Reduced synthesis of [arginine]vasopressin in spontaneously hypertensive rats

W. RASCHER, R. E. LANG, B. FINK, D. GANTEN, TH. UNGER AND F. GROSS
Department of Pharmacology, University of Heidelberg and German Institute of High Blood Pressure Research, Heidelberg, Federal Republic of Germany

Summary
1. In 12 week-old stroke-prone spontaneously hypertensive (SPSH) rats and in normotensive Wistar–Kyoto (WKY) rats plasma concentration of [arginine]vasopressin (AVP) and the AVP content in various brain areas were measured by radioimmunoassay.

2. In hydrated SPSH rats plasma AVP was lower than in WKY rats. In the hypothalamus and in the brain stem, but not in the pituitary, the content of AVP was reduced.

3. After a dehydration period of 48 h plasma AVP rose similarly in both SPSH and WKY rats. However, in the pituitary the AVP content was significantly lower in SPSH than in WKY rats. In the hypothalamus and in the brain stem, AVP content was not significantly influenced by dehydration.

4. It is concluded that in the hydrated stage the secretion of AVP and its synthesis in the hypothalamus are reduced in SPSH rats. However, the SPSH rats still respond satisfactorily to the strong stimulus of severe dehydration.

Key words: [arginine]vasopressin, brain vasopressin, spontaneously hypertensive rats.

Abbreviations: AVP, [arginine]vasopressin; SPSH rats, stroke-prone spontaneously hypertensive rats; WKY rats, Wistar–Kyoto rats.

Introduction
Recently, we have reported that young stroke-prone spontaneously hypertensive (SPSH) rats have a lower plasma concentration of [arginine]vasopressin (AVP) than age-matched normotensive Wistar–Kyoto (WKY) rats [1]. Moreover, in SPSH rats a reduced content of AVP was found in the hypothalamus, the brain stem and the amygdala [2–4].

The present study was undertaken to investigate further the nature of the diminished content of AVP in various brain regions. Stimulation of AVP release by water deprivation seemed to be a suitable procedure to differentiate between a reduced synthesis or an enhanced turnover of the hormone.

Materials and methods
Male SPSH and normotensive WKY rats of 12 weeks of age were used from the colonies bred at the Department of Pharmacology, University of Heidelberg [5]. Four groups of rats, consisting of 10 animals each, were studied: 1, SPSH rats that had access to food but were deprived of drinking water for 48 h (SPSH-dehydrated); 2, SPSH that had access to food and drinking water (SPSH-control); 3, WKY-dehydrated; 4, WKY-control.

After decapitation, blood was collected into heparinized plastic tubes and immediately centrifuged at 4°C. The plasma was stored at −25°C until measurement. The brain areas and the pituitary gland were quickly removed and dissected and the tissue was immediately frozen at −70°C and stored at −25°C until peptide extraction.

In all rats plasma concentration of AVP [1], plasma osmolality and packed-cell volume were measured and the content of AVP in the pituitary, the hypothalamus and the brain stem (medulla oblongata and pons) were determined [4]. Plasma AVP is indicated in fmol/ml (1 fmol = 1.09 pg) and brain content of AVP in mol/mg of protein.
All results are given as means ± SEM. Significance of differences was assessed by analysis of variance. In case of a difference of statistical significance, Scheffe’s test was used for further evaluation.

**Results**

In the hydrated state plasma concentration of AVP was lower in SPSH than in WKY rats (P < 0.05). The content of AVP in the hypothalamus and the brain stem was markedly reduced in SPSH rats (P < 0.01), whereas no difference was observed in the pituitary (Table 1).

During a 48 h dehydration period plasma concentration of AVP increased to similar values in both SPSH and WKY rats (Table 1).

However, in the pituitary of SPSH rats a more pronounced decrease in the AVP content was obtained compared with WKY rats (decreases of 0.26 and 0.1 nmol/mg of protein respectively) (Table 1). In contrast, dehydration had no influence on the content of AVP in the hypothalamus and the brain stem of both SPSH and WKY rats (Table 1).

**Discussion**

The formerly observed reduction of AVP in the plasma and in some brain areas of SPSH rats was confirmed, as was the lack of such a difference in the pituitary [1, 3, 4]. The reduction of AVP in the hypothalamus and in the brain stem of SPSH rats can be caused either by a diminished synthesis or by an increased release or turnover of this hormone.

