Summary

1. The effect of \(\alpha\)-adrenoceptor blockade by phentolamine on plasma arginine vasopressin, on vasopressin dependency of blood pressure and on responsiveness to exogenous lysine vasopressin was studied in conscious normotensive and in deoxycorticosterone (DOC)/salt-treated hypertensive rats.

2. Phentolamine infusion reduced blood pressure of DOC-treated hypertensive rats to levels significantly lower than those of similarly treated Wistar control animals.

3. Plasma vasopressin levels of the DOC-treated hypertensive and normotensive control rats were similar. Phentolamine infusion increased plasma arginine vasopressin levels to \(109.4 \pm 21.8\) pg/ml in the DOC-treated rats and to \(44.4 \pm 8.2\) pg/ml in the control animals. It also enhanced the pressor response to exogenous lysine vasopressin in both groups.

4. Administration of the vasopressin analogue dPVDAVP had no effect on blood pressure in either the DOC-treated or the control group but induced a similar fall in blood pressure in both groups during \(\alpha\)-adrenoceptor blockade with phentolamine.

Key words: arginine vasopressin, phentolamine.

Introduction

It has been difficult to assign to vasopressin an important role in the maintenance of blood pressure. Only in extreme situations such as baroreceptor denervation [1], hypovolaemia [2] and haemorrhage [3] or severe dehydration with associated blockade of the renin system [4] has it been possible to demonstrate that plasma vasopressin actively contributes to blood pressure maintenance. But, even in these situations, vasopressin does not seem to play a predominant role.

The present study was designed to investigate the influence of \(\alpha\)-adrenoceptor blockade on the vasopressin pressor mechanism in normotensive Wistar control animals and DOC-treated hypertensive rats. Three variables were studied: arginine vasopressin levels in the plasma, the pressor response to exogenous lysine vasopressin and the effect on blood pressure of a specific inhibitor of arginine vasopressin.

Methods

Seventy-seven male Wistar rats weighing 250–350 g were used in the study. Some were left intact and others underwent a left uninephrectomy under light ether anaesthesia. These were subsequently treated with deoxycorticosterone [30 mg/kg (Percorten, Ciba-Geigy)], which was injected once a week for a total of 4 weeks. During this time, drinking fluid was provided as 1% sodium chloride solution (171 mmol/l).

On the day of the experiment, an arterial catheter (PE 50) was inserted in the right iliac artery under light ether anaesthesia. In addition, two catheters (PE 10) were placed in the two femoral veins. After the operation, the rats were allowed to wake up and were placed in a plastic tube to restrict their movements. Throughout the experiment, blood pressure and heart rate were monitored via a transducer (Statham, Hato Rey, Puerto Rico) connected to an electrogalvanometer (Philips 2000, Eindhoven, Netherlands) and recorded on a light-sensitive oscillograph.
(Manarp 150, Electronic Institute Ltd, London). After a stabilization period of 2 h, baseline blood pressure was obtained.

In some animals, an intravenous infusion was begun at this time by using a syringe pump (model 455, Sage). The infusate contained phentolamine (Regitin, Ciba-Geigy): 125 \( \mu g \) min\(^{-1}\) kg\(^{-1}\). At the end of a 2 h infusion period, either 25 \( \mu g \) of the arginine vasopressin pressor antagonist dPVDAVP (Senn Chemicals, Dielsdorf, Switzerland) \[5\] was injected intravenously or blood was drawn through the venous catheter during a period not exceeding 30 s to determine plasma arginine vasopressin. In other rats, injections of lysine vasopressin (Vasopressin, Sandoz) 0-5, 1, 2 and 4 m-units intravenously were given 1 h after starting the infusions to establish dose-response curves. Plasma arginine vasopressin levels were determined by a radioimmunoassay to be described (M. Burnier, D. B. Brunner, H. R. Brunner & H. Gavras, unpublished work). For the statistical evaluation, an analysis of variance was used, followed by Student’s \( t \)-test for paired or unpaired data. Correlations were calculated by using Spearman’s rank correlation test.

Results

The most important results of the study are summarized in Table 1. The blood pressure of the DOC-treated hypertensive rats was 144.8 \( \pm \) 2.8 mmHg, compared with 119.9 \( \pm \) 1.0 mmHg for the Wistar control animals. Phentolamine infusion reduced the blood pressure of the DOC-hypertensive rats to 65.0 \( \pm \) 2.5 mmHg, which was significantly lower than the 90.4 \( \pm \) 3.0 mmHg measured in the Wistar control rats receiving phentolamine infusion \((P < 0.001)\). Plasma arginine vasopressin of the DOC-hypertensive rats was not different from that of the Wistar control animals. During phentolamine infusion, plasma arginine vasopressin levels increased considerably in both groups but more so in the DOC-hypertensive rats. Administration of the vasopressin analogue dPVDAVP had hardly any effect on the blood pressure of either the Wistar control or the DOC-treated hypertensive rats. However, during phentolamine infusion, it reduced blood pressure similarly in the Wistar control rats and in the DOC-treated animals, by 16.5 \( \pm \) 1.3 and 17.6 \( \pm \) 2.6 mmHg respectively. There was also no difference in the blood pressure response to exogenous lysine vasopressin between the Wistar control and the DOC-hypertensive rats. Phentolamine infusion markedly increased the blood pressure response to exogenous lysine vasopressin in both groups of animals.

