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Effect of dietary sodium on estrogen regulation of blood pressure in Dahl salt-sensitive rats

Wei Zheng,* Hong Ji,* Christine Maric, Xie Wu, and Kathryn Sandberg

Center for the Study of Sex Differences in Health, Aging and Disease, Georgetown University, Washington, District of Columbia

Submitted 11 November 2007; accepted in final form 29 January 2008

Zheng W, Ji H, Maric C, Wu X, Sandberg K. Effect of dietary sodium on estrogen regulation of blood pressure in Dahl salt-sensitive rats. Am J Physiol Heart Circ Physiol 294: H1508–H1513, 2008. First published February 1, 2008; doi:10.1152/ajpheart.01322.2007.—The effects of high-sodium (HS) and normal-sodium (NS) diets on ovarian hormone modulation of mean arterial pressure (MAP) were examined in Dahl salt-resistant (DR) and salt-sensitive (DS) rats. Ovariectomy increased MAP (OVX-Sham) to a greater extent in DS rats maintained for 2 wk on a HS (22 mmHg) compared with a NS (6 mmHg) diet. Ovariectomy had no effect on MAP in DR rats on NS but did increase MAP in rats on HS (10 mmHg) diets. On HS diets, glomerular filtration rate (GFR) was 36% less in the DS-Sham than DR-Sham animals; ovariectomy increased GFR in both strains by 1.4–1.5-fold; glomerular angiotensin II type 1 receptor (AT1R) densities were 1.6-fold higher in the DS-Sham than in the DR-Sham group; ovariectomy increased glomerular AT1R densities by 1.3-fold in DR rats but had no effect in DS rats; 17β-estradiol (E2) downregulated adrenal AT1R densities in both strains on either diet; ovariectomy reduced estrogen receptor-α (ER-α) protein expression in the renal cortex by 40–50% although renal ER-α expression was 34% lower in DS than in DR rats. These observed effects of gonadectomy were prevented by E2 treatment, suggesting that E2 deficiency mediates the effects of ovariectomy on MAP, GFR, AT1R densities, and renal ER-α protein expression. In conclusion, ovariectomy-induced increases in MAP are augmented by HS diet in both strains, and this effect is not mediated by a reduction in GFR. Aberrant renal AT1R regulation and reduced renal ER-α expression are potential contributors to the hypertensive effects of E2 deficiency in DS rats. These findings have implications for women with salt-sensitive hypertension and women who are E2 deficient, such as postmenopausal women.

17β-estradiol; estrogen receptors; angiotensin II type 1 receptors; kidney; adrenal

THE DAHL SALT-SENSITIVE (DS) and Dahl salt-resistant (DR) rats are an excellent model system in which to study salt-sensitive hypertension (10, 21). The DS rat exhibits severe and fatal hypertension. Endothelium-dependent relaxation is impaired and cardiac hypertrophy occurs in up to 32% of the animals, whereas cardiac failure is noted by 4 to 5 mo of age. Renal changes are also quite severe, and early proteinuria occurs. In contrast, the DR rat is resistant to the HS-induced hypertension and associated cardiovascular and renal damage.

The characteristics of the DS rat are remarkably similar to the phenotypic traits of hypertensive African Americans. The DS rat is salt sensitive (21), insulin resistant (2), and hyperlipidemic (22) and exhibits a low-renin form of hypertension that is resistant to angiotensin II (ANG II) type 1 receptor (AT1R) antagonists once the hypertension is established (20). The hypertensive DS rat also develops severe progressive hypertensive glomerulosis that leads to end-stage renal disease (19).

Transplantation studies suggest that the salt sensitivity in the DS rat is mediated by the kidney. If the DS kidneys are replaced with DR kidneys, the transplanted animals no longer exhibit salt-sensitive hypertension, and the corollary transplant experiments demonstrate that DR rats become susceptible to salt-sensitive hypertension when their kidneys are replaced with DS kidneys (4). Studies also indicate that central mineralocorticoid receptor agonists (e.g., aldosterone) play a role in salt-sensitive hypertension in the DS rat since central administration of mineralocorticoid receptor antagonists inhibited the development of hypertension (10).