Since during dehydration the plasma concentration of AVP rose similarly in both SPSH and WKY rats, it may be concluded that the secretion of AVP into the circulation was stimulated to about the same degree. However, the decrease in the content of AVP in the pituitary was more pronounced in SPSH rats than in WKY rats. Hence, it may be concluded that the synthesis of AVP in the hypothalamus and/or the neurosecretory transport of AVP from the hypothalamus to the neurohypophysis is impaired in SPSH rats.

Our data do not allow conclusions on the mechanism(s) underlying the reduced synthesis of AVP in SPSH rats. So far it is not clear whether this is a genetic defect, possibly unrelated to blood pressure regulation, or whether it reflects a process secondary to hypertension. Neither effective antihypertensive treatment with captopril nor sino-aortic baroreceptor deafferentation had an influence on AVP content in the hypothalamus and in the brain stem of SPSH and WKY rats (W. Rascher, R. Rettig, H. Meffe & B. Fink, unpublished work). This indicates that the reduced synthesis of AVP is not caused by the rise in blood pressure, which is known to suppress AVP by a baroreceptor reflex mechanism [6].

The presence of AVP-containing neurons in important cardiovascular control centres (e.g. nucleus tractus solitarii) [7, 8] suggests a role for AVP in the central regulation of blood pressure.

**Acknowledgments**

This study was supported by the Deutsche Forschungsgemeinschaft. Sonderforschungsbereich 90 - Cardiovasculäres System. The excellent technical assistance of Mrs Ute Rohland

---

**TABLE 1.** Body weight, packed-cell volume, plasma osmolality, plasma concentration of [arginine]vasopressin (AVP) and the immunoreactive content of AVP in the pituitary, hypothalamus and brain stem of stroke-prone spontaneously hypertensive (SPSH) rats and normotensive Wister-Kyoto (WKY) rats during a 48 h dehydration period

Values are means ± SEM, for the numbers of animals (n) per group. Statistical analysis of variance followed by Scheffe’s test.

<table>
<thead>
<tr>
<th></th>
<th>WKY control</th>
<th>WKY dehydrated</th>
<th>SPSH control</th>
<th>SPSH dehydrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>320 ± 4</td>
<td>277 ± 5*</td>
<td>240 ± 4</td>
<td>214 ± 5*</td>
</tr>
<tr>
<td>Packed-cell volume (%)</td>
<td>41.0 ± 0.4</td>
<td>51.6 ± 0.3*</td>
<td>45.7 ± 0.7†</td>
<td>52.8 ± 0.5*</td>
</tr>
<tr>
<td>Plasma osmolality (mosmol/kg of water)</td>
<td>291 ± 1.1</td>
<td>302 ± 1.5*</td>
<td>290 ± 1.0</td>
<td>303 ± 3.0*</td>
</tr>
<tr>
<td>Plasma AVP (fmol/ml)</td>
<td>2.00 ± 0.18</td>
<td>19.3 ± 1.5*</td>
<td>13.9 ± 0.17</td>
<td>16.2 ± 1.7*</td>
</tr>
<tr>
<td>Pituitary AVP (nmol/mg of protein)</td>
<td>0.90 ± 0.05</td>
<td>0.80 ± 0.06</td>
<td>0.98 ± 0.04</td>
<td>0.72 ± 0.04*</td>
</tr>
<tr>
<td>Hypothalamus AVP (pmol/mg of protein)</td>
<td>39.8 ± 1.8</td>
<td>33.1 ± 2.2</td>
<td>18.7 ± 1.2†</td>
<td>15.1 ± 1.0†</td>
</tr>
<tr>
<td>Brain-stem AVP (fmol/mg of protein)</td>
<td>20.7 ± 1.5</td>
<td>21.9 ± 1.0</td>
<td>14.6 ± 0.3†</td>
<td>12.7 ± 0.4†</td>
</tr>
</tbody>
</table>

* P < 0.01 (control versus dehydrated rats).
† P < 0.01 (WKY versus SPSH rats).
and Mr Jochen Kammer is gratefully acknowledged.

References


