Cardiovascular, endocrine, and body fluid-electrolyte responses to salt loading in mRen-2 transgenic rats

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Li, Ping, Mariana Morris, Carlos M. Ferrario, Cindy Barrett, Detlev Ganten, and Michael F. Callahan. Cardiovascular, endocrine, and body fluid-electrolyte responses to salt loading in mRen-2 transgenic rats. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1130–H1137, 1998.—We previously demonstrated that mRen-2 transgenic (Tg(+)) rats are sensitive to chronic high NaCl intake, showing increased arterial pressure and vasopressin (VP) secretion. In this study, we determined the effect of a chronic osmotic challenge, 4 days of drinking 2% NaCl, on direct arterial blood pressure, heart rate, fluid-electrolyte balance, circadian rhythm of mean arterial pressure (MAP), and changes in plasma VP and catecholamines. Under baseline conditions, male Tg(+) rats showed a significant shift in the peak in circadian MAP into the light portion of the day-night cycle. Substitution of 2% NaCl for drinking water caused a rapid increase in MAP, 20–5 mmHg in Tg(+) rats within 6 h. Whereas the amplitude of circadian MAP fluctuations increased in salt-loaded Tg(+) rats, there was no significant change in the circadian timing of peak MAP with salt loading. Tg(+) rats showed exaggerated osmotic-induced increases in plasma VP, norepinephrine (NE), and epinephrine (Epi) compared with Tg(-) rats. Plasma NE and Epi were increased two- and fourfold, respectively, in the hypertensive rats with no significant change in the Tg(-) rats. Intravenous administration of a VP antagonist did not alter arterial pressure in either Tg(+) or Tg(-) rats. Tg(+) and Tg(-) rats showed a positive sodium balance with no significant difference observed between the groups. Tg(+) rats showed a significant increase in salt consumption, plasma sodium, osmolality, and hematocrit, accompanied by a negative water balance. We conclude that Tg(+) rats are sensitive to acute and chronic osmotic stimuli in terms of blood pressure, fluid-electrolyte balance, and plasma VP and catecholamines. Whereas elevated plasma VP does not contribute to the hypertensive response, increased sympathetic drive may mediate the salt-induced blood pressure changes in this model.

hypothesis; renin; vasopressin; catecholamines; osmotic challenge

INCREASED SALT INTAKE has been incriminated as a pathogenic factor in hypertension. There is strong evidence that a genetic predisposition is involved in salt-induced hypertension in human subjects and animal models (12). Thus identification of the genetic factors involved in salt sensitivity would be a major scientific contribution and an aid in prevention and treatment of the disease. A new model of hypertension has been produced by the insertion of the mouse renin gene into the rat genome (36). This Sprague-Dawley-derived strain is characterized by overexpression of both circulating and tissue components of the renin-angiotensin system (RAS). The hypertension in this model is characterized by a shift in the circadian rhythm of arterial pressure with peak pressures seen late in the dark cycle (26). Recently, we have shown that arterial blood pressure in the Tg(+) rat is sensitive to a chronic osmotic challenge produced by forced consumption of 2% NaCl for 4 days, a typical experimental paradigm for producing activation of central peptidergic neurons (10). These hypertensive Tg(+) rats showed increased blood pressure and plasma vasopressin (VP) in response to ingestion of 2% NaCl (10), as well as a reduction in blood pressure produced by sodium depletion (5). Therefore, studies in this genetically engineered model suggest that overactivity of the renin gene causes a salt and/or osmosensitive state, a finding that may be applicable to clinical situations.

A variety of neuroendocrine and physical factors are believed to be involved in salt sensitivity, including sympathetic activation, VP secretion, baroreceptor impairment, and volume status. It has been demonstrated that the sympathetic nervous system is involved in the development of salt-sensitive hypertension in numerous animal models (7, 14, 46, 49). Sharma et al. (44) found that a high-salt diet caused a greater pressor response to norepinephrine (NE) in salt-sensitive than in salt-resistant subjects. VP is another important factor that may contribute to the pathogenesis of salt-sensitive hypertension. VP is a potent vasoconstrictor and an important hormone regulating water and salt balance. Increased secretion of VP has been found in several models of hypertension such as DOCA-salt hypertension, spontaneously hypertensive rats (SHR), and Dahl rats (17, 28, 43). The most convincing evidence for a role of VP in salt-sensitive hypertension is the fact that DOCA-salt hypertension cannot be produced in Brattleboro rats that lack VP (17, 39).

