AT₁ receptor regulation in salt-sensitive hypertension

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AT₁ receptor regulation in salt-sensitive hypertension. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H1701–H1707, 1999.—The molecular events governing salt-sensitive hypertension are currently unknown. Because the renin-ANG system plays a central role in blood pressure regulation and electrolyte balance, it may be closely involved in the phenomenon of salt sensitivity. Therefore, we examined the effect of a high-salt diet (8%) and a low-salt diet (0.4%) on ANG II-caused vascular constriction and ANG II type 1 (AT₁) receptor expression in aorta, brain, and kidney of Dahl S (salt-sensitive) and Dahl R (salt-resistant) rats by means of radioligand binding assays and quantitative PCR. NaCl diet at 8% led to a significant increase of blood pressure in Dahl S but not in Dahl R rats. High-sodium intake caused a profound decrease of ANG II-induced aortic vasoconstriction in both Dahl R and Dahl S rats. The underlying mechanism was a downregulation of aortic AT₁ receptor density and AT₁ receptor mRNA. AT₁ receptor mRNA was downregulated to 57.8% in Dahl R and 59.0% in Dahl S rats by an 8% NaCl diet compared with a 0.4% NaCl diet (P < 0.05). There was a similar decrease in aortic AT₁ receptor density. Additionally, AT₁ receptor mRNA was also downregulated in the kidney but upregulated the brain of Dahl R and S rats on a high-salt diet. Thus high NaCl intake causes organ-specific AT₁ receptor expression in Dahl R and in Dahl S rats despite the differential blood pressure regulation in these animal models in response to a high-salt diet. These findings suggest that the regulation of vascular AT₁ receptors is influenced by numerous factors such as the renin-ANG system and obviously by various other events that are currently only partly understood.

angiotensin II; salt; vascular smooth muscle cells; salt sensitivity; angiotensin II type 1 receptor

EPIDEMIOLOGICAL DATA have suggested a correlation of dietary salt to blood pressure regulation and to the prevalence and progression of essential hypertension. Nevertheless, several interventional studies have failed to establish a reproducible relationship between alterations in sodium intake and blood pressure. Therefore, the salt-blood pressure theory has remained the subject of ongoing controversy (11, 14, 20, 35). In this context, the genetic rat model of salt-induced hypertension introduced by Dahl et al. (9, 10) was of particular interest and helped to gain further insight into the molecular mechanisms of hypertension. Although the salt-resistant Dahl rat strain (Dahl R) displays no elevated blood pressure upon salt diet, the salt-sensitive Dahl rats (Dahl S) develop a fulminating hypertension in response to enhanced salt intake resulting in a short lifespan (9, 10). ANG-converting enzyme (ACE) inhibitors and ANG II type 1 (AT₁) receptor antagonists increase the life expectancy of these animals, suggesting that the renin-ANG system is involved in the development of hypertension in this particular animal model (16, 17, 19). The AT₁ receptor is a G protein-coupled receptor expressed in various tissues that mediates many effects of ANG II (7, 32). In addition to its role in the control of blood pressure and fluid and electrolyte regulation, the AT₁ receptor has been implicated in the pathogenesis of various cardiovascular diseases (7, 12, 32). In addition, dietary sodium intake is known to modulate the renin-ANG system. Low-salt diet leads to elevation of plasma renin and aldosterone activity and consequently to decreased AT₁ receptor expression via homologous downregulation. High-salt intake, which causes hypertension in some individuals, induces a decrease in the activity of the circulating renin-ANG system, and this is thought to be involved in the accompanying upregulation of AT₁ receptor expression (1, 3). To define whether a pathophysiological enhancement of AT₁ receptor gene expression in Dahl S rats could explain the phenomenon of salt-sensitive hypertension, we examined the vascular AT₁ receptor expression and the vasoconstrictory effect of ANG II in Dahl R and Dahl S rats fed with either a regular or high-salt diet.

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Aortic ring preparations and tension recording. After excision of the descending aorta, the vessel was immersed in Krebs buffer, and adventitial tissue was removed. Rings (2–3 mm) were mounted for recording of isometric tension in organ baths filled with Krebs buffer that was continuously aerated with 95% O₂ and 5% CO₂. The preparations were attached to a force transducer, and isometric tension was recorded on a polygraph. Tissues were allowed to equilibrate for 90 min. A resting tension of 2 g was maintained throughout the experiment. Drugs were added in increasing concentrations to obtain cumulative concentration-response curves. The drug concentration was increased when vasoconstriction was completed, which took an average of 5–10 min for each step.

mRNA isolation. Vessels were homogenized and lysed in 1 ml of RNA-clean (AGS) and were processed according to the manufacturer’s protocol to obtain total cellular RNA. Aliquots (2–10 µg) were electrophoresed through 1.2% agarose-0.67% formaldehyde gels and were stained with ethidium bromide to verify the quantity and quality of the RNA.

