Minearlcoriect receptor activation: a major contributor to salt-induced renal injury and hypertension in young rats

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Salt consumption among very young children has increased in developed countries at a faster rate than in developing countries (9, 28, 33). It is believed that high salt (HS) intake in life.

Recent studies have suggested that salt-induced kidney injury is mediated by mineralocorticoid receptor (MR) activation. In Dahl SS rats, although salt loading suppressed plasma aldosterone, salt-induced kidney injury was ameliorated by MR antagonist treatment (20). Serum- and glucose-regulated kinase (Sgk1) has also been shown to be upregulated in the kidneys of salt-loaded Dahl SS rats (2). In obese spontaneously hypertensive rats (SHR), SHR/Ndmp-cps, a model of metabolic syndrome, salt-induced increases in urinary protein are ameliorated by MR blockade (19). Thus MR activation may contribute to renal injury with HS intake in SS hypertension.

In addition, we previously demonstrated that an MR antagonist suppressed the salt-induced progression of hypertension and kidney injury in young Dahl SS rats, even after the discontinuation of the drug (8). The Framingham Offspring Study (31) showed that in people with HS intake, greater plasma aldosterone levels were associated with hypertension after a 4-yr follow-up. Interestingly, studies in rats and humans have shown that the renin-angiotensin-aldosterone (RAA) system is highly activated in newborns compared with adults (7, 30, 34).

Although the precise functions of this system are not known, the upregulation of the RAA system is crucial for the development of nephrons in newborns (15) and counterbalances the body water loss (22) to which newborns are susceptible. However, the upregulation of RAA activity may also weaken protective mechanisms against high BP and kidney injury resulting from excessive salt intake at a young age.

Although we recently found that salt loading in young Dahl SS rats caused hypertension and kidney injury, likely through MR activation (12), it is not clear whether MR activation is a primary mechanism of increased salt sensitivity in childhood. To test the hypothesis that MR activation plays a significant role in kidney injury in young SS hypertension, we compared salt-induced hypertension and kidney injury in young adult salt-loaded uninephrectomized (UNx) Sprague-Dawley (SD) rats, an acquired SS hypertension model. In addition, although it is unclear whether increased levels of aldosterone play a significant role in salt-induced high BP and kidney injury in young SS hypertensive models, higher plasma aldosterone has been observed in young rats and humans (7, 30, 34) and MR blockade has been shown to reduce BP and to have renoprotective effects in SS rats fed a HS diet even when serum aldosterone was suppressed (12, 19). Therefore, we also examined whether aldosterone itself is required for salt-induced renal injury in young UNx rats.

OBSERVATIONAL STUDIES HAVE suggested that increased blood pressure (BP) in childhood correlates with increased BP in adulthood (36). Hypertension is closely related to kidney dysfunction, which can cause increased BP. Therefore, both BP control and maintenance of kidney health at a young age may be critical for BP management later in life.

Salt consumption among very young children has increased in developed countries at a faster rate than in developing countries (9, 28, 33). It is believed that high salt (HS) intake during prepuberty contributes to high BP later in life (1, 23). In addition, increased BP resulting from excessive salt consumption has been shown to be enhanced in the young in several animal models of salt-sensitive (SS) hypertension (35). We previously demonstrated that in Dahl SS rats, an SS hypertension model, HS intake at a young age accelerates the development of kidney injury and hypertension (12). Interestingly, salt restriction during infant weaning has been reported to lower BP at 15 yr of age (30). Thus it is believed that HS intake in childhood may result in high BP and kidney dysfunction later in life.

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MATERIALS AND METHODS

Animals. Three-week-old male SD rats were purchased from Tokyo Laboratory Animals Science (Tokyo, Japan) and underwent a left nephrectomy. Rats were maintained in a humidity (60 ± 5%), temperature (23 ± 1.5°C), and light cycle (0700–1900 h)-regulated room. Animals had free access to food and drinking water. All animal procedures were conducted in accordance with the guidelines for the care and use of laboratory animals of the University of Tokyo Graduate School of Medicine. Body weight and systolic BP were measured before death. Systolic BP was measured using the tail-cuff method (P-98A; Softron, Tokyo, Japan). For direct measurement of mean arterial pressure (MAP), animals were put under light ether anesthesia and a left femoral arterial catheter (PE-50, Clay Adams, Parsippany, NJ) was inserted in relevant treatment groups. During MAP measurement, the rats were in a conscious and unrestrained state and a pressure transducer (model TP-200T, Nihon-Kohden, Tokyo, Japan) connected to a thermal array recorder (WS-641G, Nihon-Kohden) was used. Measurements at a stable level were then averaged. Twenty-four-hour urine samples were collected using metabolic cages after the 4-wk treatment.

