Sex and Gender Differences in Renal Physiology

Sex- and age-related differences in the chronic pressure-natriuresis relationship: role of the angiotensin type 2 receptor

Katrina M. Mirabito,1 Lucinda M. Hilliard,1 Michelle M. Kett,1 Russell D. Brown,1 Sean C. Booth,1 Robert E. Widdop,2 Karen M. Moritz,3 Roger G. Evans,1 and Kate M. Denton1

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Mirabito KM, Hilliard LM, Kett MM, Brown RD, Booth SC, Widdop RE, Moritz KM, Evans RG, Denton KM. Sex- and age-related differences in the chronic pressure-natriuresis relationship: role of the angiotensin type 2 receptor. Am J Physiol Renal Physiol 307: F901–F907, 2014. First published August 27, 2014; doi:10.1152/ajprenal.00288.2014.—Sex hormones regulate the renin-angiotensin system. For example, estrogen enhances expression of the angiotensin type 2 receptor. We hypothesized that activation of the angiotensin type 2 receptor shifts the chronic pressure-natriuresis relationship leftward in females compared with males and that this effect is lost with age. Mean arterial pressure was measured by radiotelemetry in adult (4 mo old) and aged (14 mo old) wild-type and angiotensin type 2 receptor knockout male and female mice. Chronic pressure-natriuresis curves were constructed while mice were maintained on a normal-salt (0.26%) diet and following 6 days of high salt (5.0%) diet. Mean arterial pressure was lower in adult wild-type females than males (88 ± 1 and 97 ± 1 mmHg, respectively), a difference that was maintained with age, but was absent in adult knockout mice. In wild-type females, the chronic pressure-natriuresis relationship was shifted leftward compared with knockout females, an effect that was lost with age. In males, the chronic pressure-natriuresis relationship was not influenced by angiotensin type 2 receptor deficiency. Compared with age-matched females, the chronic pressure-natriuresis relationships in male mice were shifted rightward. Renal expression of the angiotensin type 2 receptor was fourfold greater in adult wild-type females than males (33, 43). This age-related increase in arterial pressure is also observed in female spontaneously hypertensive rats (SHR) (12). However, the underlying mechanisms are not fully understood.

The renin-angiotensin system (RAS) contributes to the long-term regulation of arterial pressure by modulating pressure-natriuresis (16). We, and others, have previously demonstrated that estrogen shifts the balance of the RAS, decreasing expression of the angiotensin type 1 receptor (AT1R), while increasing expression of the angiotensin type 2 receptor (AT2R), angiotensin-converting enzyme 2 (ACE2), and the Mas receptor (MasR) (1, 5, 39). Furthermore, renal expression of the AT2R is decreased by ovariectomy (OVX) and increased by estrogen supplementation (2, 27, 30). These observations support the hypothesis that activation of the AT2R lowers arterial pressure in females and that this effect is lost with reproductive senescence (19). While it is known that expression of the AT1R increases with age in humans and rodents (6, 22, 45), few studies have investigated the influence of aging on expression of the AT2R.

The acute pressure-natriuresis relationship in females is shifted leftward compared with males, such that females excrete the same amount of sodium at a lower arterial pressure (25, 35). We have previously reported that, in anesthetized adult rats, the AT1R modulates the acute pressure-natriuresis relationship in both males and females (20). However, whether this AT2R-mediated effect changes with age is yet to be determined. Given that estrogen enhances expression of the AT2R, an age-related shift in the balance of the RAS may promote a rightward shift of the pressure-natriuresis relationship in reproductively senescent females. Such phenomena are best studied by assessing the chronic pressure-natriuresis relationship, so that neural and hormonal control of kidney function remain intact.

The two aims of the current study were 1) to determine whether the AT2R modulates the chronic pressure-natriuresis relationship to a similar extent in adult male and female mice and 2) to investigate the role of the AT2R in the chronic pressure-natriuresis relationship in aging mice. We hypothesized that the AT2R shifts the chronic pressure-natriuresis relationship to the left in females, compared with males, and that this sex difference is lost with age. To address our hypothesis, we assessed the relationship between mean arterial pressure (MAP) and sodium excretion in adult and aged wild-type (WT) and AT2R knockout (AT2R-KO) male and female mice during conditions of normal and high sodium intake.
METHODS

Experiments were conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and approved by the Monash University School of Biomedical Sciences Animal Ethics Committee. Male and female FVB/N WT and AT$_2$R-KO mice, initially established by Hein et al. (17), were obtained at 3 mo of age from Monash Animal Services. Animals were housed in an experimental room with the temperature maintained at 24–26°C and a 12:12-h light-dark cycle.

