Development of a New Strain of Spontaneously Hypertensive Rats Homozygous for Hypothalamic Diabetes Insipidus

Ursula Ganten, M.D., Wolfgang Rascher, M.D., Rudolf E. Lang, M.D., Rainer Dietz, M.D., Rainer Rettig, M.D., Thomas Unger, M.D., Roland Taugner, M.D., and Detlev Ganten, M.D., Ph.D.

SUMMARY The aim of the present study was to investigate whether the presence of arginine vasopressin (AVP) is necessary for the establishment of high blood pressure in spontaneously hypertensive rats (SHR). For this purpose we crossbred SHR of the stroke-prone substrain (SHRSP) with rats homzygous for hypothalamic diabetes insipidus of the Brattleboro strain (DI) which are unable to synthetize AVP. The successful introduction of the DI gene into the SHRSP strain (SHRDI) was demonstrated by the following observations: In 10-month-old rats, water intake was similarly elevated in SHRDI as in DI rats (137 ± 6.5 vs 125 ± 10.5 ml per 24 hours). AVP was undetectable in the plasma, in the hypothalamus, and in the pituitary of SHRDI and DI rats. Urine osmolality and urinary concentration of sodium and potassium were markedly reduced. SHRDI and DI did not adequately concentrate their urine during an 8-hour period of water deprivation, but both strains of rats responded well with a fall in urine output and a rise in urine osmolality to subcutaneous administration of the non-pressor analog of AVP, DDAVP. Mean arterial blood pressure was markedly increased in SHRDI as well as in SHRSP (184 ± 9.7 vs 197 ± 5.2 mm Hg). Thus, we have developed a new line of spontaneously hypertensive rats homzygous for hypothalamic diabetes insipidus. From this finding it is concluded that AVP is not essential for the development and maintenance of spontaneous hypertension of rats. (Hypertension 5 (supp I): 1-119-1-128, 1983)

KEY WORDS • vasopressin • crossbred rat strain

ELEVATED plasma concentrations of the antidiuretic hormone arginine vasopressin (AVP) have been demonstrated in young spontaneously hypertensive rats (SHR) during the development of hypertension1 and in adult stroke-prone SHR (SHRSP) in the established phase of hypertension. In contrast to these results, we have recently found that plasma levels of AVP were below normal in SHRSP at 6, 9, and 12 weeks of age; they were higher than in age-matched Wistar-Kyoto rats (WKY) only in SHRSP older than 24 weeks of age. Intravenous administration of specific vasopressor AVP antagonists had no significant influence on mean arterial pressure and on cardiac output or total peripheral resistance. Furthermore, reduced contents of AVP were found in the hypothalamus, in the brain stem, and in the amygdala of SHRSP. From these results we have concluded that circulating AVP does not contribute to the development and maintenance of high blood pressure. The question whether AVP is involved in the pathogenesis of spontaneous hypertension of rats or not is therefore unresolved.

The aim of the present study was to investigate whether the presence of AVP in the brain and in the periphery is necessary for the establishment of high
blood pressure in SHRSP. For this purpose we cross-bred SHRSP with rats homozygous for hypothalamic diabetes insipidus (DI) of the Brattleboro strain which are unable to synthetize AVP. This paper demonstrates the successful introduction of the DI gene into the SHRSP strain which resulted in a new line of rats that have high blood pressure despite a complete defect in the synthesis of AVP.

Methods

Animals

SHRSP and normotensive WKY rats as well as Brattleboro rats homozygous for hypothalamic diabetes insipidus (DI) and Long-Evans control rats (LE) were used. Colonies of these rats have been bred at the Department of Pharmacology, University of Heidelberg, the SHRSP and WKY rats, originally derived from Kyoto since 1975 and the Brattleboro rats from the colony in New Hampshire since 1970.

The animals received a standard diet (altromin) containing 94 ± 6 mM sodium and 204 ± 14 mM potassium per kg chow. They were housed in Macrolon cages at a room temperature of 24°C ± 1°C and a humidity of 60% ± 3%. The light in the room was switched on from 6 a.m. to 6 p.m. Demineralized water was given as drinking fluid.