Experiment 1: comparison of effects of salt loading in young and adult UNx rats. To confirm that a HS (8.0% NaCl) diet increases BP and urinary protein in young UNx rats more than in adult rats, 3- and 10-wk-old UNx rats (n = 4/group) were given a HS diet for 4 wk. Three- and 10-wk-old UNx rats fed a normal salt (NS: 0.5% NaCl) diet for 4 wk were used as a control group.

Experiment 2: drug effects on salt-induced hypertension and renal damage in young UNx rats. Three-week-old UNx rats were fed a HS diet and then divided into the following groups: 1) HS diet alone (HS); 2) HS diet plus treatment with the MR blocker eplerenone (Ep; 100 mg·kg⁻¹·day⁻¹ in chow); 3) HS diet plus treatment with the angiotensin receptor blocker (ARB) olmesartan (Olm; 10 mg·kg⁻¹·day⁻¹ in chow); 4) HS diet plus treatment with aldosterone and Olm [Olm+aldo; low-dose (8 µg·kg⁻¹·day⁻¹)]; aldosterone was infused using a subcutaneously-implanted Alzet osmotic pump 2002 (Durect, Cupertino, CA); this dose elevated plasma aldosterone to the levels observed during HS intake in adrenalectomized rats (data not shown). Three- and 10-wk-old UNx rats were fed HS diet plus treatment with the MR blocker eplerenone (Ep; 100 mg·kg⁻¹·day⁻¹ in chow) and then divided into the following groups: 1) HS diet alone (HS); 2) HS diet plus treatment with the MR blocker eplerenone (Ep; 100 mg·kg⁻¹·day⁻¹ in chow) and then divided into the following groups: 3) HS diet plus treatment with the MR blocker eplerenone (Ep; 100 mg·kg⁻¹·day⁻¹ in chow) and then divided into the following groups: 4) HS diet plus treatment with aldosterone and Olm [Olm+aldo; low-dose (8 µg·kg⁻¹·day⁻¹)]; aldosterone was infused using a subcutaneously-implanted Alzet osmotic pump 2002 (Durect, Cupertino, CA); this dose elevated plasma aldosterone to the levels observed during HS intake in adrenalectomized rats (data not shown).

Laboratory assays. Plasma aldosterone was measured using an RIA kit (TFB, Tokyo, Japan). Urinary protein was measured using a micro-TP test kit (Wako, Osaka, Japan).

RNA extraction and real-time RT-PCR. Total RNA from whole kidneys was extracted by isogen-chloroform extraction and isopropanol precipitation (5). Gene expression was analyzed quantitatively by real-time RT-PCR using an ABI PRISM 7000 (Applied Biosystems) together with assay-on-demand primers and probe sets for rat β-actin, transforming growth factor-β (TGF-β), plasminogen activator inhibitor-1 (PAI-1), macrophage chemoattractant protein-1 (MCP-1), connective tissue growth factor (CTGF), angiotensin-converting enzyme (ACE), angiotensinogen (Agt), Sphk1, and NADPH oxidase subunit gp91phox (Applied Biosystems). PCR was carried out with an initial activation of AmpliTaq Gold DNA polymerase at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, and annealing and extension at 60°C for 1 min. Relative quantification was accomplished by measuring the threshold cycle and using a standard curve. Gene expression of the target sequence was normalized to that of β-actin (10).

Measurement of NADPH-induced superoxide production. Production of NADPH-induced (final concentration, 100 µmol/l) superoxide anions in the kidney was measured by bis-N-methylacridinium (lucigenin) chemiluminescence as described previously (17 18).