Diets. Mice had ad libitum access to water and food. Mice were maintained on a semipurified standard rodent maintenance diet (normal salt, 0.26% NaCl wt/wt; AIN93M, Specialty Feeds), based on a formulation developed by the American Society of Nutritional Sciences (36). Because the ingredients in semipurified diets are refined, the nutrient levels are closely controlled and replicable across batches, making them ideal for studies of the effects of dietary modification.

The high-salt diet is a specially modified version of the standard rodent diet containing a higher salt content (5.0% salt modified AIN93M, Specialty Feeds), with all other ingredients the same as in the standard rodent diet. In addition, samples of the diets are routinely ashed to ensure the vitamin and mineral content are as specified.

Mice had ad libitum access to water and food. Mice were divided into 10 experimental groups: adult (4 mo old) male WT, male AT$_2$R-KO, and female WT and AT$_2$R-KO, and aged (14 mo old) male WT, male AT$_2$R-KO, female WT, female AT$_2$R-KO, and female aged-OVX WT and aged-OVX AT$_2$R-KO mice ($n = 6–8/group$). OVX was performed at 12 mo of age, as described previously (38). Vaginal smears confirmed that the aged mice were in persistent estrus before the start of the study.

Animal model. Mice were anesthetized (2.2–2.6% isoflurane in 40% O$_2$–60% N$_2$, Rhodia), and a radiotelemetry probe (PA-PackTech) was inserted. Baseline food and water intake was measured for 3 days, followed by 24-h urine collection. The kidneys were collected, weighed, and frozen snap frozen. RNA was extracted from the kidney using an RNeasy Mini kit (Qiagen, Doncaster, Victoria, Australia). Expression of the Renal AT$_1$aR, AT$_1$bR, AT$_2$R, MasR, and ACE2 genes was analyzed by quantitative RT-PCR Realplex software with the Applied Biosystems 7900HT Fast RT-PCR system (Applied Biosystems, Life Technologies). Samples were run in triplicate using TaqMan gene expression assays (Applied Biosystems) with 18S rRNA as the internal housekeeping gene. Reactions were setup on a 384-well PCR plate using an automated liquid handler (CASY-1200 liquid handler, Qiagen). Relative expression was calculated using the comparative cycle of threshold fluorescence ($2^{-\Delta\Delta CT}$) method, as described previously (40).

Statistical analyses. Data are presented as means ± SE. Data were analyzed using a one-way ANOVA. Where appropriate, a post hoc analysis with Tukey’s test or with selected post hoc t-tests with Holm-Sidak correction to reduce the risk of type 1 error associated with multiple comparisons were performed. Pressure-natriuresis relationships were compared using analysis of covariance (ANCOVA) with the categorical factors sex, age, genotype, or OVX as appropriate, sodium excretion as the covariate, and MAP as the dependent variable. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

MAP. MAP was significantly lower (~9 mmHg) in adult female compared with adult male WT mice on a normal-salt diet (Fig. 1; $P < 0.01$). In contrast, there was no significant difference in MAP between the adult male and adult female AT$_2$R-KO mice (Fig. 1). In female mice, MAP was greater in the adult AT$_2$R-KO than the adult WT female mice (94 ± 2 vs. 88 ± 1 mmHg, $P = 0.04$). MAP was significantly higher in aged male than adult male mice, and this age-dependent increase was apparent in both the WT and AT$_2$R-KO male mice (Fig. 1) (both $P < 0.05$). In female mice, MAP was not significantly different between adult, aged, or aged-OVX in the WT or AT$_2$R-KO groups (Fig. 1). MAP was significantly greater in aged male than aged female mice in both WT and AT$_2$R-KO groups (Fig. 1) (both $P < 0.01$).