Quantitative PCR. The aorta, brain, or kidney were isolated, quickly frozen in liquid nitrogen, and homogenized. RNA was isolated with RNA-clean (AGS) according to the manufacturer’s protocol to obtain total cellular RNA. The original AT₁ receptor cDNA (15) was digested with MSCI and self-ligated. The resulting plasmid lacking the region from base 446 to 734 (mutAT₁) was linearized by digestion with Sac I, and a deletion-mutated AT₁ receptor mRNA was in vitro transcribed using the Megascript-Kit (Ambion) following the manufacturer’s instructions (21). Two micrograms of the isolated total RNA and 10 pg of the mutAT₁ mRNA were mixed and reverse transcribed using random primers. The single-stranded cDNA was amplified by PCR reaction using Taq DNA-polymerase (Boehringer, Mannheim, Germany). Twenty-eight cycles were performed under the following conditions: 94°C, 30 s; 55°C, 45 s; 72°C, 45 s. The sequence for the AT₁ receptor sense and antisense primers were as follows: 5′-ACCCCTCCTACGCATCTTTGTTGGGGA-3′ and 5′-GGGAGGCTCGAATTCCGAGACTCAATTGA-3′, respectively. The same samples were used for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA amplification to confirm that equal amounts of RNA were reverse transcribed. The PCR reactions were performed under the same conditions described above. The PCR products were separated through 1.5% agarose gels, and DNA was visualized by etidium bromide staining. For quantification, DNA was transferred by vacuum blotting to nylon membranes that were then hybridized with a radiolabeled AT₁ receptor cDNA probe. Autoradiograms were analyzed by laser densitometry.

Radioligand binding assays. The aortic tissue was chilled in 30 ml ice-cold homogenization buffer (in mmol/l: 20 Tris-HCl, 1 EDTA, and 1 dithiothreitol (DTT), pH 8.0). Connective tissue was trimmed away, and the tissue was minced with scissors, disrupted with an Ultraturrax (I. anke and Kunkel, Staufenbreisgau, Germany), and homogenized with a motor-driven glass-Teflon Potter for 1 min. The homogenate was spun at 480 g for 10 min (J A 20; Beckman, Palo Alto, CA). The supernatant was diluted with an equal volume of ice-cold 1 mol/l KCl and was stored on ice for 10 min and centrifuged at 100,000 g for 45 min. The pellet was resuspended in 50 vol of homogenization buffer and recentrifuged at 100,000 g for 45 min. The final pellet was resuspended in an incubation buffer in the absence of DTT (50 mmol/l Tris-HCl, 50 mmol/l NaH₂PO₄, 10 mmol/l MgCl₂, 0.2% BSA, and proteinase inhibitors: 0.2 mg/ml trypsin inhibitor, 0.25 mg/ml pepstatin A, and 0.25 mg/ml leupeptin, pH 7.1). ¹²⁵I-ANG II was used as radiolabeled ligand (0.125–2 nmol/l) to assess AT₁ receptor density. Losartan (10 µmol/l) was used to determine nonspecific binding. The assay was performed in a total volume of 250 µl incubation buffer. The incubation was carried out at 24°C for 60 min. These conditions allowed a complete equilibration of the receptor with the radioligand. The reaction was terminated by rapid vacuum filtration through Whatman GF/CC filters (Whatman, Clifton, N J); the filters were washed immediately three times with 5 ml of ice-cold incubation buffer, and radioactivity was determined in a gamma counter. All experiments were performed in triplicate. The maximal density and apparent affinity of binding sites were obtained by nonlinear regression analysis.

Statistical analysis. Data are presented as means ± SE. Statistical analysis was performed using the ANOVA test.

RESULTS

Blood pressure. Figure 1 illustrates that systolic blood pressure increased only slightly in Dahl R rats on the 8% NaCl diet, whereas in Dahl S rats on 8% NaCl an increase of systolic blood pressure >200 mmHg developed (P < 0.05).