Histological examination. For morphological evaluation, paraffinized kidney sections (3-µm thickness, n = 4/group) were stained with periodic acid-Schiff (PAS) reagents and analyzed semiquantitatively for glomerulosclerosis and tubulointerstitial injury as described previously (26). The degree of glomerulosclerosis (×20 objective) was determined on the basis of the disappearance of cellular elements from the tuft, capillary loop collapse, and the folding of the glomerular basement membrane with the accumulation of amorphous material. Depending on the percentage of glomeruli involved, the sections were graded as 0 (0%), I (1–25%), II (26–50%), III (51–75%), or IV (76–100%). The glomerulosclerosis score was calculated as [(I ×%
grade I) + (2 × % grade II) + (3 × % grade III) + (4 × % grade IV)) (number of glomeruli). For each animal, between 70 and 100 glomeruli were examined. Renal sections were scored in a blinded manner. Tubulointerstitial injury was defined as tubular cast formation, sloughing of tubular epithelial cells, tubular atrophy, or thickening of the tubular basement membrane. For each kidney, 30 cortical fields (×10 objective) were scored as 0 (0%), I (1–25%), II (26–50%), III (51–75%), or IV (76–100%). Areas of injured tubulointerstitium were calculated digitally using an image-analysis program (ImageJ).

**Immunohistochemistry.** Immunostaining of CD68 was performed to assess macrophage infiltration. Sections were deparaffinized and autoclaved in pH 6.0 citrate buffer (121°C, 15 min) for antigen retrieval. Endogenous peroxidase activity was blocked using a peroxidase-blocking reagent (Dako). A primary CD68 monoclonal antibody (MCA341GA, Serotec) was incubated with the sections at room temperature for 30 min at a 1:50 dilution. A biotinylated rabbit anti-mouse secondary antibody (Dako) and LSAB streptavidin-horseradish peroxidase (Dako) were then used. The slides were lightly counterstained with hematoxylin to assist in tissue visualization, and macrophages and monocytes were identified in the renal interstitial tissues of each rat. The number of CD68-positive cells in 20 fields of tubulointerstitial tissue (×10 objective) was counted using ImageJ and averaged for each rat.

**Statistical analysis.** Data are expressed as means ± SE. Statistical analysis of simultaneous multiple comparisons was performed by two-way (experiment 1) or one-way (experiment 2) ANOVA followed by Fisher’s protected least significant difference (PLSD) test. P < 0.05 was considered to be statistically significant. Plasma aldosterone was logarithmically transformed before the performance of statistical comparisons.

**RESULTS**

**Experiment 1: comparison of salt loading in young and adult UNx rats.** Rats fed a HS diet for 4 wk starting at a young age (3 wk) developed much higher systolic BP (180.9 ± 22.6 mmHg, P < 0.01) than young NS diet-fed UNx rats (117.8 ± 9.5 mmHg) (Fig. 1A). Rats fed a HS diet starting in adulthood (at 10 wk) also exhibited significantly elevated systolic BP (NS vs. HS diet: 140.3 ± 3.4 vs. 163.5 ± 4.9 mmHg, P < 0.05). However, after 4 wk of HS intake, systolic BP was higher in the young rats than in the adult rats (P < 0.05), even though the young rats had lower systolic BP than the adult rats before salt loading (P < 0.05) (Fig. 1A). Salt-loaded young rats also had much higher urinary protein levels (100.3 ± 44.5 mg/day) than NS diet-fed young rats (8.8 ± 1.2 mg/day, P < 0.01), but adult rats in both the NS and HS groups had similar low urinary protein levels (9.6 ± 0.9, 10.4 ± 0.3 mg/day) (Fig. 1B). Thus salt loading elicited a greater increase in BP and more severe renal damage when initiated at a very young age. These results in young UNx rats are similar to those published in previous studies (4, 24).

Young NS diet-fed UNx rats had moderately higher plasma aldosterone levels than adult NS diet-fed rats at the end of treatment (355.9 ± 126.1 vs. 195.0 ± 73.5 pg/ml, respectively, P = 0.08). Although plasma aldosterone was profoundly suppressed by salt loading, it was significantly higher in young HS diet-fed rats (young vs. adult HS-fed rats, 48.1 ± 18.3 vs. 11.9 ± 13.7 pg/ml, P < 0.01) (Fig. 1C). There was no significant difference in serum potassium between young and adult rats fed either diet (Supplementary Fig. S1; all supplementary material for this article is available online at the journal web site), suggesting that serum potassium does not affect aldosterone levels in this model.