Our recent studies indicate that ovariectomy accelerates the age-induced increase in mean arterial pressure (MAP) observed in DS rats maintained on a low-sodium (LS) diet (14). The ovariectomy-induced increase in BP was prevented by 17β-estradiol (E2) treatment, suggesting that it is the loss of E2 that causes the ovariectomy-induced increase in BP. In this study, we investigated the effects of dietary sodium manipulation on factors that contribute to BP and to the effects of ovariectomy in DR and DS rats.

METHODS

Animals. Female DS and DR rats (Rapp strain), weighing 200–250 g, were purchased from Harlan Sprague-Dawley (Indianapolis, IN) and individually housed in a temperature-controlled animal facility. All rats were maintained on a phytoestrogen-free NS (0.4% NaCl) or HS (4% NaCl) diet and given tap water ad libitum under controlled environmental conditions.

* W. Zheng and H. Ji contributed equally to this study.

Address for reprint requests and other correspondence: H. Ji, 391 Bldg. D, Georgetown Univ., 4000 Reservoir Rd. NW, Washington, DC 20057 (e-mail: jih@georgetown.edu).

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conditions (12-h:12-h light-dark schedule at 24°C). All procedures were approved by the Georgetown University Animal Care and Use Committee.

Surgery. Under methoxyflurane anesthesia, bilateral incisions were made. The vascular supply was ligated, and the ovaries were then removed. The muscle layer was sutured, and the incisions were closed with wound clips. In the sham-operated rats, the animals were subjected to surgery and the ovaries were manipulated but left intact.

Drug treatments. 17β-estradiol benzoate (10 μg/day; Sigma, St. Louis, MO) was dissolved in 0.2 ml peanut oil and injected subcutaneously every day for 15 days (unless otherwise indicated); sham-operated and ovariectomized (OVX) animals were injected subcutaneously with vehicle (0.2 ml peanut oil) as previously described (18).

BP measurements. Animals were anesthetized with Inactin (100 mg/kg; Sigma) and placed on a heated table to maintain body temperature at 37°C. A tracheotomy was performed to allow spontaneous breathing. A catheter was placed in the carotid artery for BP measurements using a Blood Pressure Analyzer (Digi-Med, Louisuville, KY).

Recovery. Animals were anesthetized with Inactin (100 mg/kg ip), and catheters were placed in the jugular vein for infusion of insulin for determination of glomerular filtration rate (GFR), in the carotid artery for blood sampling, and in the bladder for urine collection. Infusions of 2% insulin in 0.9% NaCl were given intravenously at a rate of 2% body weight (BW)/h. This protocol is known to be effective in maintaining arterial hematocrit and plasma volume during preparatory surgery and throughout the period of the experiment at preanesthesia values (11). After a 60-min equilibration period, two 20-min periods of urine clearance were collected. Blood was collected at the midpoint of each urine clearance. The insulin concentration in plasma and urine was determined by the anthrone method (9). GFR was equated with the clearance of insulin.

AT1R radioligand binding. Membranes from the same DR and DS rats that were used in the MAP and GFR studies were prepared from the adrenal cortex and from isolated glomeruli as described previously (16, 29). Membranes (5–10 μg protein/tube) were incubated for 1 to 2 h at room temperature with increasing concentrations of the ANG II antagonist [125I]-[Sar9,Ile10]-ANG II (Peptide Radiodination Service Center, University of Mississippi, Oxford, MS) in the presence of 1 μM PD-123319, an ANG II type 2 receptor antagonist (so only AT1R expression was measured) (29). Binding reactions were terminated by rapid filtration through a Brandel cell harvester. For quantitation, specific AT1R binding was defined as the total amount of radioligand bound minus the nonspecific binding, defined as the amount bound in the presence of 200 nM ANG II (100 × Kd for ANG II). Data points were obtained in triplicate. Kd and maximum binding capacity (Bmax) values from Scatchard plots were determined using the nonlinear regression analysis program, PRISM.