The high-salt diet increased MAP in all groups (5–13 mmHg, all $P < 0.05$), except the male adult WT and AT$_2$R-KO mice (Fig. 1; 1–2 mmHg mean difference) ($P \geq 0.05$). Aged male mice demonstrated an enhanced pressor response to high salt intake compared with adult mice, with MAP increasing $13 ± 1$ mmHg ($P < 0.001$) in the aged WT males and $10 ± 2$ mmHg ($P < 0.001$) in the aged AT$_2$R-KO males. MAP in adult female mice was more salt sensitive than in adult male mice, irrespective of genotype (Fig. 1) (both $P < 0.05$). However, the salt sensitivity of MAP in female mice was independent of genotype, age, or OVX (Fig. 1).

Renal excretory function. There were no significant differences in water intake or sodium intake between the groups on the normal-salt diet. Urine flow and sodium excretion were not significantly different between the WT or AT$_2$R-KO mice on a...
normal-salt diet (Tables 1 and 2, respectively). As would be expected, when mice were placed on the high-salt diet their sodium intake and excretion, as well as their water intake and urine flow, markedly increased. This phenomenon was observed in all WT and AT2R-KO mice (compared with the normal-salt diet; Tables 1 and 2, respectively).

On a normal-sodium diet, albumin excretion was not significantly different between male and female mice for either genotype (Fig. 2). In response to high-salt diet, albuminuria was significantly increased in the male groups and aged AT2R-KO female mice (Fig. 2). Moreover, the increase in albumin excretion in response to the high-salt diet was greater in male than female mice (Fig. 2). The increase in albuminuria in response to high salt intake was similar across the various groups of female mice. Urine albumin levels were not determined in the aged-OVX mice.

**Chronic pressure-natriuresis.** The chronic pressure-natriuresis relationship for adult WT female mice was shifted to the left compared with that of adult WT male mice (Fig. 3) \((P_{\text{sex}} = 0.001)\). In adult male mice, the chronic pressure-natriuresis relationship did not differ significantly according to genotype (WT or AT2R-KO; Fig. 3) \((P_{\text{genotype}} = 0.2)\). In contrast, in female mice AT2R deficiency shifted the chronic pressure-natriuresis relationship to the right of the relationship for WT adult females \((P_{\text{genotype}} = 0.004)\). Consequently, the chronic pressure-natriuresis relationship in adult female AT2R-KO mice was not significantly different from that of the adult male mice of either genotype (Fig. 3).

With age, there was a significant rightward shift of the chronic pressure-natriuresis relationship in males \((P_{\text{age}} = 0.001)\), which was of a similar magnitude in AT2R-KO and WT mice \((P_{\text{genotype}} = 0.1)\). In aged WT females, the chronic pressure-natriuresis relationship was shifted rightward compared with that in their younger adult counterparts \((P_{\text{age}} = 0.008)\). However, the chronic pressure-natriuresis relationship of aged females was still shifted leftward compared with aged-matched males \((P_{\text{sex}} = 0.001)\). AT2R-KO \((P_{\text{genotype}} = 0.3)\) or OVX \((P_{\text{OVX}} = 0.1)\) did not significantly shift this relationship in aged females (Fig. 3). Moreover, construction of chronic pressure-natriuresis relationships demonstrated a significant change in the slope of the relationship in aged males compared with adult males, which was not apparent in females.

**Renal expression of components of the RAS.** In females on a normal-salt diet, expression of AT1aR, AT2R, ACE2, and MasR genes was greater than that observed in corresponding male mice (Figs. 4 and 5). Expression of the gene for the AT1aR was similar in all groups (WT and AT2R-KO), except for aged WT female mice, in which AT1aR expression was twofold greater than all other groups (Fig. 4). In females, expression of the gene for the AT1aR was slightly lower in aged compared with adult mice \((P = 0.04)\) (Fig. 4) and was not further affected by OVX \((P = 0.8)\). Expression of the gene for the AT1aR was less in aged-OVX mice than in aged female mice \((P = 0.0003)\) (Fig. 4). In males, expression of the gene for the MasR was greater in AT2R-KO mice than WT mice (Fig. 4).