Table 1. Effect of phentolamine on blood pressure, heart rate, plasma arginine vasopressin and blood pressure response to lysine vasopressin or dPVDAVP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean blood pressure (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Plasma AVP (pg/ml)</th>
<th>Blood pressure response (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To 4 m-units of LVP</td>
<td>To 25 ( \mu g ) of dPVDAVP</td>
<td></td>
<td></td>
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<tr>
<td>Normotensive</td>
<td>119.9 ( \pm ) 1.0 (18)</td>
<td>397.6 ( \pm ) 8 (18)</td>
<td>2.4 ( \pm ) 0.7 (6)</td>
<td>39.1 ( \pm ) 3.3 (7)</td>
</tr>
<tr>
<td>DOC hypertensive</td>
<td>114.8 ( \pm ) 2.8 (19)</td>
<td>384 ( \pm ) 10 (19)</td>
<td>2.8 ( \pm ) 0.9 (7)</td>
<td>43.0 ( \pm ) 6.6 (6)</td>
</tr>
<tr>
<td>+ phentolamine</td>
<td>90.4 ( \pm ) 3.0( *** ) (21)</td>
<td>396 ( \pm ) 8.3 (21)</td>
<td>44.4 ( \pm ) 8.2( *** ) (8)</td>
<td>57 ( \pm ) 4.5( ** ) (7)</td>
</tr>
<tr>
<td></td>
<td>65.0 ( \pm ) 2.5( *** ) (19)</td>
<td>427.8 ( \pm ) 6( ** ) (19)</td>
<td>109.4 ( \pm ) 21.8( *** ) (7)</td>
<td>60.3 ( \pm ) 3.7( * ) (6)</td>
</tr>
</tbody>
</table>

Discussion

There is ample evidence that increased sympathetic activity plays an important role in the maintenance of DOC-hypertension \[6\]. In the present study, phentolamine induced a rapid and marked decrease in blood pressure, which surprisingly reached levels significantly lower than those of similarly treated controls animals. Most likely, this blood pressure fall was due to a decrease in arterial tone in response to blockade of peripheral \( \alpha \)-adrenoceptors. Whether the significantly lower blood pressure observed during \( \alpha \)-adrenoceptor blockade in DOC-hypertensive rats compared with normotensive Wistar control animals was due to the lower renin levels \((13.2 \pm 4 \text{ vs } 94.3 \pm 11 \text{ ng h}^{-1}\text{ ml}^{-1})\) is a matter of debate.

Plasma vasopressin levels of the DOC-hypertensive rats were not increased when compared with those of the Wistar control animals.
Similarly, pressor responsiveness to exogenous lysine vasopressin was also unchanged. Not surprisingly, in the face of normal plasma vasopressin levels, administration of the vasopressin inhibitor dPVDAVP did not affect blood pressure. The administration of phentolamine increased plasma vasopressin levels considerably in both the normotensive control and the DOC-hypertensive animals and simultaneously enhanced the pressor response to exogenous vasopressin. Blockade of central $\alpha_2$-adrenoceptors by phentolamine has been shown to decrease the sensitivity of the baroreflex [7]. It is possible that the enhanced vascular responsiveness to exogenous vasopressin observed in rats treated with phentolamine primarily reflects an attenuation of baroreflex activity.

The considerable increase in plasma arginine vasopressin after phentolamine administration could be due to the hypotensive effect of this drug. Indeed, hypotension has been shown to provide a potent stimulus to arginine vasopressin secretion [8] and we observed a significant correlation between the decrease in mean blood pressure produced by phentolamine and the plasma level of AVP ($r = -0.76$, $n = 15$, $P < 0.001$). It is, however, important to point out that $\alpha_2$-adrenoceptor agonists have been shown to have an inhibitory effect on vasopressin secretion [9]. It is therefore possible that central $\alpha_2$-blockade might stimulate the secretion of the hormone. These findings confirm that there exists an interesting interaction between arginine vasopressin pressor mechanisms and the $\alpha$-sympathetic nervous system. It is, however, unclear how and precisely under which circumstances vasopressin interacts with the $\alpha$-sympathetic nervous system to maintain blood pressure in hypertensive or normotensive rats. These findings further enhance the impression that vasopressin participates actively in blood pressure maintenance only when normal homoeostasis is threatened.

References