Western blot analysis of estrogen receptor expression. Protein (30 μg) was extracted from rat kidney cortex from the same DR and DS rats maintained on a HS diet that were used in the MAP and GFR studies. The samples were heated (95°C, 10 min) in Laemmli buffer, separated on Criterion precasting Tris-HCl gels (Bio-Rad, Hercules, CA), and then blotted onto nitrocellulose. Nonspecific binding was separated on Criterion precasting Tris-HCl gels (Bio-Rad, Hercules, CA), and then blotted onto nitrocellulose. Nonspecific binding was equated with the clearance of inulin.

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Table 1. Effect of ovariectomy on BW and KW in DR and DS rats maintained on NS and HS diets

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>NS BW, g</th>
<th>NS KW, g</th>
<th>HS BW, g</th>
<th>HS KW, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR-Sham</td>
<td>226±4.7</td>
<td>0.86±0.02</td>
<td>232±4.1</td>
<td>1.05±0.03</td>
</tr>
<tr>
<td>DR-OVX</td>
<td>276±11*</td>
<td>0.85±0.01</td>
<td>269±7.3*</td>
<td>1.02±0.03</td>
</tr>
<tr>
<td>DR-OVX + E2</td>
<td>200±2.5*</td>
<td>0.88±0.02</td>
<td>213±2.2</td>
<td>1.11±0.02</td>
</tr>
<tr>
<td>DS-Sham</td>
<td>252±3.8*</td>
<td>0.87±0.02</td>
<td>235±13</td>
<td>1.26±0.09</td>
</tr>
<tr>
<td>DS-OVX</td>
<td>294±4.0*</td>
<td>0.91±0.01</td>
<td>297±5.1*</td>
<td>1.37±0.03</td>
</tr>
<tr>
<td>DS-OVX + E2</td>
<td>211±4.6*</td>
<td>1.1±0.07</td>
<td>229±6.1</td>
<td>1.71±0.08</td>
</tr>
</tbody>
</table>

Body weight (BW) and kidney weight (KW) values are means ± SE; rats were sham-operated (sham, n = 9 to 10) or ovariectomized (OVX, n = 9 to 10) and treated with vehicle (Sham, OVX) or 17β-estradiol (E2) (OVX + E2, n = 9 to 10) for 2 wk. HS, high-sodium diet; DS, Dahl salt-sensitive rats. *P < 0.05 compared with Sham (same strain, same diet); †P < 0.05 compared with Dahl salt-resistant (DR) rats (same treatment group, same diet); ‡P < 0.05 compared with normal-sodium (NS) diet (same strain, same treatment group).

RESULTS

Body weight. At the start of the study, the DR (212 ± 4.4 g) animals weighed ~10% less than the DS (235 ± 3.6 g) rats. There was no effect of the 2-wk NS or HS diet on BW in either the DR-Sham or DS-Sham animals (Table 1). Ovariectomy increased BW by 1.2-fold in both rat strains compared with their respective sham-operated controls under both NS and HS conditions and E2 treatment prevented the ovariectomy-induced BW gain in the DR and DS rats on either diet (Table 1). Under the NS conditions, the BW gains in the OVX + E2 groups were 12% (DR) and 16% (DS) less than their respective sham controls (Table 1). In contrast, under HS conditions, there were no significant differences in BW between sham-operated and OVX + E2 groups within either rat strain (Table 1).

Kidney weight. After 2 wk on a HS diet, kidney weight (KW) in the DR-Sham rats was 1.2-fold higher compared with KW in the NS-diet treatment group. The KW in the DS-Sham animals was even greater (1.4-fold) on the HS diet compared with the NS-diet treatment group (Table 1). Ovariectomy had no effect on KW in either rat strain on either the NS or HS diets compared with their respective sham-operated controls (Table 1).