It has been demonstrated that the central RAS plays an important role in the endocrine regulation of blood pressure and electrolyte balance. Injection of ANG II into the central nervous system (CNS) increases arterial pressure via release of VP (23) and activation of the sympathetic nervous system (27). Interestingly, angiotensin peptides and sodium act synergistically to produce exaggerated behavioral and physiological responses (2, 22). Bruner and colleagues (8) were the first to demonstrate that dietary sodium intake could produce a hypertensive response to chronic subpressor CNS infusions of ANG II. Thus overactivity of the RAS in the CNS of the renin transgenic model may cause the exaggeration of VP, sympathetic neural, and cardiovascular responses to osmotic stimulation.
In the present study, a chronic blood pressure-monitoring system was used to examine the effect of salt loading on acute and chronic cardiovascular parameters. Circadian modeling analysis was utilized to determine whether the osmotic challenge would effect a shift in circadian rhythm shown in this model of hypertension and to characterize the rapidity of the osmotically induced pressor response. The mechanisms of increased pressor responsiveness in the mRen-2 transgenic model were explored by evaluating the effects of salt loading on fluid-electrolyte balance and circulating VP and catecholamines. The role of circulating VP in exaggerated osmotic responsiveness of Tg(+) was explored by use of VP antagonist.

METHODS

All experiments were carried out in accordance with the Guiding Principles for the Care and Use of Animals as delineated by the American Physiological Society. Male 10- to 12-wk-old heterozygous Tg(+) positive for the mRen-2 gene and control Tg(-) rats were used in this study. These transgenic rats were produced by breeding female heterozygous rats with male Hanover Sprague-Dawley controls, the strain from which the transgenic animals were derived. Genotyping was used to confirm presence of the transgene, and arterial pressure was used to confirm the phenotypic expression. The rats were obtained from the breeding colony established at the Hypertension Center of Wake Forest University School of Medicine. Animals were housed in either Nalgene metabolism or regular polycarbonate cages modified by the attachment of a fluid swivel and a pressure transducer on the top of the cage. The animals had free access to regular rat chow (1% NaCl) and either water or 2% NaCl. The vivarium was maintained at 21–22°C with a 12:12-h light-dark cycle (5:00 PM lights off).

In the metabolism study, arterial catheters (PE-60 with a Silastic tip) were inserted into the common carotid artery under xylazine:ketamine anesthesia (5.7:71 mg/kg im). The catheter was tunneled through a protective spring that was attached to a fluid swivel and the animal. Catheter patency was confirmed by the attachment of a fluid swivel and a pressure transducer. Blood samples were taken over a 30-min period between 1:00 and 3:00 PM. On the second and fourth day after the start of saline ingestion, arterial pressure was measured and an intravenous bolus infusion of the VP antagonist [ß-mercapto-ß-cyclopentamethylenepropionyl]-O-Me-Tyr²,Arg⁸[VP (9 µg/100 g body wt) was given to determine whether circulating VP played a role in the elevation of arterial pressure. When given 2% NaCl as the sole drinking fluid, Tg(+) rats had significantly higher basal MAP than Tg(-) rats (142 ± 5 vs. 93 ± 2 mmHg/24 h). When given 2% NaCl as the sole drinking fluid, Tg(+) rats showed a rapid increase in MAP (20 mmHg within 6 h) compared with the same time period in the previous 24-h recording (Fig. 1). Arterial blood pressure was increased in Tg(+) rats throughout the 4-day period of salt loading (Fig. 2). Salt consumption produced no change in MAP in Tg(-) rats (Figs. 1 and 2).