Selective Breeding of SHRSP with DI Rats

SHRSP rats in the 14th generation were cross-bred with DI rats starting in 1978. The DI rats were identified from our Brattleboro colony by a drinking test in which animals are considered positive, if they drink more water per 24 hours than 50% of their body weight.

The F-1 generation of a crossing between SHRSP (+/+) and homozygous DI (di/di) animals is heterozygous for the DI allele (di/+) and characterized by a "dilution" of SHR genes. The genetic strategy therefore was to try to accumulate SHR genes as well as DI alleles in a subline of the F-1 generation. This was achieved alternatively first by inbreeding of di/+ animals and then introduction of new SHR genes from the SHRSP stock colony. This procedure led to a stepwise accumulation of SHR genes and a reappearance of DI animals from the di/+ × di/+ intercrosses (fig. 1).

Experiment 1

To characterize the new line of SHR with signs of DI, SHRDI rats (n = 7) were compared with the original SHRSP (n = 10) and normotensive control WKY (n = 10) as well as with original DI (n = 8) and control LE rats (n = 8). All rats were males between 9 and 10 months old, weighing between 220 and 350 g. They were anesthetized with ether, and a polyethylene catheter (PE 10 connected to PE 50) was implanted into the abdominal aorta via the right femoral artery. The catheter was placed under the skin in such a way as to protrude between the scapulae. It was filled with 0.9% saline solution containing heparin and then sealed until the measurements were made 1 day after the operation. At that time arterial pressure and heart rate were recorded while the rats were conscious and freely moving.

One day later the rats were decapitated, blood was collected into heparinized plastic tubes, and immediately centrifuged at 4°C. The plasma was stored at -25°C for measurement of plasma AVP concentration. The brain and pituitary gland were quickly removed and the hypothalamus isolated by cutting around its perimeter to a depth of 2 mm. The tissue was immediately frozen at -70°C and stored at -25°C until peptide extraction.

Experiment 2

In 5-month-old male WKY, SHRSP, SHRDI, DI, and LE rats (each group consisted of six rats) fluid and electrolyte balance was studied. With the rats under light ether anesthesia, systolic blood pressure was measured by tail plethysmography, and then blood (1.5 ml) was collected from the retroorbital venous plexus. Hematocrit was determined by the microcapillary technique, plasma osmolality by freezing point depression (Knauer Osmometer, Berlin, West Germany). For measurement of plasma renin concentration (PRC) the plastic tubes were kept on ice and contained 5 vol% of an angiotensinase inhibitor.

Subsequently, rats were placed in metabolic cages (Acme Research Products, Cleveland, Ohio), and allowed to adapt for 7 days. Fluid and food intake as well as urine volume, urine osmolality, and urinary concentration of sodium and potassium were measured, the latter by flame photometry of 24-hour urine collection samples. Drinking water was demineralized water and food was commercial rat chow (altromin) in paste form. In additional experiments, the response to an 8-hour period of water deprivation, and on the next day to a subcutaneous injection of 5 µg/kg 1-deamino-8-D-arginine vasopressin (DDAVP), a synthetic nonpressor analog of AVP with minimal cardiovascular activity, was investigated in all five different strains. During each of the two 8-hour periods, urine was collected and water consumption measured. The rats had free access to water during the treatment with DDAVP.

Measurement of Vasopressin (AVP) and Oxytocin (OXT)

The radioimmunoassays for AVP and oxytocin in plasma and tissue have been described elsewhere. The identity of the radioimmunological activity of AVP and OXT in various brain areas was demonstrated by high-pressure liquid chromatography (µ-Bondapak C-18, Waters, Königstein, West Germany, 0.01 ammonium acetate buffer, pH 5.4, methanol gradient, 30% to 80%).