Mean arterial pressure. Two weeks after maintenance on a NS diet, DR-Sham and DS-Sham rats exhibited indistinguishable MAP (Table 2). Although ovariectomy had no detectable effect on MAP compared with sham-operated controls in DR rats on a NS diet, it did increase MAP in DS animals, although by only 6 mmHg (Table 2). This BP-raising effect of ovariectomy in DS rats was prevented by E2 treatment, and there was no significant difference in MAP between DS-Sham and DS-OVX + E2 animals under these NS dietary conditions (Table 2). Whereas the MAP in the DS-Sham rats was 11 mmHg higher on the HS compared with NS diet, there was no effect of dietary sodium on MAP in the DR-Sham animals. On the HS diet, ovariectomy increased the MAP in the DS rats by 22 mmHg and by 10 mmHg in the DR animals (Fig. 1). Under HS conditions, E2 treatment prevented the ovariectomy-induced increases in MAP in DR and DS rats (Fig. 1). There were no
significant differences in MAP between Sham and OVX + E₂ on a HS diet; however, the MAP was significantly lower within either strain of DR animals compared with the DR rats in all three treatment groups (Fig. 1).

Glomerular filtration rate. There were no differences in GFR between DR-Sham and DS-Sham rats maintained on a NS diet (Table 2). Two weeks of a HS diet had no effect on GFR in the DR-Sham animals but markedly reduced GFR in the DS-Sham rats by 30% [GFR (HS/NS): DR-Sham, 1.24 ± 0.16 vs. DS-Sham, 0.70 ± 0.03; $P < 0.05$]. Ovariectomy had no effect on GFR in both rat strains maintained on a NS diet (Table 2). In contrast, on a HS diet, ovariectomy increased GFR in DR rats by 1.4-fold and in DS animals by 1.5-fold compared with their respective sham-operated controls (Fig. 2). This ovariectomy-induced increase in GFR on the HS diet was prevented by E₂ treatment in both rat strains, and there were no significant differences in GFR between Sham and OVX + E₂ animal groups within either strain (Fig. 2).

AT₁R density. Two weeks after maintenance on a NS diet, AT₁R expression was 1.4-fold higher in glomeruli from DS-Sham compared with DR-Sham animals (Table 2). Maintenance on a HS diet for 2 wk did not increase glomerular AT₁R densities in either rat strain [AT₁R $B_{\text{max}}$ (HS/NS): DR-Sham, 1.03 ± 0.03; DS-Sham, 1.15 ± 0.09]. On a NS diet, ovariectomy had no effect on glomerular AT₁R densities in either the DR and DS rats compared with their respective sham controls (Table 2). In contrast, after 2 wk on a HS diet, ovariectomy increased glomerular AT₁R densities by 1.3-fold in the DR rats but not in the DS animals though glomerular AT₁R expression remained 16% higher in the OVX group of the DS strain compared with the OVX group of the DR animals (Fig. 3). E₂ treatment prevented this ovariectomy-induced increase in AT₁R densities in the DR rats on the HS diet, and there were no significant differences in AT₁R densities between DR-Sham and DR-OVX + E₂ under these HS dietary conditions (Fig. 3). There were no differences in glomerular AT₁R affinities between DR-Sham and DS-Sham rats on either the NS or HS diet.

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**Table 2. Effect of ovariectomy on MAP, GFR, and glomerular AT₁R densities in DR and DS rats maintained on NS diet**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>MAP, mmHg</th>
<th>GFR, ml/min−1 g KW−1</th>
<th>Glomerular AT₁R, fmol/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR-Sham</td>
<td>122 ± 4</td>
<td>2.20 ± 0.31</td>
<td>558 ± 22</td>
</tr>
<tr>
<td>DR-OVX</td>
<td>125 ± 2</td>
<td>2.49 ± 0.20</td>
<td>611 ± 33</td>
</tr>
<tr>
<td>DR-OVX + E₂</td>
<td>112 ± 5</td>
<td>1.97 ± 0.25</td>
<td>455 ± 20</td>
</tr>
<tr>
<td>DS-Sham</td>
<td>129 ± 5</td>
<td>2.46 ± 0.060</td>
<td>782 ± 32†</td>
</tr>
<tr>
<td>DS-OVX</td>
<td>135 ± 4*</td>
<td>2.54 ± 0.13</td>
<td>759 ± 27†</td>
</tr>
<tr>
<td>DS-OVX + E₂</td>
<td>132 ± 2†</td>
<td>1.96 ± 0.040</td>
<td>798 ± 40†</td>
</tr>
</tbody>
</table>