RESULTS

Effect of 2% NaCl consumption on cardiovascular parameters. Tg(+) rats had significantly higher basal MAP than Tg(-) rats (142 ± 5 vs. 93 ± 2 mmHg/24 h). When given 2% NaCl as the sole drinking fluid, Tg(+) rats showed a rapid increase in MAP (20 mmHg within 6 h) compared with the same time period in the previous 24-h recording (Fig. 1). Arterial blood pressure was increased in Tg(+) rats throughout the 4-day period of salt loading (Fig. 2). Salt consumption produced no change in MAP in Tg(-) rats (Figs. 1 and 2).
There was no significant difference in HR between the two groups, and salt intake did not significantly affect HR (data not shown).

Nonlinear rhythm analysis showed that the rhythm-adjusted 24-h mean MAP (MESOR) and amplitude were higher in salt-loaded Tg(+) rats than water-replete Tg(+) rats (Table 1). However, the consumption of 2% NaCl did not alter the MESOR and amplitude for MAP in Tg(-) rats (Table 1). Acrophases of the dominant 24-h period for MAP occurred at 1:30 AM and 1:54 AM in salt-loaded and water-replete Tg(-) rats, respectively. In contrast, the acrophases of the dominant 24-h period for MAP in Tg(+) rats were shortly after the onset of the light phase (6:20 AM for water replete and 5:30 AM for salt loaded). A further significant improvement of fit (6–14%) was obtained by including additional harmonics in the fitting procedure (Table 1, best fit).

Effect of 2% NaCl consumption on plasma VP and catecholamines. There were no differences in the basal levels of plasma NE and Epi between Tg(1) and Tg(2) rats (Fig. 3). After 4 days of salt loading, there were significant increases in plasma Epi and NE in Tg(1) rats but no changes in Tg(2) rats. Basal plasma VP was similar in Tg(1) and Tg(2) rats, 0.4 ± 0.1 and 0.3 ± 0.2 pg/ml, respectively (Fig. 4). Plasma VP was increased to 3.9 ± 0.8 and 1.7 ± 0.4 pg/ml in Tg(1) and Tg(2) rats with a significantly greater response (P < 0.01) observed in Tg(1) rats.

Effect of 2% NaCl consumption on fluid-electrolyte balance. There were no differences in basal hematocrit and plasma osmolality and sodium between Tg(+) and Tg(-) rats (Table 2). Salt loading produced significant increases in plasma sodium, hematocrit, and osmolality in Tg(+) rats with no change observed in Tg(-) rats.

Fig. 1. Acute pressor effect of salt loading in transgenic [Tg(+)] (n = 12) and Tg(-) (n = 11) rats. Data represent means ± SE of hourly mean arterial pressure (MAP) of same animals 24 h before (water) and after being given 2% NaCl (salt) in place of drinking water. P < 0.01, salt vs. water in Tg(+) rats.

Fig. 2. Twenty-four-hour rhythms for MAP in Tg(+) and Tg(-) rats maintained on tap water for 2 days and then on 2% NaCl for 4 days. Analysis is provided in Table 4.

Fig. 3. Salt loading increased plasma epinephrine (Epi) and norepinephrine (NE) in Tg(+) rats but not in Tg(-) rats. *P < 0.01, salt vs. water in Tg(+) rats.

