Role of vasopressin in blood pressure control of spontaneously hypertensive rats

JAN MÖHRING, JACQUELINE KINTZ AND JOSIANE SCHOUN
Centre de Recherche Merrell International, Strasbourg, France

Summary

1. The role of arginine-vasopressin (AVP) and of angiotensin in blood pressure control of spontaneously hypertensive rats (SH rats, stroke-prone strain) was studied.

2. In SH rats, which drank water or 1% NaCl, plasma AVP concentrations were elevated during the benign course of hypertension and increased further when the animals entered the malignant phase. Blood pressure correlated significantly with plasma AVP concentrations in SH rats on water, but not in SH rats on saline.

3. The injection of a specific AVP antiserum lowered blood pressure significantly in SH rats on water and in SH rats on saline.

4. When the correlation between blood pressure and plasma AVP of SH rats on water was compared with the respective correlation obtained during infusion of AVP into normotensive rats, a marked shift to the left became apparent, the factor of displacement amounting to more than 1000.

5. Saralasin did not affect blood pressure of SH rats on water, except for two rats with malignant hypertension. However, in SH rats on saline, saralasin lowered blood pressure significantly.

6. It is concluded that in SH rats AVP plays an important vasopressor role in blood pressure control and that sensitization to the vasopressor effect of AVP occurs in these animals. The renin–angiotensin system is significantly involved in blood pressure control of SH rats only when they are subjected to high salt intake.

Key words: antidiuretic hormone, renin–angiotensin, spontaneous hypertension.

Introduction

In previous studies, we have shown that in hypertension induced by deoxycorticosterone and in two-kidney Goldblatt hypertension of rats, plasma concentrations of arginine–vasopressin are elevated (Möhring, Möhring, Petri & Haack, 1977; 1978). Since a specific vasopressin antiserum lowered blood pressure significantly in the hypertensive animals, we have concluded that vasopressin has a systemic vasoconstrictor action in these forms of experimental hypertension. In the present studies, we have examined the possibility that vasopressin is also involved in blood pressure control of spontaneously hypertensive rats.

Materials and methods

Spontaneously hypertensive rats (stroke-prone strain, Kyoto) and their respective normotensive controls (Wistar Kyoto, WKy) were kept under constant temperature (22 ± 1°C) and humidity (55 ± 2% OC) in a room which was lighted from 6 a.m. to 6 p.m. The animals were fed a commerical diet (U.A.R., Villemoisson-sur-Orge, France, reference AO4) and they were given tap water ad libitum.

In a first experimental series, the animals were studied at an age of 22 to 27 weeks, when blood pressure had almost stabilized. In a second experimental series, the animals were placed on 1% NaCl as sole drinking fluid at an age of 10–14 weeks; 4–8 weeks later, when blood pressure had increased to levels comparable with those of rats on water, the experiment was terminated. Body weight, and food and fluid intake were measured daily for the 4–10 weeks before the end of the
experiments. Blood pressure was measured once or twice a week by tail plethysmography under light ether anesthesia.

In heparinized blood samples, obtained by decapitation around 10 a.m., hematocrit, plasma osmolality (freezing point depression), plasma urea concentrations (urease kit, Boehringer), and plasma arginine-vasopressin (radioimmunoassay; Möhring & Möhring, 1975) were measured. In other rats, catheters were placed into the femoral artery and vein and conducted subcutaneously to emerge at the neck. At 3 h after the operation, the arterial catheter was connected to a Statham transducer (P 23 Db) and the blood pressure of the conscious, unrestrained rat was recorded continuously. After the blood pressure had stabilized for at least 30 min, 0.4 ml of a specific AVP antiserum was injected slowly via the venous catheter (for validation of the ‘biological activity’ of this antiserum see Möhring et al., 1977). In other experiments, saralasin (first, 0.7 µg/kg/min, and then 2.7 µg/kg/min) or an equivalent volume of isotonic saline (35 µl/kg/min and 130 µl/kg/min) was infused for 2–3 h.

All values in the text and in the table are means ± sem. For statistical analysis Student’s t-test and, if appropriate, Student’s t-test for paired data were used. Correlation coefficients were calculated by the method of least squares.

Results

In SH rats placed on 1% saline, blood pressure increased more rapidly than in SH rats which drank water only. In general, when blood pressure reached or surpassed a ‘critical range’ of about 180 mmHg (Möhring, Möhring, Petri, Haack & Hackenthal, 1975) signs of fluid loss (Dietz, Schömig, Haebara, Mann, Rascher, Lüth, Grünherz & Gross, 1978), i.e. retardation of daily weight gain or weight loss without reduction of food intake, became apparent. Subsequently, some of these animals developed signs of malignant hypertension, such as hypertensive encephalopathy and malignant nephrosclerosis. Therefore, it was concluded that rats exhibiting signs of fluid loss had entered the malignant phase, even if not all signs of malignant hypertension were present before the experiments were terminated. These animals will be referred to as severe or malignant hypertensive rats (MH), whereas the other SH rats will be referred to as benign hypertensive (BH) rats.

MH rats had higher blood pressure levels than BH rats (Table 1). BH and MH rats ate less food than normotensive control rats. In the BH rats, daily weight gain was less than in controls, and MH rats lost weight during the last three days of the studies (Table 1). Water intake tended to be reduced in the BH and MH rats when compared with controls. Saline intake was significantly reduced in BH rats, whereas in MH rats mean saline intake was increased (Table 1); this was due to a considerable increase in saline consumption in 4 of the 9 MH rats.