### Table 1. Body weight and 24-h renal excretory data of adult male, aged male, adult female, aged female, and aged-OVX female WT mice in response to a normal-salt diet and following 6 days of a high-salt diet

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<td>Adult</td>
<td>Aged</td>
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<tr>
<td>Body weight, g</td>
<td>NS</td>
<td>31 ± 1</td>
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<tr>
<td>Diuresis, ml/24 h</td>
<td>NS</td>
<td>0.7 ± 0.1</td>
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<tr>
<td>Sodium excretion, mmol/24 h</td>
<td>NS 0.09 ± 0.01</td>
<td>0.09 ± 0.01</td>
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<td>Osmolar excretion, mmol/24 h</td>
<td>NS 1.9 ± 0.2†</td>
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Values are means ± SE \((n = 7–9/group)\). NS, normal-salt diet; HS, high-salt diet; OVX, ovariectomized; WT, wild-type. Data were analyzed using 1-way ANOVA followed by 15 planned post hoc comparisons by Student’s unpaired t-tests with the Holm-Sidak correction to reduce the risk of type 1 error. *\(P < 0.05\) vs. male counterpart. †\(P < 0.05\) vs. NS counterpart. §\(P < 0.05\) vs. aged counterpart.

### Table 2. Body weight and 24-h renal excretory data of adult male, aged male, adult female, aged female, and aged-OVX female AT2R-KO mice in response to a normal-salt diet and following 6 days of a high-salt diet

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<th>Male</th>
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<td></td>
<td>Adult</td>
<td>Aged</td>
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<tr>
<td>Body weight, g</td>
<td>NS</td>
<td>32 ± 1</td>
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<tr>
<td>Diuresis, ml/24 h</td>
<td>NS</td>
<td>0.8 ± 0.1</td>
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<tr>
<td>Sodium excretion, mmol/24 h</td>
<td>NS 2.6 ± 0.2†</td>
<td>2.8 ± 0.2†</td>
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<tr>
<td>Osmolar excretion, mmol/24 h</td>
<td>NS 1.5 ± 0.3</td>
<td>1.9 ± 0.1</td>
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Values are means ± SE \((n = 7–9/group)\). AT2R-KO, angiotensin type 2 receptor knockout. Data were analyzed using 1-way ANOVA followed by 15 planned post hoc comparisons by Student’s unpaired t-tests with the Holm-Sidak correction to reduce the risk of type 1 error. *\(P < 0.05\) vs. male counterpart. †\(P < 0.05\) vs. adult counterpart. ‡\(P < 0.05\) vs. NS counterpart.
In male and female AT2R-KO mice and male WT mice, expression of AT1aR, AT1bR, AT2R, ACE2, and MasR genes were similar in mice placed on a high-salt diet relative to those on a normal-salt diet (Figs. 4 and 5). However, in adult WT females, expression of the gene for the AT1aR was increased ~100% in mice on a high-salt diet compared with those on a normal-salt diet ($P < 0.002$) (Fig. 4). In contrast, in aged WT females, expression of the gene for the AT1aR was 50% lower in mice on a high-salt diet than in those on a normal-salt diet ($P < 0.003$) (Fig. 4). In both intact and OVX aged WT females, ACE2 gene expression was ~50% lower in mice on a high-salt diet than in those on a normal-salt diet (both $P < 0.01$) (Fig. 5). In aged-OVX WT females, expression of the gene for the AT2R tended to be lower (~45%) when on a high-salt diet than when on a normal-salt diet ($P = 0.08$) (Fig. 4).

**DISCUSSION**

There were three major findings of the present study. First, the chronic pressure-natriuresis relationship of WT females was shifted leftward, such that females excreted the same amount of sodium as males but at a lower arterial pressure. Second, in adult females, but not aged females, absence of the AT2R was associated with a rightward shift of the chronic pressure-natriuresis relationship. Conversely, in males the chronic pressure-natriuresis relationship was similar in WT and AT2R-KO mice, regardless of age. To the best of our knowledge, this is the first study to demonstrate that, in a chronic setting, the AT2R modulates pressure-natriuresis in a sex- and age-dependent manner. Last, renal expression of the gene for the AT2R was decreased with age in WT females. Taken together, these data indicate that the AT2R contributes to regulation of arterial pressure in adult females by modulating the gene for the AT2R.
the chronic pressure-natriuresis relationship and that this protection is lost with age.