Table 1. MAP rhythm in salt-loaded and water-replete Tg(+) and Tg(-) rats

<table>
<thead>
<tr>
<th></th>
<th>24-h Component</th>
<th>MESOR, mmHg</th>
<th>Amplitude, mmHg</th>
<th>Acrophase</th>
<th>Rhythm%</th>
<th>Best fit</th>
</tr>
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<tbody>
<tr>
<td>Tg(+) Water</td>
<td>142 ± 0.9</td>
<td>6.9 ± 1.3</td>
<td>6:20 AM ± 42 min</td>
<td>70.1</td>
<td>76.4*</td>
<td></td>
</tr>
<tr>
<td>2% NaCl</td>
<td>166 ± 0.1</td>
<td>11.4 ± 0.1</td>
<td>5:30 AM ± 6 min</td>
<td>50.3</td>
<td>58.7†</td>
<td></td>
</tr>
<tr>
<td>Tg(-) Water</td>
<td>95 ± 0.4</td>
<td>6.3 ± 0.5</td>
<td>1:30 AM ± 20 min</td>
<td>74.4</td>
<td>88.2*</td>
<td></td>
</tr>
<tr>
<td>2% NaCl</td>
<td>98 ± 0.2</td>
<td>6.5 ± 0.4</td>
<td>1:54 AM ± 12 min</td>
<td>61.3</td>
<td>67.7‡</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Mean arterial pressure (MAP) was monitored for 2 consecutive days in water-replete transgenic [Tg(+)] and Tg(-) rats for next 4 days of salt loading in same animals. Partial Fourier curve, consisting of components of 24, 12, 8, and 6 h (*), 24, 12, 8, and 4.8 h (†), and 24, 12, and 6 h (‡) was fit to data. Significance of improvement of fit by adding additional harmonics to dominant 24-h period was tested by multiple-model comparisons. Shown are rhythm-adjusted 24-h mean (MESOR), amplitude, acrophase and percentage of rhythm of dominant 24-h period together with improvement by adding harmonics.
In addition, plasma potassium was decreased in Tg(1) rats, whereas no change was observed in Tg(2) subjects. The hypokalemia in Tg(1) rats is perhaps due to increased arterial pressure eliciting a kaluresis. Over the 4-day osmotic challenge, Tg(1) rats consumed significantly more 2% NaCl than Tg(2) rats (see Fig. 6A) and tended (P < 0.06) to have a greater intake of sodium (Fig. 5A). The greater intake of 2% NaCl reached significance only on day 3 (Fig. 6A). Both Tg(1) and Tg(2) groups showed positive sodium balance after consuming 2% NaCl with no significant difference between the groups (Fig. 5C). Drinking 2% NaCl caused a significant negative water balance (fluid intake-urine output) in Tg(1) rats over the 4 days of salt loading with no significant change observed in Tg(2) rats (Fig. 6C). Over the 4 days of high salt intake, water balance averaged 46.4 ± 1.1 ml Tg(1) compared with 14.6 ± 3.2 ml Tg(2) rats, indicating a significant loss of body fluids in the Tg(1) group. High salt intake significantly increased urine output, with an exaggerated diuresis in Tg(1) rats compared with Tg(2) rats (Fig. 6B).

Effect of VP antagonist on NaCl-induced blood pressure increases. Consumption of 2% NaCl for 2 or 4 days produced a significant (~30 mmHg) increase in arterial pressure in Tg(1) rats. In contrast, Tg(2) rats showed only a slight (7 mmHg) nonsignificant increase in arterial pressure. Administration of a V1 VP antagonist had no significant effect on arterial pressure in Tg(+) or Tg(−) rats after either 2 or 4 days of drinking hypertonic saline (Table 3).

**DISCUSSION**

This study presents several original findings: 1) mRen-2 transgenic rats show a rapid increase in arterial pressure when forced to consume excessive NaCl, 2) this increase in arterial pressure does not affect the shift in circadian rhythm of arterial pressure shown by Tg(+) rats, 3) plasma catecholamines are elevated in addition to plasma VP, and 4) plasma VP does not play a role in this pressor response.

A key finding in this study is that Tg(+) rats showed an acute pressor response to the ingestion of a hyper-

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**Table 2.** Effect of 2% NaCl consumption on plasma sodium, potassium, osmolality, and hematocrit

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Tg(+)</th>
<th>Water</th>
<th>2% NaCl</th>
<th>Tg(+)</th>
<th>Water</th>
<th>2% NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, meq/l</td>
<td>145 ± 2</td>
<td>169 ± 7*</td>
<td>145 ± 2</td>
<td>149 ± 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium, meq/l</td>
<td>4.2 ± 0.1</td>
<td>3.6 ± 0.2*</td>
<td>4.4 ± 0.2</td>
<td>4.2 ± 0.3</td>
<td></td>
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</tr>
<tr>
<td>Osmolality, mosm/kg H2O</td>
<td>309 ± 3</td>
<td>361 ± 1*</td>
<td>310 ± 2</td>
<td>320 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39 ± 1</td>
<td>41 ± 1*</td>
<td>42 ± 2</td>
<td>41 ± 2</td>
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Values are means ± SE. *P < 0.05 vs. Tg(+) water.
tonic saline solution. The blood pressure began to rise rapidly and was significantly elevated by 20 mmHg after 6 h of exposure to 2% NaCl. This finding complements a previous report that showed that sodium depletion (acute furosemide treatment followed by a chronic low-salt diet) caused a rapid and sustained decrease (50 mmHg) in diastolic pressure in Tg(+) rats (5). Recently, Sesoko and colleagues (42) showed that a low-salt diet alone decreased arterial pressure in Tg(+) rats. Furthermore, others have shown that dehydration produces a modest increase (<10 mmHg) in arterial pressure and that restoration of drinking water causes a profound and rapid decrease (25 mmHg within 12 h) in arterial pressure (D. B. Averill, personal communication). These data suggest that overexpression of the mRen-2 gene produces a salt- or osmotic-sensitive state in this transgenic model.