Immunocytochemistry

Specific antibodies against OXT and AVP were raised in rabbits as described in detail previously. Cross-reactivity of both antibodies with OXT or AVP was less than 0.5%. Male rats were fixed by retrograde...
Figure 1. Genealogical outline of selective breeding of stroke-prone spontaneously hypertensive rats (SHRSP) with rats homozygous for hereditary hypothalamic diabetes insipidus with stepwise accumulation of SHR genes and a reappearance of diabetes insipidus (DI) animals from the di/di × di/di intercrosses. The following symbols and abbreviations have been used: Brattleboro rats homozygous for hypothalamic diabetes insipidus (DI), genetic code: di/di; Brattleboro rats heterozygous for hypothalamic diabetes insipidus (HZ), genetic code: di/di; Long-Evans control rats (LE), genetic code: +/+ . Values on top of the symbols indicate mean arterial blood pressure (MAP) of the corresponding generation; parental (P) and filial (F) generations are indicated on the left. Heavy outlines indicate rats with di/di gene.
TABLE 1. Body Weight, Systolic Blood Pressure, Hematocrit, and Plasma Osmolality in 5-Month-Old SHRDI Rats Compared with Various Age-Matched Control Groups

<table>
<thead>
<tr>
<th>No.</th>
<th>Body weight (g)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Hematocrit (%)</th>
<th>Plasma osmolality (mOsm/kg of water)</th>
<th>Plasma renin concentration (ng Al/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>6</td>
<td>306±8.5*</td>
<td>118±3.5</td>
<td>48.2±0.6</td>
<td>297±3.1</td>
</tr>
<tr>
<td>SHRSP</td>
<td>6</td>
<td>222±3.1</td>
<td>188±10.9†</td>
<td>50.2±0.6</td>
<td>1.25±0.15</td>
</tr>
<tr>
<td>SHRDI</td>
<td>6</td>
<td>194±9.0</td>
<td>169±9.1†</td>
<td>52.2±1.0†</td>
<td>1.36±0.23</td>
</tr>
<tr>
<td>DI</td>
<td>6</td>
<td>216±12.2</td>
<td>112±1.6</td>
<td>44.2±1.1</td>
<td>2.69±0.70</td>
</tr>
<tr>
<td>LE</td>
<td>6</td>
<td>234±6.7</td>
<td>116±1.7</td>
<td>44.6±0.7</td>
<td>2.30±0.62</td>
</tr>
</tbody>
</table>

*p < 0.01 compared with the other groups. †p < 0.001 compared with the other groups. §p < 0.01 compared with DI and LE rats.

WKY = Wistar-Kyoto rat; SHRSP = stroke-prone spontaneously hypertensive rat; SHRDI = diabetes insipidus spontaneously hypertensive rat; DI = diabetes insipidus, LE = Long-Evans control rat; Al = angiotensin I.

FIGURE 2. Water intake, mean arterial pressure, and heart rate in SHRDI rats compared with various age-matched control groups. Rats were 9 to 10 months of age. n = number of animals per group. Statistical significance = water intake in SHRDI and DI rats p < 0.001 vs WKY, SHRSP, and LE rats; mean arterial pressure in SHRSP and SHRDI rats p < 0.001 vs WKY, DI, and LE rats.

FIGURE 3. Plasma arginine vasopressin (AVP) concentration and content of AVP in the hypothalamus and pituitary gland of SHRDI rats compared with various age-matched control groups. Some rats are used as in figure 2. n = number of rats per group; n.d. = not detectable; statistical significance = *p < 0.05.
Aortic perfusion with a solution of 0.1% glutaraldehyde in formaldehyde-picric-acid (50%) of a saturated picric-acid solution containing 18.5% formaldehyde. The brains of the animals were embedded in paraffin and cut in 7 μm thick sections. These paraffin sections were stained by using the peroxidase-antiperoxidase technique (PAP).

Specificity tests were carried out by preabsorbing the appropriate antibodies with AVP or OXT, and by using preimmune sera instead of antisera.

Statistics
All results are given as means ± SEM. Significance of differences was assessed by analysis of variance. In those cases in which a difference of statistical significance was obtained, Scheffe’s test was used for further evaluation.

Results

Experiment 1
Water intake was more than 4 times higher in SHRDI and DI rats than in WKY, SHRSP, and LE rats (fig. 2). SHRDI and DI rats drank similar amounts of water. Mean arterial pressure was markedly elevated in SHRSP as well as in SHRDI rats, but heart rate did not differ in the five different strains of rats tested (fig. 2).