**Experiment 2: effects of eplerenone on salt-induced hypertension and renal damage in young UNx rats.** Consistent with the results of experiment 1, the HS diet group had significantly higher systolic BP than the NS diet-fed group (177.3 ± 7.0 vs. 111.0 ± 2.1 mmHg, P < 0.01). The EP group had moderately but significantly lower systolic BP (143.8 ± 5.7 mmHg, P < 0.01) than the HS diet group (Fig. 2A). Similarly, eplerenone greatly decreased directly-measured MAP in salt-loaded rats (157.5 ± 8.5 vs. 132.5 ± 6.3 mmHg, P < 0.05). The HS diet group showed higher urinary protein than the NS diet group (127 ± 44.5 vs. 9.4 ± 1.3 mg/day, P < 0.01), but salt-induced proteinuria was completely blocked by eplerenone treatment (6.6 ± 0.9 mg/day, P < 0.01) (Fig. 2B). As shown in Fig. 3, A and B, the HS diet group had increased glomerular and interstitial injury and macrophage infiltration (P < 0.05 for all parameters) compared with the NS diet group, whereas the EP group showed less histological evidence of salt-induced renal damage (P < 0.05 for all parameters).

Renal mRNA expression of inflammatory markers, such as PAI-1 and CTGF, was significantly higher in the HS group.
than in the NS group \((P < 0.05\) for both), and the expression of both TGF-\(\beta\) and MCP-1 mRNA showed a trend of being increased in the HS group \((P = 0.07\) for both). Salt-induced changes in expression of these inflammatory markers were attenuated \((P < 0.05\) for all parameters) by eplerenone (see Fig. 4A). A lucigenin chemiluminescence assay showed stimulation of NADPH oxidase-induced reactive oxygen species (ROS) generation in the kidneys of HS diet-fed rats \((P < 0.05)\), which was attenuated by eplerenone \((P < 0.05)\). RT-PCR analysis revealed that mRNA for the renal NADPH oxidase subunit gp91phox was upregulated in HS diet rats \((P < 0.05)\) and reduced in Ep rats \((P < 0.05)\) (see Fig. 4B).

Agt and Sgk1 mRNA expression was significantly elevated by HS intake \((P < 0.05,\) respectively) and suppressed by eplerenone \((P < 0.05)\). Although a HS diet did not increase ACE mRNA, ACE expression was marginally decreased by eplerenone treatment \((P = 0.06)\) (see Fig. 4C). In contrast, Sgk1 and Agt mRNA expression was not af-

Fig. 3. Comparison of representative microphotographs of periodic acid-Schiff (PAS) and CD68 staining (arrow showing CD68-positive staining; A) and analysis of histological glomerular and tubulointerstitial scores and CD68 invasion in young UNx rats (B); \(n = 5–6\) in each group. Values are means ± SE. +\(P < 0.05\) vs. HS. *\(P < 0.05\) vs. NS.
fected by salt loading in adult UNx rats (Supplementary Fig. S2).

Experiment 2: effects of olmesartan alone and in combination with low-dose aldosterone on salt-induced hypertension and renal damage in young UNx rats. Olmesartan did not lower systolic BP (165.8 ± 8.7 mmHg) (Fig. 2A) but normalized urinary protein (18.1 ± 8.5 mg/day, \( P < 0.01 \)) in young UNx rats fed a HS diet (Fig. 2B). In the Olm group, renal damage was ameliorated (glomerular score, \( P < 0.05 \); tubulo-interstitial score, \( P < 0.05 \); macrophage infiltration, \( P < 0.05 \)) (Fig. 3, A and B) and renal ROS markers were decreased (renal NADPH oxidase activity: \( P < 0.05 \); gp91phox expression: \( P < 0.05 \)), which is similar to the effects of eplerenone (Fig. 4B). Interestingly, olmesartan also attenuated salt-induced changes