Values are means ± SE of the mean arterial pressure (MAP; $n = 9$ to 10 rats/group), glomerular filtration rate (GFR; $n = 9$ to 10 rats/group), and glomerular ANG II type 2 receptor (AT₁R) densities ($n = 4–6$ rats/group). Rats were Sham or OVX and treated with vehicle (Sham, OVX) or E₂ (OVX) for 2 wk. *$P < 0.05$ compared with Sham (same strain); †$P < 0.05$ compared with DR (same treatment group).
diets, and there was no effect of dietary sodium or ovariectomy on receptor affinities within the same rat strain (data not shown).

In the adrenal, AT1R densities were substantially lower in the OVX + E2 animal group compared with the OVX rats within both the DR or DS rat strains, and this effect of E2 treatment was observed under both NS and HS diets (Table 3). When compared with the E2-replete rats, adrenal AT1R densities in the E2-deficient animals were 2-fold higher in the DR rat and 1.4-fold higher in the DS rat on the NS diet. Similarly, under HS conditions, the E2-deficient animals had 1.6-fold (DR) and 1.5-fold (DS) higher densities than the E2-replete animals (Table 3).

**Estrogen receptor-α.** Two weeks after maintenance on a HS diet, ER-α protein expression in the renal cortex was 45% lower in the DS compared with the DR sham-operated animals (Fig. 4). When compared with their respective sham-operated controls, renal ER-α protein expression was substantially less in both the DR (57% of control) and DS-OVX (68% of control) rats. Furthermore, the renal expression of ER-α protein in the DS-OVX group was 34% lower in the DS strain compared with the DR strain (Fig. 4). E2 treatment prevented the ovariectomy-induced decreases in renal ER-α expression, and there were no significant differences between the Sham and OVX + E2 treatment groups within either rat strain under these conditions (Fig. 4).

**DISCUSSION**

We previously showed that ovariectomy increased MAP in DS rats maintained on a LS diet for 4 mo compared with the Sham and OVX + E2 treatment groups (14). Studies in DS animals maintained on a NS diet for 14 wk also demonstrated that ovariectomy increased MAP (12), and a study conducted in DS rats maintained for 2 wk on a HS diet found that ovariectomy increased MAP compared with intact animals (15). Our findings extend these previous observations by demonstrating that increasing dietary sodium from a NS to HS diet augmented the effects of ovariectomy on MAP in both DR and DS rats. The BP-raising effect of ovariectomy was greater in DS animals maintained on a HS diet compared with those maintained on a NS diet. Furthermore, whereas ovariectomy had no effect on MAP in DR rats maintained on a NS diet, on a HS diet, ovariectomy significantly increased the MAP in this salt-resistant strain. These findings are consistent with studies in numerous other animal models. Ovariectomy increased BP in transgenic rats carrying the mouse Ren-2 gene (1), the mRen2.Lewis rat (3), the ANG II-infused mouse (26), and the deoxycorticosterone-salt hypertensive rat (5). Thus the BP-raising effects of ovariectomy are widely observed, although not in all animal models of hypertension, such as the spontaneously hypertensive rat (SHR) (23). The BP-raising effects of ovariectomy in DR and DS animals are likely due to the loss of E2 as a result of gonadectomy since E2 treatment prevented these effects in both rat strains.