Functional experiments. To investigate the effect of high-salt diet on the vasoconstrictory effect of ANG II, organ chamber experiments with isolated aortic segments were performed. Developed force of contraction upon incubation with 20 or 80 mmol/l KCl was similar in all groups (data not shown). ANG II caused a profound concentration-dependent effect on aortic contraction in Dahl R and Dahl S rats fed with the low-salt diet. In Dahl R and Dahl S rats, the ANG II–induced vasoconstriction was significantly inhibited after the 8% NaCl diet (Fig. 2). Maximal force of contraction decreased in Dahl R rats from 40.7 ± 3.4 to 24.2 ± 2.1% and in Dahl S rats from 30.9 ± 6.3 to 10.1 ± 6.317% of KCl-induced vasoconstriction. ANG II–induced vasoconstriction was significantly higher in Dahl R rats than in Dahl S rats. As control experiments, phenylephrine-induced force of contraction was measured. Figure 2 shows that α-adrenergic-mediated aortic constriction

![Fig. 1. Systolic blood pressure in Dahl (D) salt-sensitive (S) and salt-resistant (R) rats. Blood pressure was measured by the tail cuff method 6 wk after either 0.4% or 8% NaCl diet. Each point represents the mean ± SE, n = 10 experiments. *P < 0.05.](http://ajpheart.physiology.org/DownloadedFrom/)
was similar in all groups, suggesting that a high-salt diet caused a selective decrease of ANG II-caused vasoconstriction in both Dahl R and Dahl S rats.

**AT1 receptor density.** To examine whether this modulation in ANG II-caused aortic constriction was based on regulation of AT1 receptor expression, radioligand binding assays on cell membranes isolated from thoracic aortas that were excised from Dahl R and Dahl S rats on regular or high-salt diet were conducted. The representative saturation binding assays with 125I-ANG II in Fig. 3 show that the 8% salt diet led, in Dahl S and Dahl R rats, to a decrease of AT1 receptor density without significant changes in receptor affinity (Table 1). These data demonstrate that high-salt intake is associated with a downregulation of vascular AT1 receptor density in vivo in Dahl R and in Dahl S rats.

**Aortic AT1 receptor mRNA.** To assess whether the decrease of aortic AT1 receptor density during high-salt diet was caused by a decrease in mRNA, AT1 receptor mRNA was detected by means of a quantitative PCR. The RT and PCR reaction of the AT1 receptor mRNA was monitored by including an internal standard. This deletion-mutated AT1 receptor mRNA yielding a substantially shorter PCR product (191 bp) enabled distinction of the wild-type and mutated AT1 receptor mRNA (479 bp). Quantity and quality of the included RNA was controlled by an additional PCR reaction from the same RT samples using an external standard (GAPDH). The exponential phase for the used amounts of wild-type and mutated RNA was found to be in a range between 20 and 36 cycles (data not shown). Therefore, 28 cycles were used in our experimental setup. Figure 4 illustrates a representative ethidium bromide-stained agarose gel loaded with PCR reactions generated from aortic RNA of Dahl R rats fed with 0.4 or 8% NaCl diet, indicating that the AT1 receptor mRNA expression was markedly decreased in aortas isolated from rats on a high-salt diet. Figure 5 shows the quantitative analysis indicating that the AT1 receptor mRNA was decreased to 57.8% in Dahl R rats and to 59.0% in Dahl S rats on the high-salt diet. AT1 receptor mRNA-to-internal standard ratio 8.13 ± 1.7 (8% NaCl) vs. 4.7 ± 1.1 (0.4% NaCl) in Dahl R rats and 11.0 ± 3.1 (8% NaCl) vs. 6.5 ± 0.9 (0.4% NaCl) in Dahl S rats. AT1 receptor mRNA expression was slightly higher in Dahl S than in Dahl R rats irrespective of the dietary intake. However, these differences were not statistically significant. GAPDH mRNA was similar between groups (data not shown).

**Kidney and brain AT1 receptor mRNA.** In addition, AT1 receptor mRNA expression was assessed in brain
and kidney of Dahl S and R rats by quantitative PCR. Figure 6 displays that the high-salt diet led to a corresponding downregulation of AT1 receptor mRNA expression in kidney but to an upregulation in brain in both animal models. Basal brain AT1 receptor expression was comparable between Dahl R and Dahl S rats; however, the increase in AT1 receptor expression in response to the high-salt diet was more pronounced in Dahl S than in Dahl R rats. No significant difference of GAPDH mRNA expression was measured between groups (data not shown).