Increased plasma or CNS RAS components in Tg(+) rats may exaggerate the input of osmotic information from peripheral and/or central osmoreceptors to effect an acute pressor response to the hypertonic solution. There is evidence that animals show drinking behavior and endocrine changes before consumed fluids have produced significant effects on systemic osmolality (1, 15). Peripheral osmoreceptors are located in the regions served by the mesenteric and portal circulation. Morita and colleagues (33) have shown that in dogs consumption of high-salt chow elicits frank increases in plasma sodium and decreases in renal nerve activity without altering MAP or plasma AVP. Osmosensitive information derived from peripheral osmoreceptors is transmitted to a number of CNS areas involved in autonomic and neurohumoral regulation, including the area postrema and nucleus tractus solitarius, lateral parabrachial nucleus, and possibly ventral medulla (24, 25). Hypertonic stimulation of peripheral osmoreceptors without a frank elevation in plasma osmolality can also activate the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei and thus increase VP secretion (4, 13, 34). Although we found that drinking 2% NaCl does not significantly elevate plasma sodium or osmolality at 6 and 48 h (unpublished observations), it is possible that small nondetectable increases in portal plasma sodium or osmolality may occur shortly after exposure to the hyperosmotic stimulus. This may activate the sympathetic nervous system and release VP to increase blood pressure and restore fluid-electrolyte balance in the early period of salt loading. After 4 days of drinking 2% NaCl, plasma sodium and osmolality are elevated in the Tg(+) rats. Recently, our laboratory found that an equivalent hypertonic saline load given by either intravenous (37) or intracerebroventricular (unpublished observations) routes elicits greater pressor responses in Tg(+) rats compared with Tg(−) rats. Because the cardiovascular response to osmotic stimulation is dependent on forebrain osmoreceptive regions, our findings may indicate that the central osmoreceptors in Tg(+) rats are more sensitive to osmotic challenges.

Alterations in the circadian variation in blood pressure have been shown to affect cardiovascular morbidity and mortality (35). In hypertensive populations, failure to show nocturnal decreases in arterial pressure...
is associated with microalbuminuria (6) and increases in left ventricular mass (48). In the present study, we used continuous, hour-by-hour monitoring of blood pressure to examine the cardiovascular response to high salt intake in Tg(+) and Tg(-) rats. Under baseline conditions, the acrophase (peak) in blood pressure in Tg(+) rats was shifted to about 6:00 AM (shortly after the onset of the light cycle) compared with Tg(-) rats, which peaked at approximately 2:00 AM. This finding is similar to that of Lemmer and colleagues (26, 40), who reported that the acrophase for arterial pressure was shifted into the early to midpart of the light cycle in Tg(+) rats. In the current study, the osmotic challenge did not change the circadian blood pressure pattern in either Tg(+) or Tg(-) rats but increased MESOR and amplitude in Tg(+) rats. These results are consistent with the report that high salt intake did not disrupt the circadian rhythm of blood pressure in either NaCl-sensitive SHR or NaCl-resistant Wistar-Kyoto rats (9). These findings are interesting in light of the recent observation that salt-sensitive hypertensive patients fail to show nocturnal decreases in arterial pressure compared with non-salt-sensitive patients (47) and suggests a possible pathophysiological link between salt sensitivity and alterations in circadian blood pressure control. The manifestations of that salt sensitivity may be different in human vs. animal subjects because salt-sensitive humans show an absence of diurnal rhythms, whereas mRen-2 transgenic rats show a shift in blood pressure rhythms.