In the present study, WT females had lower arterial pressure than age-matched WT males. This finding is consistent with evidence from clinical and experimental studies that arterial pressure is lower in females than males of reproductive age (21, 44). Moreover, this sex difference in arterial pressure was still apparent at 14 mo of age. Previous studies have demonstrated that aged mice enter reproductive senescence, which is characterized by persistent estrus, by 11–16 mo of age (9, 28). Consistent with these findings, we confirmed using serial vaginal smears, that our cohort of aged mice had entered reproductive senescence by 11–16 mo of age. Previous studies have demonstrated that aged mice enter reproductive senescence, which is characterized by persistent estrus, by 11–16 mo of age (9, 28). Consistent with these findings, we confirmed using serial vaginal smears, that our cohort of aged mice had entered reproductive senescence by 11–16 mo of age. However, it has been demonstrated in aged female SHR, which cease regular estrus cycling at ~10 mo of age, that arterial pressure rises to match that of males at 18 mo of age (12, 34). In accordance with this finding, we have recently observed a similar increase in arterial pressure in 18-mo-old female mice, such that arterial pressure in females matches that measured in male mice (Mirabito et al., unpublished data unpublished observations). Thus there appears to be a time lag between reproductive senescence and the increase in arterial pressure in aged female rodents.

Our current data support the hypothesis that activation of the AT2R acts to shift the chronic pressure-natriuresis relationship to the left in female mice and that this effect is lost with age. Considering that the AT2R modulates natriuresis and that AT2R expression is increased by estrogen (1, 31), loss of AT2R expression and/or activation in aged females appears to play a pivotal role in the resetting of the chronic pressure-natriuresis relationship. Furthermore, it is well established that the AT2R exerts its actions through a pathway mediated by nitric oxide (NO) (7). Given that NO opposes the renal actions of ANG II, it is plausible that greater activation of the renal AT2R in adult females contributes to the functional role of NO in female kidneys as well as slowing the progression of age-dependent NO deficiency and renal dysfunction (3, 4). Consistent with this hypothesis, the salt sensitivity of arterial pressure increased with age in male, but not female, mice. In contrast, previous studies have provided evidence that arterial pressure in females becomes more salt sensitive with age (8, 22, 32). However, this may reflect the timing of the studies, as cardioprotection in females has been shown to persist for a number of years postmenopause.

Remarkably, we could not detect an effect of the AT2R on the chronic pressure-natriuresis relationship in males. This finding contrasts with those of previous studies demonstrating that the AT2R modulates the acute pressure-natriuresis relationship in males, and moreover, that the AT2R tonically modulates natriuresis to a similar extent in males and females (14, 18, 20, 42). The discrepancy between these findings may be related to the experimental setting. In the present study, chronic pressure-natriuresis relationships were constructed by manipulating dietary sodium intake and observation of the resultant effect on MAP in unanesthetized mice. In contrast, acute pressure-natriuresis relationships are constructed by manipulating renal artery pressure in anesthetized animals and observing the resultant change in sodium excretion. Importantly, the chronic pressure-natriuresis relationship is generated under physiological conditions and incorporates neurohumoral changes that occur as part of the integrated response to altered dietary sodium intake.

The chronic pressure-natriuresis relationship in aged males was shifted to the right of that of adult males. In males, testosterone shifts the acute pressure-natriuresis relationship to the right, castration shifts the acute pressure-natriuresis relationship to the left, and androgen receptor blockade lowers arterial pressure (35). Given that it has been previously demonstrated that testosterone levels increase with age in male SHR (11), increased circulating levels of testosterone could drive the rightward shift in the chronic pressure-natriuresis relationship we observed in aged male mice. Moreover, elevated testosterone levels in aged male SHR are also associated with increased proteinuria, a marker of renal injury (11). Consistent with this, aged males had greater urinary albumin excretion in response to a high-salt diet than adult males. Albuminuria was also present in the aged females, but to a lesser extent. Moreover, it has been reported previously that albuminuria is greater with OVX in aged SHR (12). Thus both testosterone and estrogen appear to influence renal injury. Interestingly, expression of the gene for the MasR was greater in male AT2R-KO than male WT mice. Enhanced MasR expression may explain why male AT2R-KO mice do not have greater basal arterial pressure than their WT counterparts. Moreover, these data suggest that the ACE2/Ang(1–7)/MasR pathway may play a prominent role in modulating the chronic pressure-natriuresis relationship in AT2R-KO males.