Renin plasma levels. Figure 7 illustrates renin plasma concentrations in Dahl R and Dahl S rats after either a

Table 1. AT1 receptor density and affinity in aortas isolated from Dahl R and Dahl S rats on a low- or high-salt diet

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Density, fmol/mg protein</th>
<th>Affinity, nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4% NaCl diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl S</td>
<td>11.1 ± 0.6</td>
<td>0.3 (0.18–0.4)</td>
</tr>
<tr>
<td>Dahl R</td>
<td>7.9 ± 0.9</td>
<td>0.3 (0.04–0.56)</td>
</tr>
<tr>
<td>8% NaCl diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl S</td>
<td>8.5 ± 0.9</td>
<td>0.2 (0.11–0.24)</td>
</tr>
<tr>
<td>Dahl R</td>
<td>5.6 ± 0.21</td>
<td>0.38 (0.11–0.6)</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ranges are in parentheses. AT1, ANG II type 1 receptor; Dahl R, Dahl salt resistant; Dahl S, Dahl salt sensitive.

Fig. 4. Quantitative ANG II type 1 (AT1) receptor mRNA PCR. Representative ethidium bromide-stained agarose gel of an RT-PCR of RNA isolated from aortas excised from Dahl R rats on regular and high-salt diet. The 496-bp DNA fragment corresponds to the AT1 receptor mRNA, and the 191-bp DNA fragment resulted from the mutated AT1 receptor mRNA (mutAT1-R; internal standard); 1 kb DNA marker (GIBCO-BRL) on left.

GAPDH mRNA expression was measured between groups (data not shown).

Fig. 5. Aortic AT1 receptor mRNA levels. Relative AT1 receptor expression in aorta from Dahl R (A) and S (B) rats subjected to regular or high-salt diet is shown. AT1 receptor mRNA level is expressed in relation to the mutated AT1 receptor mRNA, which was used as internal standard. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA expression, which was independently assessed from the same RT reaction, was not different between groups (data not shown). Each point represents data from 5 separate experiments ± SE.*P < 0.05.
low- or high-salt diet. As expected, renin was suppressed in Dahl R rats upon high-salt intake. Additionally, renin plasma concentrations were significantly lower in Dahl S rats than in Dahl R (low-salt diet) rats, and a high-salt diet led to a paradoxical increase in renin levels in Dahl S rats.

**DISCUSSION**

The present study demonstrates that increased intake of NaCl decreases vascular AT1 receptor gene expression in Dahl R and Dahl S rats. Because many of the known biological effects of ANG II are mediated by the AT1 receptor, modulation of the responsiveness of this receptor has been a prominent subject of recent research. Conditions of increased renin-ANG system activity cause downregulation of AT1 receptors, whereas a decrease in the activity of the renin-ANG system upregulates the AT1 receptor expression (1, 3, 7, 12, 32). It is thought that ANG II circulating in the plasma may influence AT1 receptor regulation. Namely, reduced ANG II concentration may lead to upregulation, and increased ANG II plasma levels may cause downregulation of vascular AT1 receptors (1, 3, 13, 18, 22, 23, 28).