AVP was slightly higher in the plasma of 10-month-old SHRSP compared with WKY and LE rats, but AVP was not measurable in the plasma of SHRDI and DI rats (fig. 3). The AVP content in the hypothalamus was reduced in SHRSP rats compared to age-matched WKY rats, and similar amounts of AVP were found in the pituitary of SHRSP, WKY, and LE rats. AVP could not be detected in the hypothalamus and the pituitary of SHRDI and DI rats (fig. 3).

The OXT content in the pituitary was markedly reduced in SHRDI and DI rats as compared to WKY, SHRSP, and LE rats (fig. 4). Similarly, reduced amounts of OXT were detected in the hypothalamus of SHRDI and DI rats; but also in SHRSP rats OXT content was lower than in WKY and LE rats (fig. 4).

Experiment 2
Body weight and systolic blood pressure of 5-month-old WKY, SHRSP, SHRDI, DI, and LE rats are given in table 1. In DI rats, hematocrit was not elevated compared with LE rats; however, in SHRSP and SHRDI hematocrit was higher than in DI rats. Plasma osmolality was slightly but not significantly elevated in SHRDI and DI rats, and plasma renin concentration did not differ among all five groups tested.

In balance studies, a tremendous intake of water and output of urine was observed in SHRDI and DI rats (table 2). Consequently, urine osmolality and urinary

### Table 2. Fluid and Food Intake, Urine Volume, and Electrolyte Excretion in 5-Month-Old SHRDI Rats Compared with Various Age-Matched Control Groups

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHRSP</th>
<th>SHRDI</th>
<th>DI</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Water intake (ml)</td>
<td>13 ± 2.2</td>
<td>18 ± 3.0</td>
<td>151 ± 22*</td>
<td>122 ± 12*</td>
<td>11 ± 0.9</td>
</tr>
<tr>
<td>Food intake (g)</td>
<td>36.1 ± 3.9</td>
<td>38.5 ± 1.5</td>
<td>34.3 ± 3.0</td>
<td>42.6 ± 1.3</td>
<td>43.3 ± 1.1</td>
</tr>
<tr>
<td>Urine volume (ml/24 hr)</td>
<td>11.5 ± 1.3</td>
<td>11.2 ± 1.5</td>
<td>123 ± 17*</td>
<td>113 ± 12*</td>
<td>9.5 ± 0.7</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg of water)</td>
<td>2026 ± 279</td>
<td>1695 ± 198</td>
<td>190 ± 33*</td>
<td>262 ± 26*</td>
<td>2195 ± 68</td>
</tr>
<tr>
<td>Urinary sodium concentration (mmol/liter)</td>
<td>135 ± 19</td>
<td>93 ± 17</td>
<td>10 ± 0.7*</td>
<td>18 ± 2.4*</td>
<td>131 ± 7.4</td>
</tr>
<tr>
<td>Urinary potassium concentration (mmol/liter)</td>
<td>316 ± 46</td>
<td>252 ± 23</td>
<td>23 ± 6.7*</td>
<td>29 ± 3.1*</td>
<td>367 ± 19</td>
</tr>
</tbody>
</table>

*p < 0.001 compared with the other groups. See table 1 for abbreviations.
concentration of sodium and potassium were markedly reduced. During an 8-hour period of water deprivation, SHRDI and DI rats were unable to concentrate their urine adequately, but urine volume was reduced to some extent (table 3). However, SHRDI and DI rats did concentrate their urine three- to fourfold after subcutaneous administration of DDAVP (table 4), but they did not reach maximal urinary concentration as observed in WKY, SHRSP, and LE rats.

Immunocytochemistry

In all animals, positive reaction was observed in the hypothalamus for OXT. AVP immunocytochemistry was negative in DI and SHRDI rats (figs. 5 and 6).