As shown previously, the GFR was significantly reduced in DS rats maintained on a HS diet compared with the NS diet, whereas no significant effects of the HS diet on GFR were observed in the DR strain (7). What was surprising, however, was our finding that GFR was markedly increased by ovariectomy in both DR and DS rats maintained on a HS diet compared with their respective E2-replete intact or E2-treated OVX animals. These effects of ovariectomy on GFR could not be explained by changes in KW since ovariectomy had no effect on KW in either strain under both NS or HS conditions. These findings also indicate that the BP-raising effects of ovariectomy are not a result of reduced GFR. The fact that E2 treatment prevented this GFR-raising effect of ovariectomy suggests that the loss of E2 due to gonadectomy is responsible for the increase in GFR. E2 may modulate GFR by regulating renal blood flow or renal vascular resistance since both of these factors contribute to GFR. In contrast to these effects observed in DR and DS rats, ovariectomy reduced the GFR in the SHR compared with E2-replete SHR; however, in this same SHR study, ovariectomy had no effect on MAP (8). Taken together, these observations suggest that GFR can be modulated by ovariectomy in a manner that is independent of BP.

We previously showed that the ovariectomy-induced increase in MAP correlated with increased AT1R densities in the kidney compared with E2-replete intact or E2-treated OVX DS rats maintained on a LS diet (14). Likewise in this study, we found that the ovariectomy-induced increase in MAP in DR rats maintained on a HS diet correlated with higher AT1R densities in the glomeruli compared with E2-replete animals, whereas on the NS diet, both MAP and glomerular AT1R densities were not modulated by E2. This positive correlation

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Table 3. Effect of E2 replacement on adrenal AT1R densities in OVX DR and DS rats maintained on NS and HS diets

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>NS AT1R, fmol/mg protein</th>
<th>HS AT1R, fmol/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR-OVX</td>
<td>204±38</td>
<td>154±24</td>
</tr>
<tr>
<td>DR-OVX + E2</td>
<td>103±13*</td>
<td>94.8±9.2*</td>
</tr>
<tr>
<td>DS-OVX</td>
<td>117±7.3†</td>
<td>138±10</td>
</tr>
<tr>
<td>DS-OVX + E2</td>
<td>82.7±5.8*</td>
<td>90.2±9.9*</td>
</tr>
</tbody>
</table>

Values are means ± SE of the adrenal AT1R densities (n = 4-6 rats/group). Rats were OVX and treated with vehicle (OVX) or E2 for 2 wk. *P < 0.05 compared with OVX (same strain); †P < 0.05 compared with DR (same treatment group).
between MAP and glomerular AT\(_1\)R densities was lost in the DS rat when maintained on the NS diet but becomes aberrant when dietary sodium increases to the level present in a HS diet. This loss in E\(_2\) regulation of the glomerular AT\(_1\)R was tissue specific since E\(_2\) was able to modulate adrenal AT\(_1\)R densities in the DS rat in a manner similar to the DR rat under both NS and HS conditions. This finding of aberrant AT\(_1\)R regulation in the DS rat kidney may contribute to why AT\(_1\)R antagonists are able to attenuate the development of hypertension in the DS animal maintained on a LS diet but are less effective at preventing the development of hypertension on a HS diet (30).

One study found that ovariectomy increased the expression of immunoreactive AT\(_1\)R protein in kidney homogenates of the DS rat maintained on a NS diet (12). This finding coupled with our AT\(_1\)R binding data raises the possibility that ovariectomy increases the expression of AT\(_1\)R protein in the glomerular membrane but that these receptors are not functional and thus unable to bind ligand. Furthermore, since these immunoblots were performed in whole kidney homogenates, the possibility exists that the immunoreactive AT\(_1\)R protein is functionally sequestered and not available for ligand binding in the OVX kidney. Alternatively, the longer time course of this previous study (14 wk) compared with our 2-wk NS treatment may explain the differences in ability of ovariectomy to increase AT\(_1\)R expression in the DS rat.