Hematocrit of BH rats was elevated, which was most likely due to erythrocytosis (see Sen, Hoffman, Stowe, Smey & Bumpus, 1972). In MH rats hematocrit was higher than in BH rats, reflecting fluid loss (Dietz et al., 1978). Plasma osmolality tended to be lower in BH and MH rats, except for 2 MH rats on water in which it was higher than in controls. Plasma urea concentrations of BH rats were lower than those of control rats, which corresponds to the reduced food intake of these animals (Table 1). In MH rats on saline, plasma urea concentrations were increased by about 50%, whereas in MH rats on water this increase was small (Table 1).

Plasma AVP concentrations of BH rats were increased about 2-fold when compared with control rats (Table 1). In MH rats on water, plasma AVP concentrations were increased about 5-fold, whereas in the MH rats on saline this increase was about 3-fold (Table 1). The height of blood pressure correlated significantly with the logarithm of plasma AVP in the SH rats on water \( (Y = 45.8 \log x + 135.0, r = 0.66, P < 0.01) \), while in MH rats on saline no such correlation was found \( (r = 0.32, P > 0.1) \). In comparison with the respective correlation obtained during AVP infusion into normotensive rats \( (Y = 16.9 \log x + 86.8, r = 0.96, P < 0.001; \) see Möhring, 1978), a marked displacement to the left was found for the curve correlating blood pressure and plasma AVP of SH rats on water.

The injection of 0.4 ml of the AVP antiserum to four MH rats on water lowered blood pressure by 60, 90, 80 and 100 mmHg and in four BH rats on water by 45, 85, 40 and 20 mmHg; in three MH rats on saline blood pressure fell by 40, 20 and 50 mmHg, and in four BH rats on saline by 35, 15, 0 and 30 mmHg. The infusion of saralasin over 2–3 h did not lower blood pressure in BH rats \( (+2.2 \pm 2.9, n = 7) \) and in only two of seven MH rats on water (by 20 mmHg; mean of MH rats: \(-3.9 \pm 4.6 \) mmHg). However, in BH and MH rats on saline a significant \( (P < 0.01) \) reduction of blood pressure was induced (WKy controls: \(-2.5 \pm 1.4 \) mmHg, \( n \)}.
TABLE I. Blood pressure, fluid and food intake, weight gain, haematocrit, and plasma osmolality, urea, and arginine-vasopressin (AVP) in spontaneously hypertensive rats

Values are means ± SEM; *P < 0.05, **P < 0.01 when compared with either control rats (C) or benign hypertensive rats (BH); MH refers to rats with severe or malignant hypertension. Values of fluid and food intake and weight gain are daily means for the last three days before blood sampling.

<table>
<thead>
<tr>
<th>n</th>
<th>Blood pressure (mmHg)</th>
<th>Fluid intake (ml/day)</th>
<th>Food intake (g/day)</th>
<th>Weight gain (g/day)</th>
<th>Haematocrit (%)</th>
<th>Plasma osmolality (mosmol/kg)</th>
<th>Plasma urea (mmol/l)</th>
<th>Plasma vasopressin (fmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>9 109 ± 2</td>
<td>38.3 ± 1</td>
<td>22.6 ± 0.4</td>
<td>+2.5 ± 0.1</td>
<td>42.2 ± 0.5</td>
<td>293.8 ± 0.6</td>
<td>5.7 ± 0.2</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>BH</td>
<td>7 162** ± 2</td>
<td>34.0 ± 3.4</td>
<td>19.1** ± 0.5</td>
<td>+2.2 ± 0.3</td>
<td>43.0* ± 0.7</td>
<td>291.0** ± 0.8</td>
<td>5.1** ± 0.1</td>
<td>4.9** ± 0.0</td>
</tr>
<tr>
<td>MH</td>
<td>12 183** ± 3</td>
<td>32.8 ± 1.3</td>
<td>18.6 ± 0.4</td>
<td>-0.8** ± 0.3</td>
<td>46.3** ± 0.5</td>
<td>293.8 ± 0.9</td>
<td>6.2* ± 0.6</td>
<td>12.2** ± 3.5</td>
</tr>
<tr>
<td>C</td>
<td>8 111 ± 2</td>
<td>48.0 ± 3.60</td>
<td>20.4 ± 0.5</td>
<td>+3.0 ± 0.2</td>
<td>45.0 ± 0.2</td>
<td>295.4 ± 1.1</td>
<td>6.9 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>BH</td>
<td>9 163** ± 5</td>
<td>40.1* ± 2.4</td>
<td>17.6** ± 0.3</td>
<td>+2.5* ± 0.2</td>
<td>46.6** ± 0.5</td>
<td>292.2* ± 0.8</td>
<td>5.6** ± 0.3</td>
<td>3.3** ± 0.5</td>
</tr>
<tr>
<td>MH</td>
<td>9 192** ± 5</td>
<td>60.0 ± 10.5</td>
<td>16.6 ± 0.6</td>
<td>-1.3** ± 0.5</td>
<td>48.8** ± 0.5</td>
<td>290.4 ± 1.8</td>
<td>8.3** ± 0.6</td>
<td>4.7 ± 0.6</td>
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Discussion

The present studies show that plasma AVP concentrations are elevated in SH rats. In rats exhibiting severe or malignant hypertension plasma AVP concentrations were higher than in rats exhibiting a benign course of hypertension. In SH rats kept on a standard sodium intake, the height of blood pressure was quantitatively related to plasma AVP concentrations, whereas in SH rats on high salt intake no such relationship was found. The elevated plasma AVP concentrations observed for instance in malignant renal hypertension. After cessation of saralasin infusion, blood pressure returned to preinfusion levels within 1–2 h.

References