**FIGURE 5.** Upper Left and Right: Normotensive Wistar-Kyoto control rats. Positive immunoreaction for oxytocin (left) and AVP (right) of cells in the nucleus supraopticus (SO) and paraventricularis (PV). Perfusion fixation with Bouins solution containing 0.1% glutaraldehyde. Antiserum dilution 1:5000. PAP-method. ×60. Lower Left and Right: Rats with hypothalamic diabetes insipidus (DI) (Brattleboro strain). Positive reaction for oxytocin (left) and negative reaction for AVP (right) of cells in the nucleus supraopticus (SO) and paraventricularis (PV). ×60.
Discussion

Both DI and SHRSP rats have been studied extensively during the past decade. To investigate whether AVP is necessary for the development and maintenance of high blood pressure in SHRSP, we have crossbred SHRSP with Brattleboro DI rats. The successful breeding of a new line of SHR rats with hereditary hypothalamic diabetes insipidus clearly demonstrates that AVP is not essential for the development and maintenance of high blood pressure in spontaneous hypertension of rats.

In SHRD1 rats, high blood pressure was similarly elevated (a mean arterial pressure more than 180 mm Hg) as in SHRSP rats of the same age, indicating that

FIGURE 6. Upper Left and Right: Spontaneously hypertensive rats (SHRSP) (Wistar-Kyoto strain). Positive immunoreaction for oxytocin (left) and AVP (right) of cells in the nucleus supraopticus (SO) and paraventricularis (PV). ×60. Lower Left and Right: Rats with spontaneous hypertension and hereditary hypothalamic diabetes insipidus (SHRD1). Positive reaction for oxytocin (left) and negative reaction for AVP (right) of cells in the nucleus supraopticus (SO) and paraventricularis (PV). For technical details see figure 5. ×60.
TABLE 3. Response to an 8-Hour Period of Water Deprivation in SHRDI Rats Compared with Various Age-Matched Control Groups

<table>
<thead>
<tr>
<th>No.</th>
<th>WKY</th>
<th>SHRSP</th>
<th>SHRDI</th>
<th>DI</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine volume (ml/24 hr)</td>
<td>4.0 ± 0.4</td>
<td>3.3 ± 0.3</td>
<td>13.3 ± 1.4*</td>
<td>18.5 ± 1.6*</td>
</tr>
<tr>
<td></td>
<td>Urine osmolality (mOsm/kg of water)</td>
<td>2174 ± 150</td>
<td>1939 ± 90</td>
<td>376 ± 33*</td>
<td>358 ± 22*</td>
</tr>
<tr>
<td></td>
<td>Urine sodium concentration (mmol/liter)</td>
<td>200 ± 15</td>
<td>150 ± 7.9</td>
<td>25 ± 4.8*</td>
<td>36.6 ± 1.9*</td>
</tr>
<tr>
<td></td>
<td>Urinary potassium concentration (mmol/liter)</td>
<td>365 ± 17</td>
<td>340 ± 13</td>
<td>69 ± 9.5*</td>
<td>51 ± 3.1*</td>
</tr>
</tbody>
</table>

*p < 0.001 compared with the other groups.

TABLE 4. Response to Subcutaneous Injection of 5 μg/kg 1-Desamino-8-D-Arginine Vasopressin (DDAVP) in SHRDI Rats Compared with Various Age-Matched Control Groups

<table>
<thead>
<tr>
<th>No.</th>
<th>WKY</th>
<th>SHRSP</th>
<th>SHRDI</th>
<th>DI</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine volume (ml/24 hr)</td>
<td>2.2 ± 0.5</td>
<td>2.0 ± 0.3</td>
<td>3.0 ± 0.6</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Urine osmolality (mOsm/kg of water)</td>
<td>2877 ± 337</td>
<td>3080 ± 87</td>
<td>976 ± 65*</td>
<td>717 ± 88*</td>
</tr>
<tr>
<td></td>
<td>Urinary sodium concentration (mmol/liter)</td>
<td>210 ± 20</td>
<td>189 ± 32</td>
<td>52 ± 5.8*</td>
<td>49.4 ± 4.5*</td>
</tr>
<tr>
<td></td>
<td>Urinary potassium concentration (mmol/liter)</td>
<td>460 ± 36</td>
<td>526 ± 20</td>
<td>211 ± 16*</td>
<td>169 ± 10*</td>
</tr>
</tbody>
</table>