The finding of aberrant regulation of the glomerular AT\(_1\)R is significant given the evidence that the kidney is a major contributor to salt sensitivity in the DS rat (4). We have previously shown in the adrenal that the ability of E\(_2\) to regulate AT\(_1\)R densities is dependent on the ability of E\(_2\) to modulate tissue levels of ANG II (25). A recent report suggests that ANG II levels are elevated in the kidney of DS rats maintained on a HS diet (17). Thus one possibility is that E\(_2\) loses its ability to regulate glomerular AT\(_1\)R densities in the DS rat when dietary sodium is increased above a certain threshold due to dietary sodium-induced increases in the renal tissue levels of ANG II.

Although we and others have previously shown that ovarectomy increases the degree of renal injury in DS rats, this renal damage takes weeks to occur (19). Therefore, it is unlikely that the ovariectomy-induced BP increase is due to glomerulosclerosis since our study was conducted after a 2-wk exposure to dietary sodium manipulation.

Under HS conditions, strain differences in MAP inversely correlated with strain differences in renal ER-\(\alpha\) protein expression. DS-Sham rats exhibited higher MAP and expressed lower levels of ER-\(\alpha\) in the renal cortex compared with DR-Sham rats. Renal ER-\(\alpha\) protein expression also inversely correlated with ovariectomy-induced increases in MAP in both rat strains. The fact that E\(_2\) replacement prevented this effect of gonadectomy suggests that renal ER-\(\alpha\) protein expression is modulated by E\(_2\). These findings raise the possibility that under HS conditions, ovariectomy increases MAP in both rat strains through the loss of renal ER-\(\alpha\)-mediated antihypertensive actions.

Inadequate nitric oxide (NO) production is thought to participate in the pathology of salt-sensitive hypertension in the DS rat, but “NO deficiency” is a relative term. It is likely that the degree of NO deficiency in the DS rat is greater in the ovariectomized female compared with the E\(_2\)-replete intact female or compared with the E\(_2\)-replaced ovariectomized female. This idea is supported by many studies showing that NO synthase activity in key target tissues including the kidney is upregulated by E\(_2\) (13). Furthermore, E\(_2\) has multitudinous effects in the DS rat that could contribute to its ability to attenuate the adverse effects of NO deficiency on MAP, such as the ability of the hormone to reduce superoxide production (27), lower ANG II levels (12), and improve vascular reactivity in renal arteries (28).

A recent study supports our finding that ovariectomy down-regulates ER-\(\alpha\) protein expression in the DS renal cortex; however, the same study, which was conducted in animals maintained on a LS diet for 8 wk, showed that ER-\(\alpha\) expression was greater in the DS rat compared with the DR animal (6). Thus ER-\(\alpha\) expression in the kidney may be differentially regulated by dietary sodium.

In conclusion, this study demonstrates that the ability of ovariectomy to increase MAP is augmented by a HS diet in both DR and DS rats. This BP-raising effect of ovariectomy is not explained by an attenuation in GFR since ovariectomy actually increased GFR in both rat strains. In contrast to the DR animal, E\(_2\) was unable to downregulate the density of glomerular AT\(_1\)Rs in the DS rat kidney maintained on HS conditions. This lack of effect on AT\(_1\)Rs was specific to the kidney since E\(_2\) was able to downregulate AT\(_1\)Rs in the DS renal cortex. This aberrant regulation of the renal AT\(_1\)R may reflect why MAP in the hypertensive DS rat is resistant to AT\(_1\)R antagonists. The inverse correlation between MAP and renal ER-\(\alpha\) protein expression that we observed in both rat strains suggests that ER-\(\alpha\) could play a role in the antihypertensive effects of E\(_2\) in the E\(_2\)-replete female rat. The clinical significance of these findings is that the incidence of hypertension increases significantly after menopause, and salt-sensitive BP is associated with an increased risk for becoming hypertensive. This study also raises the possibility that aberrant upregulation of the glomerular AT\(_1\)R by dietary sodium and reduced renal ER-\(\alpha\) protein expression may contribute to this disease process in salt-sensitive hypertension.

GRANTS

This research was supported by an American Heart Association Beginning Grant-in-Aid (to H. Ji) and National Institutes of Health Grants HL-57502 and AG-19291 (to K. Sandberg).

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