It has been shown that a high-salt diet causes suppression of plasma renin levels, whereas a low-salt intake leads to increased renin plasma levels (1, 3). Accordingly, AT1 receptors are regulated in a reciprocal manner in response to dietary changes. AT1 receptors are reportedly upregulated after high-salt intake in the kidney (27) and in the brain (29). More recently, it has been shown that increased dietary salt intake induces an upregulation of vascular AT1 receptors in Sprague-Dawley and Wistar rats (25, 33). Consistently, kidney AT1 receptor expression is enhanced in Sprague-Dawley rats on a high-salt diet (30). Salt-induced AT1 receptor upregulation may potentially be involved in salt sensitivity. We hypothesized that some individuals may react with a more pronounced AT1 receptor overexpression upon high-salt intake leading to salt-sensitive hypertension. To explore this theory, we examined Dahl rats, which represent a well-established animal model for salt-sensitive hypertension. The Dahl S rats develop a low-renin hypertension after a high-salt diet (5). Interventional studies in Dahl rats showed that ACE inhibitors and AT1-receptor antagonists are capable of lowering blood pressure, reducing cardiac hypertrophy, and decreasing mortality (16, 17, 19, 31), suggesting a central role of the renin-ANG system and the AT1 receptor in this animal model. It was therefore reasonable to assume that AT1 receptor regulation may participate in the salt sensitivity of Dahl S rats. Surprisingly, our data show that vascular AT1 receptors are downregulated in Dahl S and Dahl R rats regardless of the development of salt-sensitive hypertension in Dahl S rats, suggesting that AT1 receptor regulation is not
decisively involved in salt-sensitive hypertension in Dahl S rats. Renal cross-transplantation of the kidney of Dahl S and Dahl R rats has illustrated that the kidney of Dahl S rats plays an important role in the development of hypertension (8). It is of note that suppression of plasma renin concentrations to a high-salt diet is blunted in Dahl S rats (6). Moreover, it has been shown that renin activity gradually increased in Dahl S rats after a high-salt diet for 4 wk (29). On the basis of these data, it is thought that the renin-ANG system is inefficiently suppressed during salt loading, which contributes to salt-sensitive hypertension. The present data illustrate downregulation of vascular AT1 receptors and decreased ANG II-induced vasoconstriction after a high-salt diet. This is obviously independent of the circulating renin-ANG system because the suppression of plasma renin concentration in response to a high-salt diet should lead to AT1 receptor upregulation. Our data on renin plasma levels are in agreement with previous findings (6, 26) which demonstrate that renin plasma concentrations are suppressed in Dahl R rats but may be paradoxically increased in Dahl S rats after a high-salt intake. The latter may be due to progressive renal damage and heart failure in Dahl S rats, leading to an activation of the renin-ANG system, which overcomes the initial suppression of renin after salt loading (6, 26). Accordingly, AT1 receptor downregulation may be of compensatory nature in Dahl S rats. This does not apply for Dahl R rats, which display observed downregulation of vascular AT1 receptors in Dahl rats is probably influenced by additional factors besides the renin-ANG system. The fact that AT1 receptor downregulation occurred not only in aortic but also in kidney tissue supports the idea of a general regulative phenomenon in these animals. It may be speculated that, e.g., the increased catecholamine plasma levels induce AT1 receptor downregulation (4). It is presumable, since stimulation of β-adrenergic receptors with isoproterenol causes AT1 receptor downregulation in vascular smooth muscle cells (34). In addition, it is well established that the vascular AT1 receptor is subjected to heterologous regulation by, e.g., growth factors and lipoproteins (22, 24). The nitric oxide system may also influence blood pressure regulation in Dahl rats. Namely, it has been reported that renal and aortic constitutive nitric oxide synthase activity is significantly lower in Dahl S rats on a high-salt diet than in Dahl S rats on a low-salt diet or Dahl R rats (15). This could possibly explain the increase in blood pressure in Dahl S rats despite the observed AT1 receptor downregulation.

Interestingly, in Sprague-Dawley rats, salt loading causes an upregulation of vascular AT1 receptor expression (25), suggesting that AT1 receptor regulation in Dahl rats is per se subjected to differential regulatory pathways. On the basis of our data, this does not apply to the brain, since salt loading causes upregulation of brain AT1 receptors, especially in Dahl S rats, suggesting organ-specific regulation of the AT1 receptor. Acting through the AT1 receptor in the brain, ANG has effects on fluid and electrolyte homeostasis, neuroendocrine systems, and autonomic pathways regulating cardiovascular function and behavior. The distribution of ANG receptors in the brain indicates that they play diverse and important physiological roles in the nervous system (2). There is a greater increase of AT1 receptor expression in the brain after a high-salt diet (basal levels are comparable) in Dahl S rats compared with Dahl R rats. It may be speculated that this AT1 receptor upregulation may drive in part the salt-sensitive hypertension in those animals. If so, AT1 receptor downregulation in the aorta and kidney would be considered a compensatory step, although the molecular mechanisms leading to this differential and organ-specific regulative pathways are not clear.

There is a trend toward higher AT1 receptor expression in the aorta and kidney in Dahl S rats on a low-salt diet compared with Dahl R rats on a low-salt diet. This could be explained by the reduced renin levels in Dahl S rats. On the other hand, the lower renin levels may be induced through AT1 receptor overexpression in Dahl S rats. Nevertheless, the present data cannot clarify this question.

Further investigations concerning the molecular mechanisms underlying this differential AT1 receptor regulation will lead to a better understanding of the role of the AT1 receptor and its regulation in the setting of hypertension. Our results suggest that the renin-ANG system-independent factors, such as the sympathetic nervous system, are involved in this pathophysiologically important modulatory process of AT1 receptor gene.

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