*p < 0.01 compared with the other groups.

the new strain has a severe form of hypertension. The fluid and electrolyte studies leave no doubt that the SHRDI rats had hypothalamic diabetes insipidus. The severity of the disease was manifested by the very high intake of water and output of urine, which in some rats exceeded the total body weight during a 24-hour period. Urine osmolality in SHRDI was very low, as it was in DI rats, and both strains of rats did not adequately concentrate their urine during water deprivation. The marked reduction of urine volume and the profound increase in urine osmolality to exogenously applied DDAVP in SHRDI and in DI rats demonstrates that the kidney tubules responded normally to vasopressin and that the defect in the ability to concentrate urine in SHRDI was not the result of acquired kidney disease, which confirms that SHRDI respond like DI rats in this respect. Thus, lack of AVP is responsible for the distinct disturbance of water balance in these rats.

As in DI rats, no AVP was detectable in the plasma of SHRDI rats by radioimmunoassy. The plasma AVP levels of WKY, SHRSP, and LE rats corresponded to those reported previously. 2, 3, 20 AVP was also undetectable in the hypothalamus and in the pituitary of SHRDI rats, again similar to the original DI rats. We can therefore conclude that SHRDI rats have high blood pressure and an absolute inability to synthesize AVP.

With bioassay methods, it has been shown that the pituitary content of OXT is about one-third in DI rats compared with that of LE rats. 21 We confirmed this finding in the present experiments in which pituitary OXT was measured radioimmunologically. In the hypothalamus of DI rats, OXT content was only one-half that found in LE rats. As in DI, SHRDI rats also had reduced contents of OXT in the hypothalamus and pituitary gland when compared to WKY or LE rats. This striking finding warrants further investigation, as discussed elsewhere. 33

The role of AVP in the pathogenesis of hypertension is still unclear. We can definitely conclude from the results obtained with the new SHRDI strain that AVP in the plasma and in the brain is not essential for the development and maintenance of high blood pressure in SHRSP rats. This does not exclude the possibility that AVP, when present, may contribute to the hypertensive process. No data are available as yet as to the stroke incidence in these rats.

From recent studies, it appears that two different AVP systems exist. First, there is the hormonal AVP system, originating from the paraventricular and supraoptic nuclei in the hypothalamus and secreted from the posterior pituitary into the blood. Second, there is the neurohormonal or neurotransmitter brain AVP system, which projects from the paraventricular and su-
prachiasmatic nuclei to several brain nuclei known to play a role in cardiovascular regulation. In histochemical studies, a dense vasopressinergic innervation of cell groups in nuclei of the brain stem was demonstrated; these nuclei are known to relay baroreceptor signals to other areas of the brain stem, including the vasomotor center, the hypothalamus, and the spinal cord. Microinjection of AVP into the nucleus tractus solitarii elicited a dose-dependent increase in arterial pressure and heart rate and a marked depressor effect was found after microinjection of a vasopressor AVP antagonist in this area. This extrahypothalamic AVP may therefore contribute to the volume-preserving and blood-pressure-increasing effects of circulating plasma AVP.

On the basis of indirect evidence, however, it was postulated that circulating AVP enhances the reflex bradycardia and reflex-induced reduction in cardiac output by a central mechanism, and it cannot be excluded that the increase in cardiac output observed in DOCA hypertensive rats after intravenous injection of a vasopressor AVP antagonist was brought about by a central action of this compound. Depressor effects of brain AVP have also been suggested by experiments in which AVP was administered into the lateral brain ventricle. In these experiments the pressor response after electrical stimulation of the mesencephalic reticular formation was attenuated by AVP. Thus, in the central nervous system AVP may also activate blood-pressure-lowering pathways. We therefore have to consider the possibility that AVP, similar to the adrenergic nervous system and to opioid peptides, may not only activate pressor but also depressor mechanisms. The high blood pressure in SHRDI rats might then not occur "despite" the fact that AVP is absent, but this defect may even contribute to the development of high blood pressure, since other pressor stimuli such as an increased sympathetic tone remain unopposed in the AVP-deficient SHRDI rats.

Acknowledgments

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