection of a specific antagonist of the vasopressor action of arginine-vasopressin \( \text{d(CH\textsubscript{2}})\text{DAVP} \) in conscious unrestrained DOCA hypertensive rats.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Cardiac output (ml min(^{-1}) 100 g(^{-1}))</th>
<th>Total peripheral resistance (mmHg/100 g ( \times ) min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (8)</td>
<td>0 115 ( \pm ) 3.3</td>
<td>44.7 ( \pm ) 2.7</td>
<td>2.64 ( \pm ) 0.15</td>
</tr>
<tr>
<td></td>
<td>0.5 113 ( \pm ) 3.5</td>
<td>44.1 ( \pm ) 2.7</td>
<td>2.64 ( \pm ) 0.18</td>
</tr>
<tr>
<td></td>
<td>5 112 ( \pm ) 3.7</td>
<td>43.2 ( \pm ) 2.3</td>
<td>2.64 ( \pm ) 0.14</td>
</tr>
<tr>
<td>DOCA + (8)</td>
<td>0 138 ( \pm ) 5.1</td>
<td>43.1 ( \pm ) 2.0</td>
<td>3.26 ( \pm ) 0.21</td>
</tr>
<tr>
<td>water</td>
<td>0.5 142 ( \pm ) 6.4</td>
<td>48.3 ( \pm ) 2.1*</td>
<td>2.97 ( \pm ) 0.16*</td>
</tr>
<tr>
<td></td>
<td>5 141 ( \pm ) 7.5</td>
<td>45.5 ( \pm ) 2.7</td>
<td>3.04 ( \pm ) 0.23</td>
</tr>
<tr>
<td>NaCl (7)</td>
<td>0 116 ( \pm ) 7.3</td>
<td>42.0 ( \pm ) 1.3</td>
<td>2.73 ( \pm ) 0.22</td>
</tr>
<tr>
<td></td>
<td>0.5 112 ( \pm ) 6.8</td>
<td>40.4 ( \pm ) 1.3</td>
<td>2.83 ( \pm ) 0.23</td>
</tr>
<tr>
<td></td>
<td>5 114 ( \pm ) 6.4</td>
<td>41.9 ( \pm ) 1.4</td>
<td>2.79 ( \pm ) 0.18</td>
</tr>
<tr>
<td>DOCA + (8)</td>
<td>0 173 ( \pm ) 8.5</td>
<td>41.6 ( \pm ) 1.9</td>
<td>4.23 ( \pm ) 0.25</td>
</tr>
<tr>
<td>NaCl</td>
<td>0.5 172 ( \pm ) 8.7</td>
<td>44.8 ( \pm ) 1.6**</td>
<td>3.87 ( \pm ) 0.23**</td>
</tr>
<tr>
<td></td>
<td>5 170 ( \pm ) 10.7</td>
<td>43.4 ( \pm ) 2.1</td>
<td>3.95 ( \pm ) 0.25</td>
</tr>
</tbody>
</table>

Results are means \( \pm \) SEM. Numbers of animals are shown in parentheses. Statistics (paired t-test): \( *P < 0.05; **P < 0.01, \) as compared with the control value (0).
Acknowledgments

This study was supported by the Deutsche Forschungsgemeinschaft within the SFB 90, Cardiovasculäres System. We thank Dr M. Manning, Toledo, Ohio, U.S.A., for the generous gift of \( \text{d(CH}_2\text{)}_2\text{VDAVP} \). The skillful technical assistance of Mrs U. Rohland, Mr B. Fertig and Mr J. Kammer is gratefully acknowledged.

References