Since we could not reliably measure plasma estrogen levels, an aged-OVX cohort was included in the study. Although we did not detect differences between aged-intact and aged-OVX females with respect to AT2R expression or the chronic pressure-natriuresis relationship, AT1aR expression was greater in...
aged-intact than aged-OVX females. Thus an aged-OVX animal is not equivalent to an aged-intact animal. Our conclusion is supported by previous observations of differential effects of OVX in the adult, OVX in aged animals, and aging alone (8, 12).

As has been observed previously, adult WT females had greater renal gene expression of the depressor components of the RAS (AT1R, ACE2, and MasR) than males (1, 39). While there were no significant changes in expression of the genes for ACE2 or MasR with age in females, expression of the gene for the AT2R was 35% lower in aged than adult WT females. In contrast, expression of the gene for the AT1aR was increased 115% with age in WT female mice. The age-dependent increase in AT1aR expression is consistent with previous observations from studies of postmenopausal women and rodents (22, 24, 45). Consequently, with age, the balance of the renal RAS appears to be shifted toward the pressor RAS in WT female mice.

Given that the impact of the AT2R on the chronic pressure-natriuresis relationship was lost in reproductively senescent female mice, it is tempting to speculate that loss of the protective effects of AT2R activation may contribute to the increase in arterial pressure observed in postmenopausal women. It is known that the chronic pressure-natriuresis relationship is shifted rightward after menopause (32) and that plasma renin activity is increased (10, 41). This suggests that activation of the pressor RAS is enhanced in postmenopausal women. However, to the best of our knowledge, neither AT2R expression, nor expression of other components of the depressor RAS, have been measured in postmenopausal women. Moreover, there is little functional information from animal studies about the role of the AT2R during aging. The only observation of diminished AT2R expression in aged female mice was seen in response to vascular injury in the femoral artery (29). In female SHRs, renal AT2R expression appears to change little with age (29, 47).

We must acknowledge some limitations of our study. First, we cannot exclude the possibility that our findings were confounded by changes in renal development associated with the absence of the AT2R. However, previous studies have documented the absence of renal abnormalities in AT2R-KO mice (14, 17, 23). Second, plasma concentrations of estrogen in mice are below the limit of detection of commercially available assays, so we were unable to measure circulating estrogen levels in the mice we studied. Third, we did not include an adult-OVX group. Therefore, we cannot conclude that the rightward shift of the chronic pressure-natriuresis relationship in aging female WT mice was solely attributable to changes in ovarian hormone production. Rather, it is likely that the rightward shift of the chronic pressure-natriuresis relationship in aging females is multifactorial. Indeed, age-related increases in the levels of vasoconstrictor factors (e.g., endothelin-1 and reactive oxygen species) and their receptors (e.g., AT1R), may occur independently of alterations in ovarian hormone production (46). Finally, we assessed sodium intake and excretion on only two occasions, rather than continuously during the experiment. The first 24-h urine sample was collected while mice were maintained on their standard diet. Thus by definition they were in sodium balance. Furthermore, chronic metabolic balance studies, in which sodium was delivered intravenously, demonstrated that sodium intake and output are in equilibrium 2–3 days after a switch from normal to high salt intake in mice (26). Because our second urinary measurement was collected 6 days after a switch from a normal-salt diet to a high-salt diet, we can be confident our animals were in sodium balance.

The AT2R mediates a leftward shift in the chronic pressure-natriuresis relationship in adult females compared with males, and this effect is lost with age. Therefore, the AT2R appears to modulate the chronic pressure-natriuresis relationship in a sex- and age-specific manner. Consequently, age-related deficits in AT2R expression and/or signaling may contribute to the pathophysiology of hypertension in postmenopausal women. Restoration of AT2R expression levels in older women or upregulation of the AT2R in men may represent a novel target for antihypertensive therapy.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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