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**Fig. 4. A:** comparison of inflammatory markers plasminogen activator inhibitor-1 (PAI-1), macrophage chemoattractant protein-1 (MCP-1), connective tissue growth factor (CTGF), and transforming growth factor-\( \beta \) (TGF-\( \beta \)) mRNA in the kidney. **B:** comparison of NADPH oxidase activity and mRNA expression of the NADPH oxidase subunit gp91phox. **C:** kidney expression of components of the renin-angiotensin-aldosterone (RAA) system angiotensin converting enzyme (ACE), angiotensinogen (Agt), and serum- and glucose-regulated kinase (Sgk1) mRNA. actb, \( \beta \)-Actin; \( n = 5–6 \)/group. See the legend to Fig. 2 for explanation of other abbreviations. Values are means ± SE. \(+ P < 0.05 \) vs. HS. \(* P < 0.05 \) vs. NS.
in renal Agt and ACE mRNA expression (P < 0.05 for all parameters) (Fig. 4C). Olmesartan decreased renal expression of Sgk1 (P < 0.05), although plasma aldosterone was not further suppressed by olmesartan (56.6 ± 3.0 pg/ml) compared with HS diet-fed rats (43.7 ± 5.2 pg/ml) (Fig. 5). Low-dose aldosterone administration resulted in a complete nullification of the normalizing effect of olmesartan on urinary protein (94.8 ± 26.8 mg/day, P < 0.01) in HS diet-fed rats (Fig. 2B) without affecting BP (Fig. 2A). However, plasma aldosterone levels in Olm+aldo (131.8 ± 29.3 pg/ml, P = 0.17) rats were marginally higher than in Olm rats.

**Experiment 2: effects of FAD286 on salt-induced hypertension and renal damage in young UNx rats.** It has been suggested that aldosterone-induced MR activation is required for salt-induced renal injury because the renoprotective effects of olmesartan are nullified by low-dose aldosterone infusion. However, plasma aldosterone levels were similar in HS diet-fed and Olm rats. Thus, to elucidate the role of aldosterone in this process, we examined the effects of the aldosterone synthase inhibitor FAD286. FAD286 had no effect on tail-cuff systolic BP (Fig. 2A) or MAP (157.5 ± 4.8 mmHg) in HS diet-fed rats but significantly reduced urinary protein (15.9 ± 5.8 mg/day, P < 0.05) (Fig. 2B). Again, FAD286 did not further attenuate plasma aldosterone (40.8 ± 9.8 pg/ml) (Fig. 5). The effects of FAD286 were similar to the effects of olmesartan.

**Experiment 2: effects of tempol on salt-induced hypertension and renal damage in young UNx rats.** Tempol did not affect systolic BP (160.1 ± 8.9 mmHg) (Fig. 2A) or plasma aldosterone (39.9 ± 10.7 pg/ml) but significantly ameliorated changes in urinary protein (15.3 ± 6.0 mg/day, P < 0.05) in HS diet-fed rats (Fig. 2B). Similar to eplerenone, salt-induced changes in renal expression of Sgk1, Agt, and ACE mRNA were attenuated by tempol treatment (P < 0.05 for all parameters) (Fig. 3C).

**DISCUSSION**

This study has demonstrated that in salt-loaded UNx rats, an acquired SS hypertension model, salt loading at a young age induced a greater increase in BP and more severe kidney injury than salt loading in adults, in agreement with our previous report on Dahl SS rats (12). Moreover, we found that MR blockade moderately ameliorated hypertension and normalized kidney function in young salt-loaded UNx rats, which showed greater kidney expression of Sgk1. Taken together, these data suggest that MR activation plays an important role in the progression of hypertension and kidney injury in both inherited (12) and acquired (the present study) models of SS hypertension in young animals.

In the present study, the treatment of rats with ARB suggested an important renoprotective effect of MR. Olmesartan greatly reduced urinary protein excretion without lowering BP. In a previous study (21), transient angiotensin receptor blockade during puberty was shown to suppress salt-induced progression of hypertension and renal dysfunction in Dahl SS rats. However, the primary mechanism of the renoprotective effect of olmesartan may occur not through angiotensin receptor blockade itself but rather through decreased MR activity because ARB-induced renoprotection was completely reversed when combined with low-dose aldosterone infusion. Therefore, angiotensin receptor stimulation may play a secondary role when aldosterone-stimulated MR activation exceeds a certain threshold value, although this threshold is low. The aldosterone synthase inhibitor FAD286 also normalized urinary protein in HS-fed rats. These data suggest that aldosterone-mediated MR activation is necessary for the onset and progression of kidney injury in young HS diet-fed UNx rats. High aldosterone levels during salt loading may be critical for the modulation of kidney function in young HS diet-fed rats. In the Framingham Offspring Study, a slight increase in plasma aldosterone within the normal range was found to result in increased urinary albumin (8) and hypertension (31) in people with moderately HS intake.