Consistent with a previous report from our laboratory (10), 4 days of drinking 2% NaCl produced elevated levels of plasma VP in Tg(+) rats. Brain RAS is involved in osmotic stimulation of the hypothalamic VP axis (27). Recent studies demonstrated that osmotic-induced VP release was blocked by angiotensin receptor antagonists (21) or antisense directed against angiotensin receptors (31). Senanayake et al. (41) found that Tg(+) rats have elevated levels of angiotensin peptides in brain regions participating in the neuroendocrine regulation of blood pressure, such as hypothalamus and brain stem. Thus the elevated brain RAS in Tg(+) rats may exaggerate the osmotic input, resulting in increased secretion of plasma VP. Increased osmotic-induced levels of plasma VP have been observed in other models of salt-sensitive hypertension (16) and have been shown to play a role in the expression of salt sensitivity in DOCA salt hypertension and acute sinoaortic denervation (18, 38). In the current study, we found that increased plasma VP did not play a role in the arterial pressure response to salt loading in Tg(+) rats. In this respect, these rats resemble Dahl salt-sensitive rats and the elevation of plasma VP may be an attempt to compensate for greater osmotic challenges in Tg(+) rats. Alternatively, the elevation of plasma VP may be a reflection of increased CNS sensitivity to osmotic challenges. We have recently observed that intracerebroventricular injection of hypertonic NaCl produces exaggerated pressor and plasma VP responses in Tg(+) rats (unpublished observations).

Sympathetic activation must also be considered as mediating the cardiovascular response to the osmotic challenge in Tg(+) rats. Salt loading produced significant increases in plasma NE and Epi in Tg(+) but not in Tg(-) rats. A salt-induced increase in plasma catecholamines has been observed in salt-sensitive subjects and animals (12). Support for a role of catecholamines in the development of hypertension is provided by the demonstrations that peripheral 6-hydroxydopamine lesions of catecholamine neurons and neonatal guanethidine-induced sympathetotomy attenuated or prevented the development of salt-sensitive hypertension (19, 46). Both central ANG II injection and osmotic stimulation cause an increase in arterial pressure by activation of sympathetic nervous system (22, 27). The pressor response to intracerebroventricular ANG II is potentiated by a NaCl load administered by intravenous infusion or in the diet (3, 8). Furthermore, Katahira and colleagues (22) showed that reversing the routes of administration still results in synergistic interaction of ANG II and NaCl on arterial pressure, which is dependent on activation of the sympathetic nervous system (22). Thus in Tg(+) rats the sympathetic output is probably exaggerated by the elevated plasma sodium/osmolality, and this may be contributing to the elevation of arterial pressure at this time point. Further studies are needed to explore the role of sympathetic activation at different time points and to determine whether alterations in portal sodium receptors mediate these responses at early time points in the response.

There was no significant difference in sodium balance between salt-loaded Tg(+) and Tg(-) rats. However, only Tg(+) rats significantly increased hematocrit and plasma sodium and osmolality. In addition, urine output during salt loading was significantly greater for Tg(+) rats. During the 4 days of salt loading, Tg(+) rats demonstrated an overall negative water balance and increased hematocrit, suggesting that these animals became dehydrated. This fluid loss could have resulted in higher plasma sodium and osmolality. These abnormal physiological responses may be related to alterations in renal function in Tg(+) rats. For example, isolated perfused kidneys of Tg(+) rats show increased renal perfusion flow and GFR, but urinary sodium excretion is normal, suggesting that the sodium reabsorption is greater in Tg(+) rats (45). Gross and colleagues (20) reported that the pressure-diuresis-natriuresis relationship is shifted to higher pressure levels in Tg(+) rats. Thus pressure natriuresis/diuresis may play a role in the handling of the osmotic challenge in the transgenic rats. Indeed, salt-induced increase in blood pressure may have led to a diuresis in Tg(+) rats.

In conclusion, the genetic overexpression of angiotensin peptides in mRen-2 transgenic rats leads to exaggerated cardiovascular, endocrine, and body fluid-electrolyte responses to acute and chronic osmotic stress. These findings provide further evidence that central angiotensin systems are critical in the regulation of osmotic responsiveness and that the renin gene may be a candidate marker for salt-sensitive hypertension.
REFERENCES