Nevertheless, plasma aldosterone was not significantly decreased in the Olm and FAD groups. This discrepancy might be due to limitations in the sensitivity of our aldosterone assay. Alternatively, stimulation of regional (renally synthesized) rather than systemic (adrenally synthesized) aldosterone may play an important role in renal injury (32). Interestingly, similar treatment with FAD286 (4 mg·kg⁻¹·day⁻¹ for 4 wk) decreased angiotensin II-stimulated levels of plasma aldosterone but not baseline levels in UNx rats (16). As renal aldosterone is increased in SS hypertension models (3), FAD286 may exert its renoprotective effects by inhibiting aldosterone synthesis in the kidney. In fact, local aldosterone production induces kidney injury, which is reversible by FAD286, and has been suggested to contribute to renal injury in adrenalectomized diabetic rats (27). In the present study, because the renal components of the RAA system were enhanced, angiotensin II-stimulated aldosterone synthesis in the kidney may have contributed to the progression of renal damage in young salt-loaded UNx rats and angiotensin receptor-mediated suppression of such regional aldosterone synthesis by olmesartan may improve renal function. Indeed, olmesartan decreased renal Sgk1 expression without affecting plasma aldosterone. Interestingly, low-dose aldosterone nullified the renoprotective effects of olmesartan, so a slight increase in aldosterone may be sufficient to induce renal injury by excessive salt intake.

In the kidneys of young salt-loaded UNx rats, the inflammatory cytokines PAI-1, CTGF, TGF-β, and MCP-1 were
MINERALOCORTICOID RECEPTOR ACTIVATION IN YOUNG RATS

upregulated, and ROS and NADPH oxidase were stimulated. Macrophage infiltration was also enhanced. Similarly, aldosterone treatment in conjunction with excess salt has been shown to cause glomerulosclerosis and tubulointerstitial fibrosis associated with increased expression of inflammatory cytokines (6, 29). However, aldosterone treatment under sodium-deficient conditions does not cause kidney damage. Thus excessive salt intake is needed for the development of aldosterone-induced kidney injury (25). The antioxidant tempol also ameliorated kidney injury in the present study. Thus we believe that HS intake-generated ROS (14) may trigger and strengthen MR activation. In this study, these phenomena were more apparent when salt-induced aldosterone suppression was modest, for example, in young HS diet-fed UNx rats. It was recently reported that MR expression is increased in distal tubules soon after birth and declines thereafter (17). This may not explain the increased susceptibility of young rats to glomerular injury but suggests a possible mechanism for enhanced salt retention in young rats. Thus, when young rats were fed a HS diet, more salt may have been retained. This caused greater ROS generation than in adult rats, which resulted in greater MR activation even in the presence of only slightly increased aldosterone levels. Further experiments are needed to clarify this alternative hypothesis.

This study also found that Agt expression was upregulated in young HS diet-fed rats, but that MR blockade, as well as angiotensin receptor blockade, suppressed Agt and ACE expression. These data suggest that in this SS hypertension model, regional MR stimulates the RA system, which leads to a vicious cycle in the RAA system, as demonstrated previously (11, 13). Therefore, the enhanced effects of salt loading on BP and renal injury in young rats may be attributable to increased renal RAA system activity, including high plasma aldosterone.

In conclusion, this study has suggested that even in an acquired model of SS hypertension (12), excessive salt intake during early life can have far greater detrimental effects on renal function than during adulthood and that this effect is at least partly mediated by MR activation. This study, along with our recent report on Dahl SS rats (12), suggests that MR activation might be a universal mechanism of increased salt sensitivity and may play a particularly important role in kidney injury after salt loading early in life. Also, we believe that small increases in aldosterone synthesis during periods of excessive salt intake may be important for salt-induced excessive renal injury in young SS hypertension. Furthermore, ROS and angiotensin receptor stimulation may enhance aldosterone-stimulated MR activity, which causes a salt-induced increase in BP and renal damage.

DISCLOSURES

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